Prof. dr. D.L. Knook lezing : Tweelingen en veroudering

door Prof. dr. Dorret Boomsma [di.boomsma@vu.nl]

Tweelingen, genetica en levensloop.

MZ

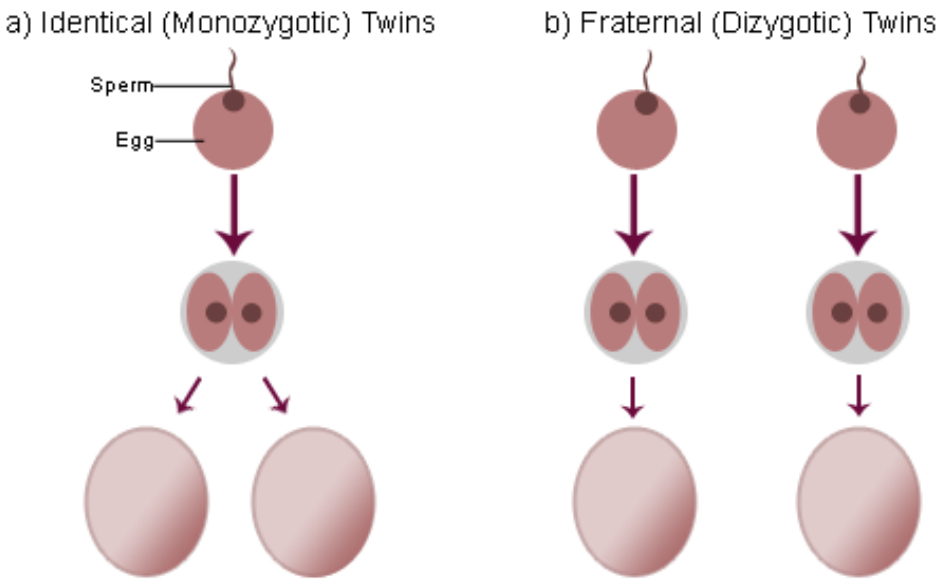
DZ

Why Twins

Classical twin design:
heritability = 2(rMZ – rDZ)
(where r stands for correlation)

Monozygotic (MZ) :
“100% “ genetically identical

Dizygotic (DZ):
Share 50% of segregating genes



Biometrical model

Phenotype = Genes + Environment + Chance

Measured	Measured or latent	Measured or latent	????

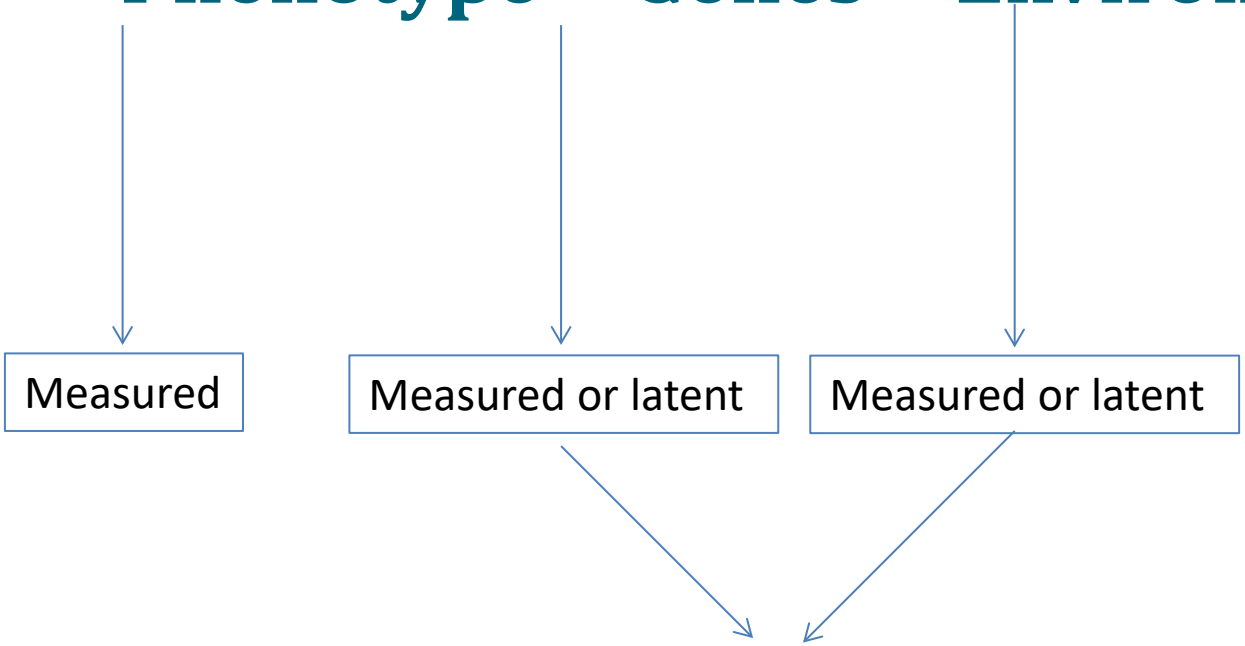
Biometrical model

$$P = G + E + \text{Chance}$$

$$\text{Variation } (P) = \text{Variation } (G) + \text{Variation } (E)$$

Biometrical model

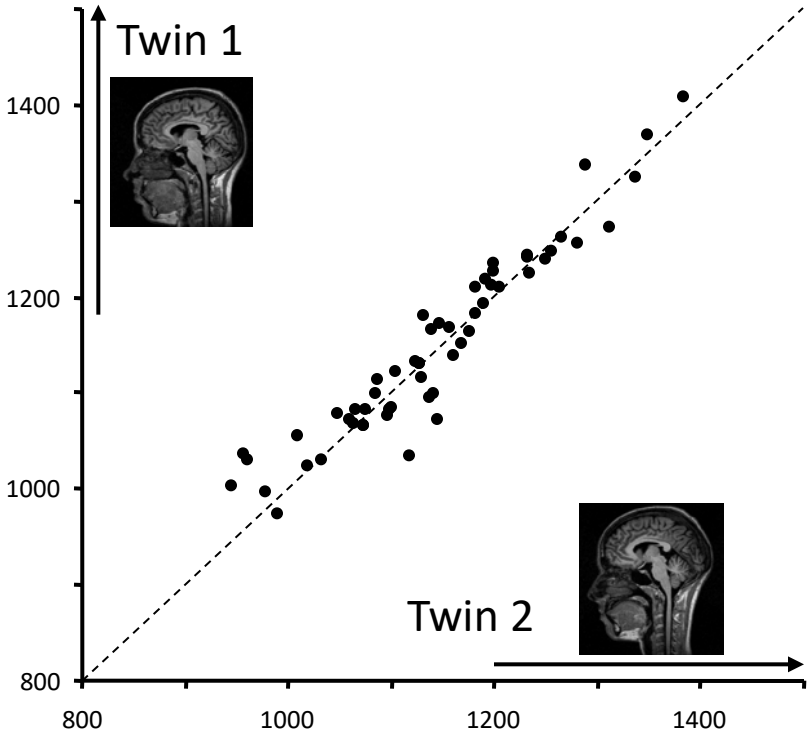
Phenotype = Genes + Environment



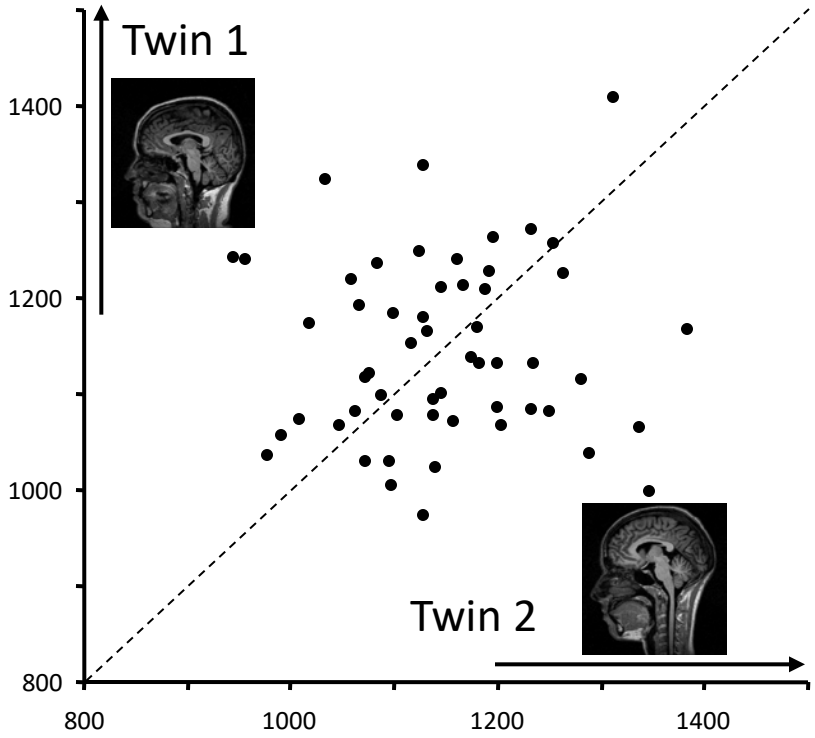
When both are not directly measured (unobserved or latent) we apply a twin, adoption, or family design and methods from genetic epidemiology and behavior genetics to estimate genetic and non-genetic variation.

Adoptions of twins into separate homes are rare.

The classic twin design relies on comparing resemblance of mono- and dizygotic twin pairs reared together.



Brain volume MZ twin pairs (milliliter) in twin and co-twin



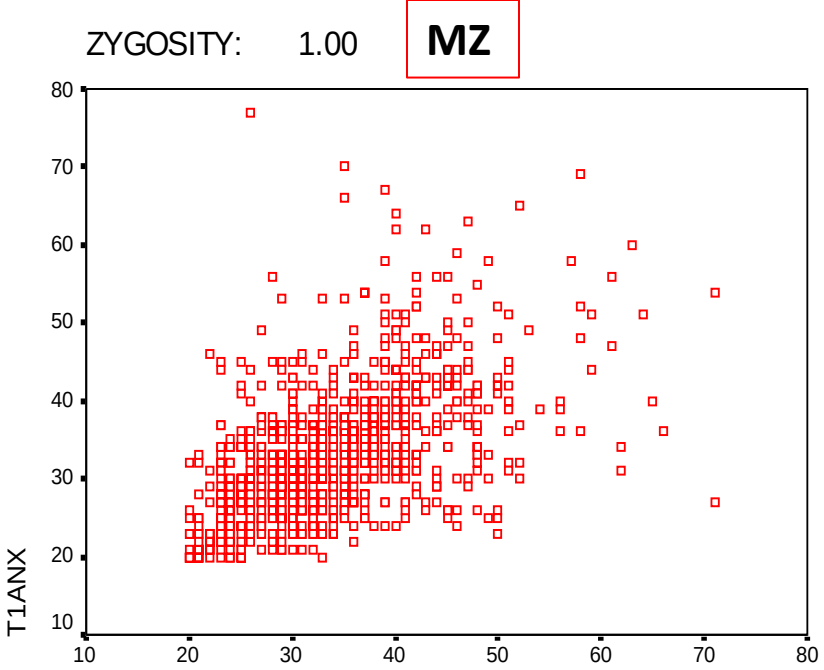
Brain volume DZ twin pairs (milliliter) in twin and co-twin

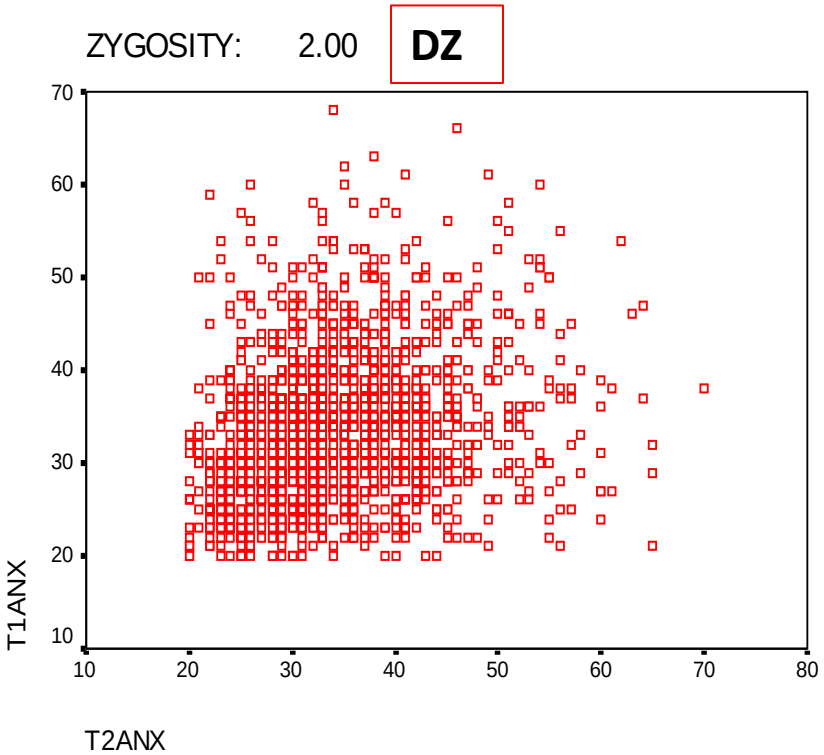
Example: MRI-based Brain volumes
Resemblance of MZ ('identical') and DZ twins (sibs)

Twin Model

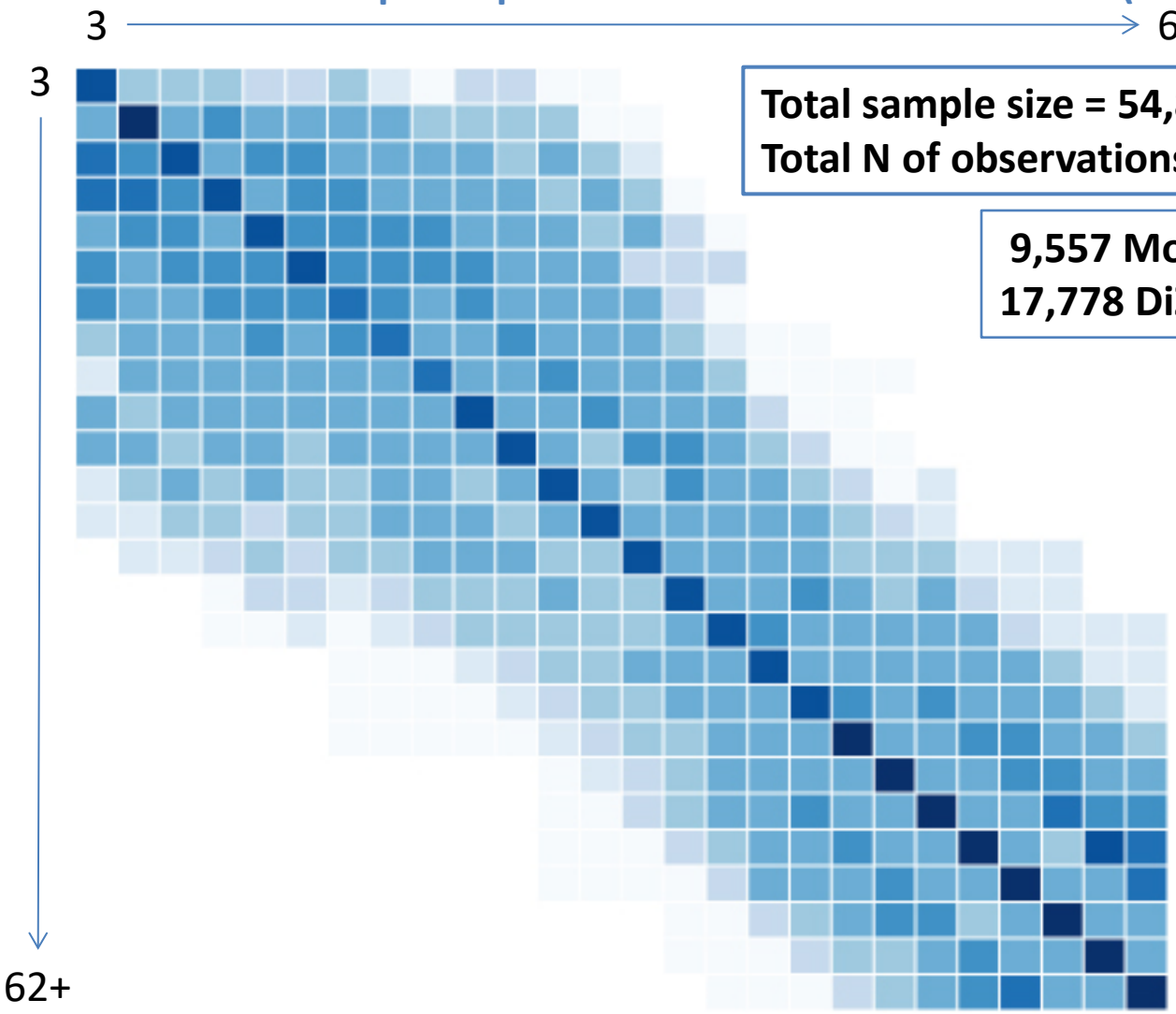
- Twin correlations for anxiety (young adult twins)

- Correlation (MZ) = 0.54
- Correlation (DZ) = 0.25
- Difference = .54-.25 = .29
- Heritability =2 * .29 = 58%





Longitudinal data: each participant is at most rated 8 or 9 times (over ~20 years).

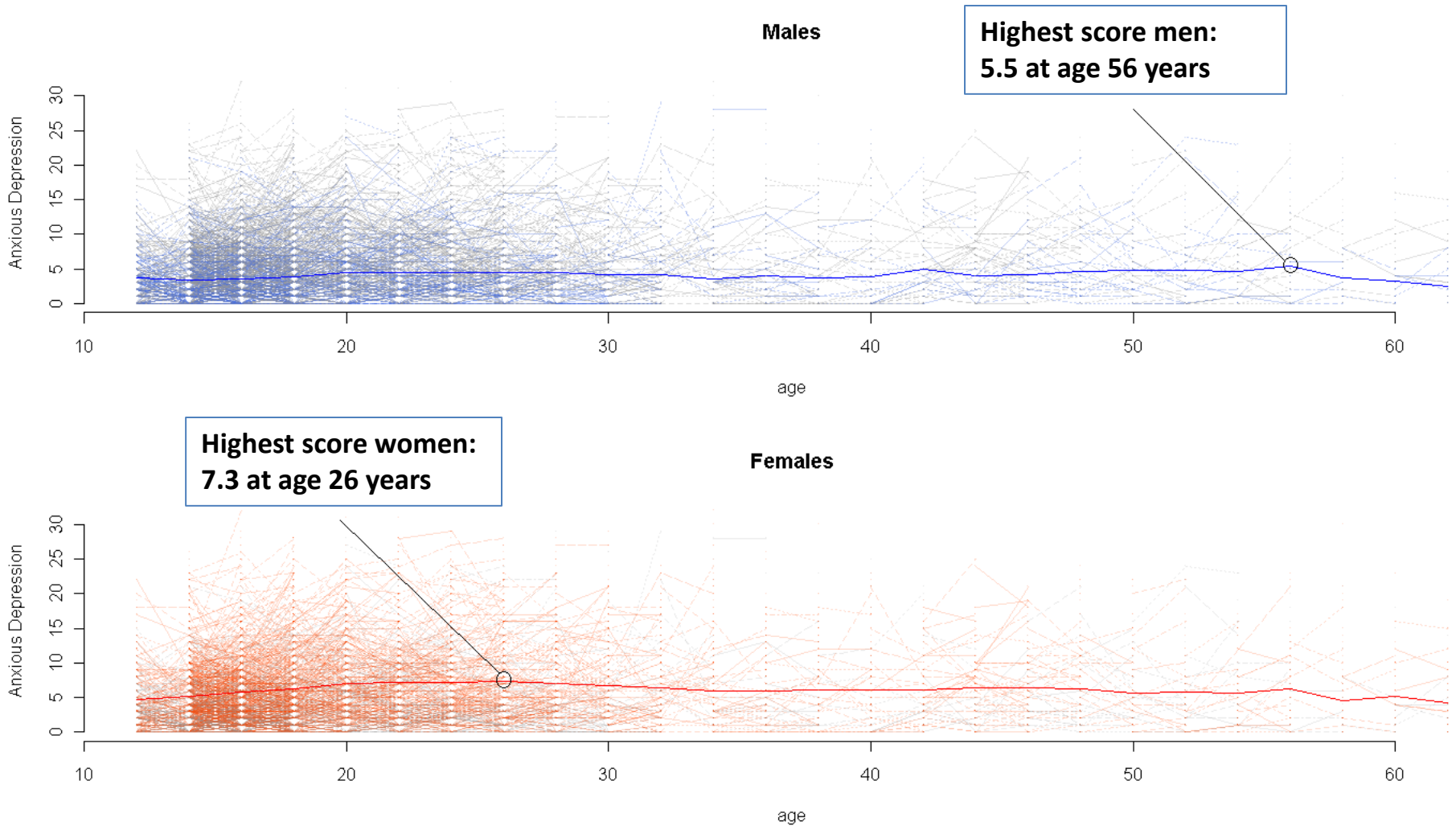


Total sample size = 54,896
Total N of observations = 170,446

9,557 MonoZygotic pairs
17,778 DiZygotic pairs

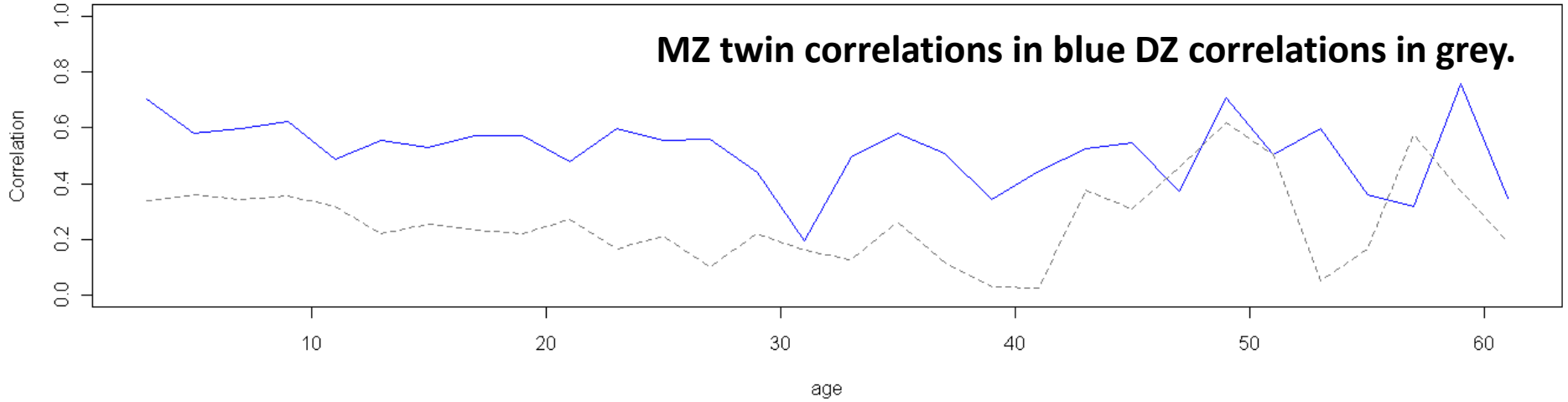
Cells in the matrix with Anx/dep observations are in Blue, darker indicates more data

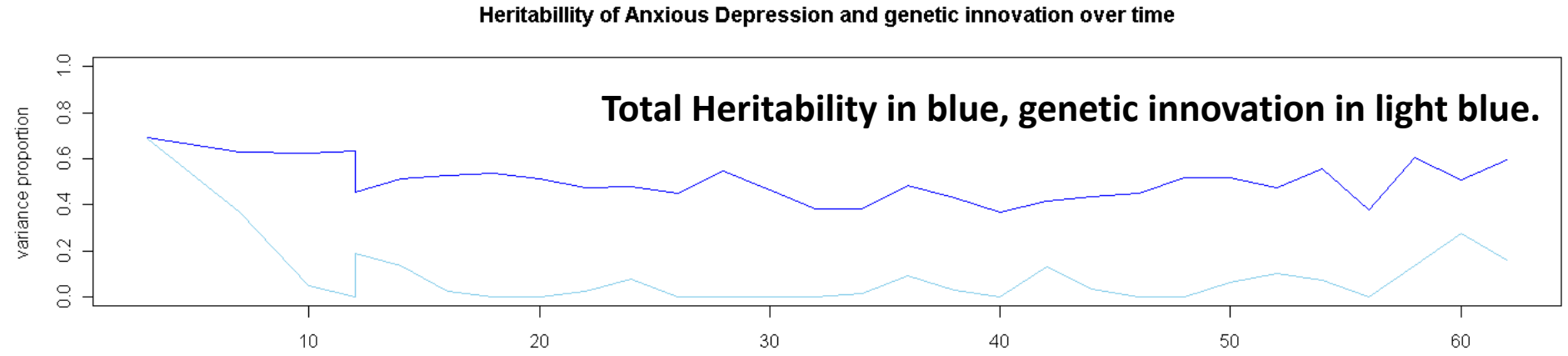
Anx/Dep: Mean *self* ratings and individual trajectories per subject over age



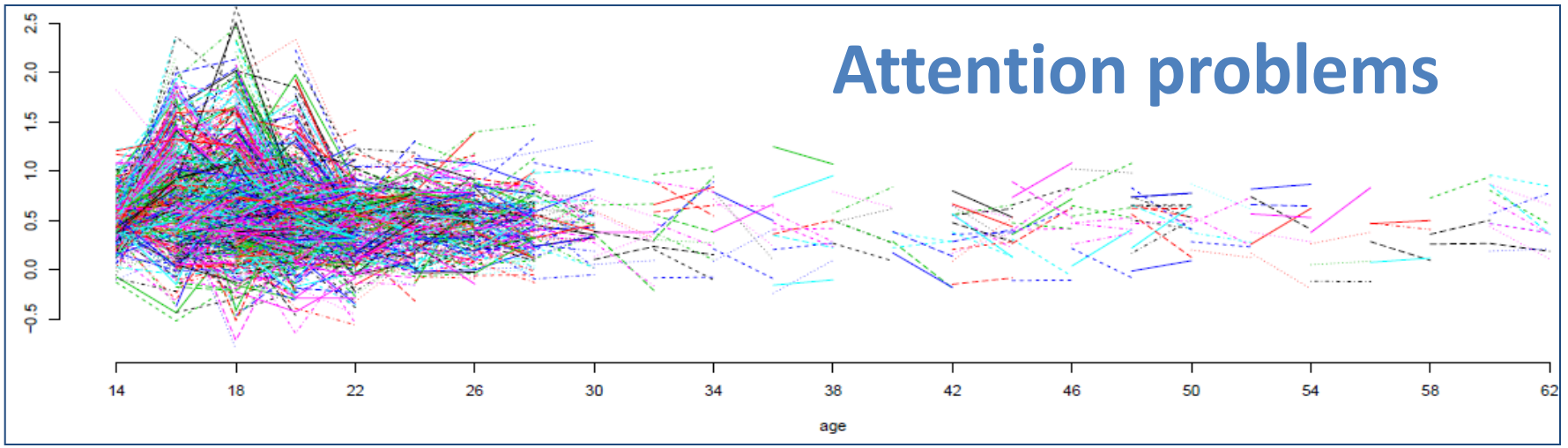
Males: blue against grey (women) background.
Females: red against grey (men) background.

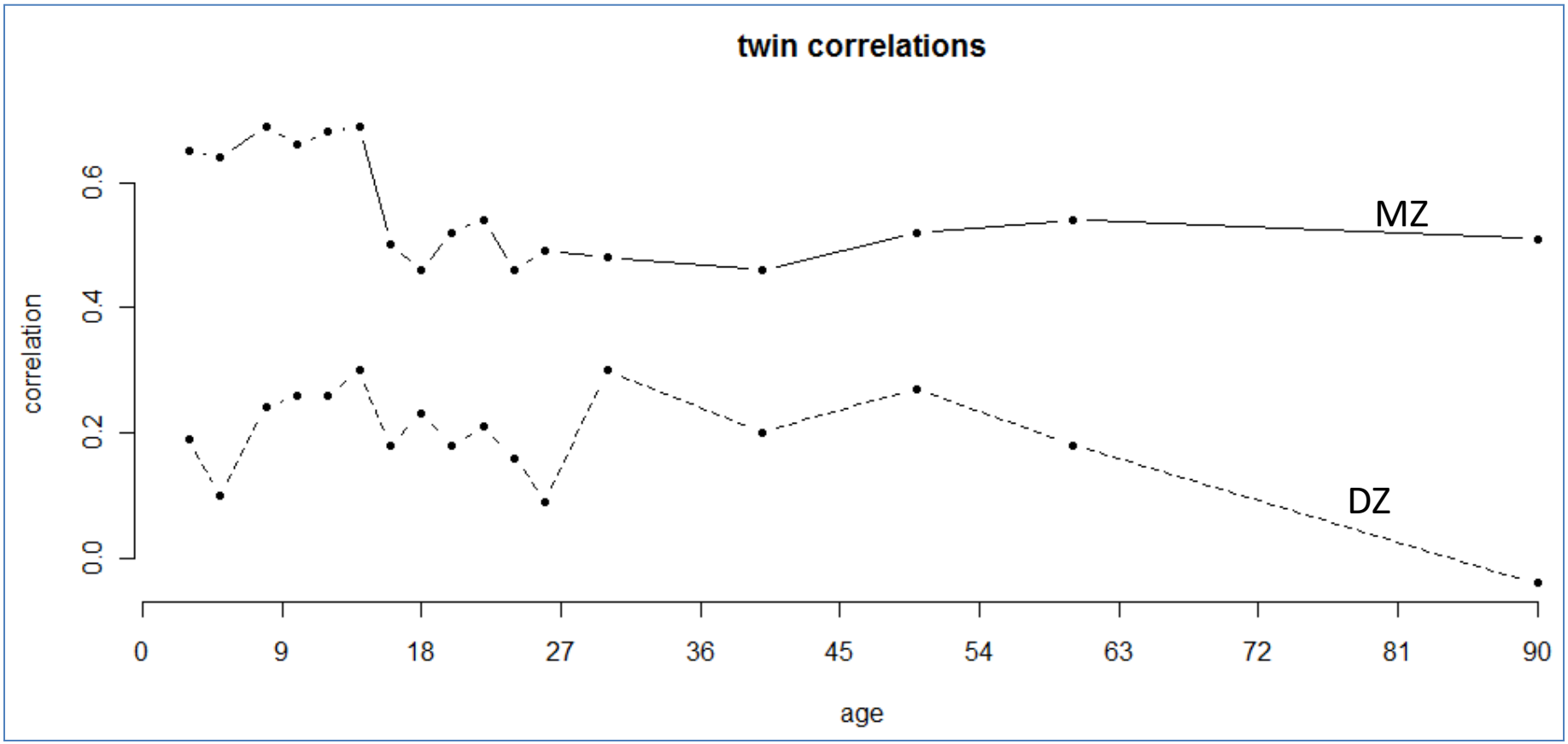
Anxious depression: Twin correlations for MZ and DZ twin pairs across age





Nivard et al. Psychol Med. 2015


Attention problems
-0.5
0.0
0.5
1.0
1.5
2.0
2.5
14
18
22
26
30
34
38
42
46
50
54
58
62
age


twin correlations
correlation
0.0
0.2
0.4
0.6
MZ
DZ
0
9
18
27
36
45
54
63
72
81
90
age

Attention problems

Age	3-5	5	6-8	10	12	14	16	18	20	22	24	26	30	40	50	60	90
h^2	**66**	**66**	**83**	**86**	**75**	**75**	**48**	**52**	**57**	**58**	**52**	**50**	**59**	**47**	**59**	**59**	**52**
h^2_{new}	-	35	52	00	16	01	26	10	01	02	00	00	00	00	00	00	00
h^2_{stable}	-	31	31	86	59	74	22	42	56	56	52	50	59	47	59	59	52

Total heritability as a function of age (blue shades)

Heritability that is innovation (**new genetic variance**)

Heritability that is shared across age **(stable genetic variance**)

After adolescence no genetic innovation, the variation in Attention problems is still mainly explained by Genes

Kan et al. JAACAP, 2013

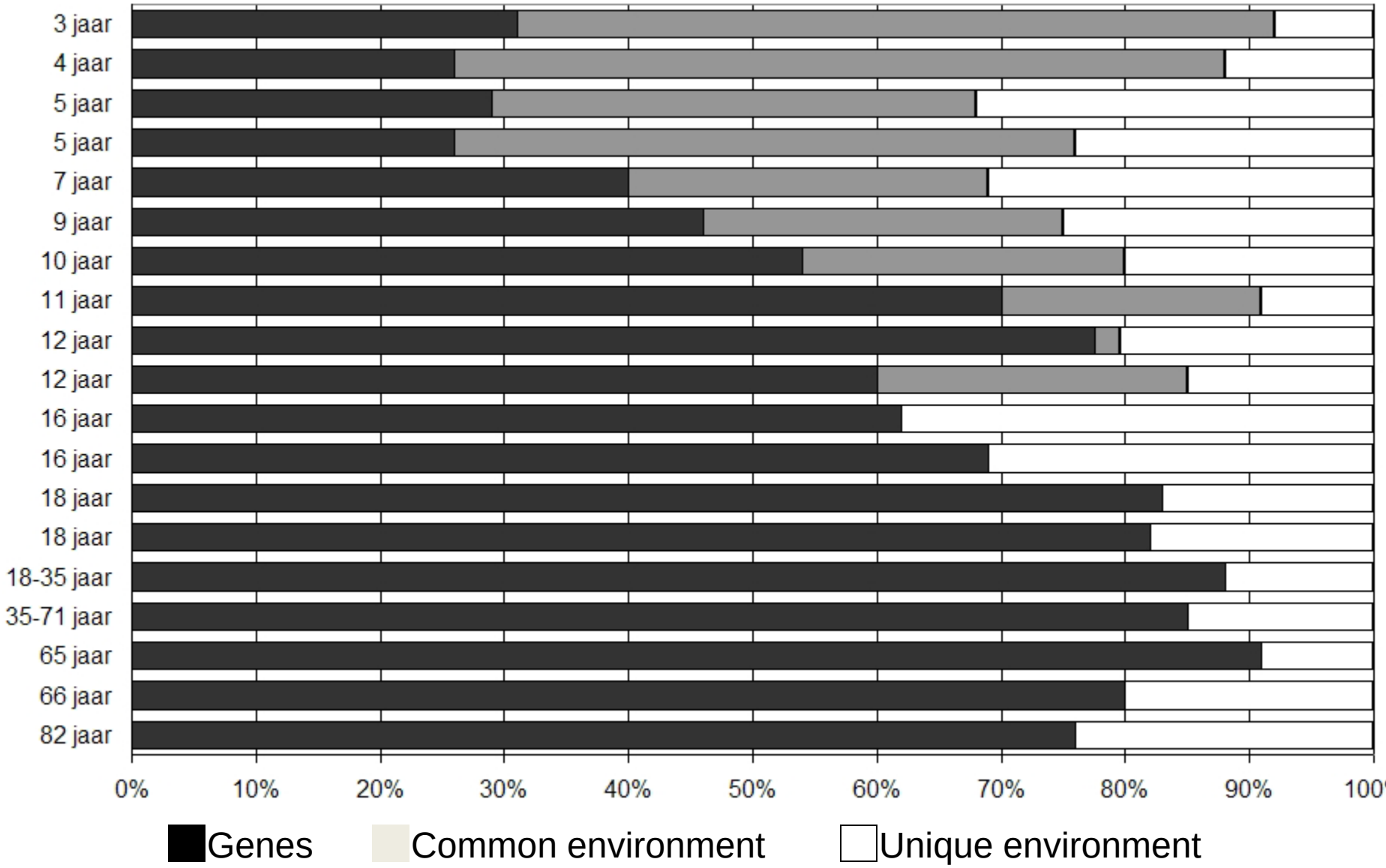
In conclusion

Very little / no evidence for genotype x age interaction for depression or ADHD / AP

Very little evidence for genetic innovation between ages 18 and 60+: no new genes expressed

Cognition, genetics, lipids, ageing

IQ heritability (low at early ages)



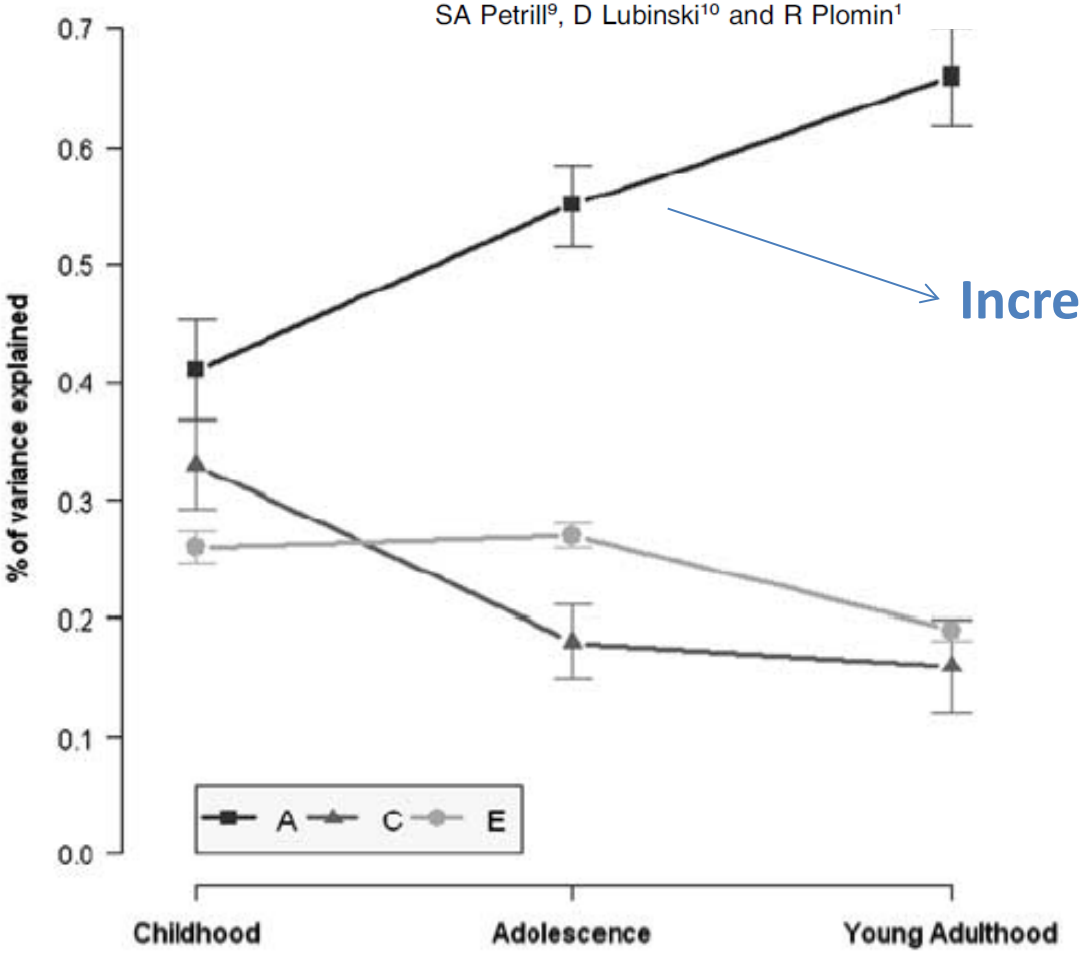
Molecular Psychiatry (2009), 1–9

www.nature.com/mp

ORIGINAL ARTICLE

The heritability of general cognitive ability increases linearly from childhood to young adulthood

CMA Haworth[1], MJ Wright[2], M Luciano[2], NG Martin[2], EJC de Geus[3], CEM van Beijsterveldt[3], M Bartels[3], D Posthuma[3,4,5], DI Boomsma[3], OSP Davis[1], Y Kovas[1], RP Corley[6], JC DeFries[6], JK Hewitt[6], RK Olson[6], S-A Rhea[6], SJ Wadsworth[6], WG Iacono[7], M McGue[7], LA Thompson[8], SA Hart[9], SA Petrill[9], D Lubinski[10] and R Plomin[1]



Increase in heritability

This is observed across all studies: Three US studies: Minnesota, Ohio, Colorado. One from Australia. Two from EU: Netherlands, UK. Age ranged from 6 to 71 years

Substantial Genetic Influence on Cognitive Abilities in Twins 80 or More Years Old

Gerald E. McClearn, Boo Johansson, Stig Berg, Nancy L. Pedersen, Frank Ahern, Stephen A. Petrill, Robert Plomin*

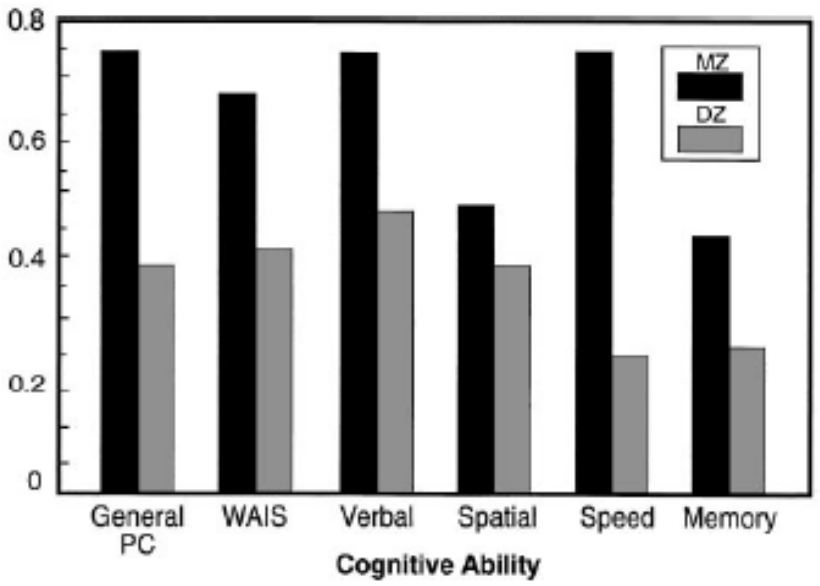


Fig. 2. Intraclass correlations for identical twins (MZ; black bars) and fraternal twins (DZ; gray bars) for general cognitive ability (PC and WAIS) and specific cognitive abilities.

Science, 1997

Heritability of lipids in different age groups from 3 countries

Heritabilities of Apolipoprotein and Lipid Levels in Three Countries

Marian Beekman[1,2], Bastiaan T. Heijmans[1], Nicholas G. Martin[3], Nancy L. Pedersen[4], John B. Whitfield[5], Ulf DeFaire[6], G. Caroline M. van Baal[7], Harold Snieder[8,9], George P. Vogler[10], P. Eline Slagboom[1], and Dorret I. Boomsma[7]

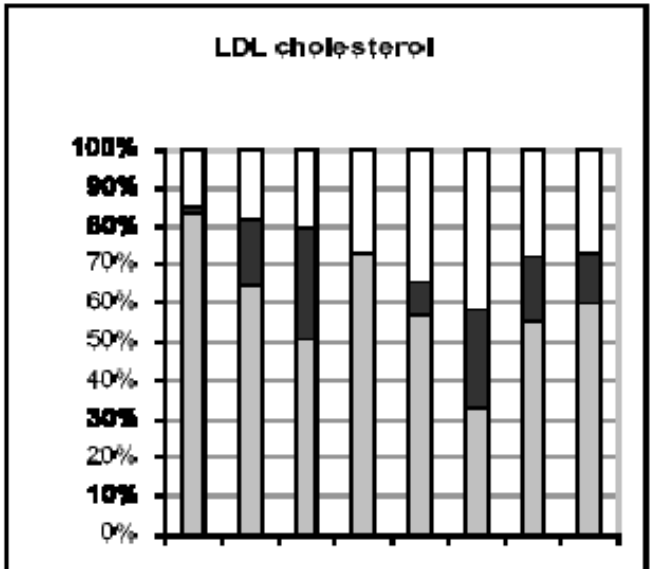
Table 1

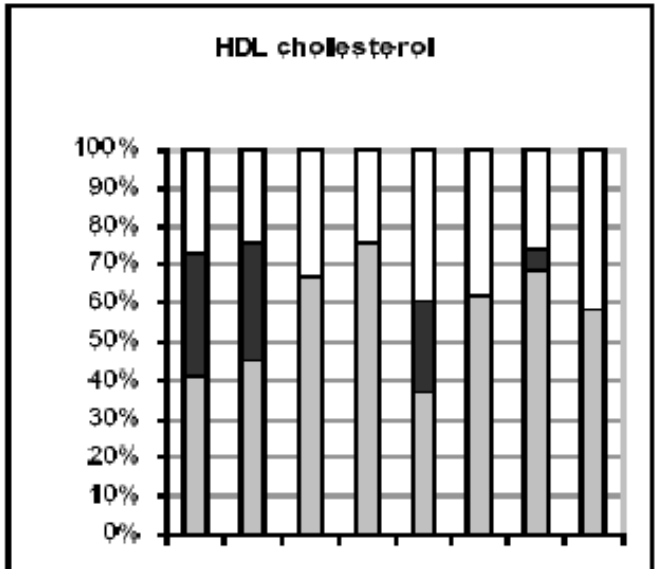
Descriptives of the Twin Samples, Means (and Standard Deviations) for Each Sample by Sex, for Levels of Apolipoprotein E, AII, AI and B and for Levels of Total, Low-density-lipoprotein, High-density-lipoprotein Cholesterol and the Natural Log of Triglyceride Levels

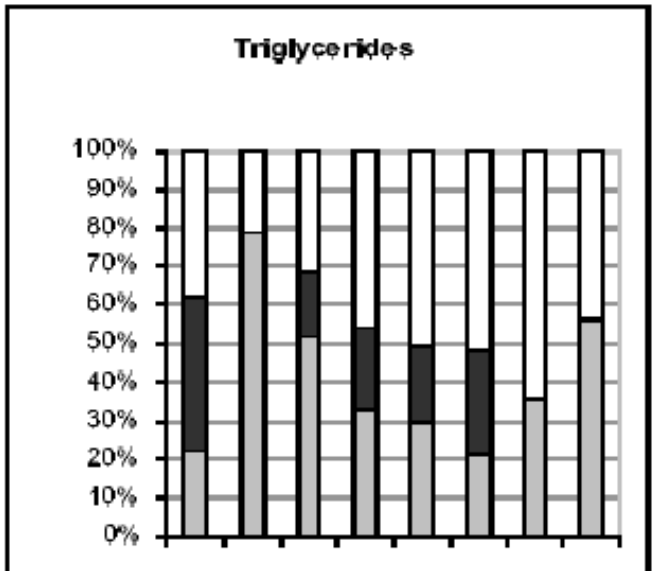
Twin sample	Young Dutch twins		Middle-aged Dutch twins		Australian twins		Swedish twins	
Mean (SD)	Men	Women	Men	Women	Men	Women	Men	Women
Number of individuals	161	159	192	218	874	1850	234	350
Age (yr)	16.77 (1.78)	16.71 (2.20)	43.55 (6.47)	44.70 (6.79)	44.10 (10.41)	45.88 (11.69)	65.02 (7.51)	66.09 (8.99)

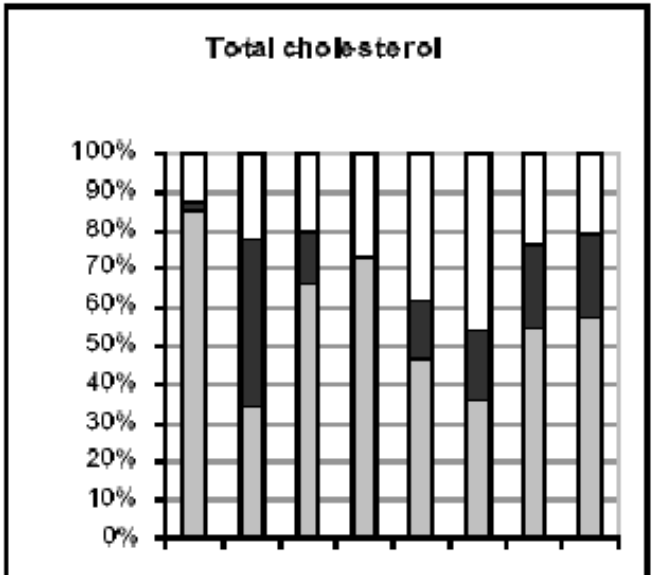
Twin Research, 2002

Heritability (gray bars) for LDL, HDL, triglycerides, total cholesterol









Young Dutch / middle-age Dutch / Australian, Old Swedish twins: M-F within cohort

WILEY ONLINE LIBRARY Journal of the American Geriatrics Society Volume 58, Issue 3, Article first
published online: 11 MAR 2010
Abstract | Full Article (HTML) | References | Cited By

Serum Lipid Levels and Cognitive Change in Late Life

Chandra A. Reynolds, PhD, Margaret Gatz, PhD,†‡ Jonathan A. Prince, PhD,‡ Stig Berg, PhD,§ and Nancy L. Pedersen, PhD†‡*

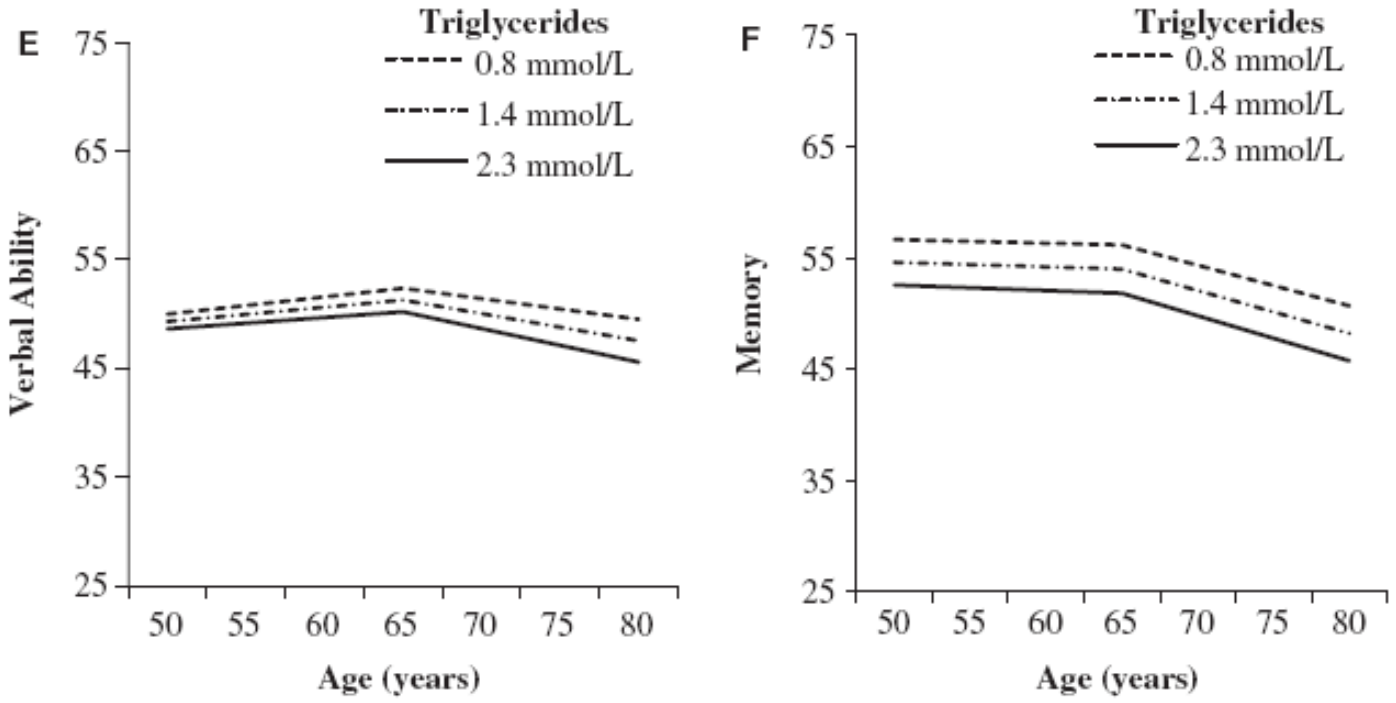


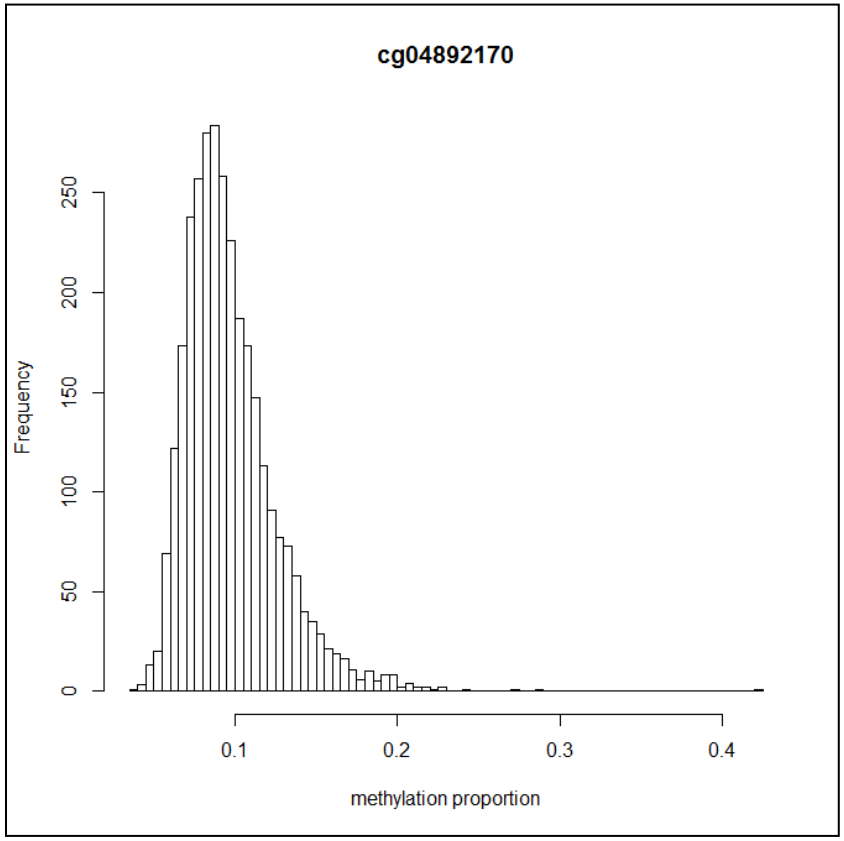
Table 3. Paired *T*-Test Analyses of Lipid Values for Twin Pairs Discordant for Dementia

Variable	Pairs, n	Mean Difference Untransformed	Mean Difference Log Transformed	*T*	*P*-Value
High-density lipoprotein cholesterol (HDL-C)	17	0.024	0.009	0.176	.86
ApoA1	21	0.030	—	0.566	.58
ApoB	21	0.103	0.078	2.362	.03
ApoB/ApoA1	21	0.069	0.069	1.692	.11
Triglycerides	21	0.067	0.017	0.164	.87
Total cholesterol	21	0.395	—	2.363	.03

T-tests for differences between log transformed variables shown where transformation applied. The lipid values for the unaffected twin were subtracted from their affected co-twin, with positive differences indicating higher lipid values associated with dementia status.
Apo = apolipoprotein; log = natural log of values.

The study included twin pairs discordant for dementia later in life: The twin who remained healthy had lower apoB and cholesterol levels early on.

Epigenetics: DNA methylation level at one locus in a population of cells (e.g. whole blood) is a quantitative trait



What are the total effects of genetic and environmental factors?

- **Do these effects depend on age or sex?**
- **Do these effects vary between different genomics regions?**

nature COMMUNICATIONS

ARTICLE

Received 10 Jun 2015 | Accepted 23 Feb 2016 | Published 7 Apr 2016

DOI: 10.1038/ncomms11115 OPEN

Genetic and environmental influences interact with age and sex in shaping the human methylome

Jenny van Dongen[1,*], Michel G. Nivard[1,*], Gonneke Willemsen[1], Jouke-Jan Hottenga[1], Quinta Helmer[1], Conor V. Dolan[1], Erik A. Ehli[2], Gareth E. Davies[2], Maarten van Iterson[3], Charles E. Breeze[4], Stephan Beck[4], BIOS Consortium[†], H. Eka Suchiman[3], Rick Jansen[5], Joyce B. van Meurs[6], Bastiaan T. Heijmans[3,**], P. Eline Slagboom[3,**] & Dorret I. Boomsma[1,**]

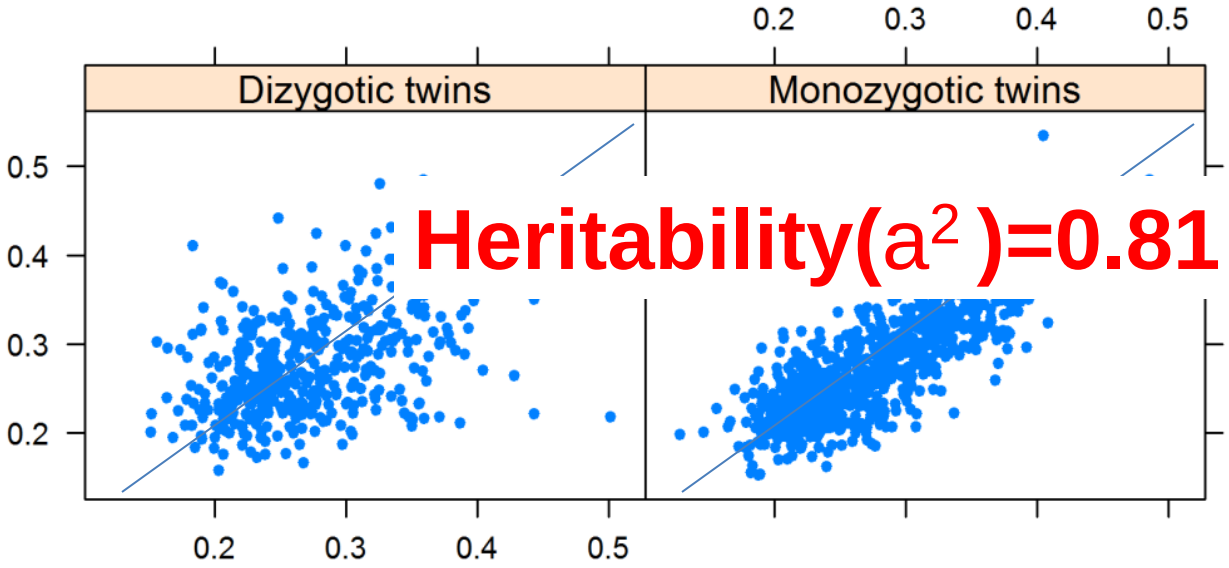
-We applied the classical twin model to DNA methylation levels to estimate components of variation and their interactions with age.
-We also estimated 'SNP heritability' and heritability due to other genetic effects.

The classical twin design

Differences= V_E (Unique environment, stochastic, measurement error)

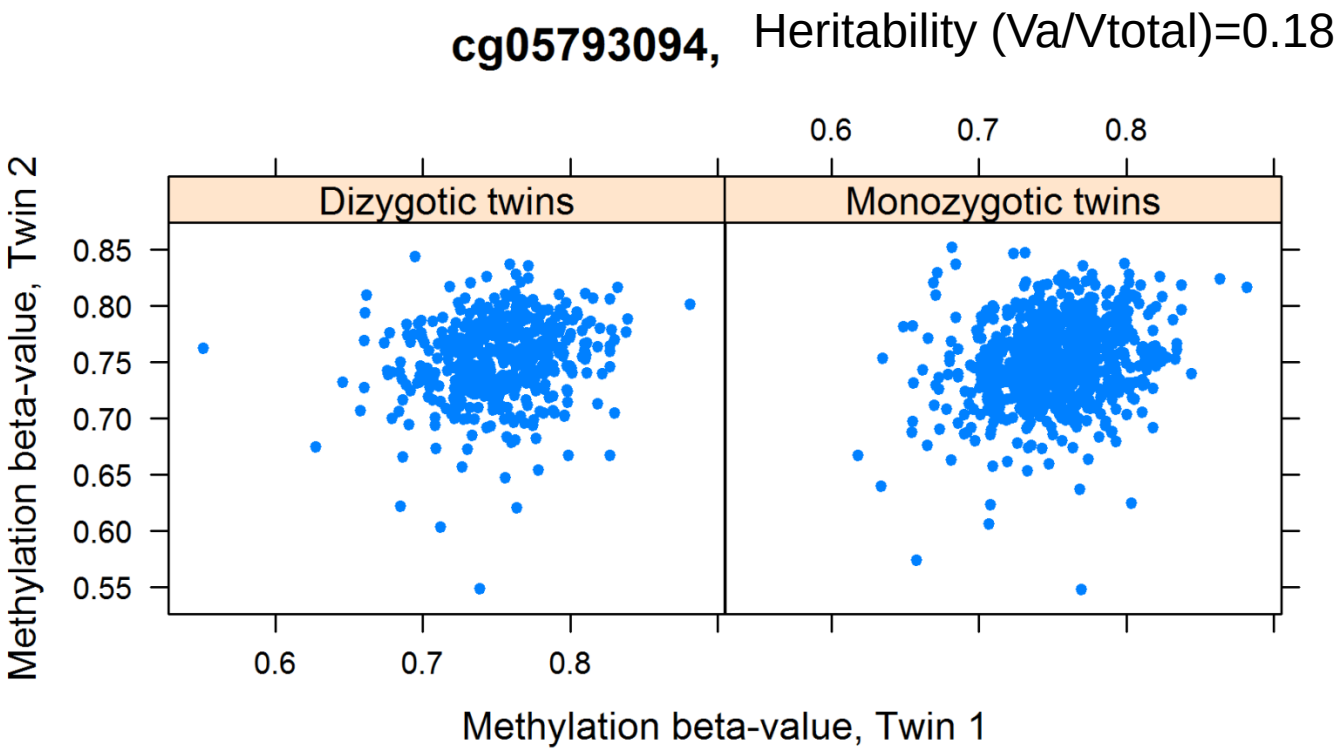
Covariance (MZ)= **100**% V_A + **100**% V_D + **100**% V_C

Covariance (DZ) = **50%** V_A + **25%** V_D + **100%** V_C



$$\text{Heritability } (a^2) = \frac{\text{additive genetic variance } (V_A)}{\text{total variance}}$$

Example of a methylation site with a ***low*** *heritability*



Partitioning the total heritability into 'SNP heritability' and other genetic effects

SNPs

Other genetic effects

Unique environmental variance (V_E)

$$covar(CpGi) = \boldsymbol{GRM}^{\boldsymbol{IBS}}_{\boldsymbol{n*n}} \otimes \sigma^2_{SNPs} + \boldsymbol{GRM}^{\boldsymbol{IBS>0.05}}_{\boldsymbol{n*n}} \otimes (\sigma^2_{IBD} - \sigma^2_{SNPs}) + I_{n*n} \otimes \sigma^2_e$$

Covariance (methylation level) between individuals (matrix)

Additive genetic variance due to all SNPs

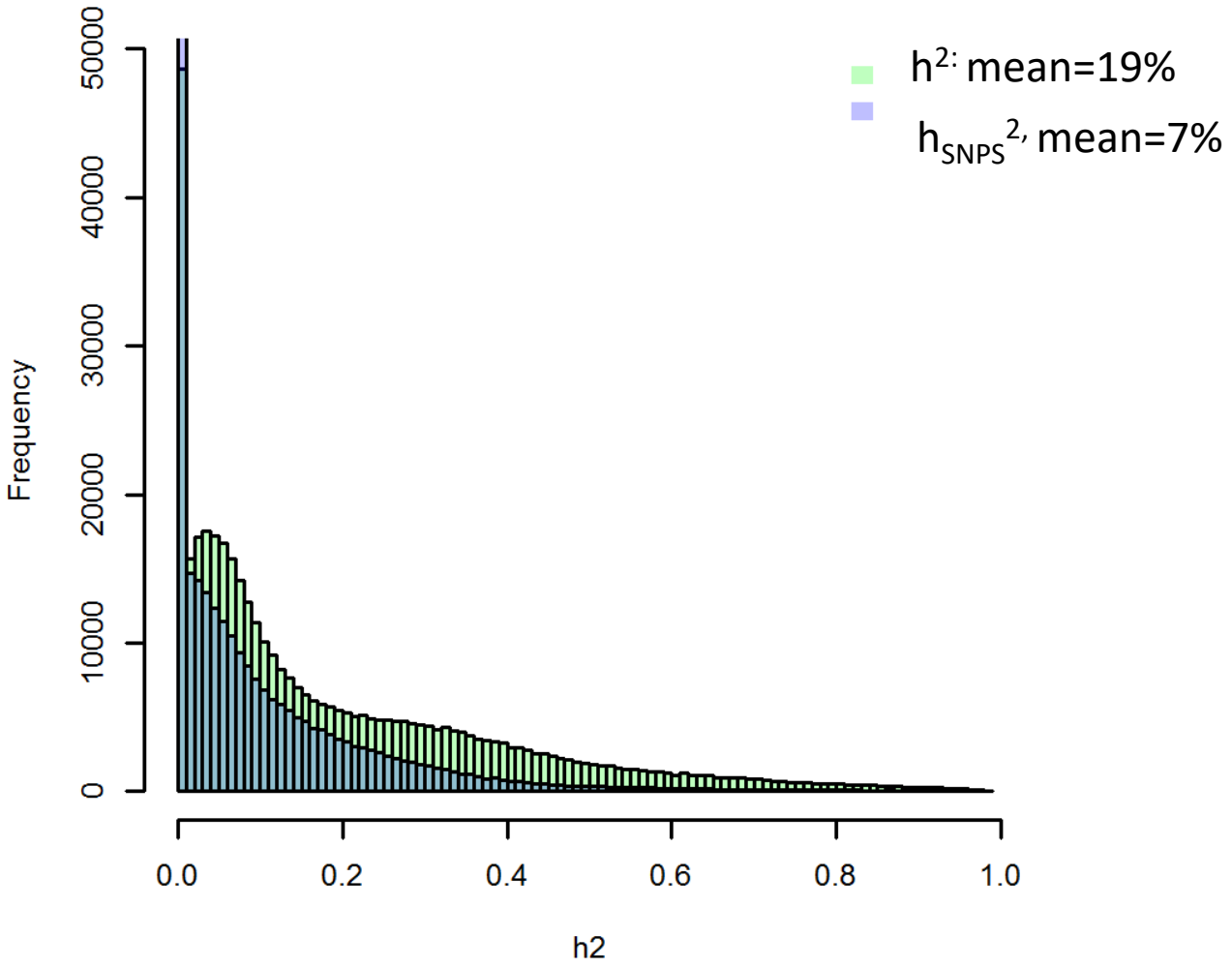
Genetic relatedness (IBD)
e.g.
0 between unrelated individuals
0.5 between parent-offspring,
0.5 on average between DZ twins
1 between monozygotic (MZ) twins,

Additive genetic variance not explained by SNPs

$\boldsymbol{GRM}^{\boldsymbol{IBS}}_{\boldsymbol{n*n}}$: Genetic relationship matrix (IBS) all individuals, from **G**

$\boldsymbol{GRM}^{\boldsymbol{IBS>0.05}}_{\boldsymbol{n*n}}$: Same matrix, but IBS set to zero for distant relativ

Total and SNP heritability of DNA methylation level at 411,169 sites in the genome

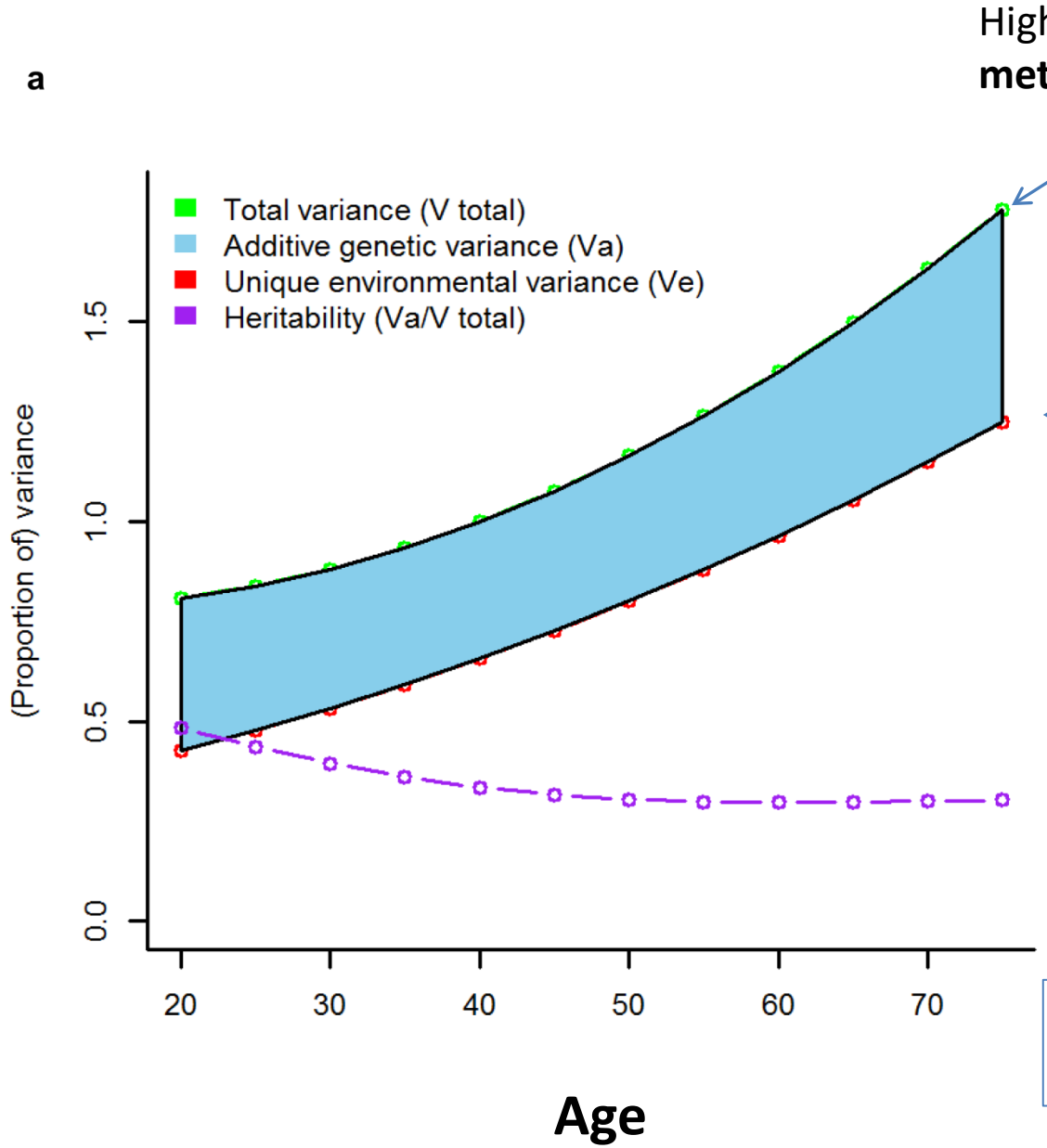


Age

- 33% of methylation sites: significant change in **mean** methylation level with age
- 10% of methylation sites: significant change of the genetic or environmental **variance** with age

There is an age related shift in the causes of variation in DNA methylation between people

- At 39,455 methylation sites

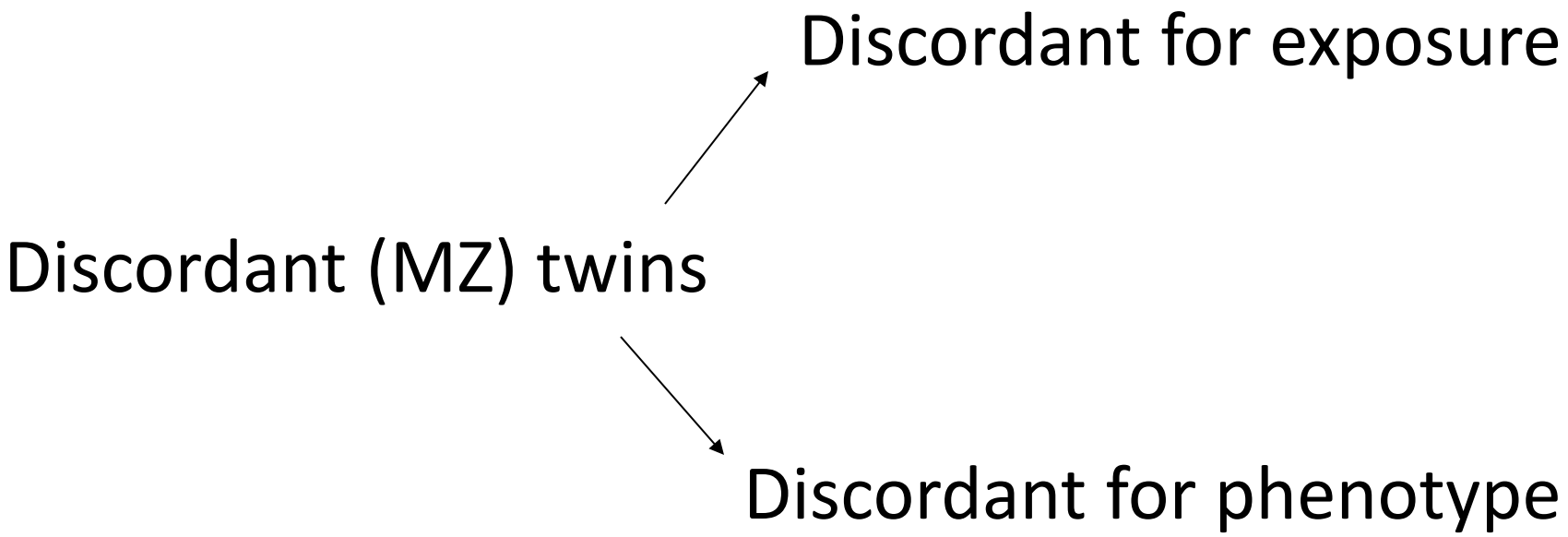


Higher age → **more variation in DNA methylation** between people

Environmental or stochastic influences on methylation increase

Heritability of methylation decreases

In general not more discordance with increasing age


Discordant for exposure
Discordant (MZ) twins
Discordant for phenotype

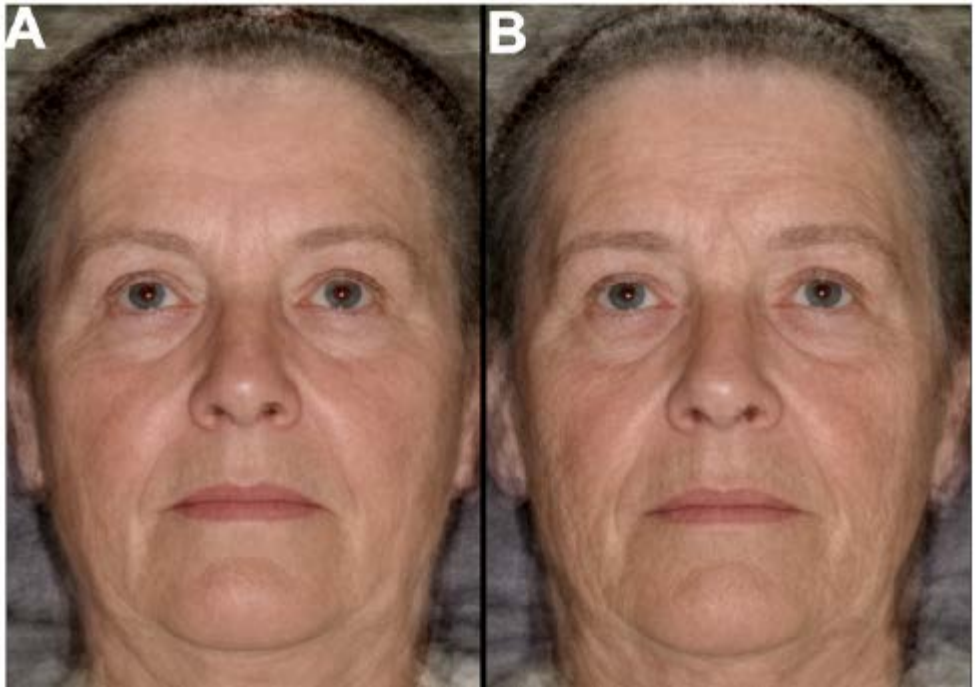
OPEN ACCESS Freely available online

PLoS one

Why Some Women Look Young for Their Age

David A. Gunn[1]*, Helle Rexbye[2], Christopher E. M. Griffiths[3], Peter G. Murray[1], Amelia Fereday[1], Sharon D. Catt[1], Cyrena C. Tomlin[1], Barbara H. Strongitharm[1], Dave I. Perrett[4], Michael Catt[5], Andrew E. Mayes[1], Andrew G. Messenger[6], Martin R. Green[1], Frans van der Ouderaa[7], James W. Vaupel[8], Kaare Christensen[2]

1 Unilever Discover, Sharnbrook, Bedfordshire, United Kingdom, 2 The Danish Twin Registry and Danish Aging Research Center, Institute of Public Health, University of Southern Denmark, Odense, Denmark, 3 Dermatological Sciences, University of Manchester, Salford Royal Hospital, Manchester, United Kingdom, 4 Perception Lab, School of Psychology, University of St Andrews, St Andrews, United Kingdom, 5 Institute for Ageing and Health, Newcastle University, Newcastle Upon Tyne, United Kingdom, 6 Department of Dermatology, Royal Hallamshire Hospital, Sheffield, United Kingdom, 7 Netherlands Consortium for Healthy Ageing, Leiden University Medical Centre, Leiden, Netherlands, 8 Max Planck Institute for Demographic Research, Rostock, Germany



Younger looking Older looking

Composite images of the effects of environment on variation in perceived age in MZ twins.

The older looking twin sister composite shows signs of **increased skin wrinkling, increased nasolabial fold shadowing and a grayer skin color, a thinner face and reduced lip fullness.**

Each composite was derived from 14 twin images, chronological age was 67 [60–76] for the composites.

Discordant Monozygotic Twins

- Different chromosome constitutions because of post-zygotic non-disjunction: e.g. MZ male-female 46,XY - 45,XO
- Differences in DNA sequence
- Differential *methylation* (imprinted genes)
- CNV (copy number variation)
- Skewed X chromosome inactivation in female MZ twins
- Differential trinucleotide repeat expansion
- Post-zygotic mutation
- *Prenatal* differences
- *Postnatal* environmental differences

Martin, Martin N, Boomsma DI, Machin G. (1997) *Nature Genetics*

Twin Research and Human Genetics
Volume 16 ▮ Number 6 ▮ pp. 1026–1032 ▮ © The Authors 2013 ▮ doi:10.1017/thg.2013.73

Aging as Accelerated Accumulation of Somatic Variants: Whole-Genome Sequencing of Centenarian and Middle-Aged Monozygotic Twin Pairs

Kai Ye,[1] Marian Beekman,[1,2] Eric-Wubbo Lameijer,[1] Yanju Zhang,[1] Matthijs H. Moed,[1] Erik B. van den Akker,[1,3] Joris Deelen,[1,2] Jeanine J. Houwing-Duistermaat,[4] Dennis Kremer,[1] Seyed Yahya Anvar,[5] Jeroen F. J. Laros,[5] David Jones,[6] Keiran Raine,[6] Ben Blackburne,[7] Shobha Potluri,[8] Quan Long,[9] Victor Guryev,[10] Ruud van der Breggen,[1] Rudi G. J. Westendorp,[11] Peter A. C. 't Hoen,[12] Johan den Dunnen,[12] Gert Jan B. van Ommen,[12] Gonneke Willemsen,[13] Steven J. Pitts,[8] David R. Cox,[8] Zemin Ning,[6] Dorret I. Boomsma,[13,*] and P. Eline Slagboom[1,2,*]

Eight single base substitutions between co-twins were supported by two platforms and validated as somatic variants.

The number of somatic variants may be substantially larger but those present in smaller fractions of cells go undetected. Consistent, detectable somatic variation likely includes somatic mosaicism in blood generated during development or clonal expansion of mutations generated at any point during the lifetime. The frequency of these variants is limited in blood even after 100 years of life.

This study showed that the number of detectable somatic variants in blood by NGS is very low and that accumulation of somatic mutations is not necessarily a consequence of a century of life.

Discordant MZ twin design

MZ concordance

for complex disease (heritability) and MZ and DZ twin concordance

	Probandwise concordance (%)	
	MZ	DZ
Diabetes Type 1 (88%)	**42.9**	7.4
Diabetes Type 2 (64%)	**34**	16
Multiple Sclerosis (25-70%)	**25.3**	5.4
Alzheimer's Disease (48%)	**32.2**	8.7
Parkinson Disease (34%)	**15.5**	11.1
Schizophrenia (81%)	**40.8**	5.3
Major Depresssion (37%)	**31.1**	25.1

Two sides of the coin

Personalized medicine?
Incomplete concordance of MZ twins indicates that a genome cannot predict individual outcome.

- Twin pairs a good way of recruiting **families**.
- Twins are **representative** of the population (no difference in mortality / (cancer) morbidity, many other traits too).
- Unique value of **MZ pairs** for e.g. epigenetics .
- Twin registers have (very long) **follow-up** / longitudinal data and/or biological samples; often **prospective**.
- Twins are usually phenotyped for **multiple traits**.
- Twin registers often have **environmental exposure** data.

Parental Education and Genetics of BMI from Infancy to Old Age: A Pooled Analysis of 29 Twin Cohorts. Silventoinen

Genetic and environmental influences on adult human height across birth cohorts from 1886 to 1994. Jelenkovic A

Stability in symptoms of anxiety and depression as a function of genotype and environment: a longitudinal twin study from ages 3 to 63 years. Nivard MG

Genetic and environmental stability in attention problems across the lifespan: evidence from the Netherlands twin register. Kan KJ

The Computerized Neurocognitive Battery: Validation, **aging** effects, and heritability across cognitive domains. Swagerman SC

Association of amyloid pathology with memory performance and cognitive complaints in cognitively normal older adults: a monozygotic twin study. Konijnenberg E

Genetic influences on individual differences in longitudinal changes in global and subcortical brain volumes: Results of the ENIGMA plasticity working group. Brouwer RM

Age-related accrual of methylomic variability is linked to fundamental **ageing** mechanisms. Slieker RC

Genetic and environmental influences interact with age and sex in shaping the human methylome. van Dongen J

The Influence of Age and Sex on Genetic Associations with Adult Body Size and Shape: A Large-Scale Genome-Wide Interaction Study. Winkler TW,

Genome-wide patterns and properties of de novo mutations in humans. Francioli LC