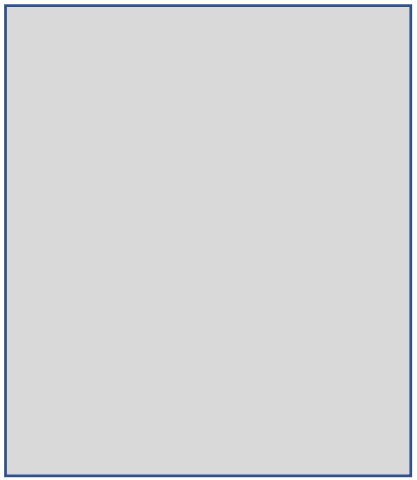
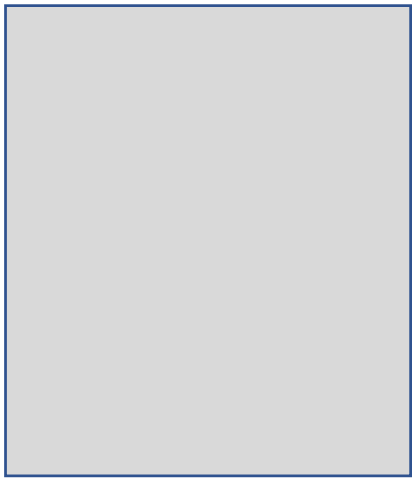
Twin Studies of Aging and Longevity



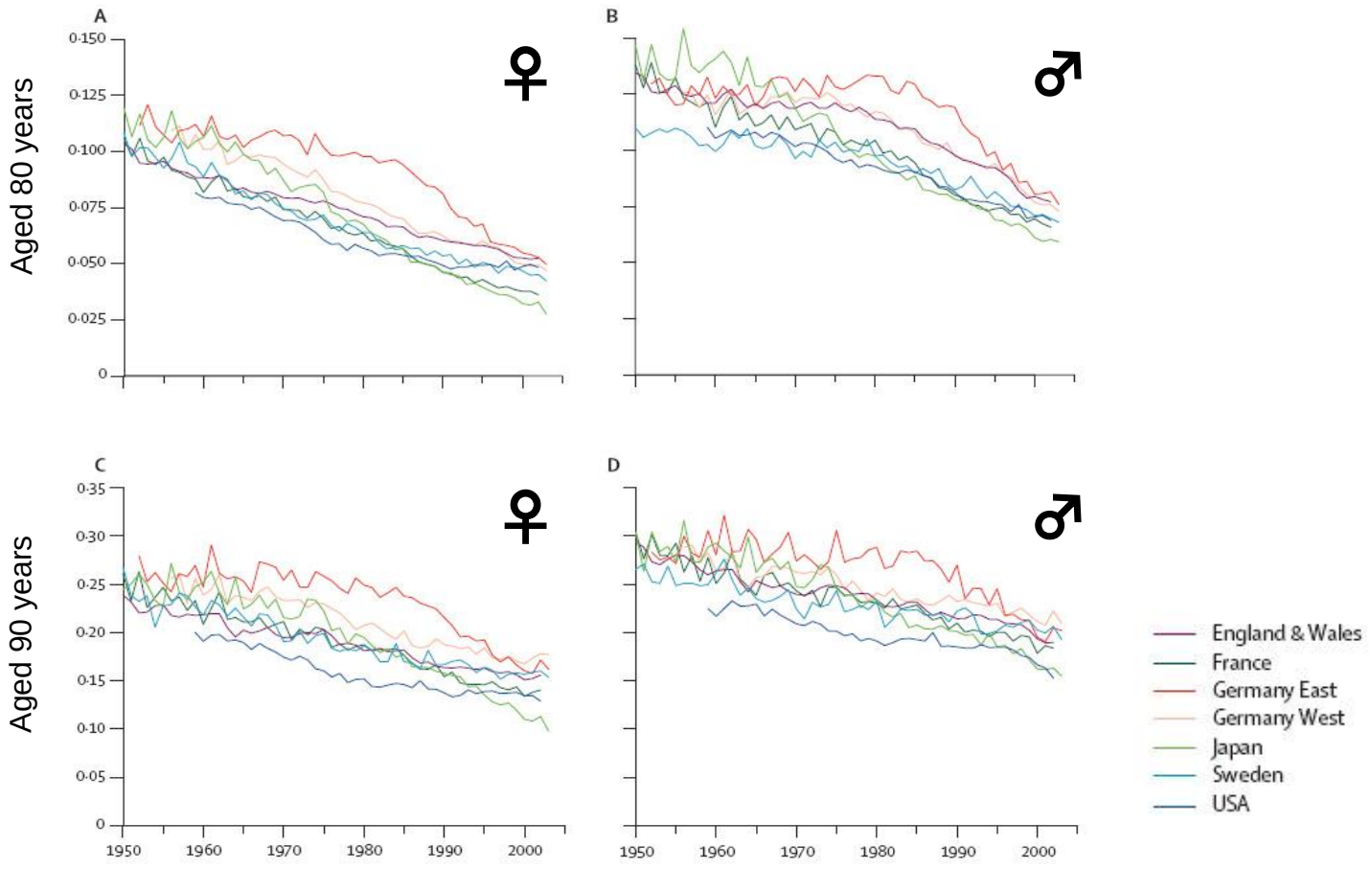


Kaare Christensen

University of Southern Denmark

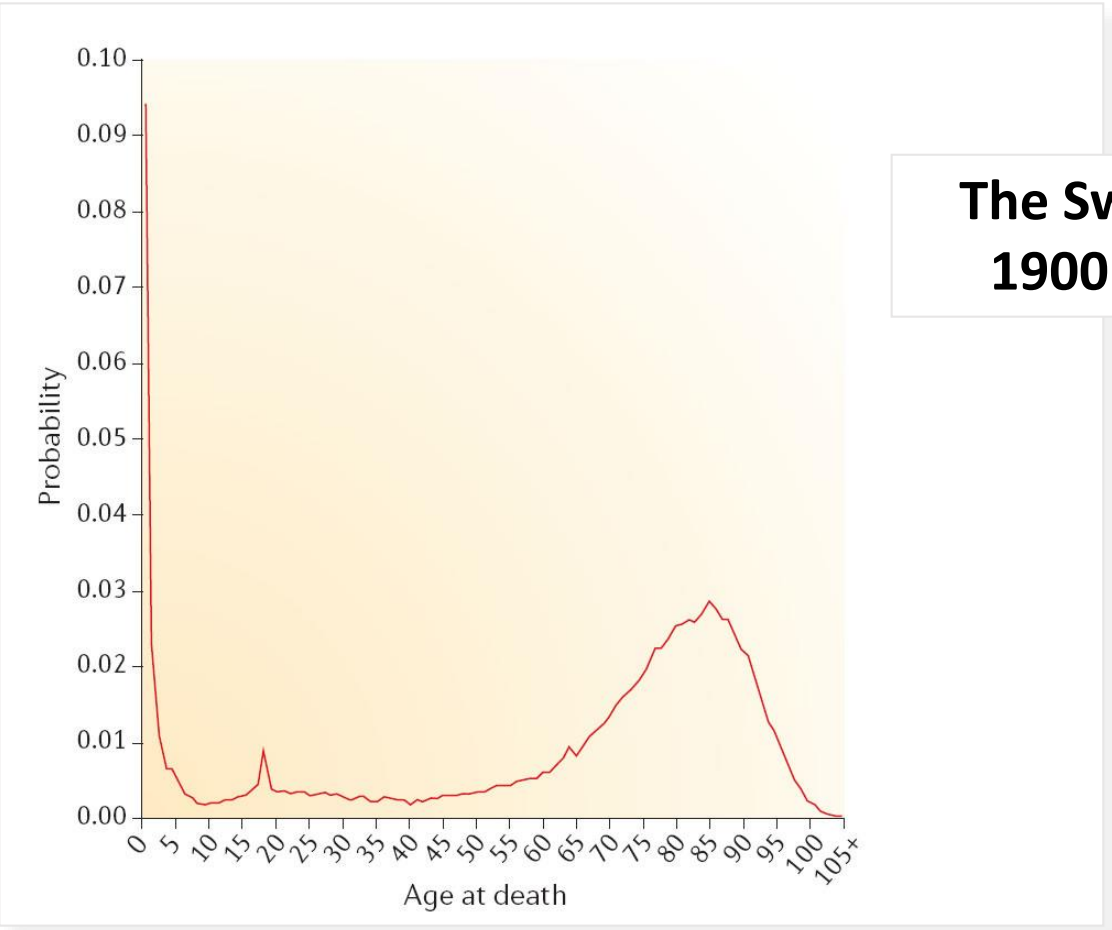
SDU
UNIVERSITY OF
SOUTHERN DENMARK

Probability of dying for elderly men and women 1950-2003



Christensen, Doblhammer, Rau, and Vaupel; Lancet 2009

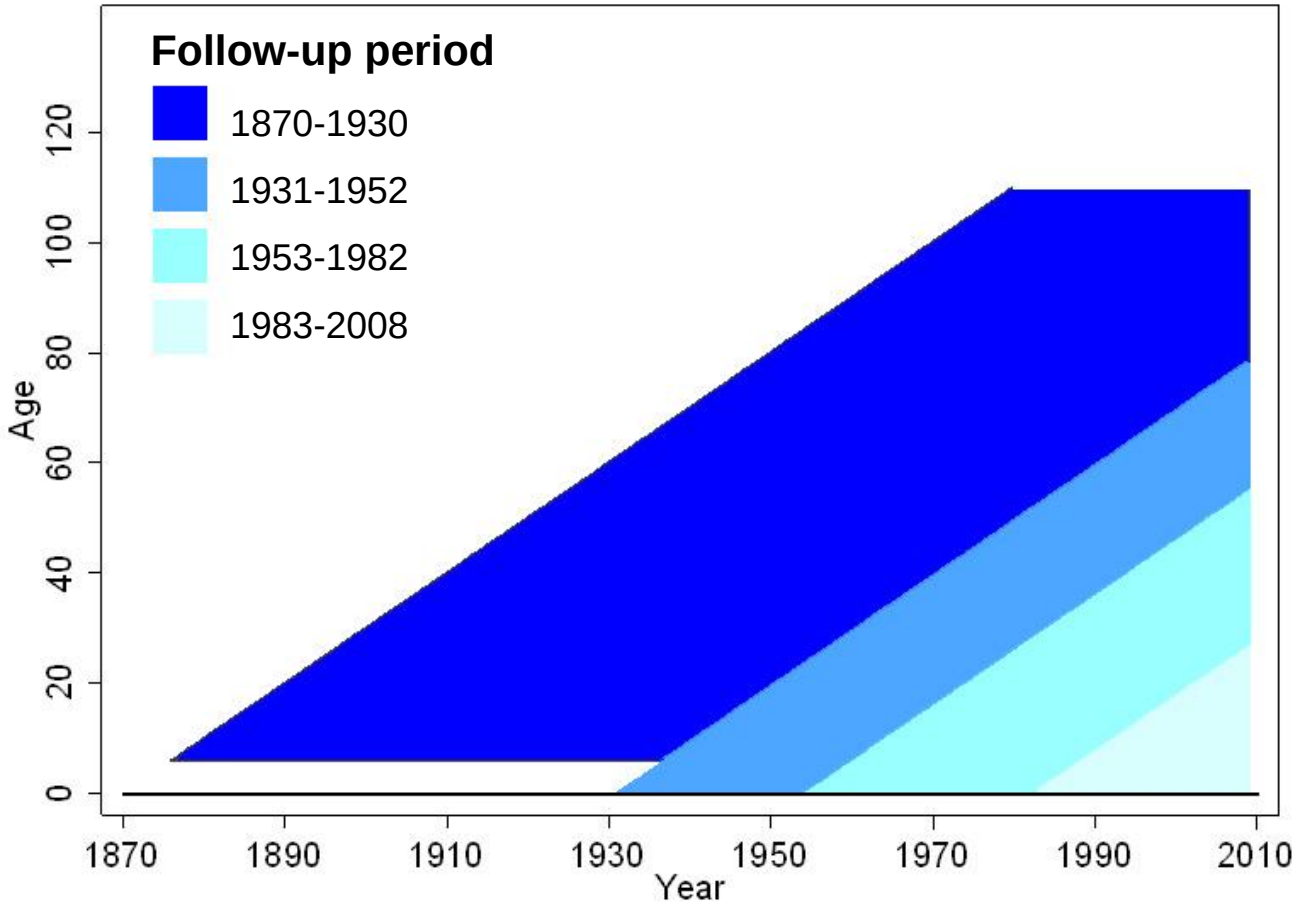
Large variation in lifespan within a birth cohort



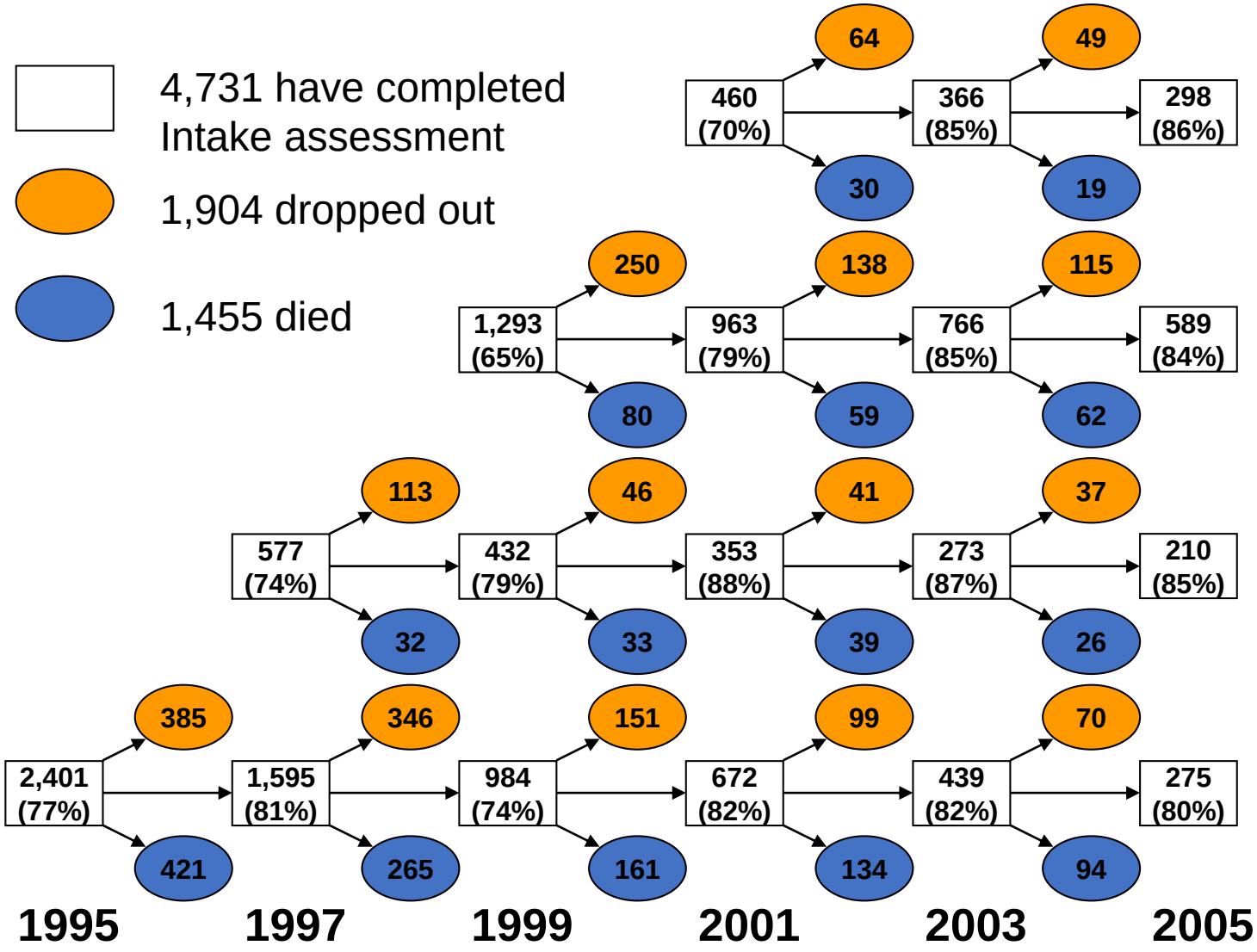
The Swedish female 1900 birth cohort

Berkeley Mortality Database; http:// demog.berkeley.edu/wilmoth/mortality/

Danish Twin Registry

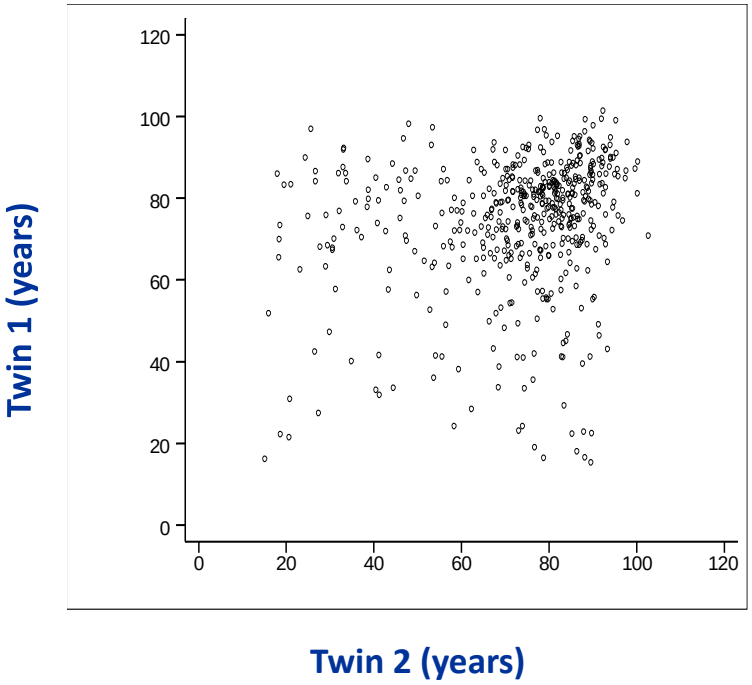


LSADT

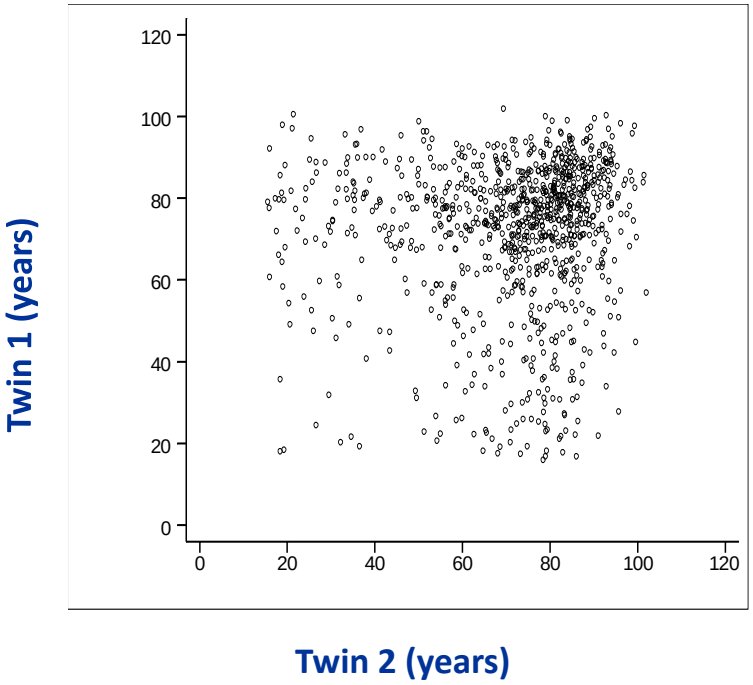

4,731 have completed Intake assessment
1,904 dropped out
1,455 died
2,401 (77%)
385
421
1,595 (81%)
346
265
984 (74%)
151
161
672 (82%)
99
134
439 (82%)
70
94
275 (80%)
577 (74%)
113
32
432 (79%)
46
33
353 (88%)
41
39
273 (87%)
37
26
210 (85%)
1,293 (65%)
250
80
963 (79%)
138
59
766 (85%)
115
62
589 (84%)
460 (70%)
64
30
366 (85%)
49
19
298 (86%)
1995
1997
1999
2001
2003
2005

Human Co-Twin Lifespan

Monozygotic



Dizygotic



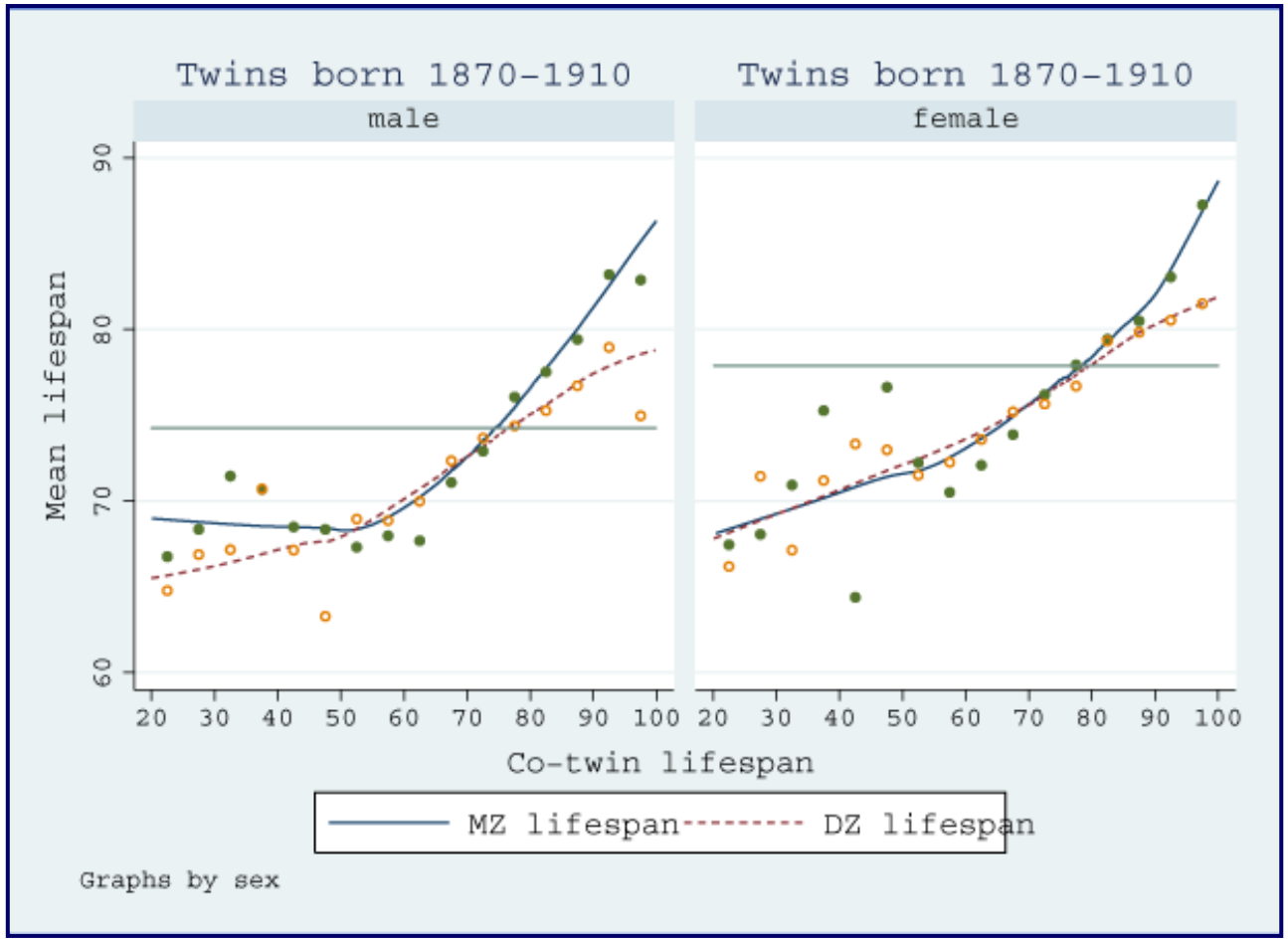
Herskind et al., Hum Genet 1996

Relative Recurrence Risk

Age	MZ male	DZ male	p
	Both survived past age 6		
75+	1.3 (1.2,1.3)	1.1 (1.0,1.2)	< 0.0001
80+	1.4 (1.3,1.6)	1.2 (1.1,1.4)	0.003
85+	2.0 (1.6,2.4)	1.7 (1.4,2.0)	0.03
90+	3.6 (2.1,5.0)	1.9 (0.8,2.9)	0.004

Hjelmborg et al., Hum Genet 2006

Lifespan of Twin by Lifespan of Co-Twin



Hjelmborg et al., Hum Genet 2006

Conclusion

- **Constant or increasing heritability of lifespan at the highest ages**

- **Limited genetic influence before age 60**

- **Focus on the highest ages when looking for genetic variants influencing lifespan**

Hjelmborg et al., Hum Genet 2006

Twin Design

- **Heritability**

  - **Life span 25%**

Twin Design

- **Heritability**

  - **Life span 25%**
  - **Functioning 50%**

Twin Design

- **Heritability**

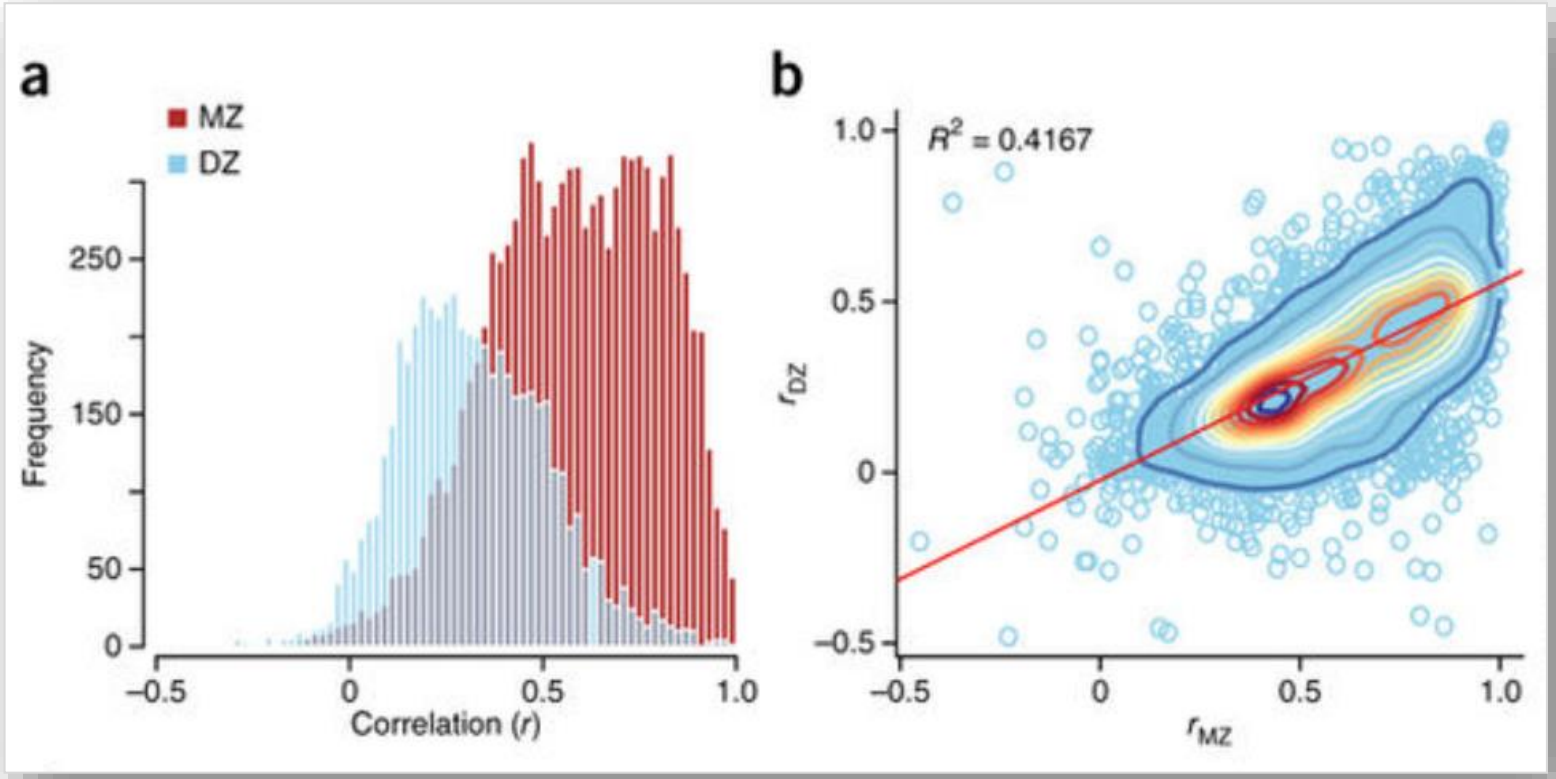
  - **Life span 25%**
  - **Functioning 50%**
  - **Alzheimer 70%**

Twin Design

- **Heritability**

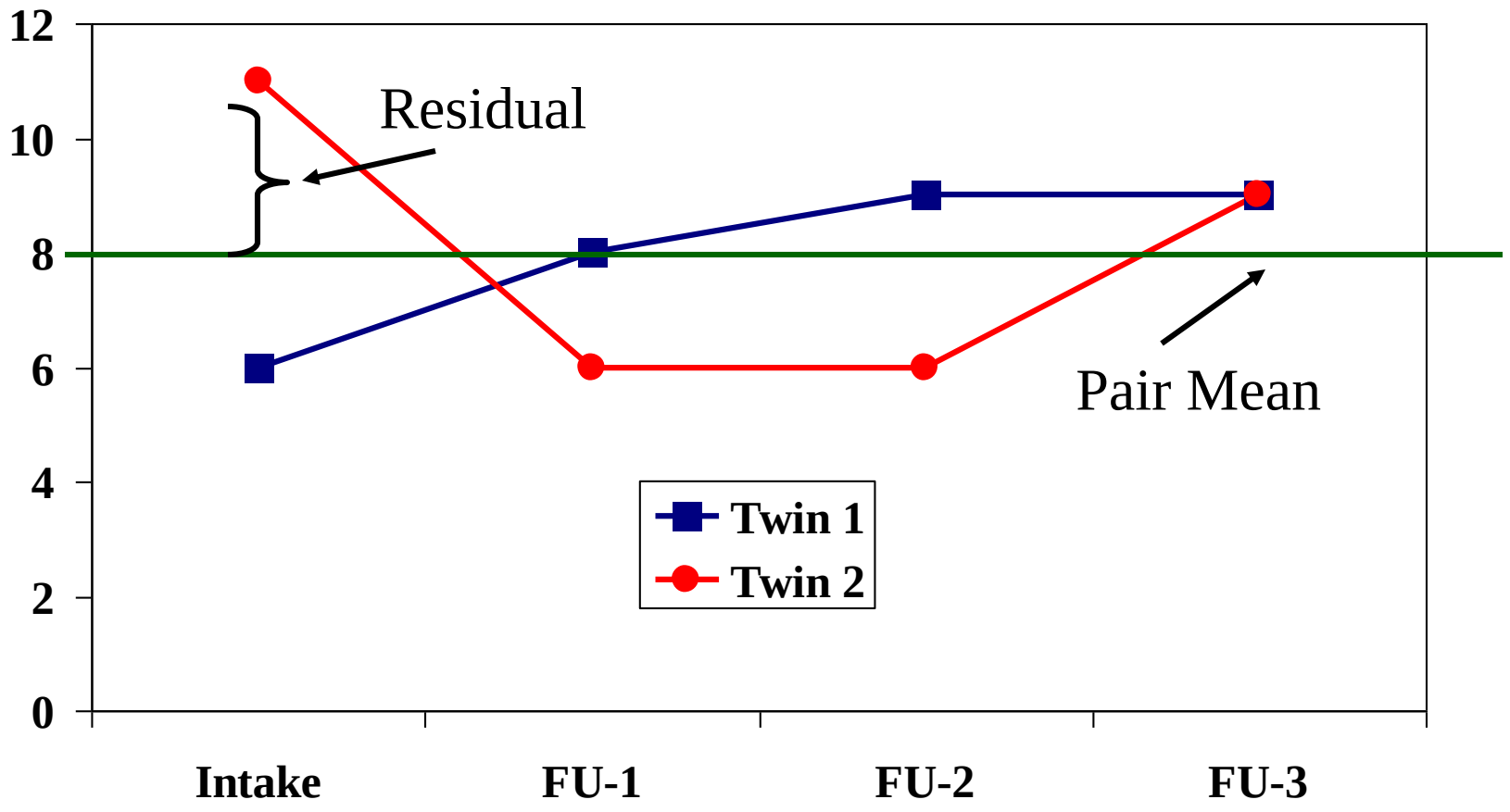
-	**Life span**	**25%**
-	**Functioning**	**50%**
-	**Alzheimer**	**70%**
-	**Parkinson**	**35%**

Meta-analysis of the heritability of human traits based on fifty years of twin studies

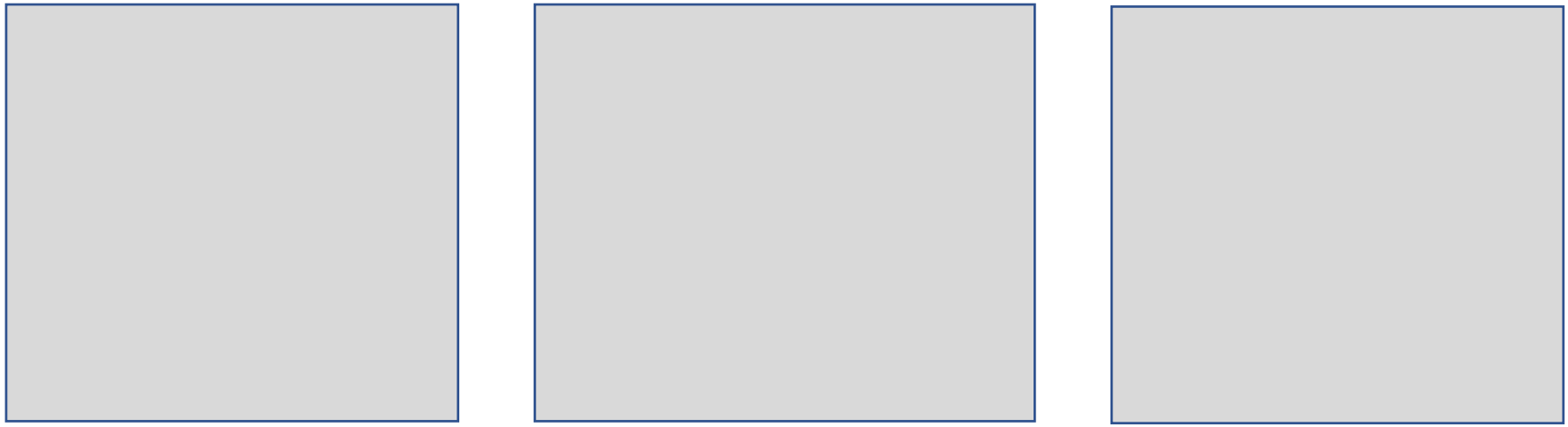


Polderman et al., Nature Genet, 2017

Genetics: MZ Twin Pairs Concordant for Level but Discordant at Specific Assessments



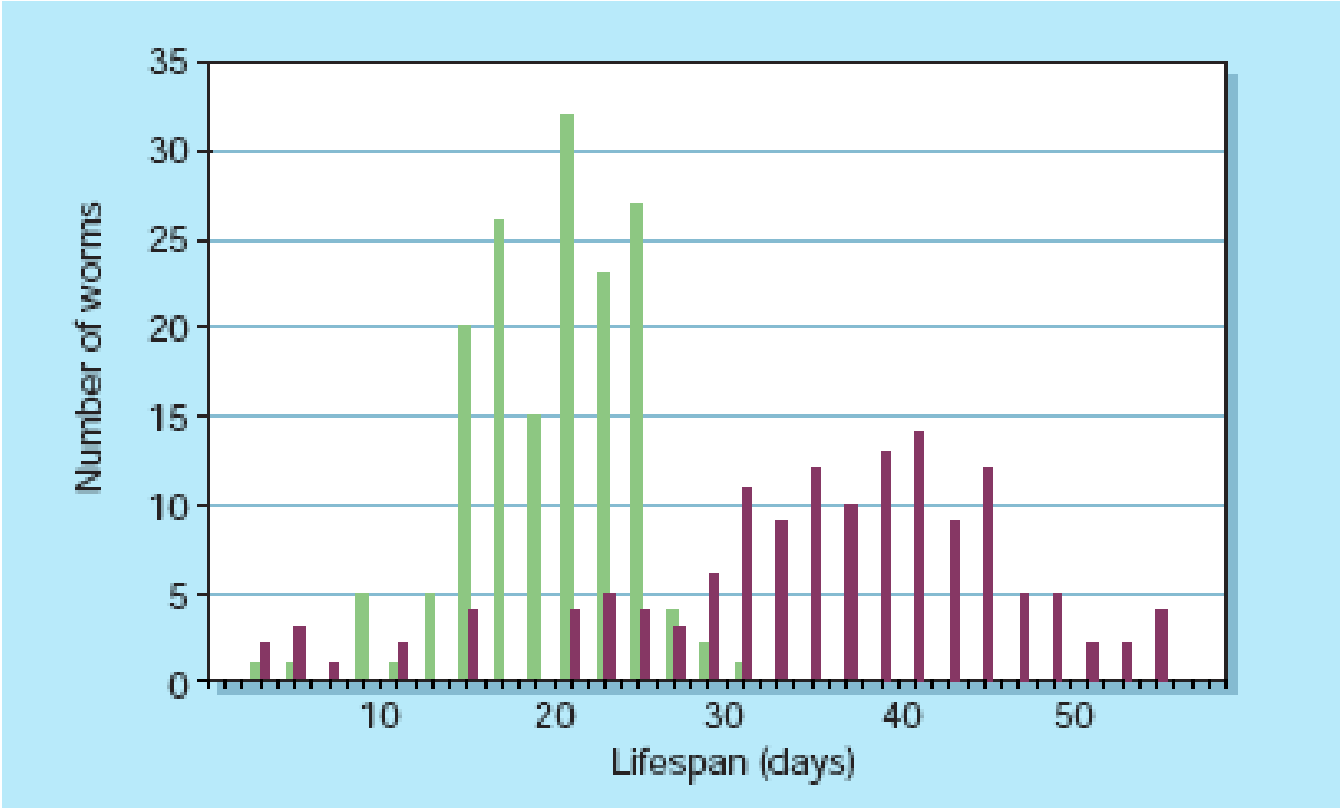
Chance!



Gene + environment

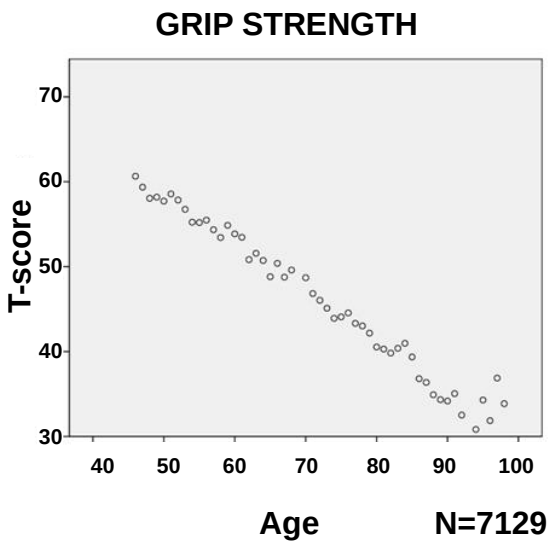
fixed

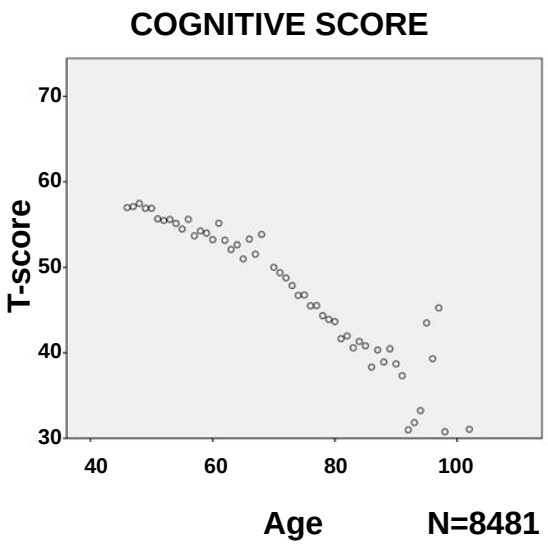
Lifespan C. elegans

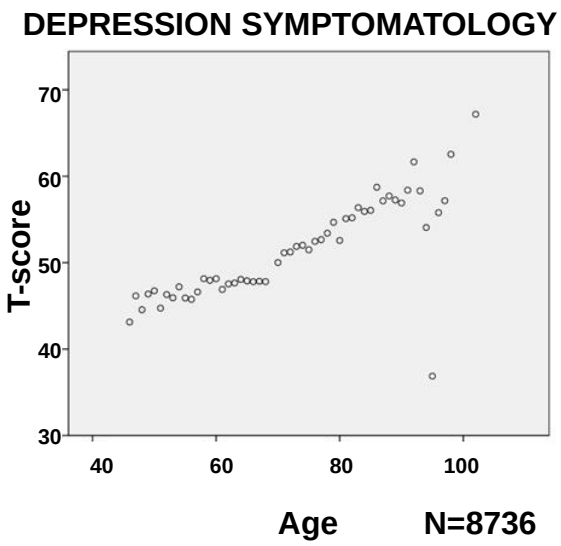


Kirkwood & Finch, Nature 2002; Data from Johnson, Science 1990

Age-Related Traits
Age 45-90

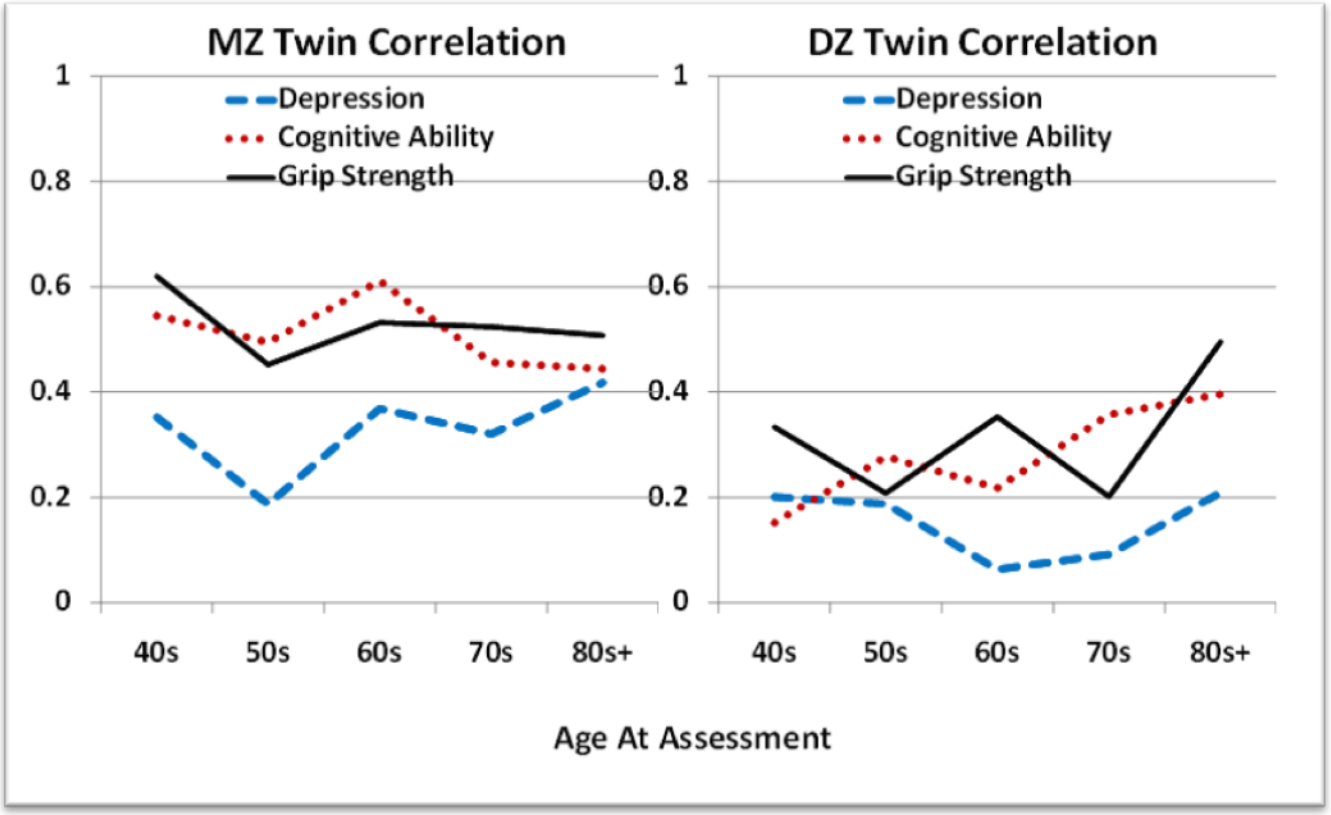






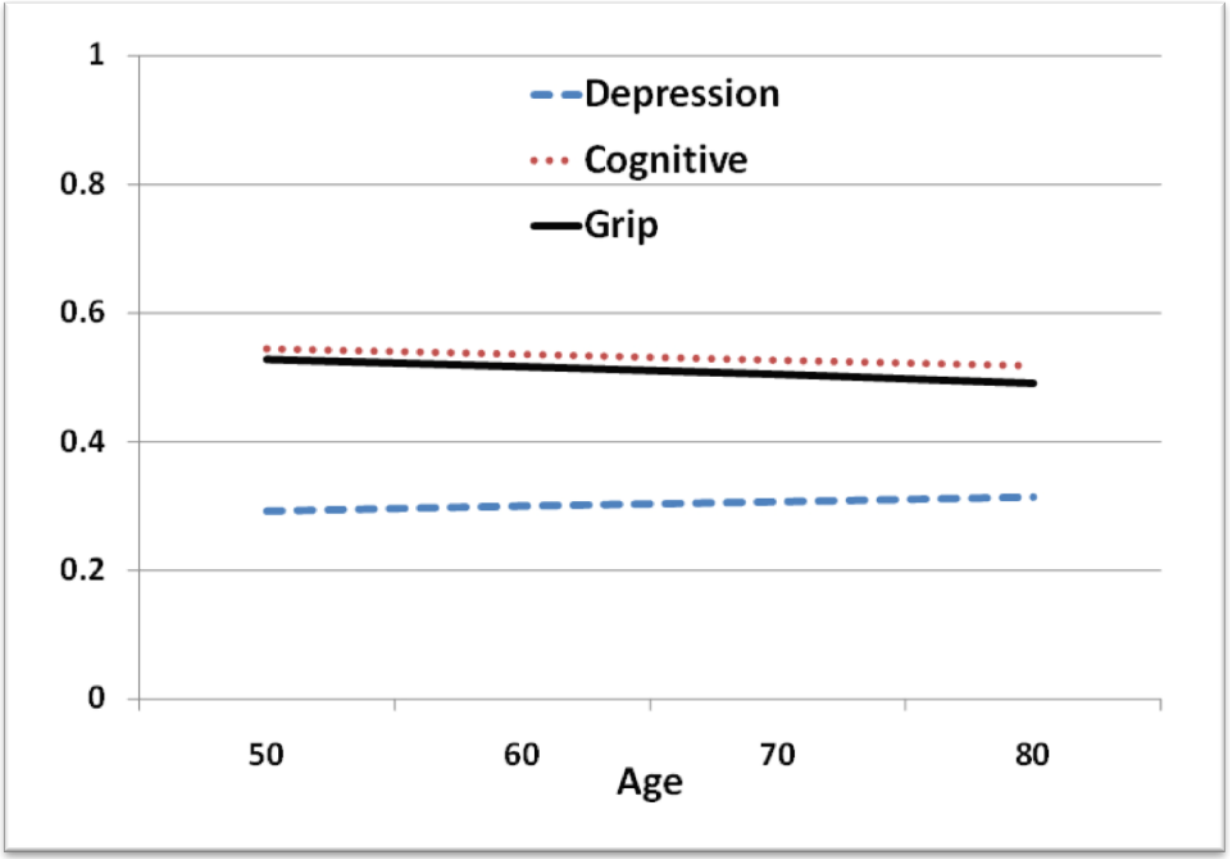
McGue & Christensen, Behav Genet, 2013

Twin Similarity



McGue & Christensen, Behav Genet, 2013

Heritability in the Latter Half of the Lifespan



McGue & Christensen, Behav Genet, 2013

Middle Age Danish Twin Study

Intake (MADT):

- Completed in 1998
- N=4314 born 1931-1952
- 83% of surviving eligible twins

Follow-up (MADT & MIDT):

- Completed in 2008-2011
- N=2402 (MADT) and 10,281 (MIDT) born 1931-1969
- ~50% eligible twins participated

McGue, Skytthe & Christensen, Int J Epi, 2014

MADT Lifestyle Assessment

Domain	# Items	Reliability	Description/Sample Items
Physical Activity	6	a=.64	Go on a rapid walk for exercise? Cycle at least 3 km?
Intellectual Activity	8	a=.67	Visit a museum or art exhibit? Read a book, news magazine, or similar?
Social Activity	6	a=.71	Attend a party or social event? Visit family or friends in their homes?
Healthy Diet	5	a=.56	Frequency of eating fruit, vegetables, etc.
Smoking Packyears	2	NA	Number of cigarettes etc. smoked daily times number of years smoked
Drinks per week	5	NA	Average number of drinks/week in past 6 months

McGue, Skytthe & Christensen, Int J Epi, 2014

Twin Correlations and Biometric Estimates

Lifestyle Factor	r_{MZ} (N=1069)	r_{DZ} (N=1390)	a^2	c^2	e^2
Physical Activity	.45	.23	.45 (.32, .49)	.01 (.00, .11)	.54 (.51, .59)
Intellectual Activity	.52	.31	.47 (.30, .55)	.06 (.00, .20)	.47 (.44, .52)
Social Activity	.38	.19	.38 (.24, .43)	.01 (.00, .12)	.61 (.57, .66)
Healthy Diet	.38	.21	.32 (.19, .42)	.06 (.00, .17)	.62 (.58, .67)
Smoking	.69	.34	.69 (.62 ,.72)	.00 (.00, .07)	.31 (.28, .34)
Drinking	.43	.24	.45 (.28, .49)	.01 (.00, .13)	.54 (.51, .61)

McGue, Skytthe & Christensen, Int J Epi, 2014

Genetics of Aging

May be (largely?) constructed to reinforce and complement heritable tendencies

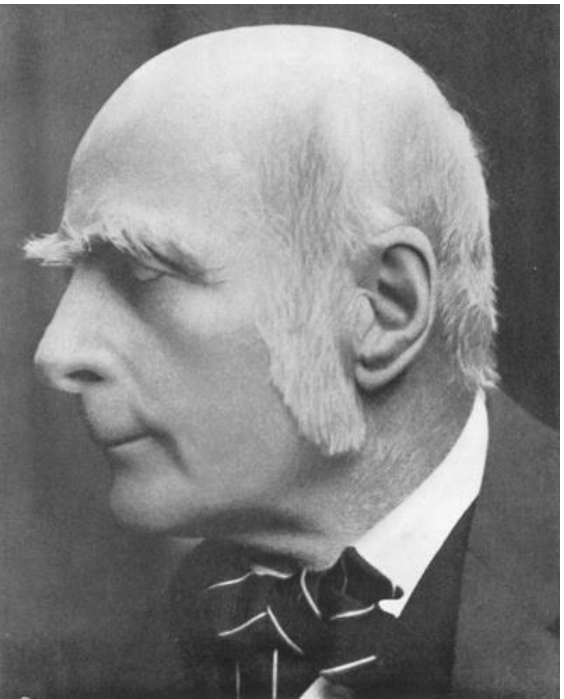
May be the basis for stable heritable influences

McGue, Skytthe & Christensen, Int J Epi, 2014

Twins - An old-timer in family design

ANTHROPOLOGICAL MISCELLANEA.

The History *of* Twins, *as a Criterion of the* Relative Powers *of* Nature *and* Nurture. By Francis Galton, F.R.S.*



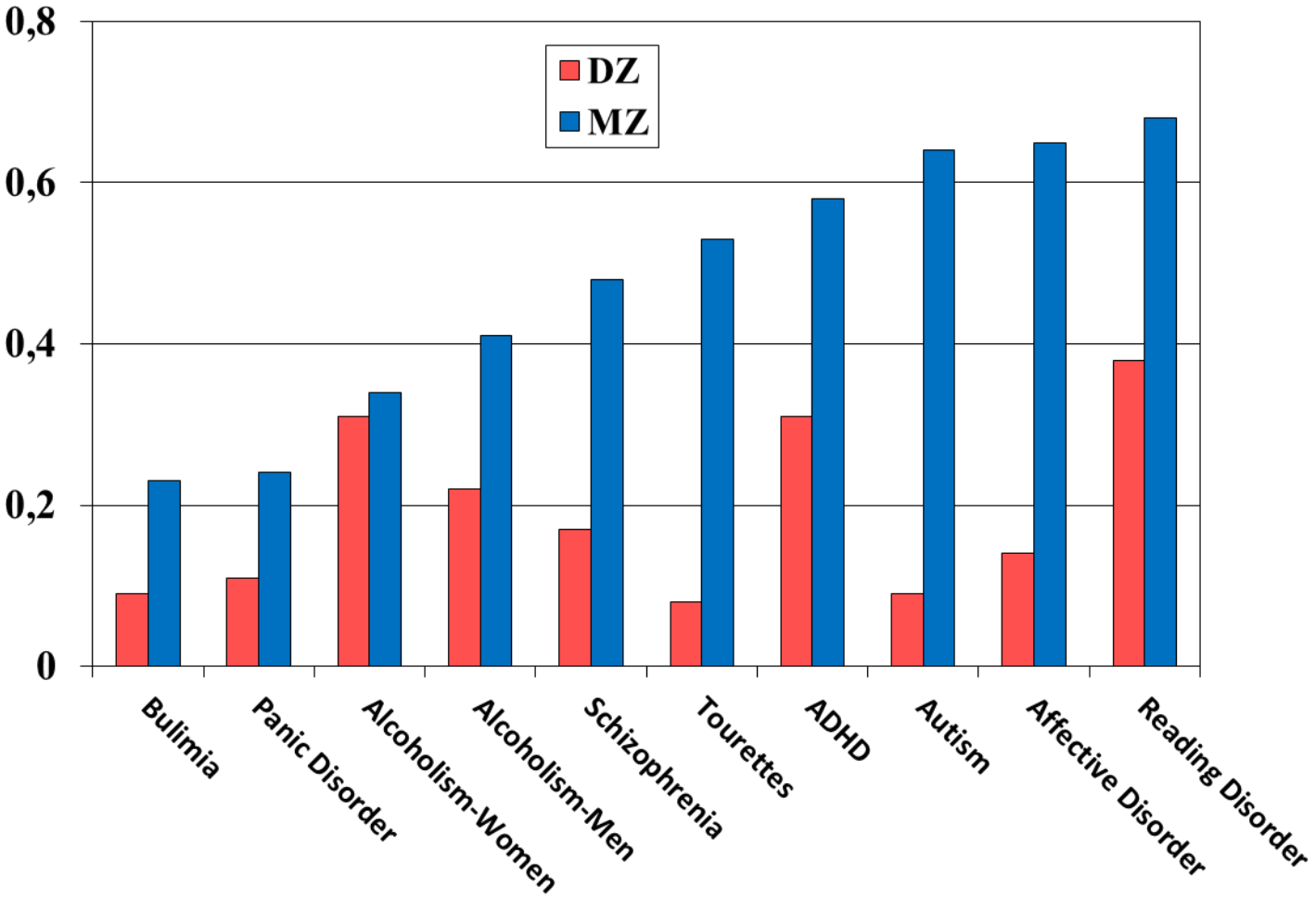
"Extreme similarity and extreme dissimilarity between twins of the same sex are nearly as common as moderate resemblance." *F. Galton (1876)*

JB Watson (Behaviorism) on Twins

"Suppose we were to take individual twins into the laboratory and begin rigidly to condition them along utterly different lines… Those of us who have spent years in the conditioning of children and animals cannot help but realize that the two end products would be as different as night and day."

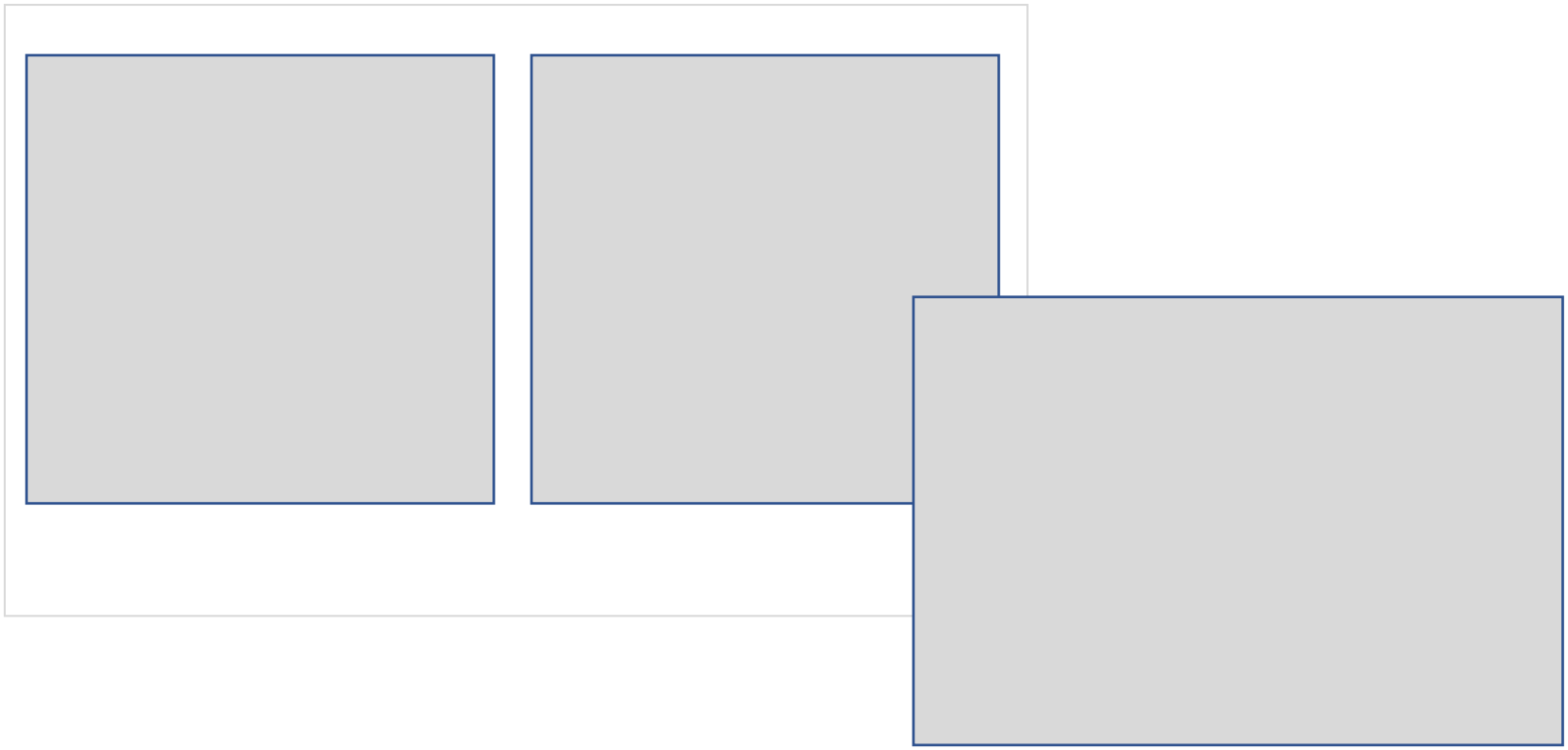
John B. Watson (1928)

Twin Concordance for Behavioral Disorders



McGue & Bouchard (1997). Annual Review of Neuroscience, 21: 1-24

Controlling for genetic factors and shared environment through twin studies



Leukocyte Telomere Length

- **Inversely correlated with age**
- **Shorter in men than in women**
- **Associated with aging-related diseases**
- **Associated with mortality?**

Kimura et al. AM J Epidemiol, 2008

Telomere Length and Mortality

- **274 twin pairs age 73-94**

- **Blood samples 1997**
- **Follow-up to 2007**

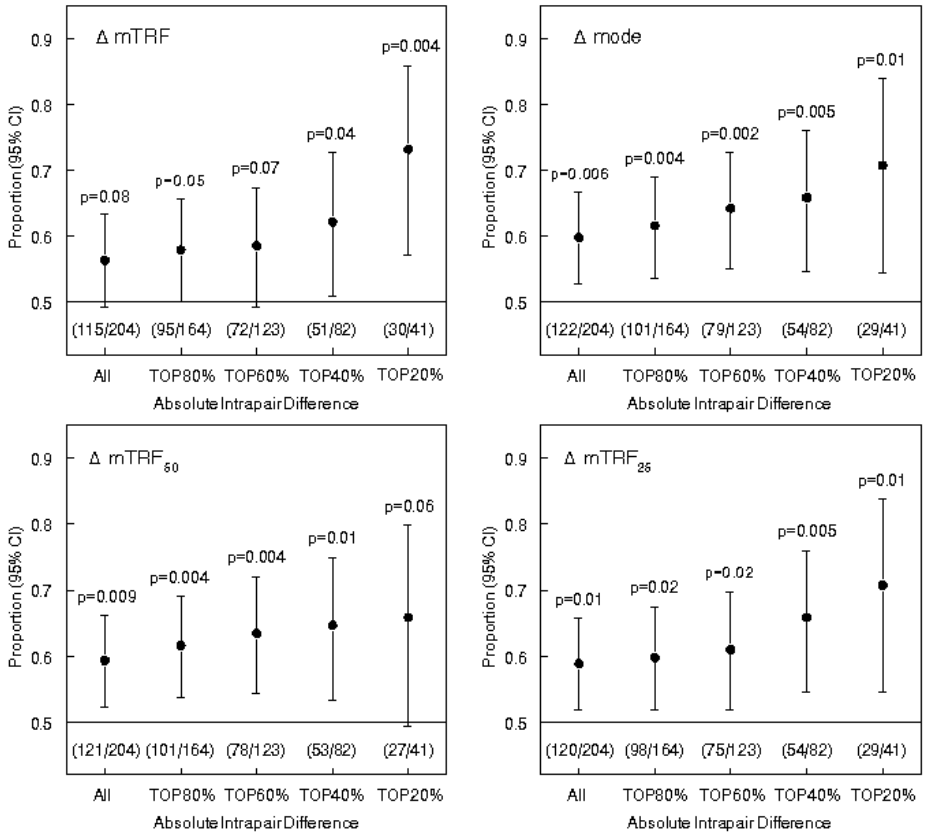
- **Deaths:** 289 twins
  204 pairs with at least one dead twin

- **Intrapair comparison:**
  Control for age, sex, genetic factors

Kimura et al. AM J Epidemiol, 2008

Telomeres and Survival

Intrapair comparisons



Kimura et al. AM J Epidemiol, 2008

Anesthesia and Postoperative Cognitive Dysfunction

Anesthesia - a potential risk factor for accelerated cognitive decline in elderly

- Exposure to anesthesia is associated with loss of cognition in elderly

(Moller et al. 1998, Abildstrom et al. 2000, Canet et al. 2003, Monk et al. 2008)

- Anesthetic agents may be important for the loss of cognition after surgery

(Xie et al. 2006, 2008, Wiklund et al. 2009)

- Alternative explanations:
  Surgical procedure, patient vulnerability, the disease leading to surgery

- Few and small studies

Up to 75 percent of the population has been exposed to anesthesia

Dokkedal et al. Anesthesiology 2016

Materials

Surveys including cognitive performance tests (N=8,503)

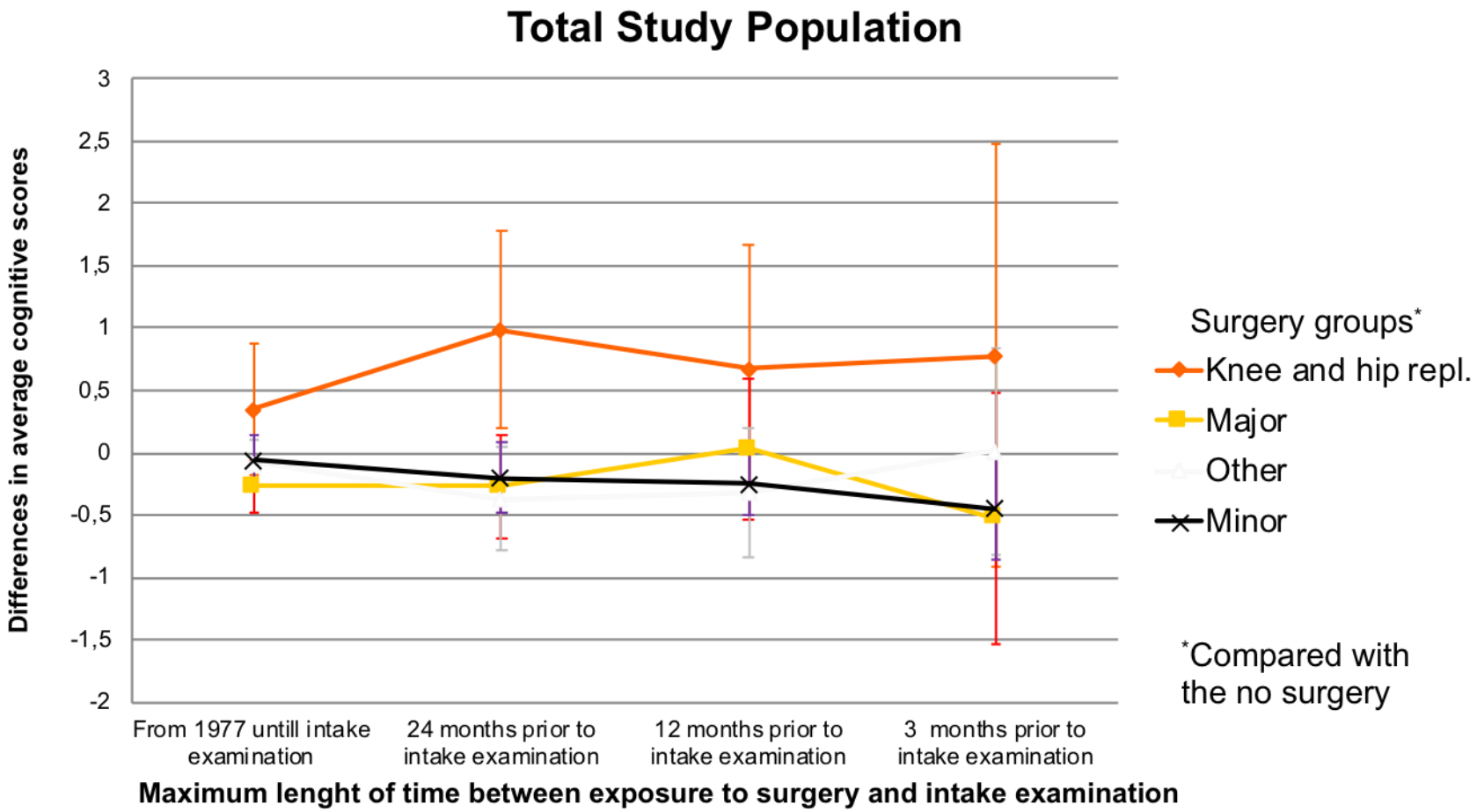
- **Study of Middle-Aged Danish Twins (1931-52)**
  - <70 years
  - N=4,299
  - Intake assessment in 1998/99 and follow-up in the period 2008-2011
- **Longitudinal Study of Aging Danish Twins (-1930)**
  - ≥70 years
  - N=4,204
  - First wave in 1995 with follow-up every 2nd year from 1997 to 2005

Cpr no.

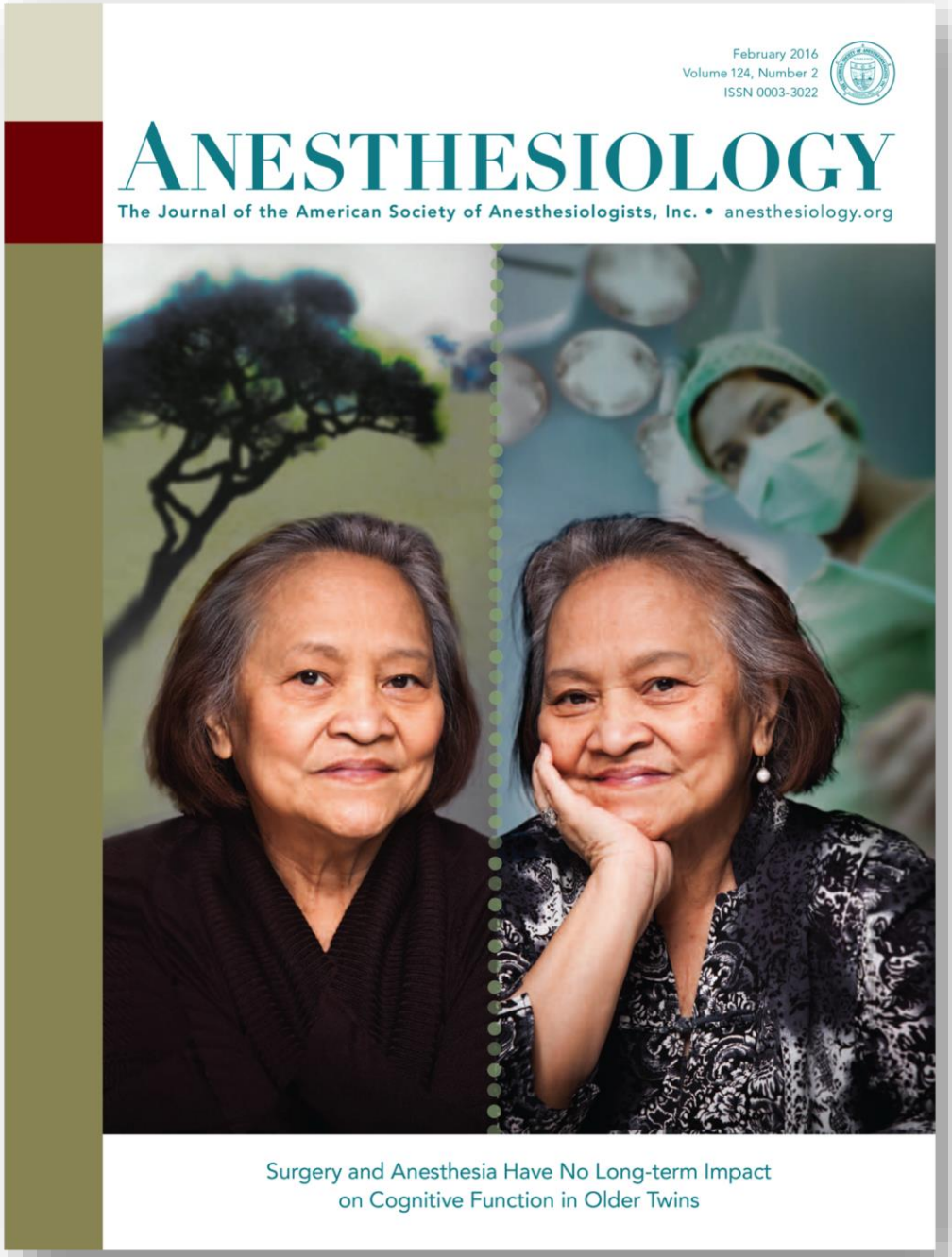
Danish National Patient Register (1977→)

Surgery data
- Type of surgery
- Date of surgery
- Date of admission and discharge

Results



Dokkedal et al. Anesthesiology 2016



SDU

Dokkedal et al. Anesthesiology 2016

Fertility, Ageing, and Longevity

A tooth per child?

- Germany

- Denmark

- Russia

- Japan

Fertility and Old-Age Health

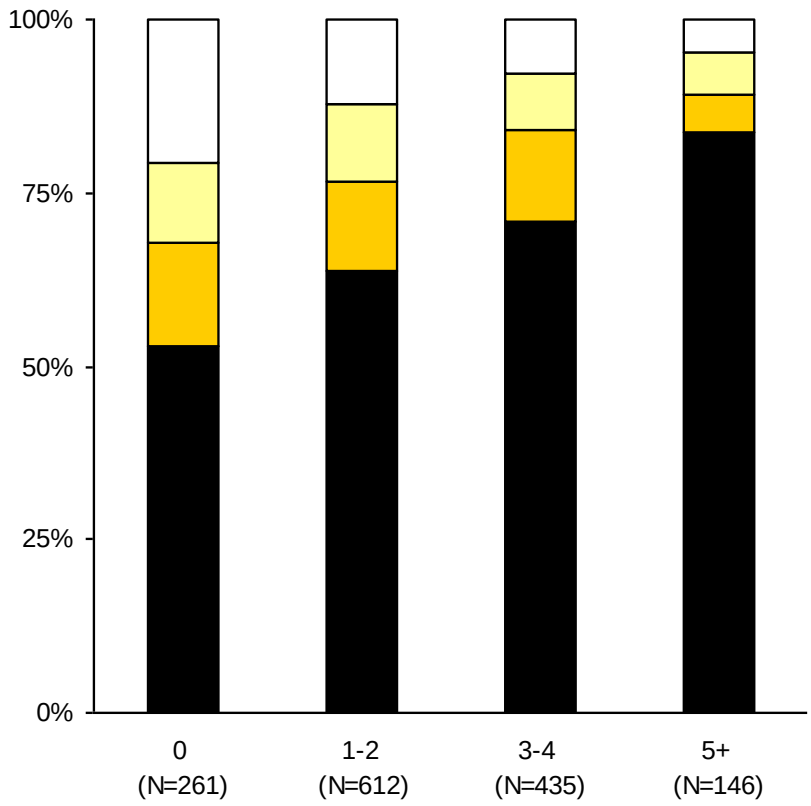
- A tooth per child?
- Cost of reprodution?
  - LSADT 1995 and 1997

    2,978 twins aged 73+

    - teeth
    - children
    - SES
    - females and males

A Tooth per Child?

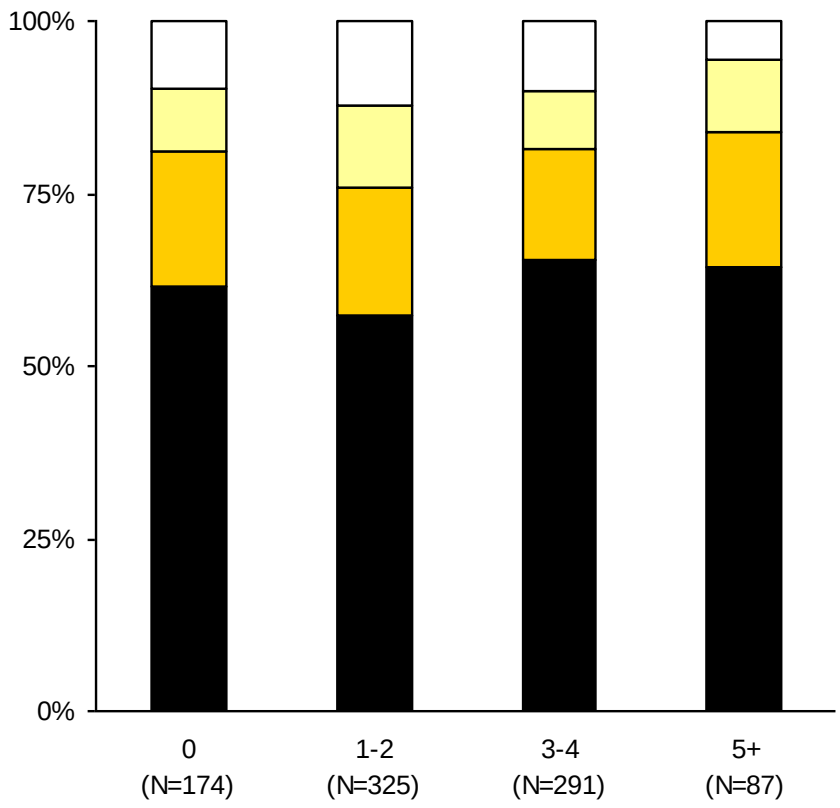
females



Christensen et al. Lancet 1998

A Tooth per Child?

males

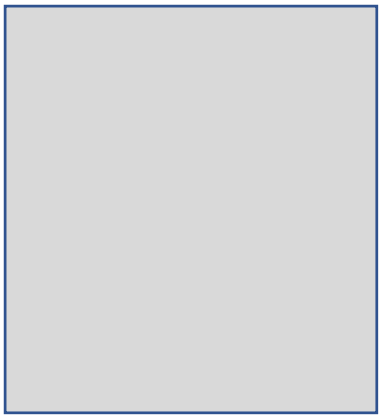


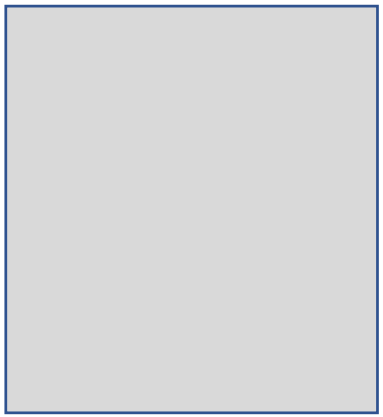
No. of children

Christensen et al. Lancet 1998

Biomarkers of Aging

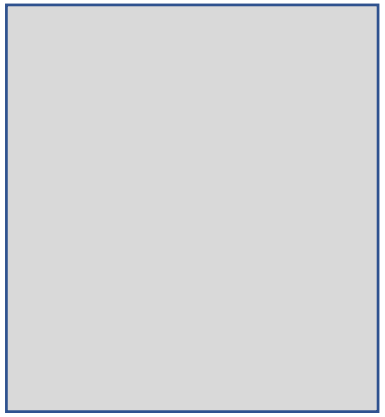
Théodore Rousseau
45 years

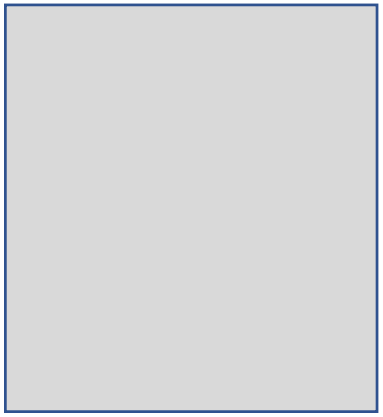




Harrison Ford
50 years

Gérard de Nerval
47 years





Clint Eastwood
58 years

”Looking Old for Your Age”

A Genetic Condition Associated with Mortality?

”Looking Old for Your Age”

A Genetic Condition Associated with Mortality?

- **Pictures of 387 twin pairs age 70-91**
- **20 nurses act as assessors**
- **No knowledge about real age**
- **First day twin As, second day twin Bs**

Christensen et al. Epidemiology, 2004

”Looking Old” and Mortality

Within twin pair comparisons:

- **49 deaths in twin pairs**
- **Oldest looking died first?**

Youngest looking die first	No diff. in perceived age (< 2 years)	Oldest looking die first
7	**23**	**19**

(p < 0.03)

Christensen et al. Epidemiology, 2004

”Looking Old” and Mortality

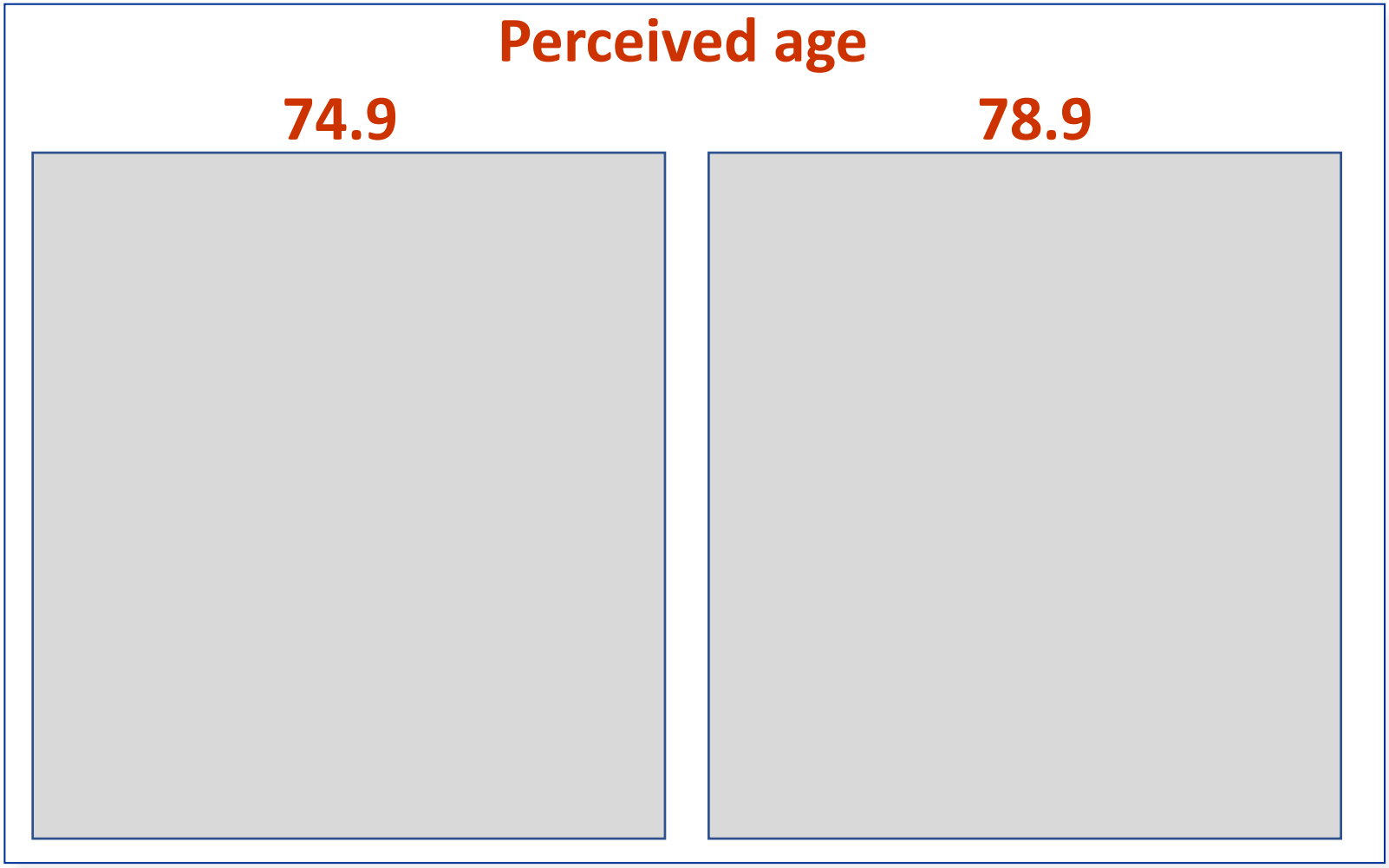
Within twin pair comparisons:

- **126 deaths in twin pairs (January 2006)**
- **Oldest looking died first?**

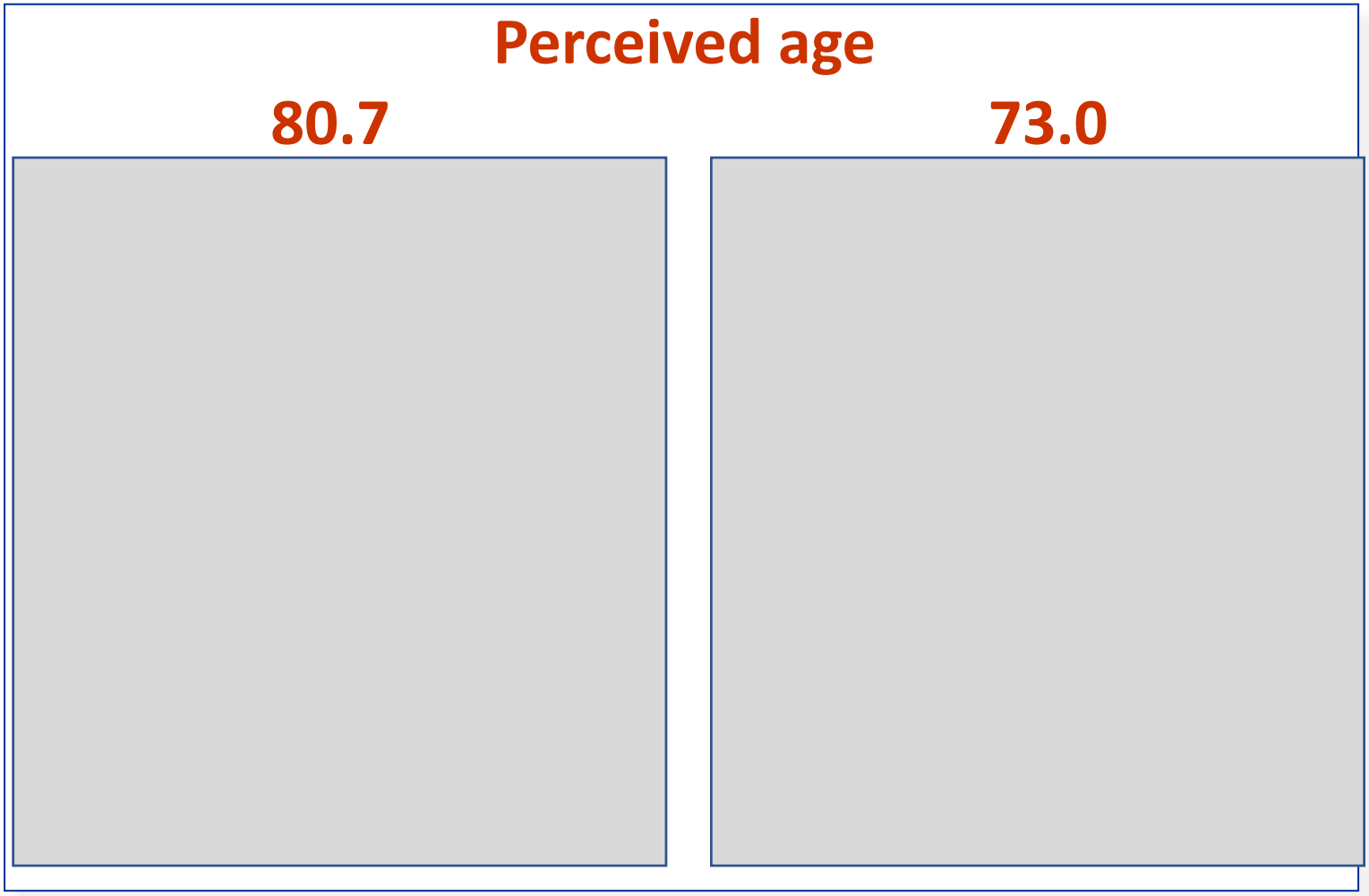
Assessor group	Nurses	Male students	Elderly ladies
Youngest looking die first	19	26	31
No diff. in perceived age (< 2 years)	55	45	46
Oldest looking die first	52	55	49
p (one-sided, two-sided)	(0.000,0.000)	(0.001,0.002)	(0.028,0.057)

Christensen et al. BMJ, 2009

Dizygotic Twins Age 72



Dizygotic Twins Age 72



Sex, chronological age, perceived age - and mortality

	N	Hazard ratios (95% CI)
Sex	1826	0.60 (0.52-0.70)
Chronological age		1.11 (1.10-1.13)
Sex	1826	0.67 (0.57-0.78)
Perceived age		1.15 (1.13-1.17)
Sex	1826	0.59 (0.51-0.69)
Chronological age		1.08 (1.07-1.10)
Perceived age		1.08 (1.05-1.10)

Christensen et al. BMJ, 2009

Environmental and Genetic Influences – Facial Averages

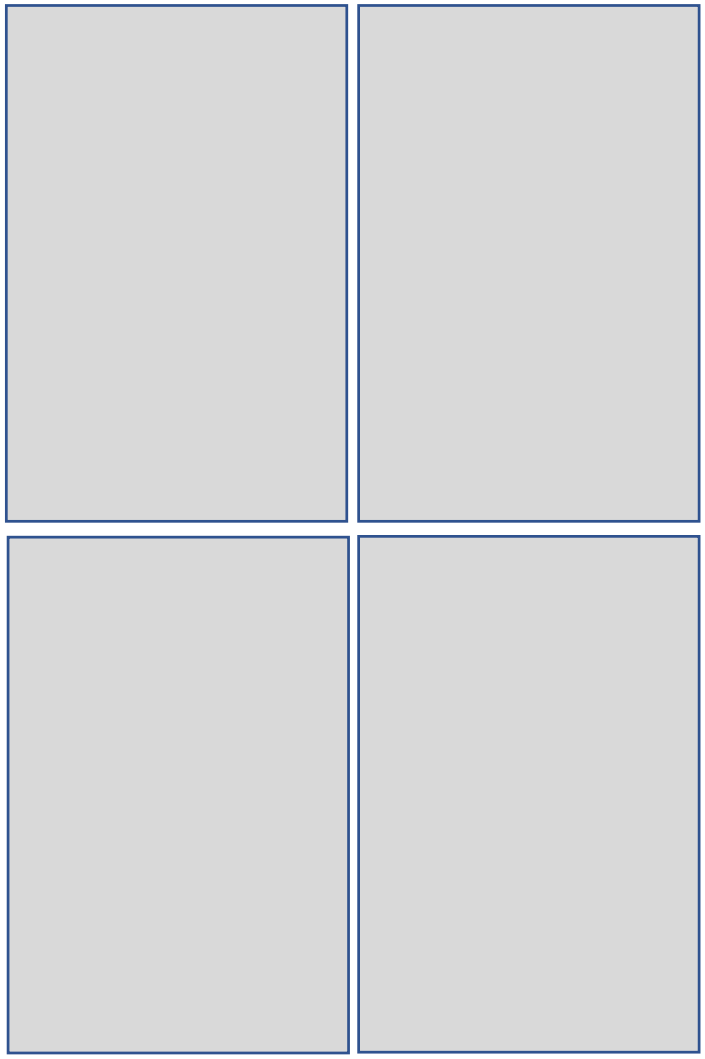
Dizygotes: Better and Worse Agers

Average actual age: 69.35

Average perceived Age: 64.59 Average perceived Age: 75.19

N=14

Acknowledgements: Unilever and University of St. Andrews



Skin wrinkling

Hair graying

Lip height

Gunn et al, PLoS ONE, Nov 2009

Heritability

Feature	Monozygotic correlation	Dizygotic correlation	Heretability (%)
Pigmented Spots	0.44	0.15	41 [14, 61]
Sun-damage	0.60	0.06	60 [40, 73]
Wrinkles	0.58	0.09	55 [34, 70]
Wrinkle Depth	0.60	0.16	57 [35, 73]
Lip Height	0.67	0.25	66 [48, 78]
Hair Graying	0.90	0.34	90 [80, 94]
Hair Recession	0.81	-0.03	80 [51, 94]
Hair Thinning	0.06	0.31	0 [0, 49]

Gunn et al, PLoS ONE, Nov 2009

Cancer and longevity - is there a trade-off?

A Study of Co-occurrence in Danish Twin Pairs Born 1900-1918

Christensen et al, J Gerontol, 2012

Family co-occurrence of cancer and longevity

Predictions of the two hypotheses:

- **”Causal”:** Low cancer risk in relatives of long-lived individuals

- **”Trade-off”:** High cancer risk in relatives of long-lived individuals

Christensen et al, J Gerontol, 2012

Nature Reviews Genetics | AOP, published online 31 July 2012; doi:10.1038/nrg3243

STUDY DESIGNS

The continuing value of twin studies in the omics era

Jenny van Dongen[1], P. Eline Slagboom[2], Harmen H. M. Draisma[1], Nicholas G. Martin[3] and Dorret I. Boomsma[1]

Abstract | The classical twin study has been a powerful heuristic in biomedical, psychiatric and behavioural research for decades. Twin registries worldwide have collected biological material and longitudinal phenotypic data on tens of thousands of twins, providing a valuable resource for studying complex phenotypes and their underlying biology. In this Review, we consider the continuing value of twin studies in the current era of molecular genetic studies. We conclude that classical twin methods combined with novel technologies represent a powerful approach towards identifying and understanding the molecular pathways that underlie complex traits.

Epigenetics

Aging Cell (2012) **11**, pp694–703 Doi: 10.1111/j.1474-9726.2012.00835.x

Epigenetic variation during the adult lifespan: cross-sectional and longitudinal data on monozygotic twin pairs

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Introduction

The risk of most common diseases increases with age. A lifetime of accumulated epigenetic changes was proposed to contribute to the development of such diseases (Bjornsson *et al.*, 2004). Epigenetic mechanisms determine the expression potential of genes without changing the DNA sequence (Jaenisch & Bird, 2003). The molecular basis includes the methylation of cytosines in CpG dinucleotides, which, together with histone modifications, noncoding RNAs, and localization, influence the accessibility of a genomic locus to the transcriptional machinery (Bernstein *et al.*, 2007; Cedar & Bergman, 2009). DNA methylation can be measured on DNA samples that are commonly available in biobanks (Talens *et al.*, 2010).

Various studies have investigated whether DNA methylation can change with increasing calendar age. A cross-sectional study of limited sample size reported the genome-wide absence of changes in mean DNA methylation between young (26 years) and old (68 years) individuals

Twins, the epigenetic clock and survival

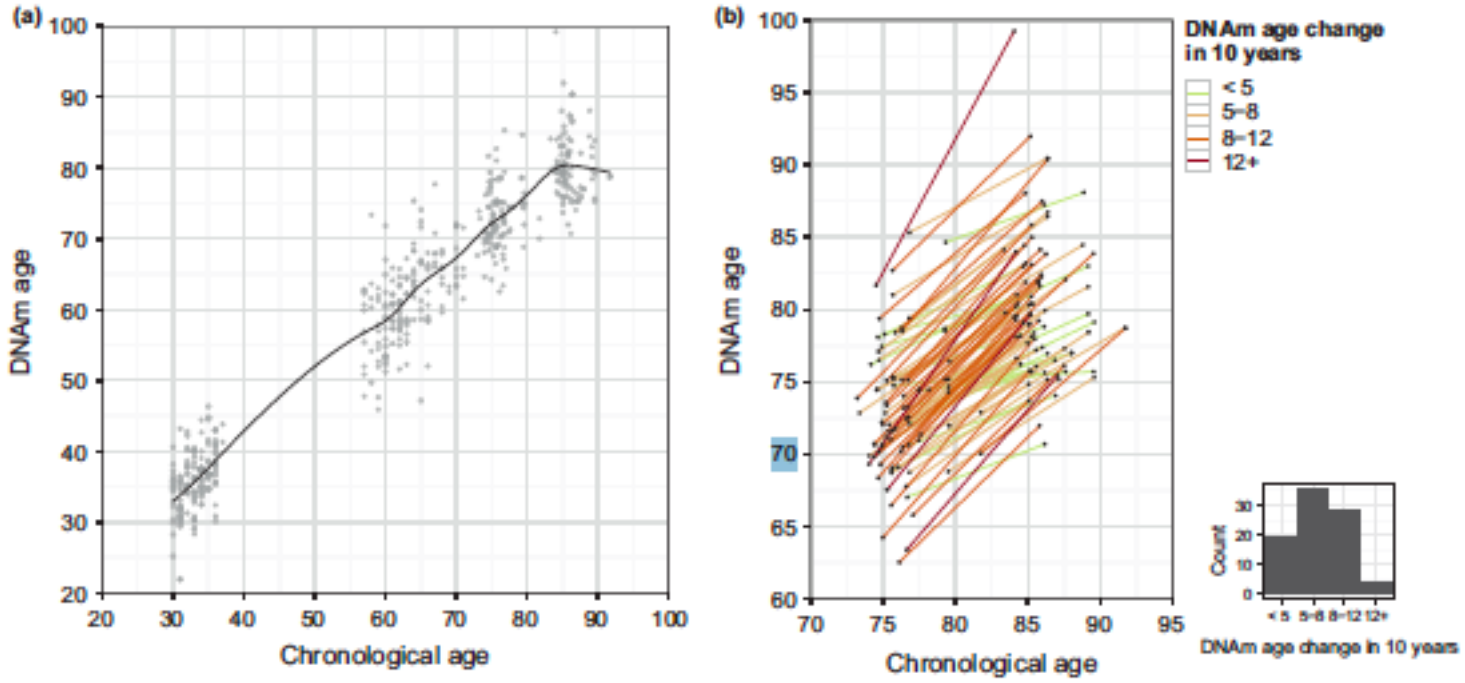
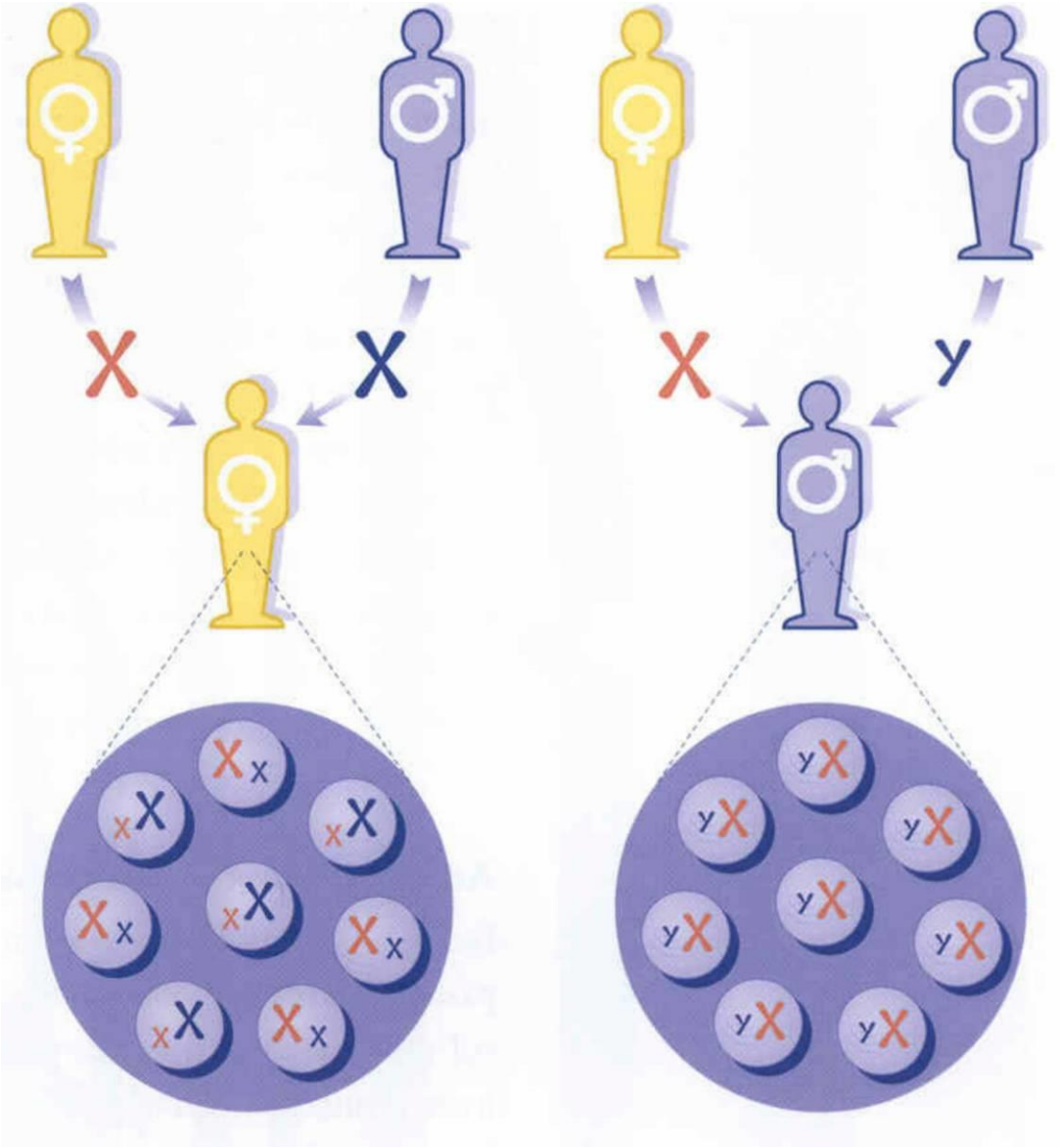
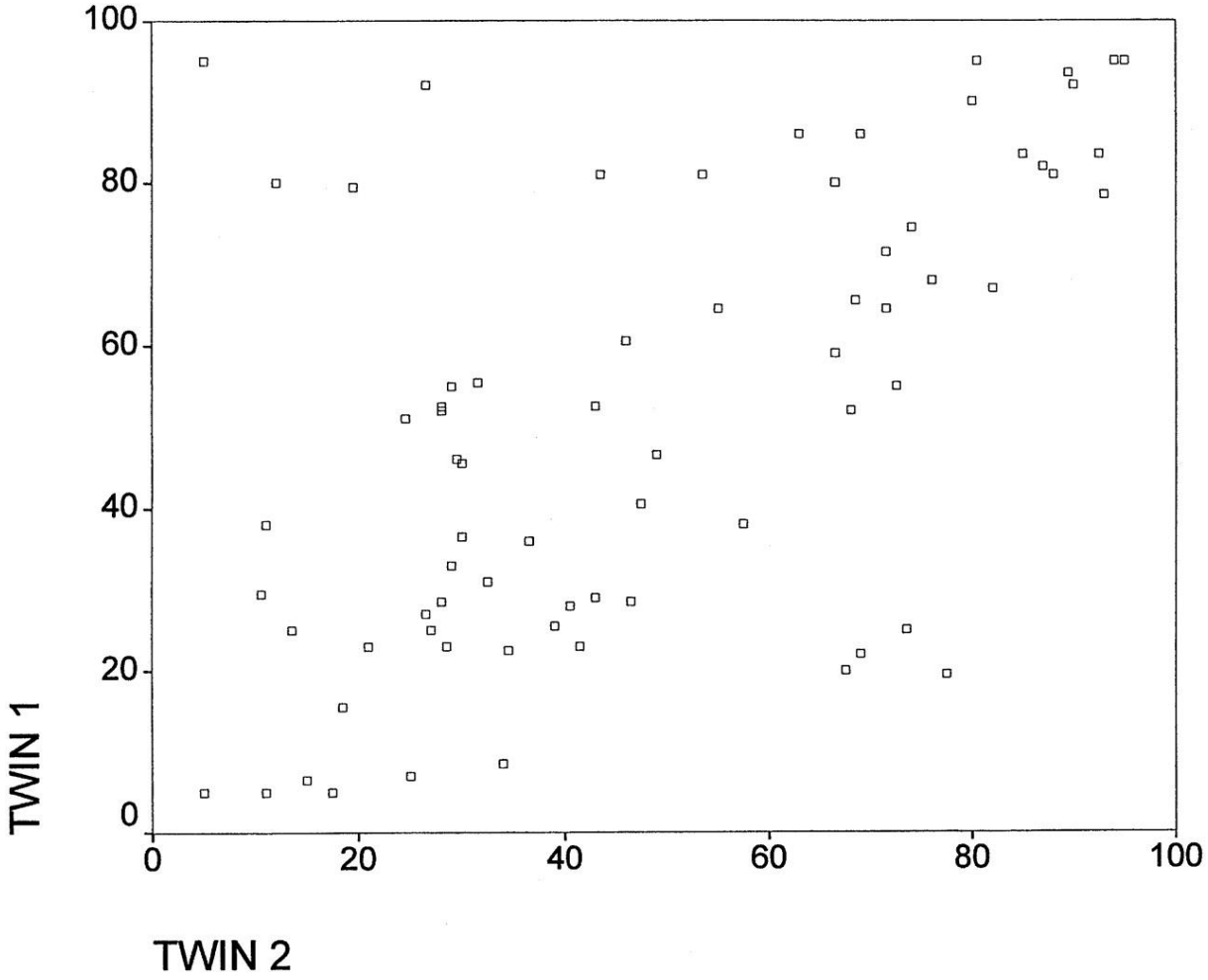


Fig. 1 Horvath DNAm age against chronological age. (a) Correlation between the methylation age using the Horvath model. The relation is visualized by a smoothing spline. (b) DNAm age trajectories of each individual in the longitudinal study of oldest-olds. The lines are colored by intervals of slow to fast agers, and the histogram indicates the distribution within the intervals.

Christiansen et al. Aging Cell, 2016


X
X
X
y

X inactivation patterns in female monozygotic twins aged 73 to 93 years. Percentage of inactivation of an X chromosome (percentage of smaller allele)

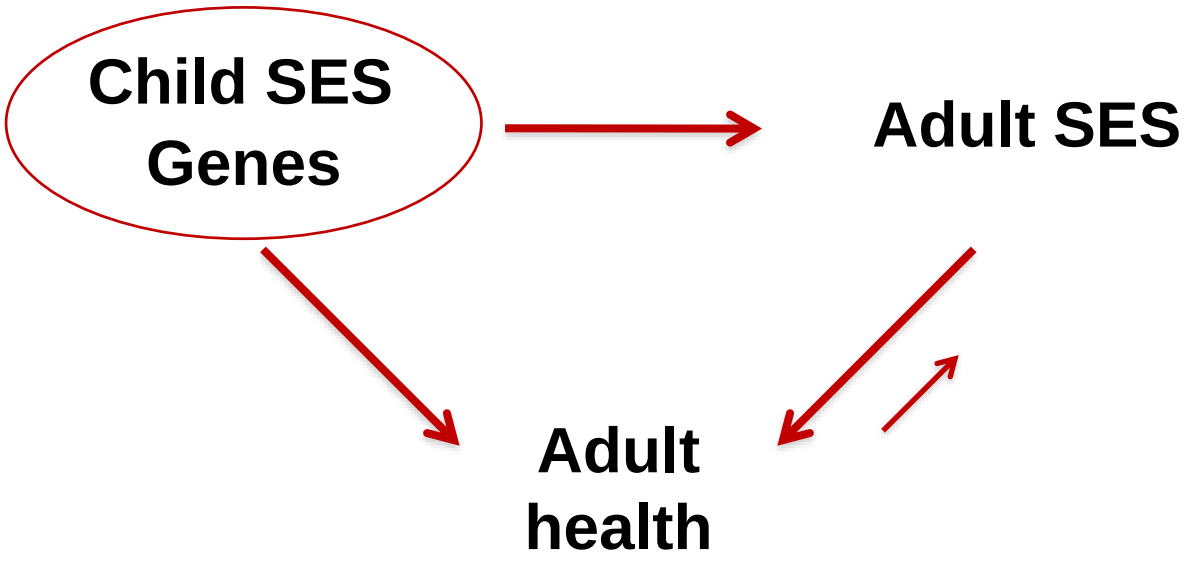


Christensen K et al. Blood 2000;95:2449-2451

MZ discordant
– SNPs, CNV, epigenetics, omics

Kondo et al, Nat Genet, 2002

Controlling for familial factors



Danish twin findings

An attenuation of the SES association in the intrapair analyses (in particular for MZ)

- Mortality
- Self-reported health measures
- Cardiovascular disease
- Breast cancer
- Prescription medicine

Suggest that the causal health effect of SES may be overstated in regular cohort studies in Denmark

Osler et al., 2007; Madsen et al. 2010, 2011a, 2011b;

Methodological challenges

- Power and lack of precision
- Equal environment assumption
- Social interaction
- Measurement error
- Bigger impact of non-shared confounders

Frisell et al, Epidemiology, 2012

- Twins are different

Fetal origin

Twins 1 kg lighter at birth

+

Older parents (DZ)

+

Assisted reproduction technologies

+++

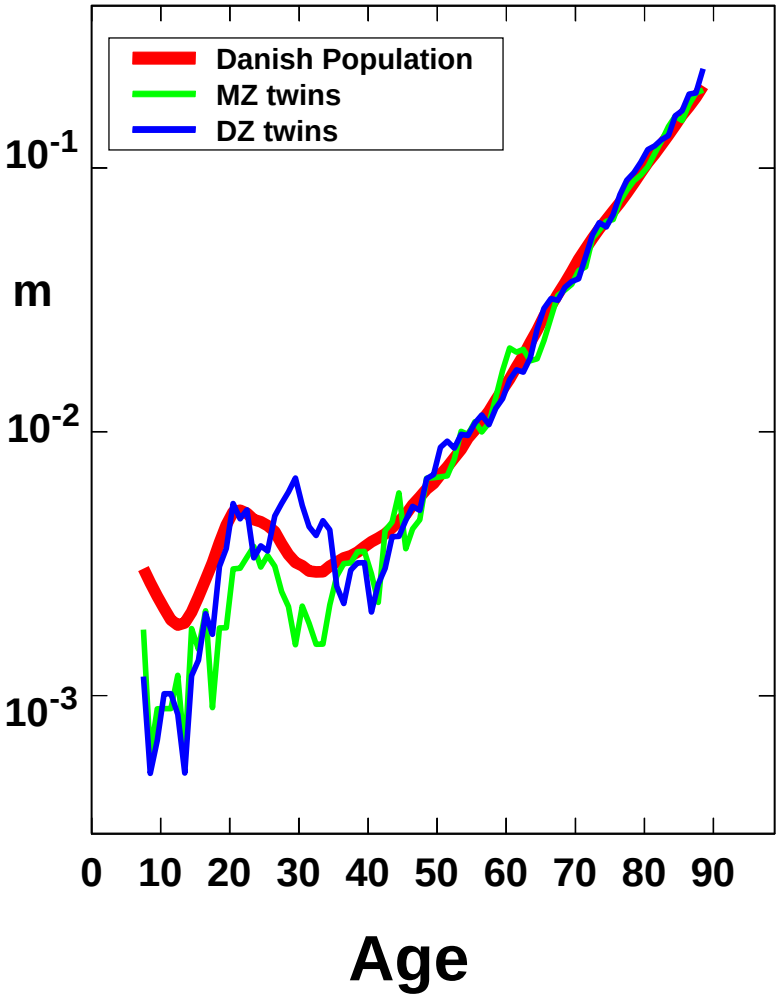
2-5 times higher infant mortality

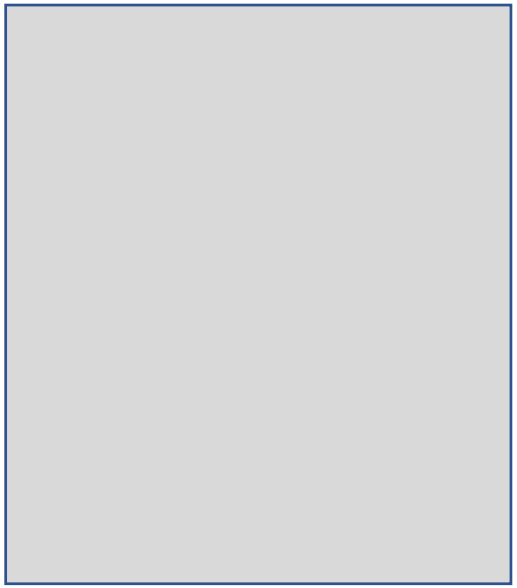
+++

Key Question

How important is early life for later life health and functioning?

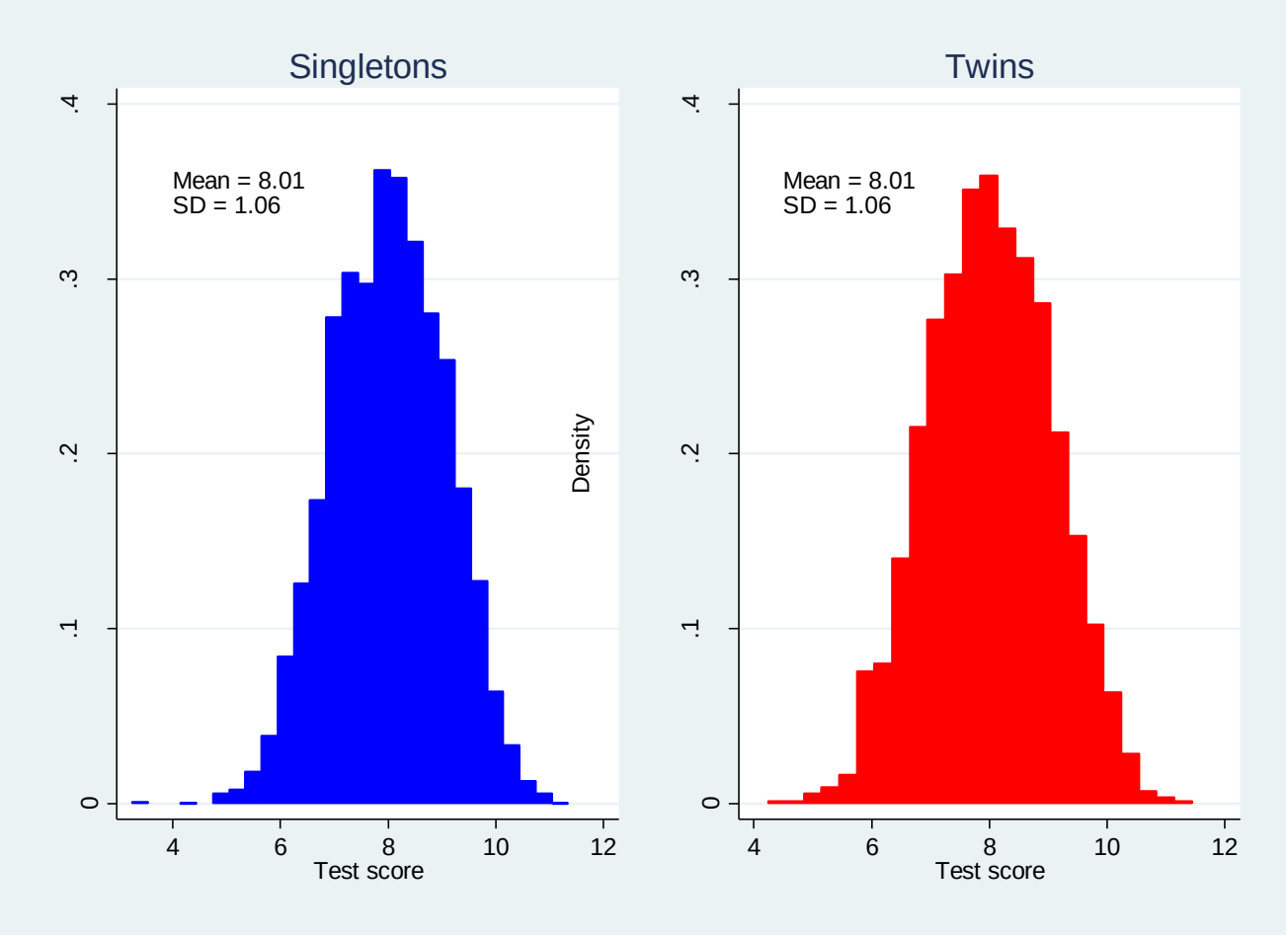
Fetal programming



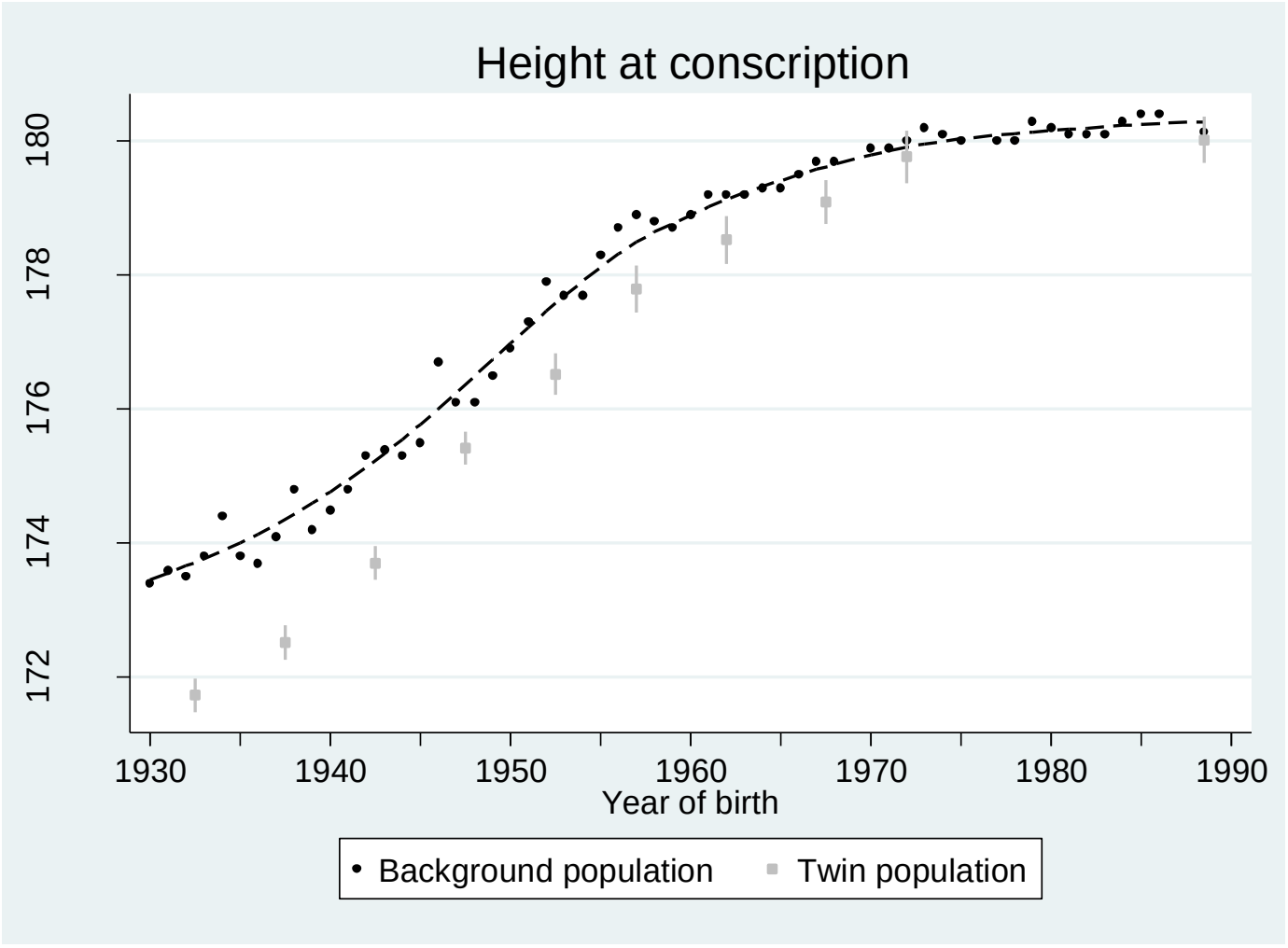


Christensen et al. BMJ 1995, 2003, 2006

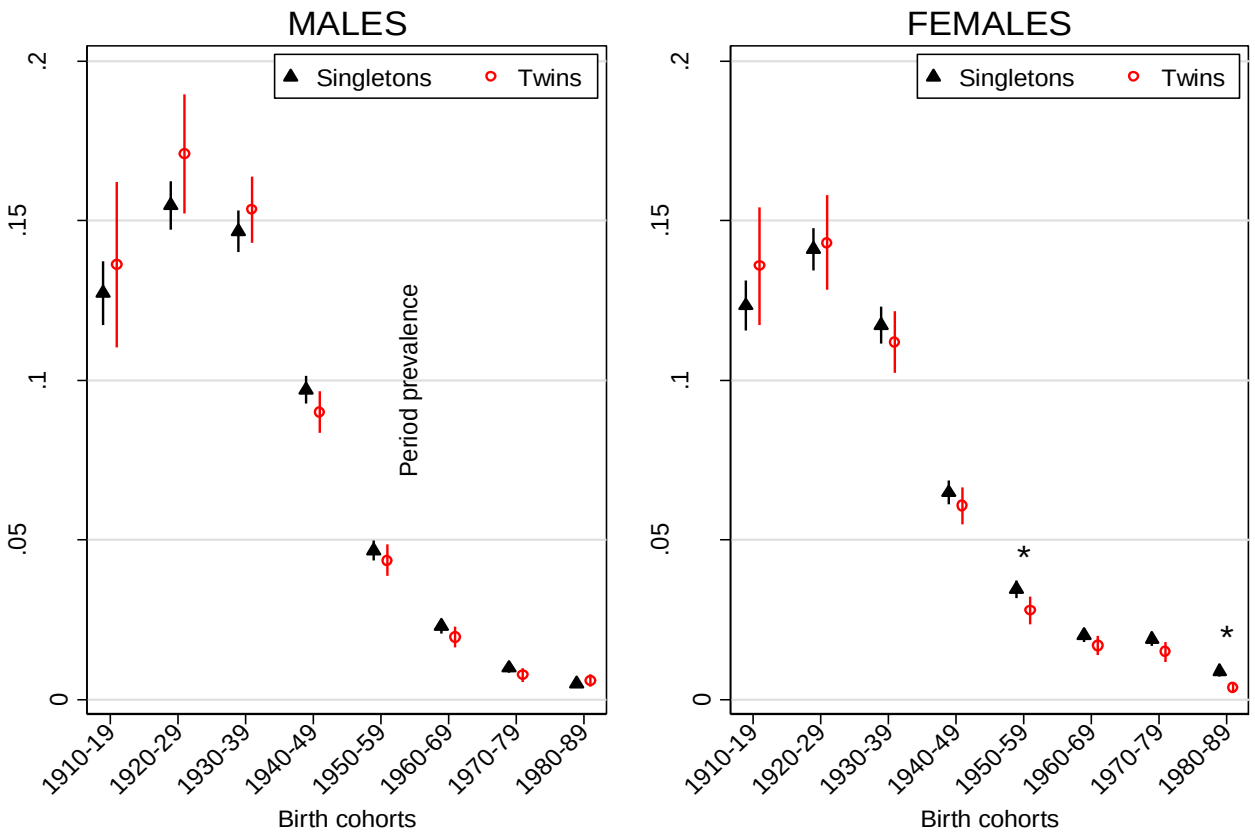
Educational achievement



Christensen et al., BMJ, 2006

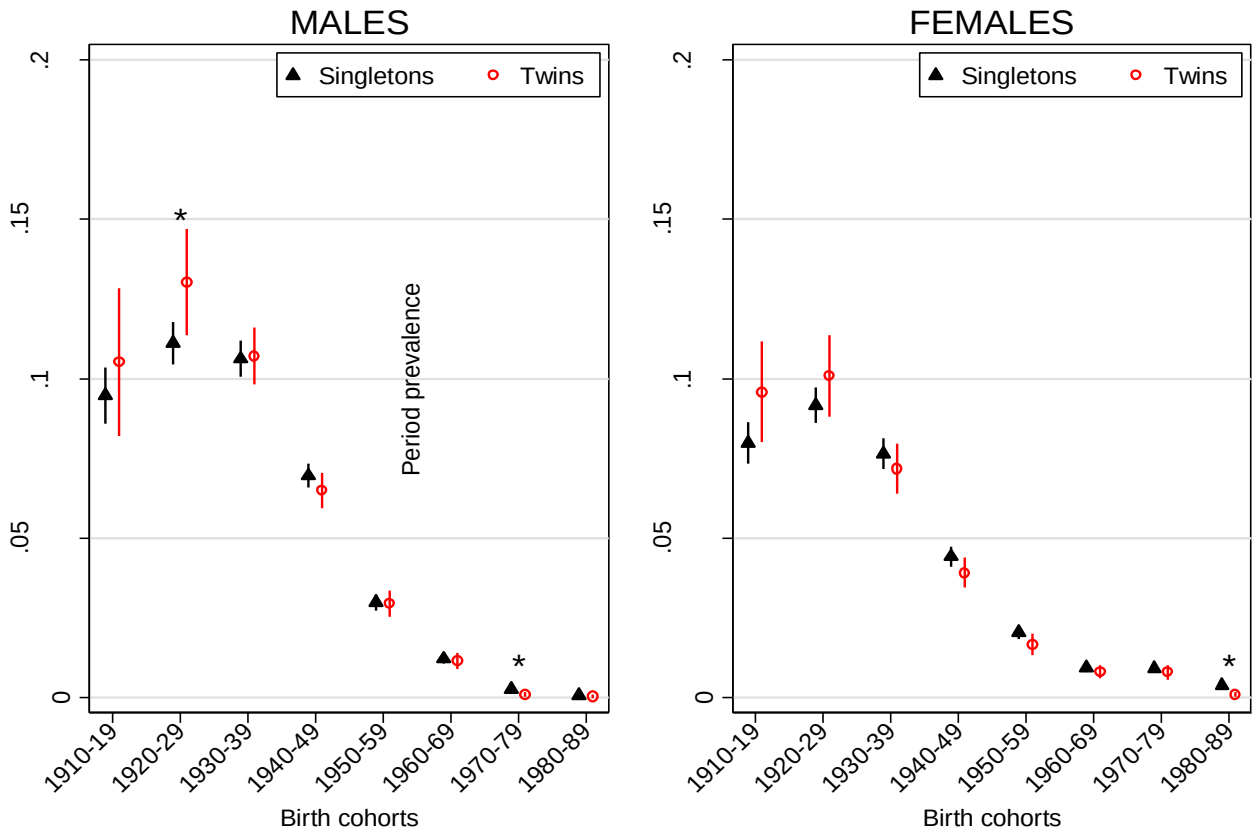

Height at conscription
180
178
176
174
172
1930
1940
1950
1960
1970
1980
1990
Year of birth
Background population
Twin population

Diabetes - All cases



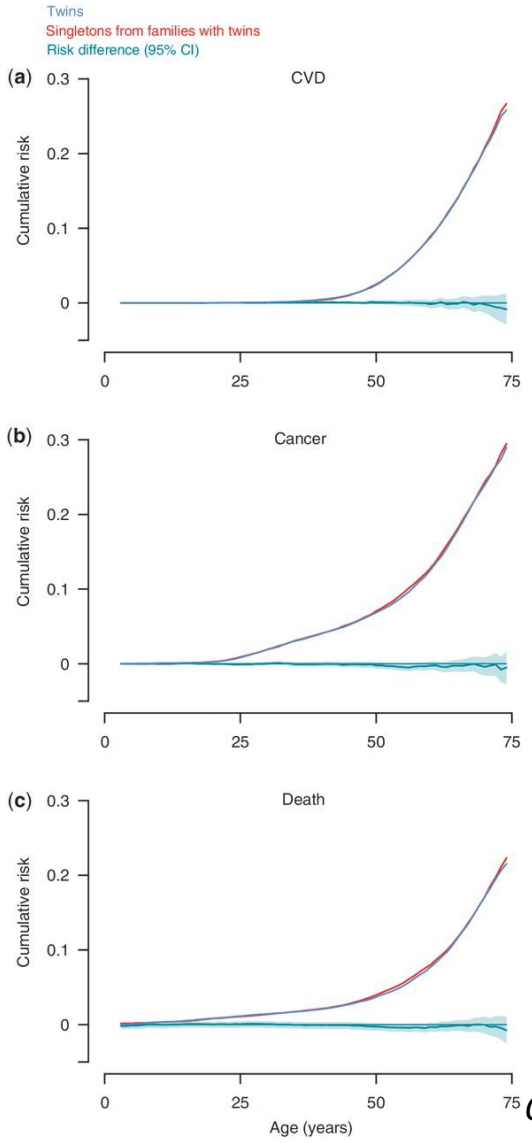
Petersen et al., Diabetologia, 2011

Known type-2 diabetes cases



Petersen et al., Diabetologia, 2011

Cumulative risks of CVD, cancer and death in 49,000 Swedish twins and 35,000 siblings



International Journal of Epidemiology

Öberg S et al. Int. J. Epidemiol. 2012;ije.dys067

155 extremely birth weight discordant MZ twin pairs (age 30-74 years, median 58 years)

Median birth weight difference 0.5kg ~ 25%

Frost et al., Diabetologia, 2012

155 extremely birth weight discordant MZ twin pairs (age 30-74 years, median 58 years)

Median birth weight difference 0.5kg ~ 25%

<u>Low birth weight twins NOT disadvantaged in</u>

2-h oral glucose tolerance test with sampling of

p-glucose, insulin, C-peptide, GIP and GPL-1

Homeostasis models for

beta-cell function (HOMA-β), insulin resistance (HOMA-IR), insulin sensitivity index (BIGTT-Si), and acute insulin response (BIGTT-AIR)

Frost et al., Diabetologia, 2012

Twins, worms and life course epidemiology

Christensen & McGue, Int J Epidemiol, 2012

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