The future of twin studies

Odense workshop
May 14, 2018

Jaakko Kaprio, MD, PhD

Consulted for Pfizer on nicotine dependence in 2012-2015

Mid-summer 2017

Genes, developmental history and environment as determinants of health and lifecourse

In complex traits and diseases a person's susceptibility genotypes and environmental history combine to establish present status.

The genotype's norm of reaction determines future developmental and health trajectory.

Maximum human lifespan is 100+ years.

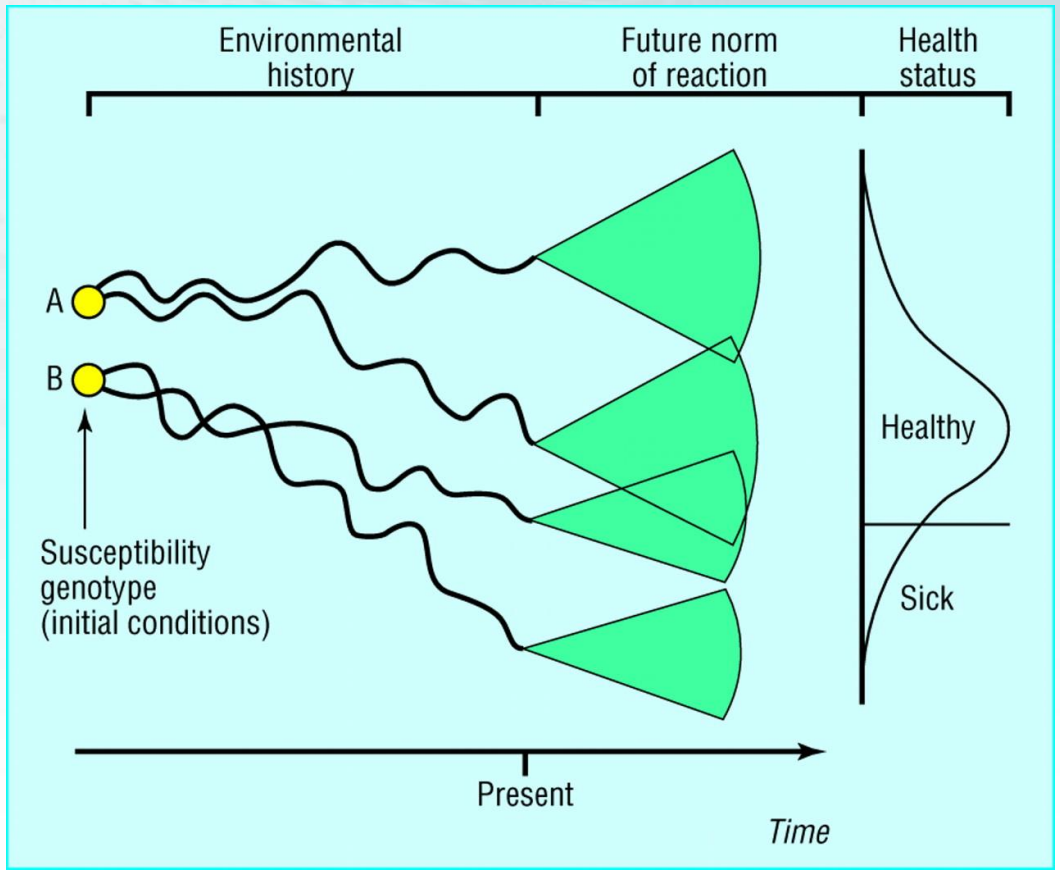
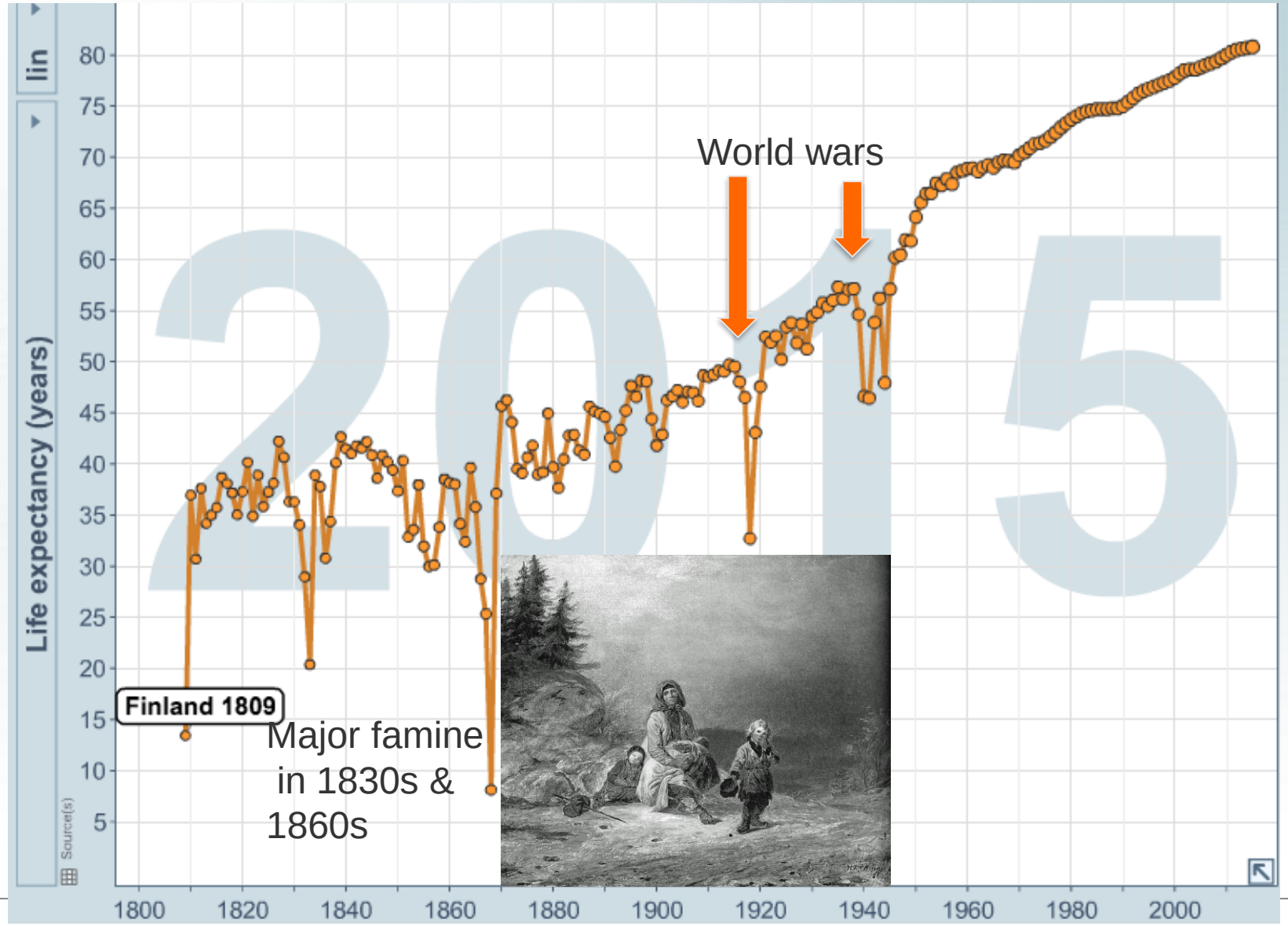


Figure courtesy of Charles F Sing (my post-doc mentor in Ann Arbor 1989)

Finnish life-expectancy 1809-present day

www.gapminder.org

Globally dramatic Improvements in health while our gene pool has not essentially changed



Institute for Molecular Medicine Finland
Nordic EMBL Partnership for Molecular Medicine

Outline:

Causality and observational epidemiological studies

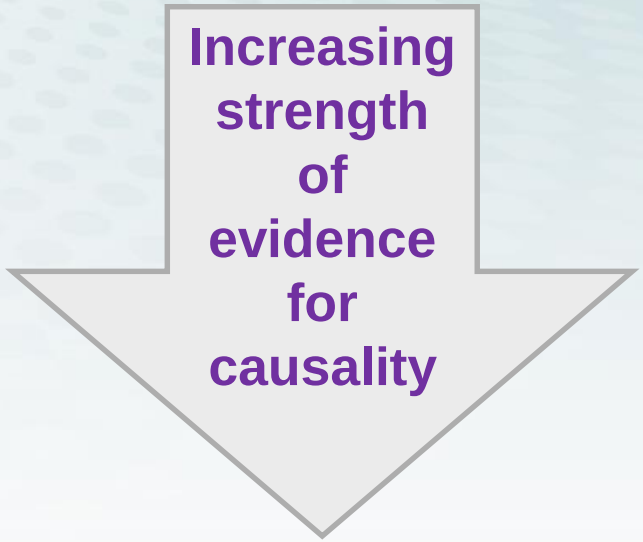
Value of heritability estimates

Assessing causation

Analytic epidemiology studies the relationship of exposures and outcomes

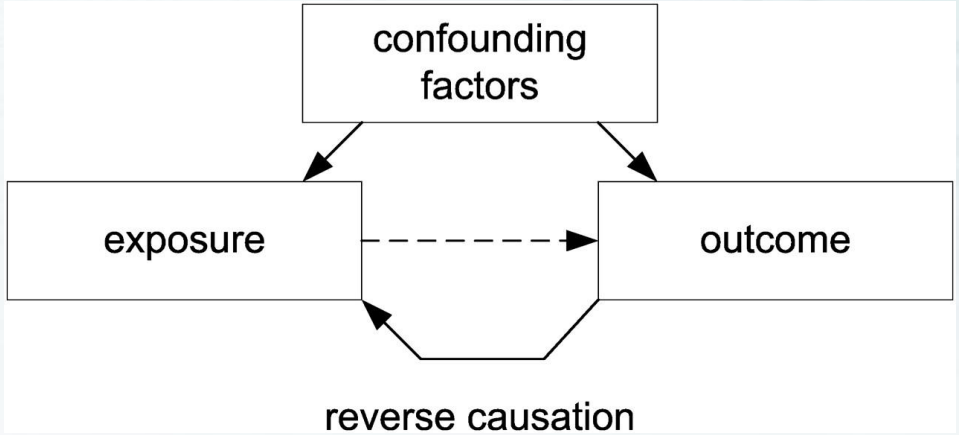
Study designs include:

- case-control studies
- cohort studies
- Quasi-experimental designs
- Interventions



Observational studies are prone to:

- confounding,
- residual confounding
- reverse causation
- and bias (systematic error)



Randomized clinical trial (RCT) considered gold standard for assessing causality. i.e. does changing the exposure yield to a change in the outcome?

RCTs are generally short-term, involve generally a new exposure (such as a medication) and target highly selected participants

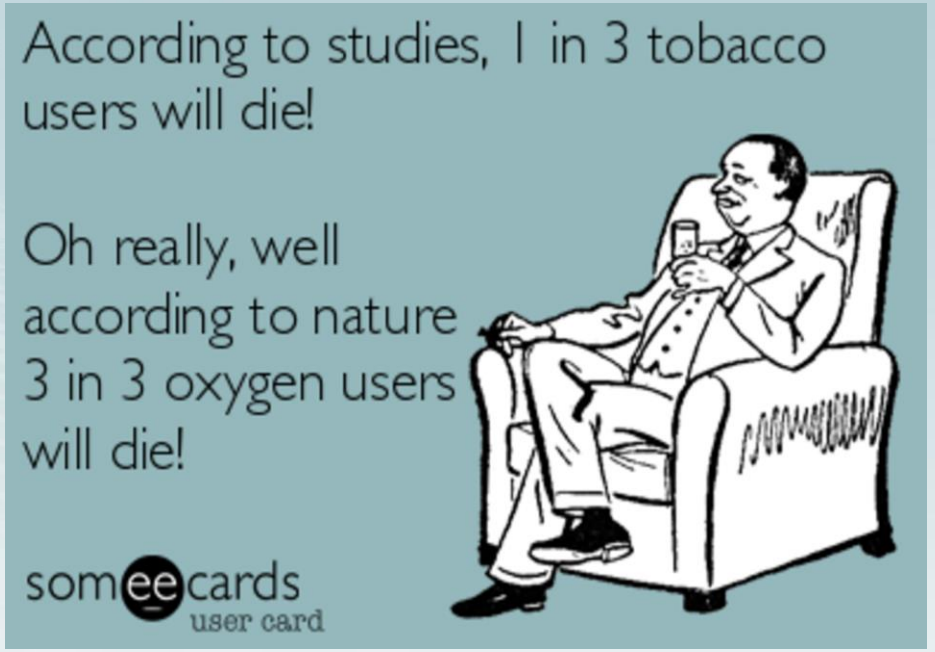
How to assess existing exposures & long-term effects in the whole population?

We cannot assign children to be maltreated or not, and then see if the maltreated are at higher risk of say ADHD

Confounding may be due to known or unknown factors

Observational studies do not resolve causality

- Need clinical trials (generally short-term) or field interventions (longer term), but these cannot be done in all situations.
- Within-family studies can adjust for confounding due to familial effects
- Studies of MZ pairs discordant for a trait have been the prototypical design for within-family studies (Gesell 1940 and Cederlöf et al, several papers in the 1960s)
- The Finnish Twin Cohort study was set up to test the causal vs constitutional hypotheses of smoking effects on chronic disease



SMOKING

IN RELATION TO

CORONARY HEART DISEASE

AND

LUNG FUNCTION IN TWINS

A co-twin control study

By

TORBJÖRN LUNDMAN

Also published as supplement 455 to
Acta Medica Scandinavica, Vol. 180, 1966

STOCKHOLM 1966

ALCOHOL CONSUMPTION
IN RELATION
TO FACTORS ASSOCIATED
WITH ISCHEMIC HEART DISEASE

A co-twin control study

By

MÅRTEN MYRHED

Also published as supplement 567 to
Acta Medica Scandinavica 1974

STOCKHOLM 1974

Kansanterveystieteen julkaisuja M 84: 1984

THE INCIDENCE OF CORONARY HEART DISEASE IN TWIN PAIRS DISCORDANT FOR CIGARETTE SMOKING

A SIX YEAR FOLLOW-UP OF ADULT LIKE-SEXED MALE TWIN PAIRS

JAAKKO KAPRIO

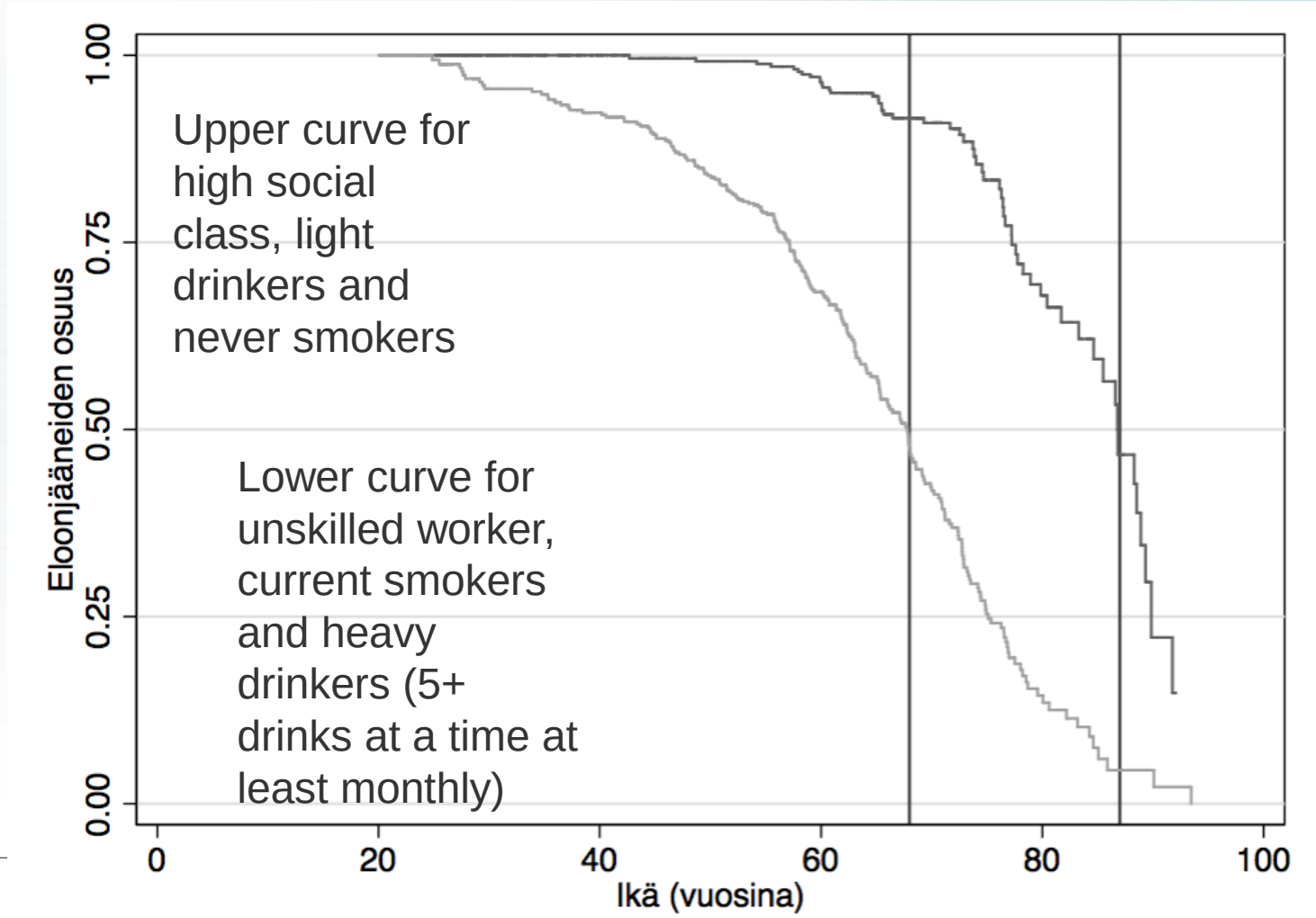
Kansanterveystieteen laitokset
Helsinki, Kuopio, Oulu,
Tampere ja Turku

Helsinki 1984

Cohort of Older Like-sexed Finnish Twins

- The older Finnish Twin Cohort consists of all Finnish twin pairs of the same gender born before 1958 with both co-twins alive in 1975.
- These twin pairs were selected from the Central Population Registry of Finland in 1974.
- Four questionnaire surveys of the cohort have been carried out. The first questionnaire was mailed to all pairs in August-October 1975. The follow-up questionnaire studies have been carried out in 1981, 1990 and 2011.
- Twin zygosity was determined by a validated questionnaire method initially in the entire cohort. In sub-studies of selected twin pairs, genetic markers have been used for validation.
- The total number of MZ and DZ twin pairs was 13,888 in the beginning of prospective follow-up in August 1975.

Two “metabolites” and one “cognitive measure” are powerful predictors of mortality – survival curves by age **among individuals**

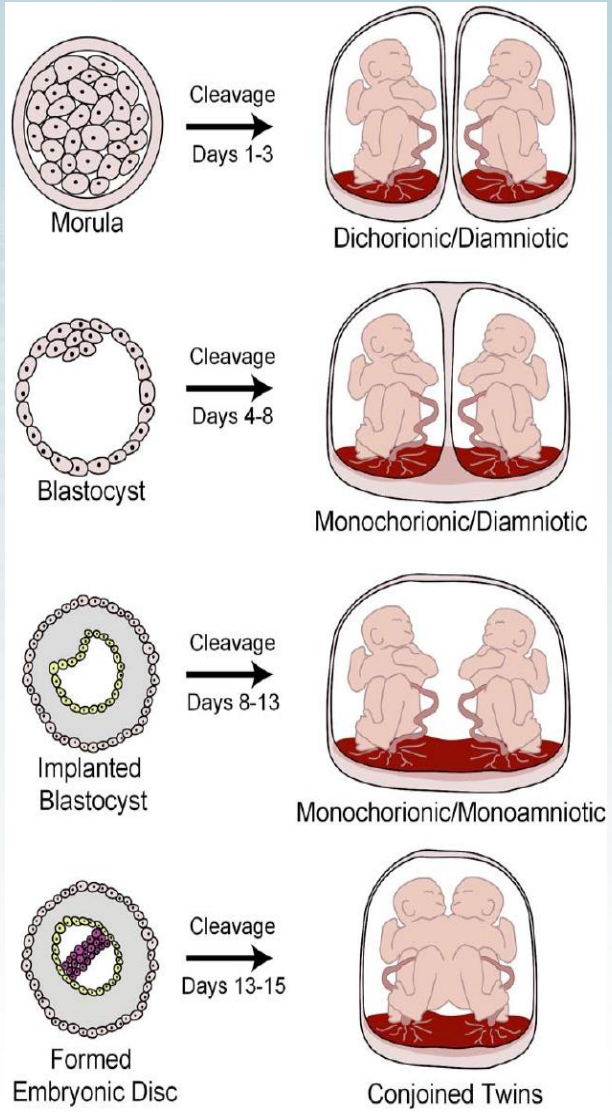


15 797 men followed for 35.7 years as of 1976 in the Finnish twin cohort

Life expectancy of two groups were 68 yrs & 87 yrs

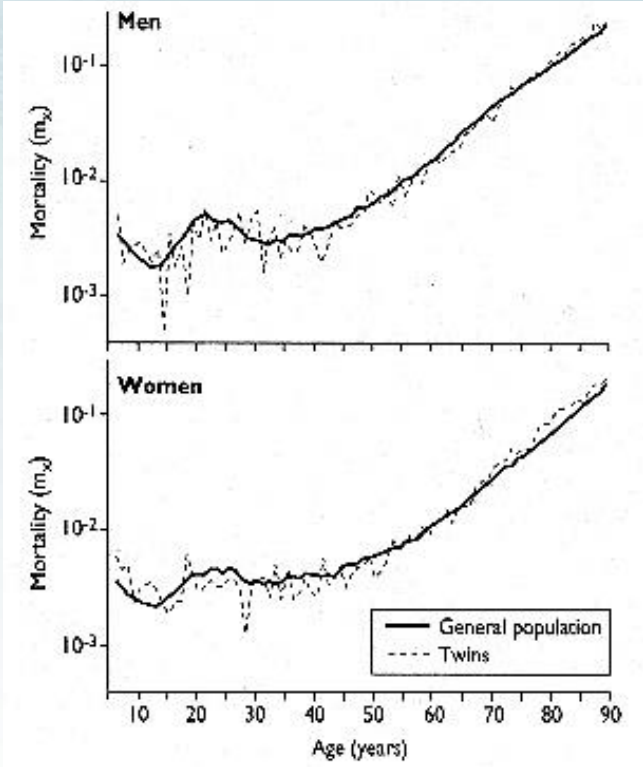
Monozygotic twins

- Approximately 1 to 1.5% of births are multiples (twins, triplets, etc)
- Twin births can be monozygotic (MZ), rising from the cleavage after fertilization of a single ovum, thus giving rise to two individuals with the same genetic sequence
- OR dizygotic (DZ), due to implantation of two fertilized ova simultaneously. DZ twins can be of the same or different sex, and are genetically full siblings.
- MZ twins can have a shared placenta or separate ones, depending on time of cleavage.
- MZ twins hence have some specific potential abnormalities (like feto-fetal transfusion), lower birthweight and higher perinatal morbidity and mortality



MZ twins

- As adults, there are no substantial differences in health, personality and behaviors of MZ twin individuals, DZ twins individuals and singletons on means and variation.
- The dyadic interactions of MZ twin pairs is often closer and more intense than among DZ pairs or siblings.
- As genetic clones, MZ pairs are ideal subjects for quasi-experimental studies



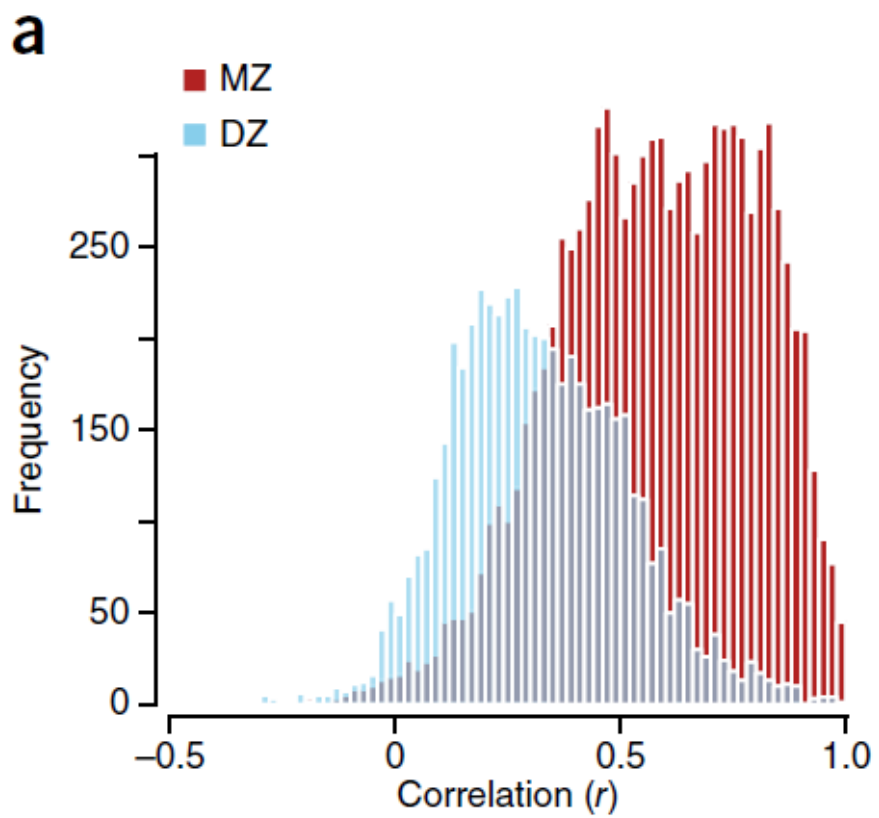
Christensen K et al. BMJ 1995;310:432-436

nature genetics

Though MZ pairs are genetically identical, they do differ phenotypically

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

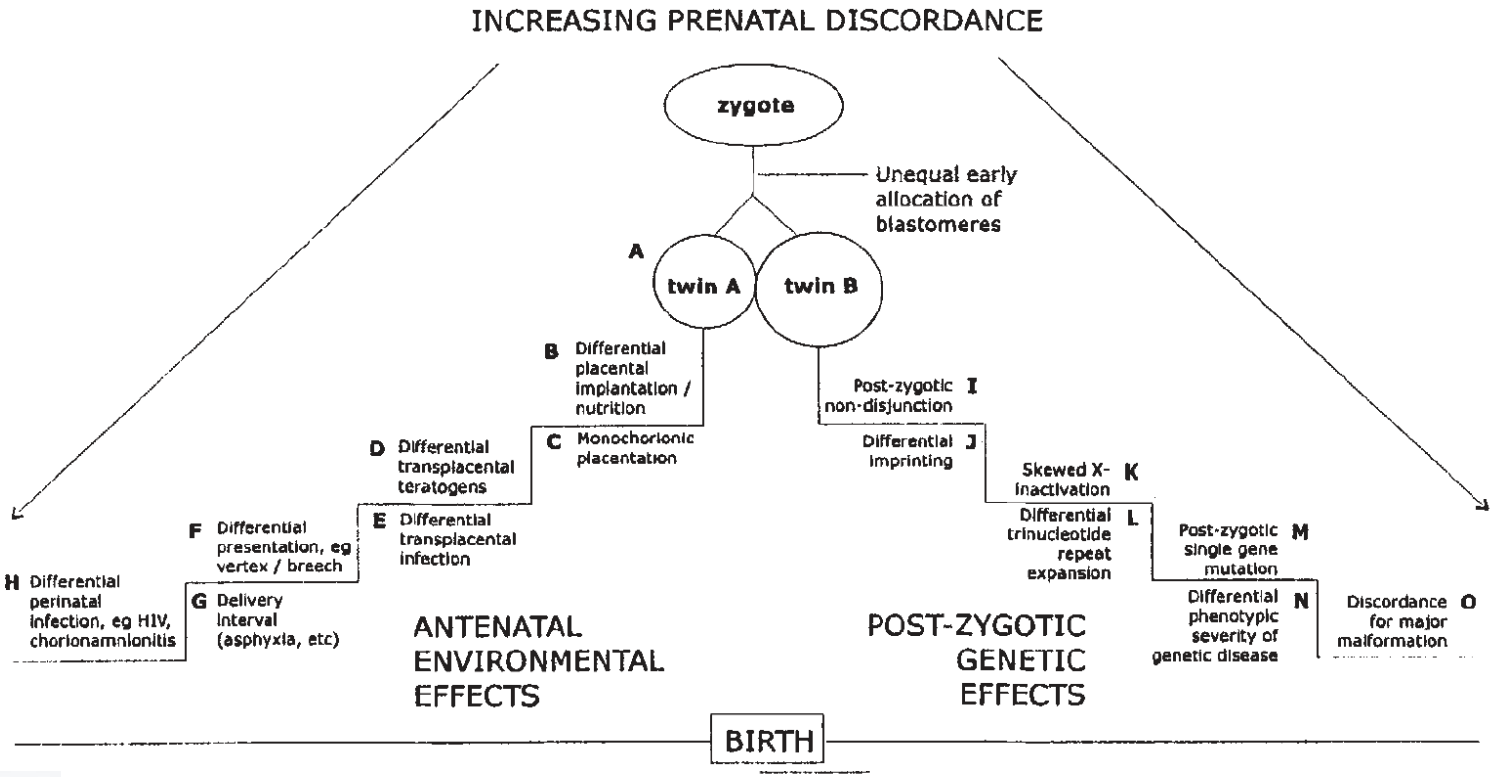
Tinca J C Polderman[1,10], Beben Benyamin[2,10], Christiaan A de Leeuw[1,3], Patrick F Sullivan[4–6], Arjen van Bochoven[7], Peter M Visscher[2,8,11] & Danielle Posthuma[1,9,11]



Despite a century of research on complex traits in humans, the relative importance and specific nature of the influences of genes and environment on human traits remain controversial. We report a meta-analysis of twin correlations and reported variance components for 17,804 traits from 2,748 publications including 14,558,903 partly dependent twin pairs, virtually all published twin studies of complex traits. Estimates of heritability cluster strongly within functional domains, and across all traits the reported heritability is 49%. For a majority (69%) of traits, the observed twin correlations are consistent with a simple and parsimonious model where twin resemblance is solely due to additive genetic variation. The data are inconsistent with substantial influences from shared environment or non-additive genetic variation. This study provides the most comprehensive analysis of the causes of individual differences in human traits thus far and will guide future gene-mapping efforts. All the results can be visualized using the MaTCH webtool.

Box 2 · How identical are MZ twins?

There are many reasons why MZ twins might be less than fully identical[61]. A wide range of ante-natal genetic and environmental influences can cause phenotypic and genotypic divergence. Reconvergence may occur after birth because the twins do not passively undergo differing experiences; on the contrary, it now seems likely that they actively seek, select and perceive similar environments because of genetic similarities in brain physiology.



Martin NG et al.
Nat Genet 1997

The discordant pair design

		Twin with lung cancer	
		Non-smoker	Smoker
Cotwin (alive or death from other causes)	Non-smoker	A	B
	Smoker	C	D

Pairs from cells A and D are non-informative

The ratio B/C is an estimate of the CHD risk associated with sedentarines controlling for family/genes. Statistical significance tested by McNemar's test, and conditional logistic regression

Observational studies do not resolve causality

- While powerful by design, MZ discordant pairs are rare and require large and well-studied cohorts and registries to identify sufficient numbers
- In the Nordic Twin study of Cancer, we identified over 100,000 twins with baseline smoking data and follow-up for lung cancer incidence

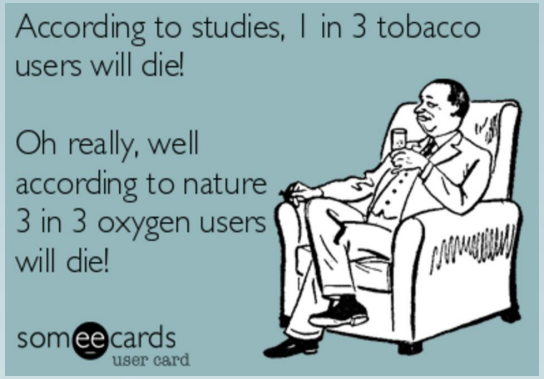


Table 5 Lung cancer in twin pairs discordant for smoking at baseline by zygosity and smoking status

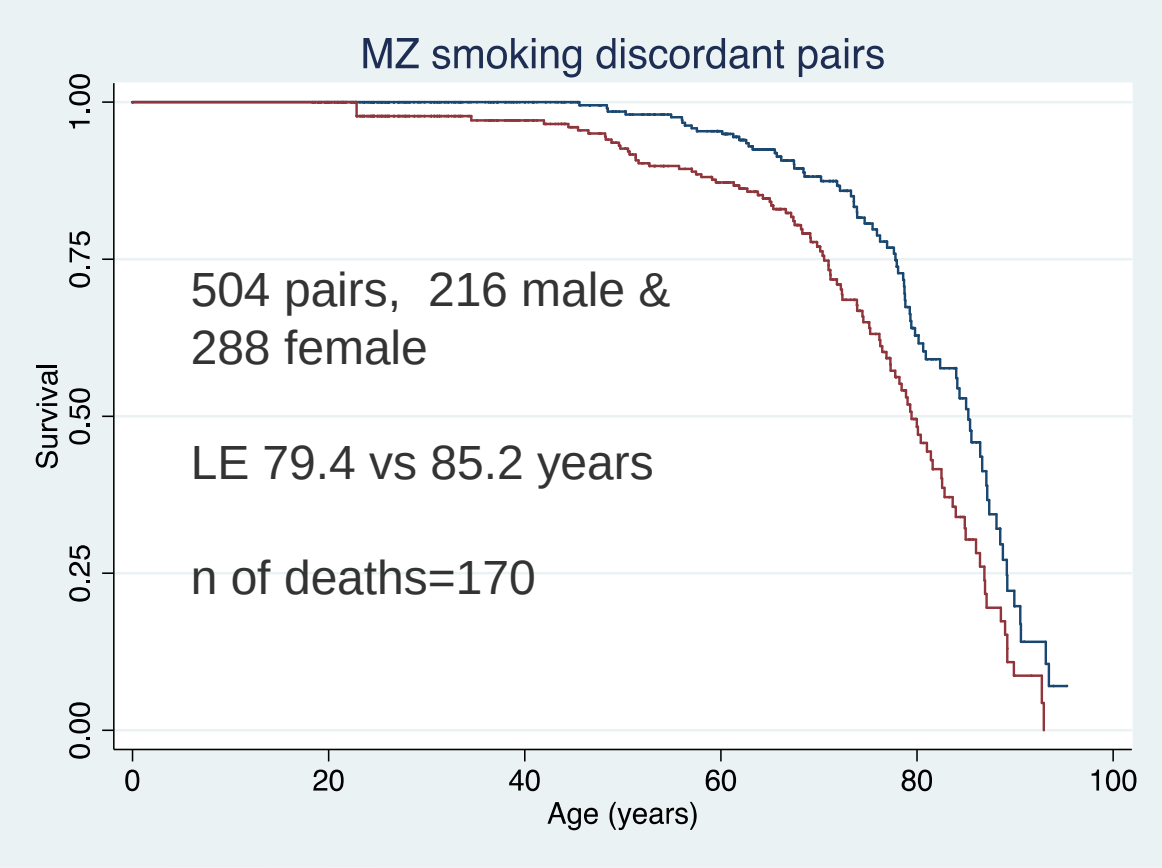
Smoking discordance	Zygosity	Pairs in which smoker had lung cancer and the non-smoking co-twin did not	Pairs in which non-smoker had lung cancer and the smoking co-twin did not	HRs (95% CI); p Value
Ever/never	MZ	35	5	5.4 (2.1 to 14.0); p=0.0005
	DZ	145	28	5.0 (3.2 to 7.9); p=1.4e–12
Current/never	MZ	31	4	6.0 (2.1 to 17.3) p=0.001
	DZ	124	20	5.9 (3.5 to 9.8) p=1.4e–11

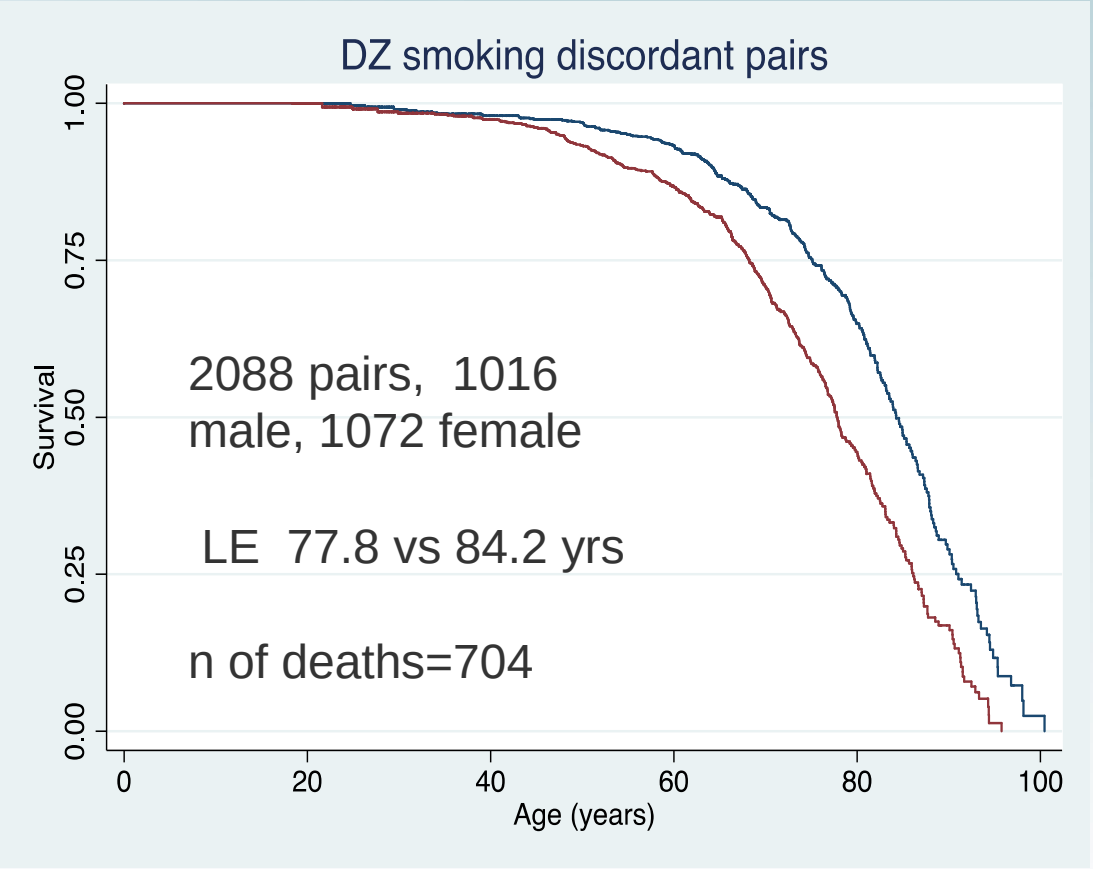
DZ, dizygotic; MZ, monozygotic.

Four Nordic twin registries, decades of follow-up

Hjelmborg et al, *Thorax* 2017

Four decades of follow-up of smoking discordant pairs





Follow-up of mortality from 1976 to end of 2016, for the current and never smoker twins from twin pairs discordant for smoking. Survival curves with person's age as the time axis (unpublished data)

Smoking and income – testing the causality of a well-established association

Petri Böckerman, Ari Hyytinen and Jaakko Kaprio. *Tobacco Control* 2014

PB: Labour Institute for Economic Research and IZA, Helsinki, Finland.
AH: Jyväskylä University School of Business and Economics, Jyväskylä, Finland.
JK: University of Helsinki, Helsinki, Finland

Smoking and income

- Current smokers earn less than non-smokers, the income gap being up to 24%.

- Most earlier studies cross-sectional, short-term and sometime self-reported income.

Leigh J. P., Berger M. Effects of smoking and being over weight on current earnings. *Am J Prev Med* 1989; **5**: 8-14.

Levine P. B., Gustafson T. A., Velenchik A. D. More bad news for smokers? The effects of cigarette smoking on wages. *Ind Labor Relat Rev* 1997; **50**: 493-509.

Grafova I., Stafford F. P. The wage effects of personal smoking history. *Ind Labor Relat Rev* 2009; **62**: 381-393.

Neumann T. The effect of drinking and smoking on the labor market outcomes of low-income young adults. *Appl Econ* 2013; **45**: 541-553.

Van Ours J. C. A pint a day raises a man's pay; but smoking blows that gain away. *J Health Econ* 2004; **23**: 863-886.

Auld M. C. Smoking, drinking, and income. *J Hum Resour* 2005; **40**: 505-518.

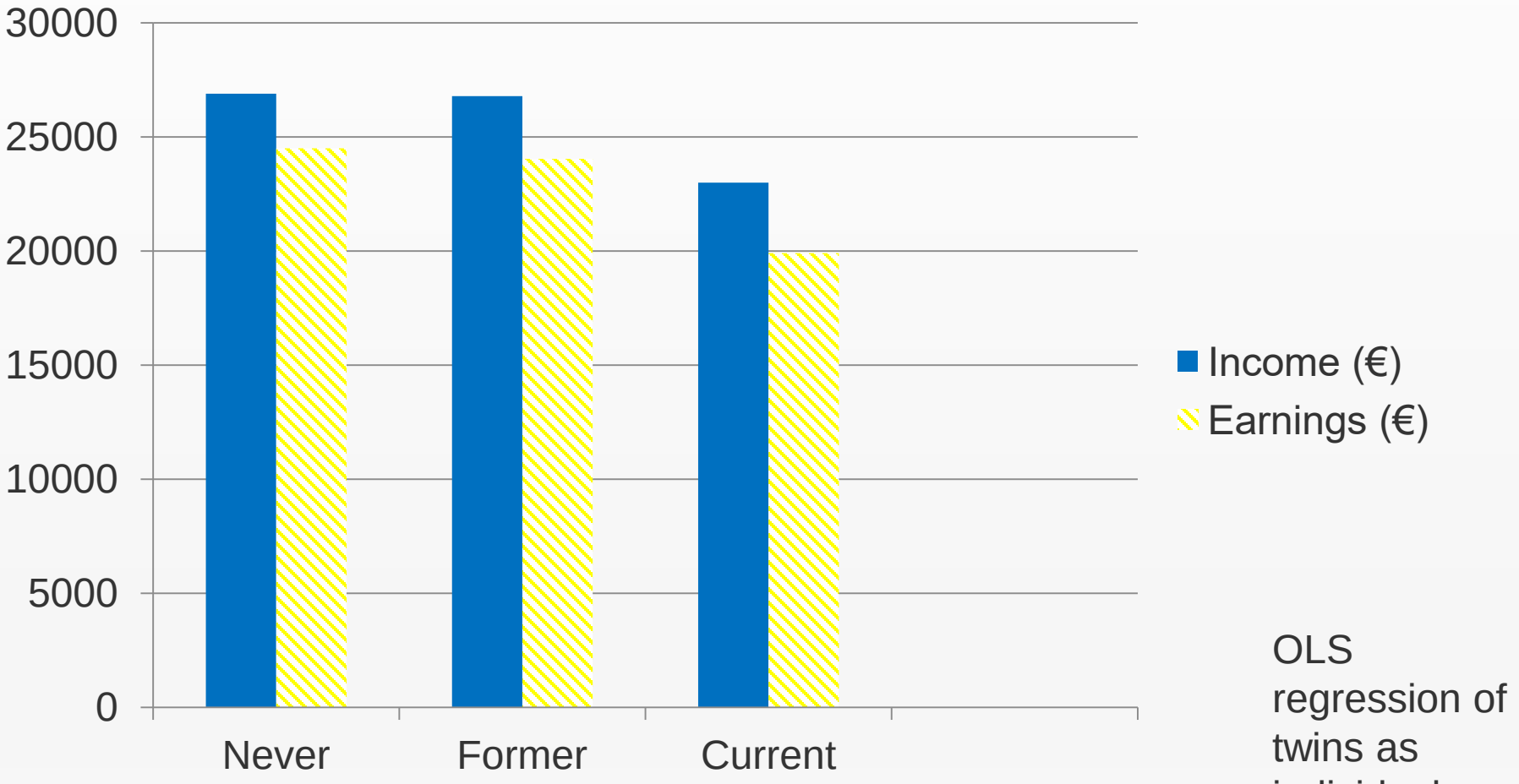
Purpose and data sources

- To study the relationship between smoking and future income using the twin design to minimize confounding

- Smoking and covariate data from the older Finnish Twin Cohort surveys in 1975, 1981 and 1990 (Kaprio & Koskenvuo, Twin Res 2002)
- Administrative (exact and unbiased) data from tax authorities on annual income (wages, salary, capital income and social security benefits/income transfers) from 1990-2004 and available through Statistics Finland
- Income (all sources) and earnings (wages and salaries) examined separately for entire 15 year period and on a annual basis.
- # of employment months/yr and # of employment years taken into account in additional analyses
- Information on employer (company type, size, # of employees, turnover) is available
- Focus on men in best earning years (ages 33-59)

Income and earnings in 1990-2004 by smoking status of 1981 (adjusted to year 2000 values)

Men born 1945-1957 and aged 33-59 during income period



OLS regression of twins as individuals

Withinpair comparisons of smoking pairs with income

Sample	DZ and MZ individuals	DZ and MZ pairs	DZ pairs	MZ
Estimation method	OLS	Twin differences	Twin differences	Twin differences
Dependent variable	Log income	Log income	Log income	Log income
Cigarette pack years	-0.0099***	-0.0097***	-0.0087***	-0.0138**
95% CI	[-0.0126, -.0072]	[-0.0144, -0.0049]	[-0.0140, -0.0034]	[-0.0250, -0.0027]
N	3914	1957	1350	607

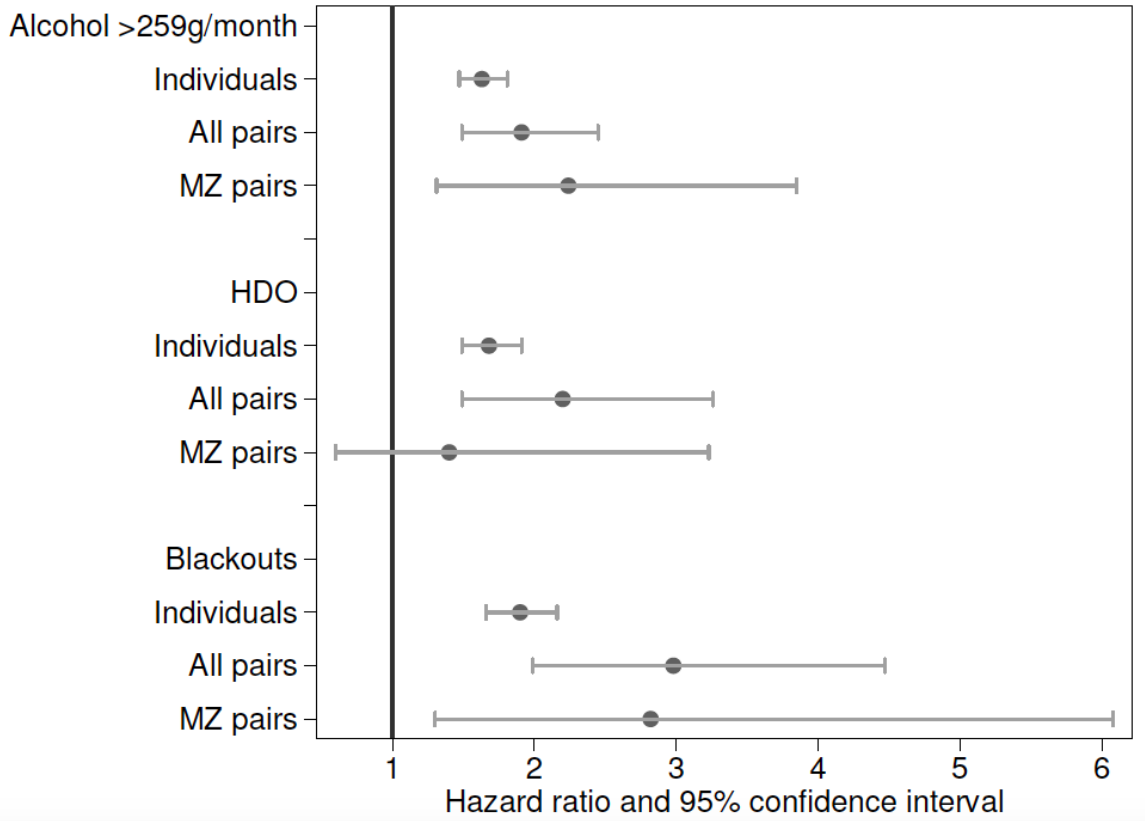
Summary

- Even within MZ pairs a 1 SD increase in cigarette pack years decreased income by 8% (c 1700 euros and equivalent to one year of schooling)
- Relationship was robust to adjustments for education, # of chronic diseases , heavy alcohol use and BMI
- Negative effect of smoking larger in recession years
- Findings support causal contribution of smoking to reduced future earnings

Other phenotypes

Extensions to other risk factors

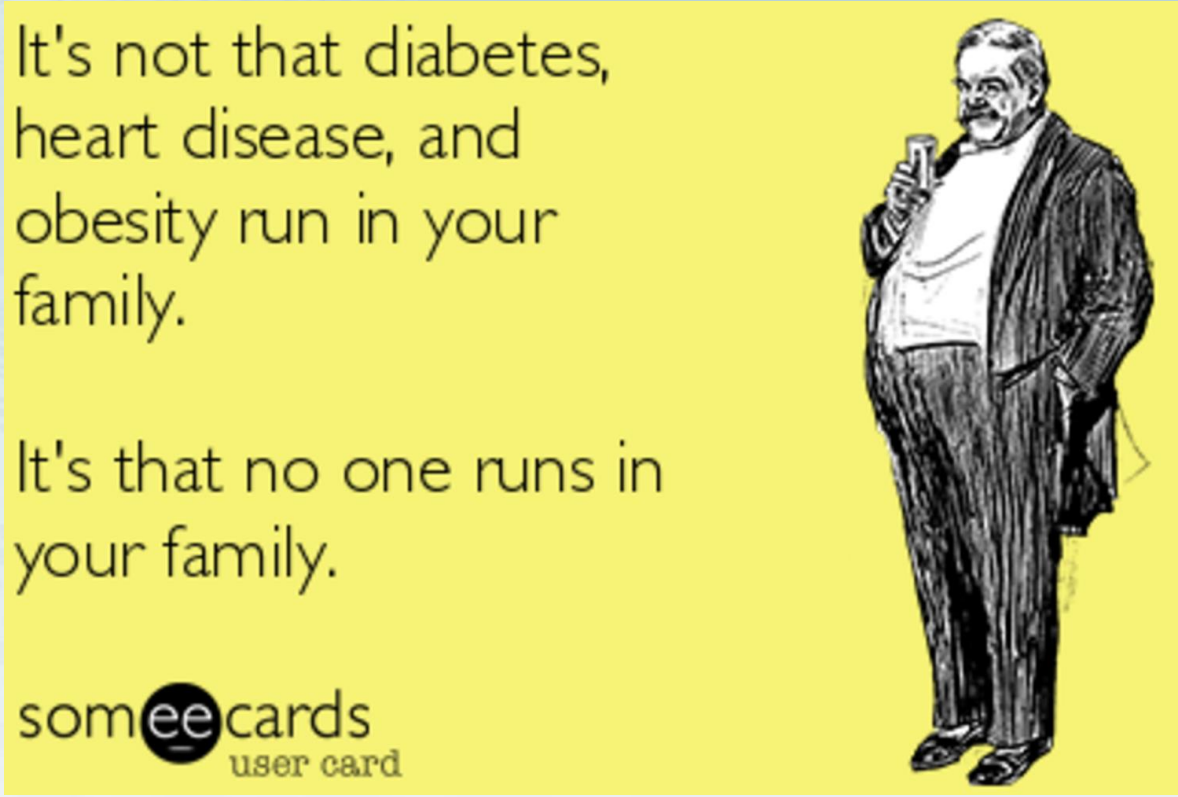
When extended to physical activity and alcohol use, no differences in mortality within discordant pairs were seen in contrast to smoking (Kujala et al, Am J Epidemiol 2002) for the first two decades of follow-up



On further follow-up, we see an effects for alcohol. Thus within-pair analyses support a causal effect of alcohol use and drinking pattern on overall mortality. N=14,878 adults follow-up for 30 years (Sipilä P, Rose RJ, Kaprio J. Addiction 2015)

Physical activity and health

- Numerous epidemiological observational studies indicate that physical activity in the general population is associated with better health, less onset of disease and longer lifespan.
- The lifespan of former elite athletes is also increased, in particular that of endurance athletes (Kettunen JA et al, Br J Sports Med 2015)
- Intervention studies show numerous short-term benefits

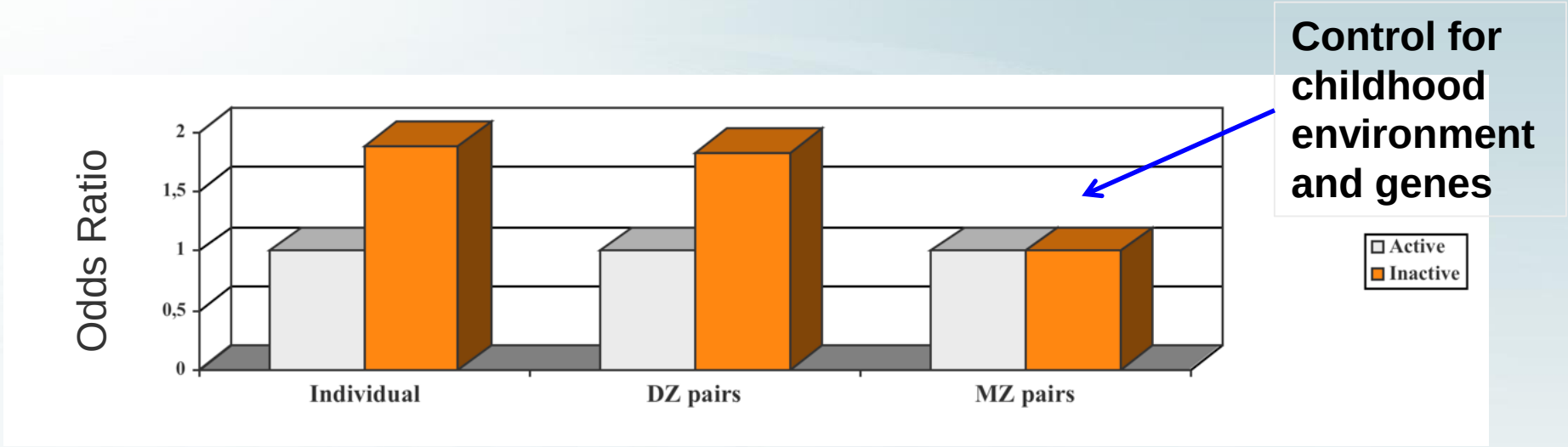


We see this also in the Finnish Twin Cohort:

25831 twins who replied to physical activity items in 1975
Mortality follow-up to end of 2016, # of deaths 9802

Compared to non-active persons (defined as in Kujala et al, JAMA 1998), the mortality of conditioning exercisers was 40% less (HR=0.60, 95%CI .54 to .66) and that of the intermediate was 17% less. The effect is stronger in men (HR=0 .57) than in women (HR=0.69). (unpublished data)

Modifiable Risk Factors as Predictors of All-Cause Mortality: The Roles of Genetic and Childhood Environment



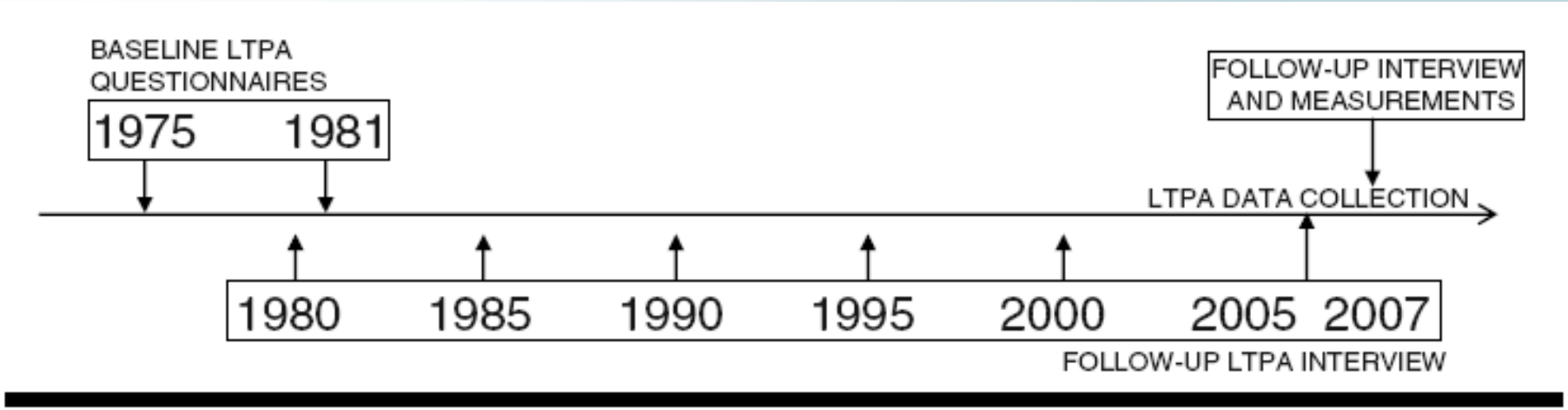
'Active' participated in leisure-time physical activity which was more strenuous than normal walking in 1975 and in 1981; 'inactive' did not.

Follow-up of deaths from 1983 to 2001.

Data sources for baseline health: Exclusion of subjects with chronic disease based on questionnaires in 1975 & 1981, hospital discharge reports, reimbursable medication reports, malignant cancer reports, deaths before Jan 1983.

Kujala et al. Am J Epidemiol 2002;156:985-993.

TWINACTIVE co-twin control study



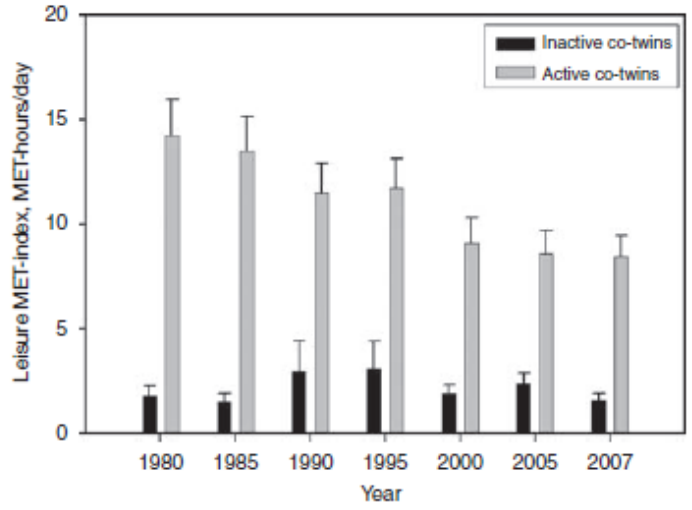
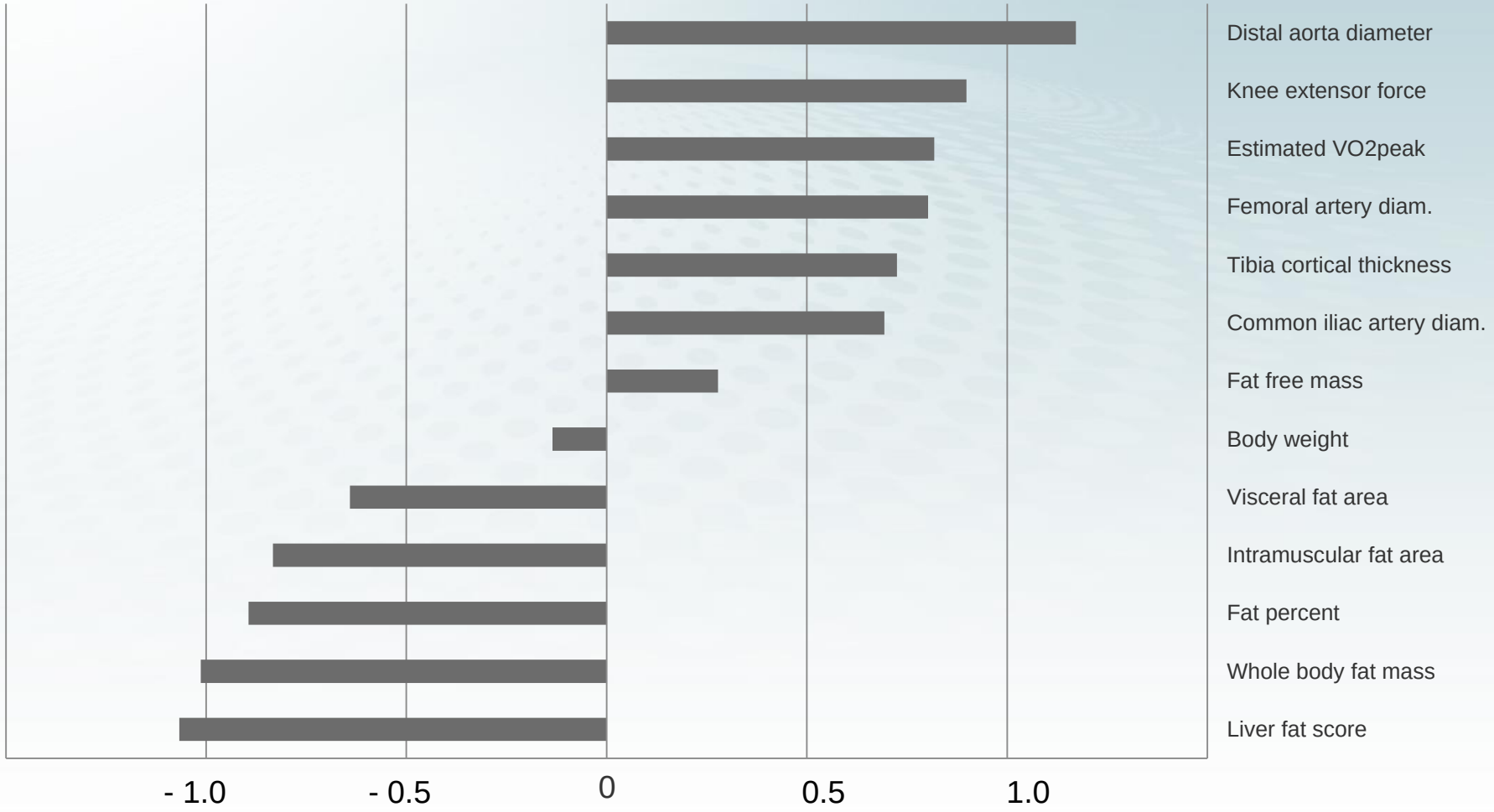


Figure 1 Follow-up leisure-time physical activity recorded by the retrospective interview among the inactive and active co-twins. The mean age of twins was 33 years (range 23–47 years) in 1980 and 60 years in 2007. Data are mean ± s.e.m. $P = 0.005$ to < 0.001 for comparisons between the inactive and active co-twins (for more details, see Leskinen *et al.*[19]).

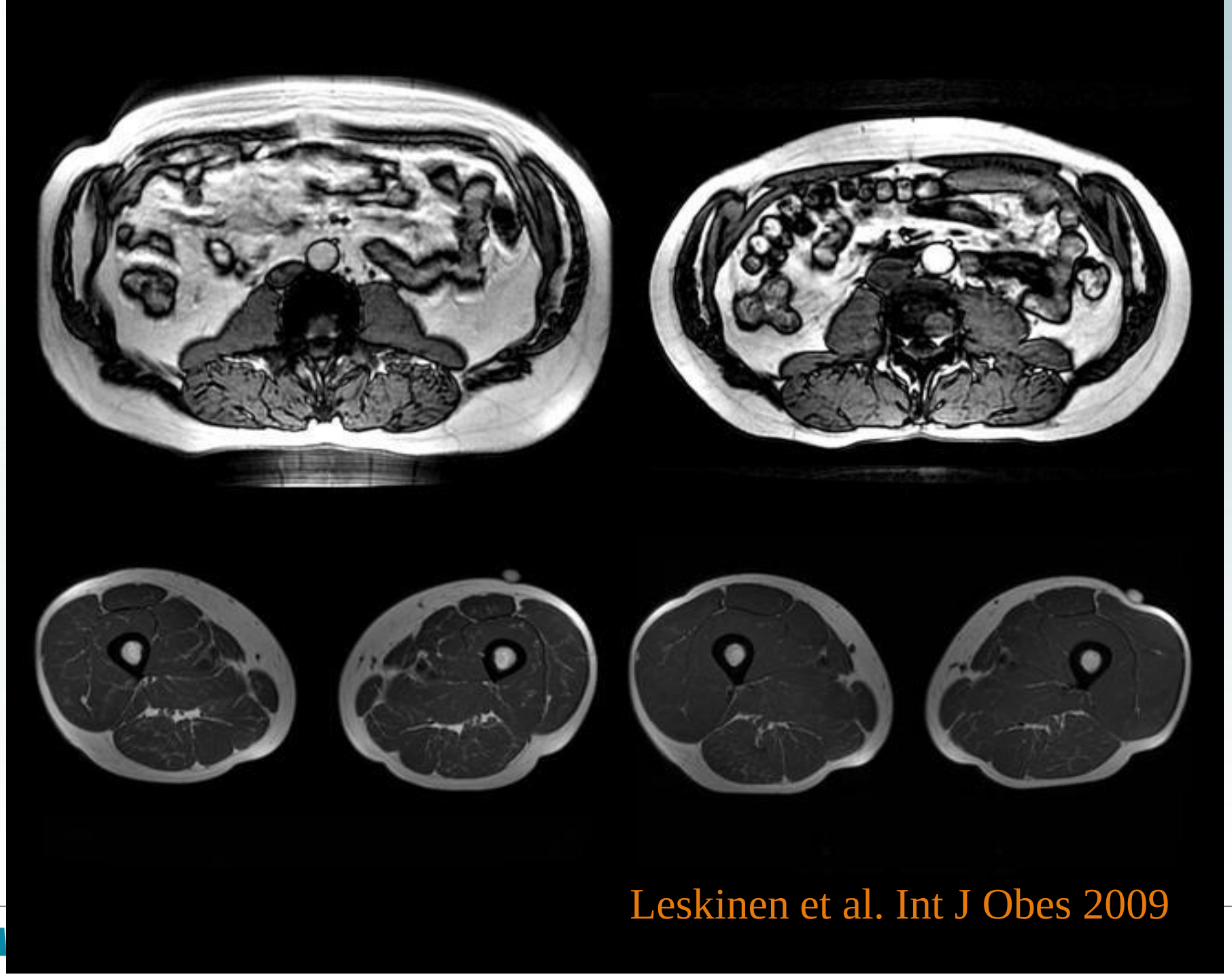
>> 16 twin pairs consistently discordant for leisure-time physical activity studied in-person

Leskinen et al.
Twin Research Human Genetics 2009;12:108-117
& Int J Obesity 2009;33:1211-1218.

Summary of differences between active vs. inactive members of MZ twin pairs



TWINACTIVE study; Leskinen & Kujala. Twin Research & Human Genetics 2015;18:266-272.



Leskinen et al. Int J Obes 2009

Interpretation and implications

- **Previous observational follow-up studies in humans suggested that increasing physical activity levels could prolong life**
  - We did not see the suggested association in pairwise analysis among monozygotic twin pairs
  - **Increasing follow-up-time did not resolve this**
  - **HR for MZ pairs 1975-2016 is 0.98, p=0.94**
- **Genetic pleiotropy might explain at least part of the previously observed associations between high baseline physical activity and later reduced mortality in humans**
- **Molecular genetic data is needed to resolve this,**
- **A couple of 2018 gwas papers on self-reported physical activity have yielded only a few gwas hits**
- **Divergence in physical activity starts typically in early adulthood for physical activity-discordant MZ twin pairs**
  - More studies are needed to determine whether physical inactivity might affect lifespan differently when started early in life
  - The reasons for discordance merit much more study

Outline:

Causality and observational epidemiological studies

Value of heritability estimates

nature genetics

Twins have been the major source of evidence for genetic influences

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

Tinca J C Polderman[1,10], Beben Benyamin[2,10], Christiaan A de Leeuw[1,3], Patrick F Sullivan[4–6], Arjen van Bochoven[7], Peter M Visscher[2,8,11] & Danielle Posthuma[1,9,11]

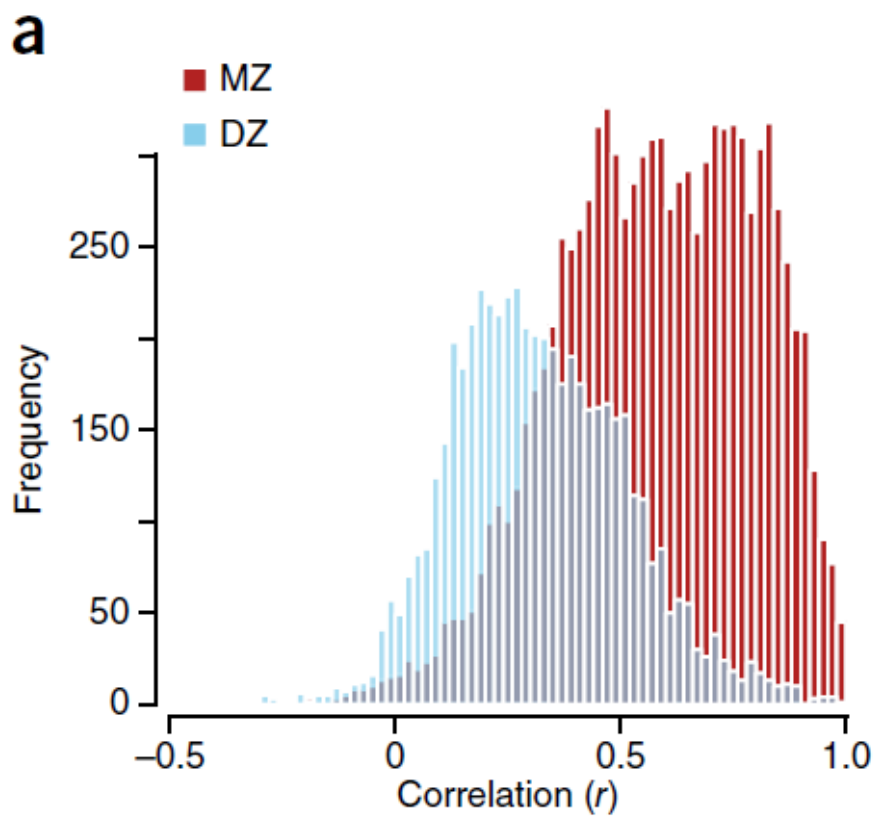


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Table 1 Overview of study designs estimating heritability of BMI

Study design	Heritability estimate (s.e.)	Benefits	Pitfalls
Classical twin design[a]	0.63 (0.01) 0.75 (0.02)	High precision	Limited by two correlation estimates Environmental sharing among different relatives difficult to separate Confounding by nonadditive sources of genetic variance
Family studies[b]			
Siblings raised together or apart	0.44 (0.04)	High precision Low bias by environmental sharing	Large sample sizes required
Pedigree estimates	0.46 (0.06) 0.39 (0.04)	High precision	No separation of environmental sharing from genetic similarity
Within-family segregation[c]	0.42 (0.02) 0.42 (0.17)	No confounding by population stratification Not reliant on assumptions of environmental sharing	Low precision due to high standard errors Large sample sizes required
Population studies[d]			
HapMap3 SNPs	0.22 (0.02)	Unrelated individuals unlikely to share environments Unbiased by nonadditive genetic effects	Captures only variance attributable to loci in LD with genetic markers
Whole-genome imputation	0.27 (0.03)	Unrelated individuals unlikely to share environments Unbiased by nonadditive genetic effects Imputation provides better genome coverage	Captures only variance attributable to loci in LD with genetic markers

Robinson et al. Nature Genetics 2017

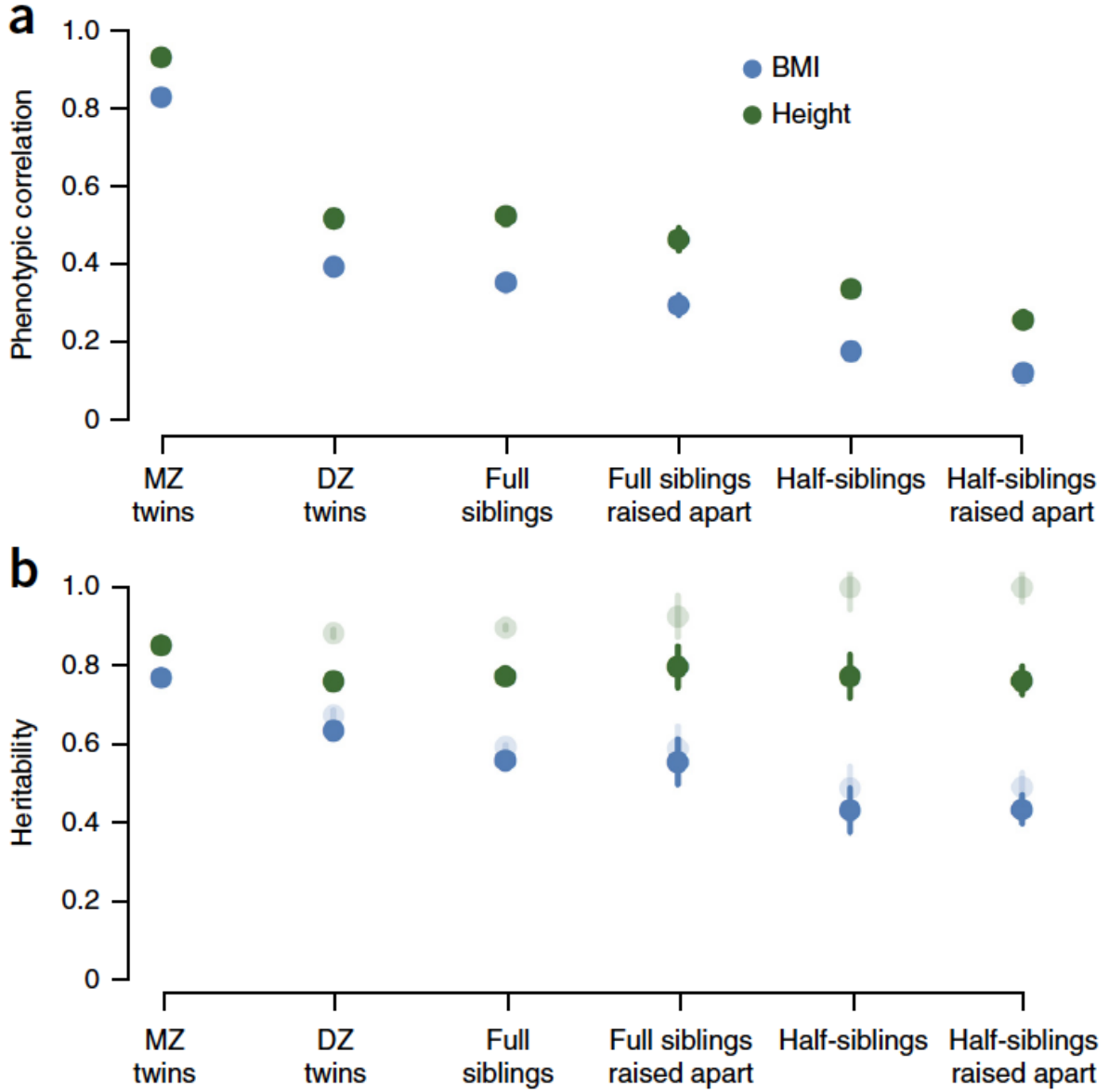
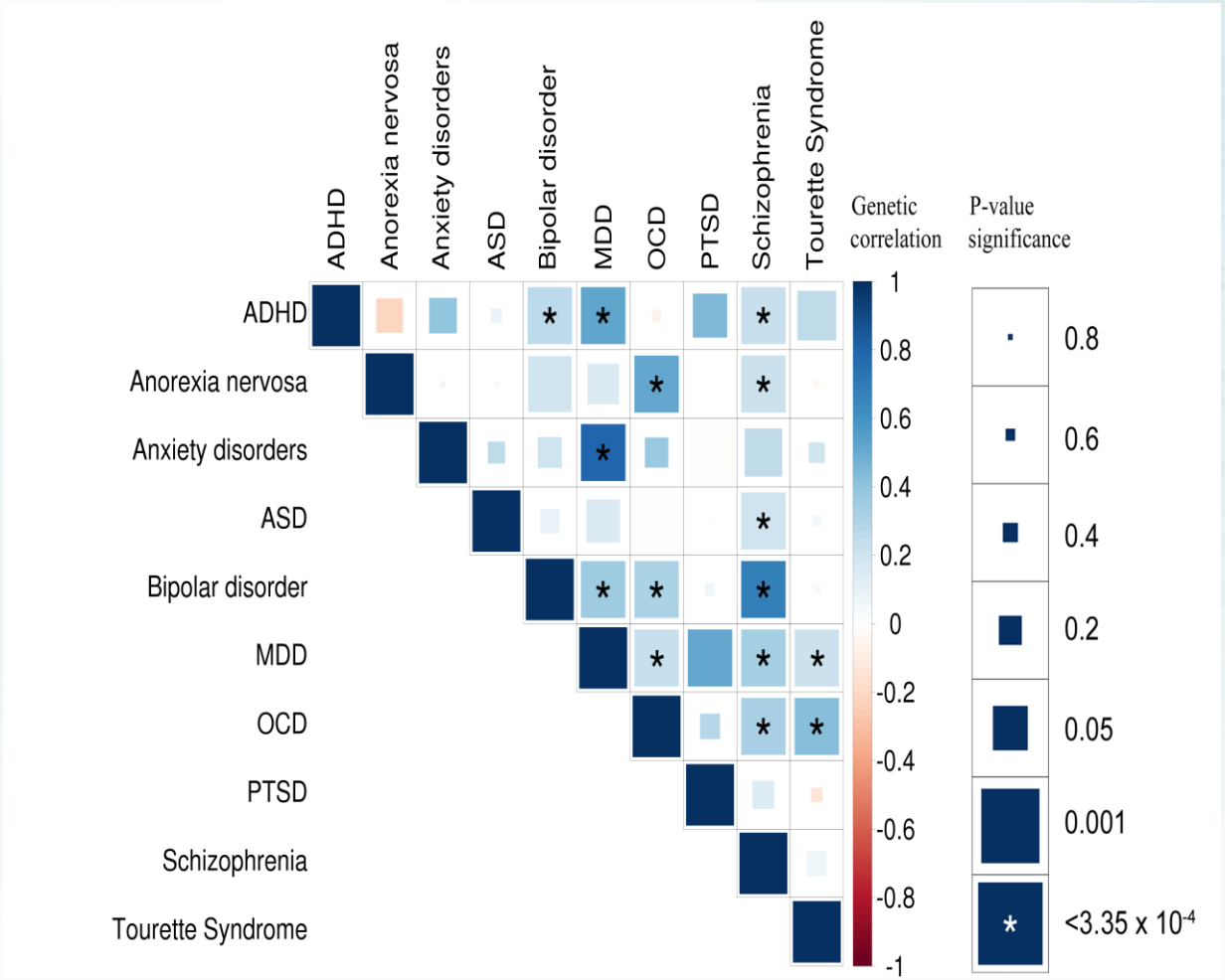


Figure 1 Systematic inflation of BMI heritability estimates in close relatives that share developmental environments. (**a**,**b**) Phenotypic correlations (**a**) and heritability estimates (**b**) from behavioral genetic models (see Online Methods) among different male sibling pairs taken from Swedish army conscription BMI (blue) and height (green) records

Complex genetic and environmental architecture of traits



Anttila V et al, Science (in press)

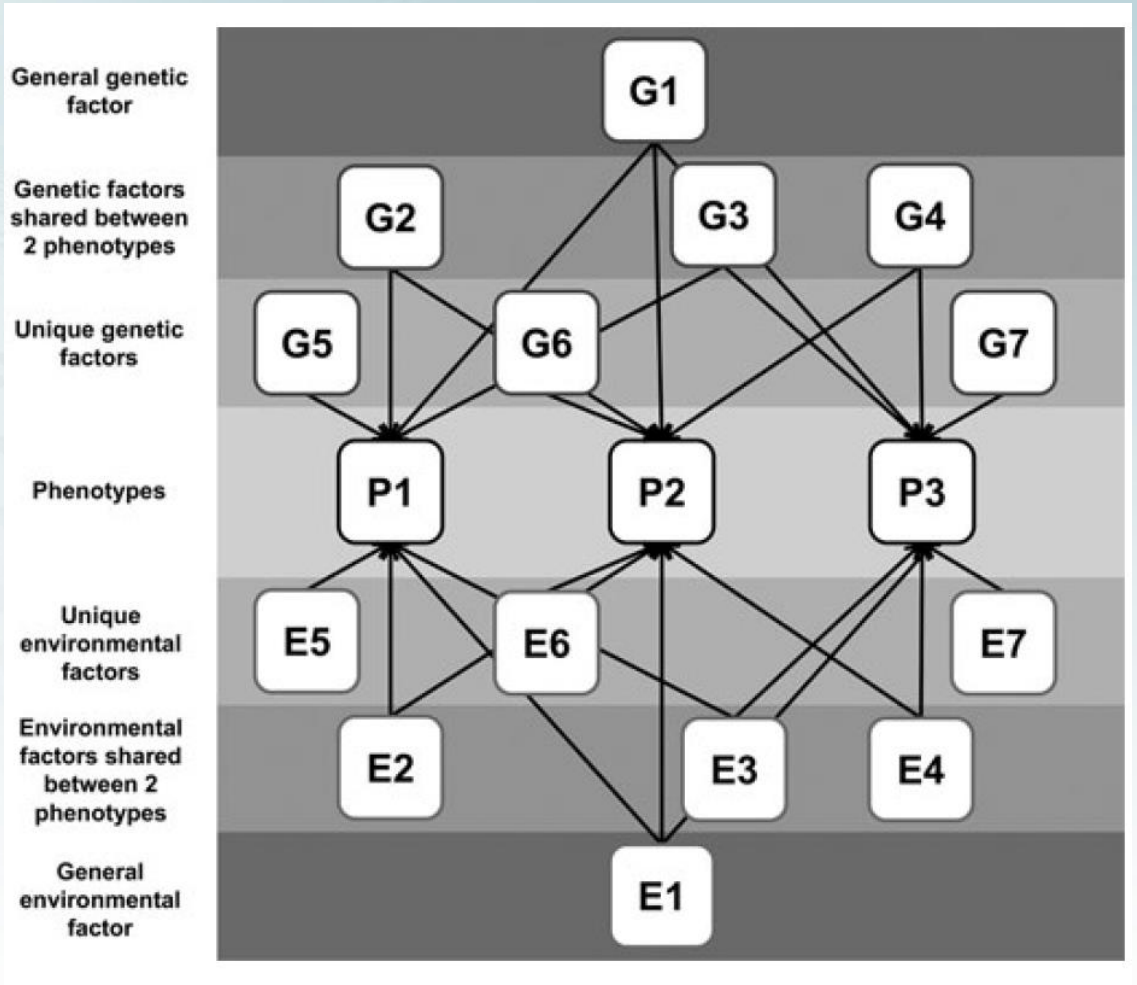


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Fig. 2. **Potential interpretations of genetic correlation across phenotypes**: (a) true biological pleiotropy, where the same genetic risk variant is causally associated with two phenotypes; (b) unmeasured phenotype, where a third phenotype is on the causal pathway between genetic risk and the outcome phenotypes of interest; (c) correlated genetic risk, where different genetic risk variants that are highly correlated are causally associated with each phenotype; (d) mediation, where a genetic risk variant only acts on one of the phenotypes, which in turn influences a second phenotype; (e) Nosological issues, which blur the distinction between phenotypes, for example comorbidity, ascertainment bias, heterogeneity or diagnostic misclassification; (f) assortative mating, where individuals with the two phenotypes of interest are more likely to mate than expected at random, thereby leading to clustering of genetic risk for both phenotypes in the offspring.

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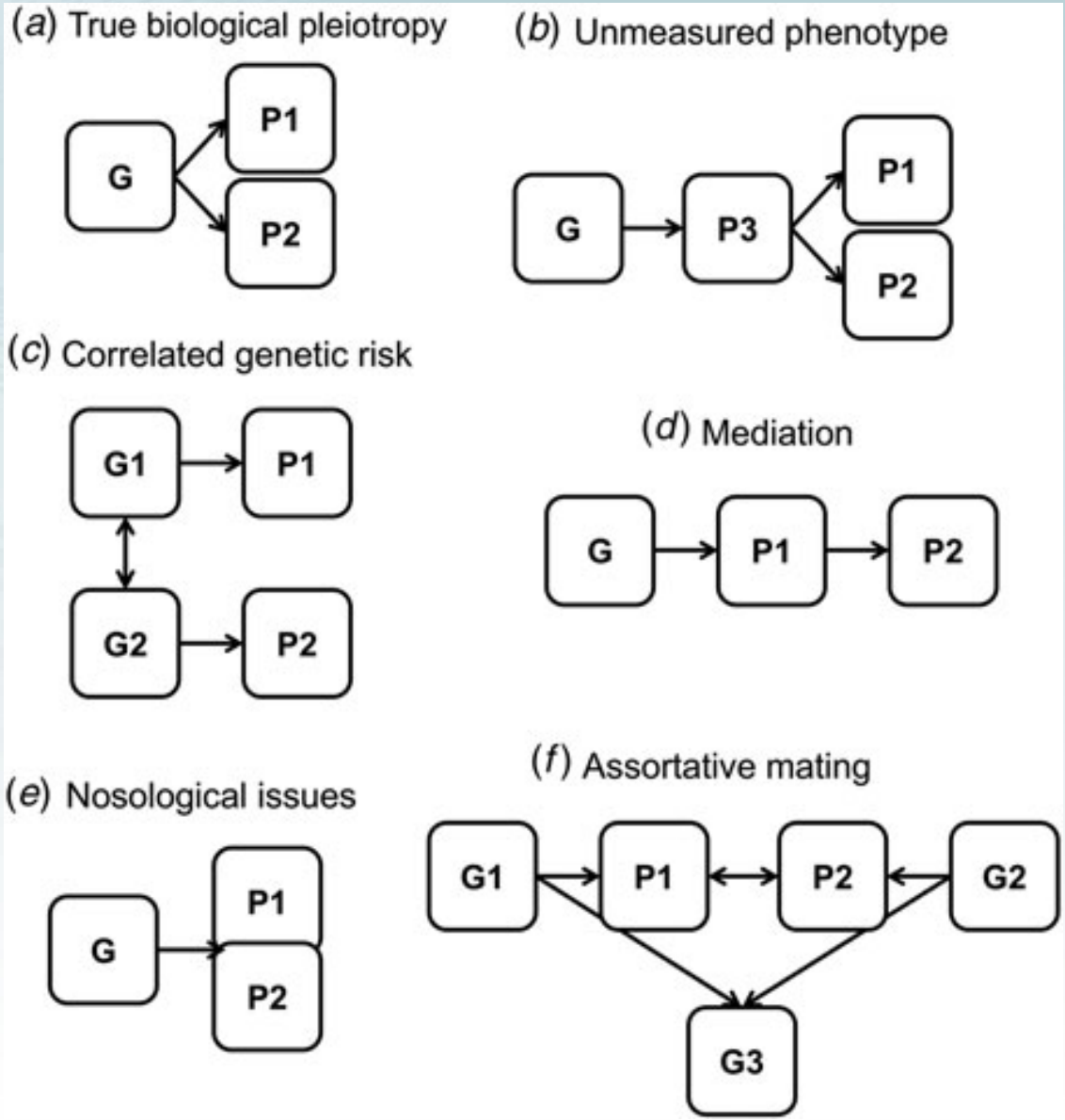

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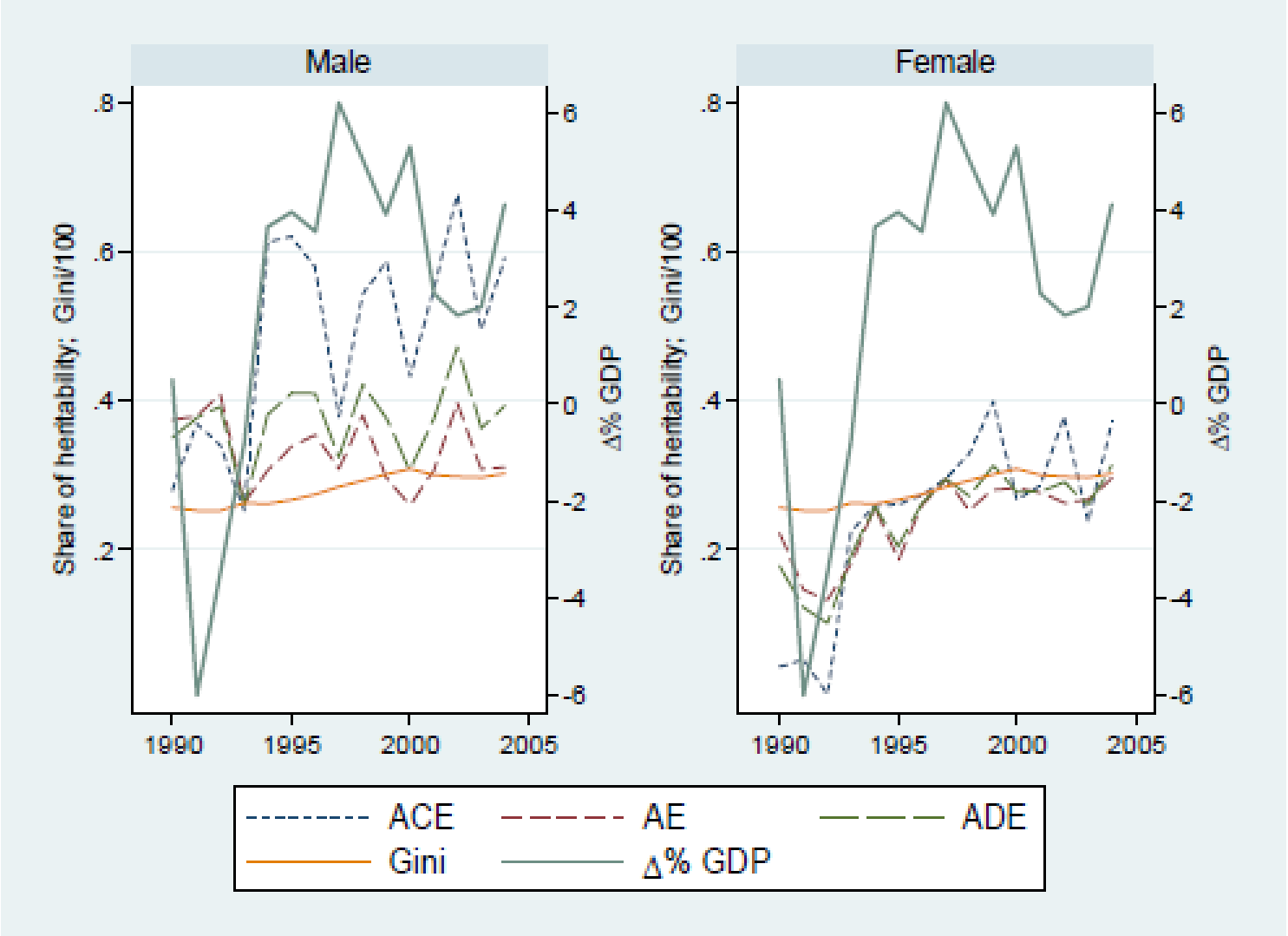
How major environmental effects buffer genetic influences ?

Effect of a major recession on twin similarity of income

Table 1: Earlier studies on the genetic heritability of income

Source	Income measure	Gender	Country	r_{MZ}	r_{DZ}
Taubman (1976, Table 2)	Log of annual income	Men	USA	0.54	0.30
Ashenfelter, Krueger (1994, Table 2)	Log of hourly wage	Both	USA	0.56	0.36
Ashenfelter, Rouse (1998)	Log of hourly wage	Both	USA	0.63	0.37
Johnson, Krueger (2005, Table IV)	Log of annual household income	Both	USA	0.38	0.13
Schnittker (2008, Table 1)	Log of annual income	Both	USA	0.40	0.26
Miller, Mulvey, Martin (1995, Table 2)	Log of average occupational income	Both	Australia	0.68	0.32
Miller, Mulvey, Martin (1997, Table 2)	Log of average occupational income	Men	Australia	0.59	0.56
Miller, Mulvey, Martin (1997, Table 2)	Log of average occupational income	Women	Australia	0.56	0.28
Miller, Mulvey, Martin (2006, Table 2)	Log of annual income	Both	Australia	0.50	0.14
Isacsson (1999, Table 2)	Average of 3 year log incomes	Both	Sweden	0.68	0.46
Björklund, Jäntti, Solon (2005, Table 1)	Average of 3 year log incomes	Men	Sweden	0.36	0.17
Björklund, Jäntti, Solon (2005, Table 1)	Average of 3 year log incomes	Women	Sweden	0.31	0.12
Cesarini (2010, Table III.III)	Log of 3-year average income	Men	Sweden	0.49	0.29
Benjamin et al. (2012, Table 1)	Average of 20 year log incomes	Men	Sweden	0.63	0.27
Benjamin et al. (2012, Table 1)	Average of 20 year log incomes	Women	Sweden	0.48	0.22
Benjamin et al. (2012, Table 1)	Average of 5 year log incomes	Men	Sweden	0.51	0.20
Benjamin et al. (2012, Table 1)	Average of 5 year log incomes	Women	Sweden	0.30	0.20
Benjamin et al. (2012, Table 1)	Log of annual income	Men	Sweden	0.41	0.16
Benjamin et al. (2012, Table 1)	Log of annual income	Women	Sweden	0.27	0.14
			Avg. U.S.	0.50	0.28
			Avg. Australia	0.58	0.32
			Avg. Sweden	0.44	0.22

Figure 1: Annual variation in heritability estimates



During the recession in 1990-1993, unemployment went to 15%, and then the economy recovered with rapid growth until 2001 (tech bubble) – solid green line

Income inequality did not change very much due to social policy and unemployment benefits (Gini index).

Substantial changes in apparent genetic contributiuon to year-on-year income

Based on Finnish twin pairs born 1950-1957

Hyytinen A et al. The Genetic Heritability of Lifetime Income

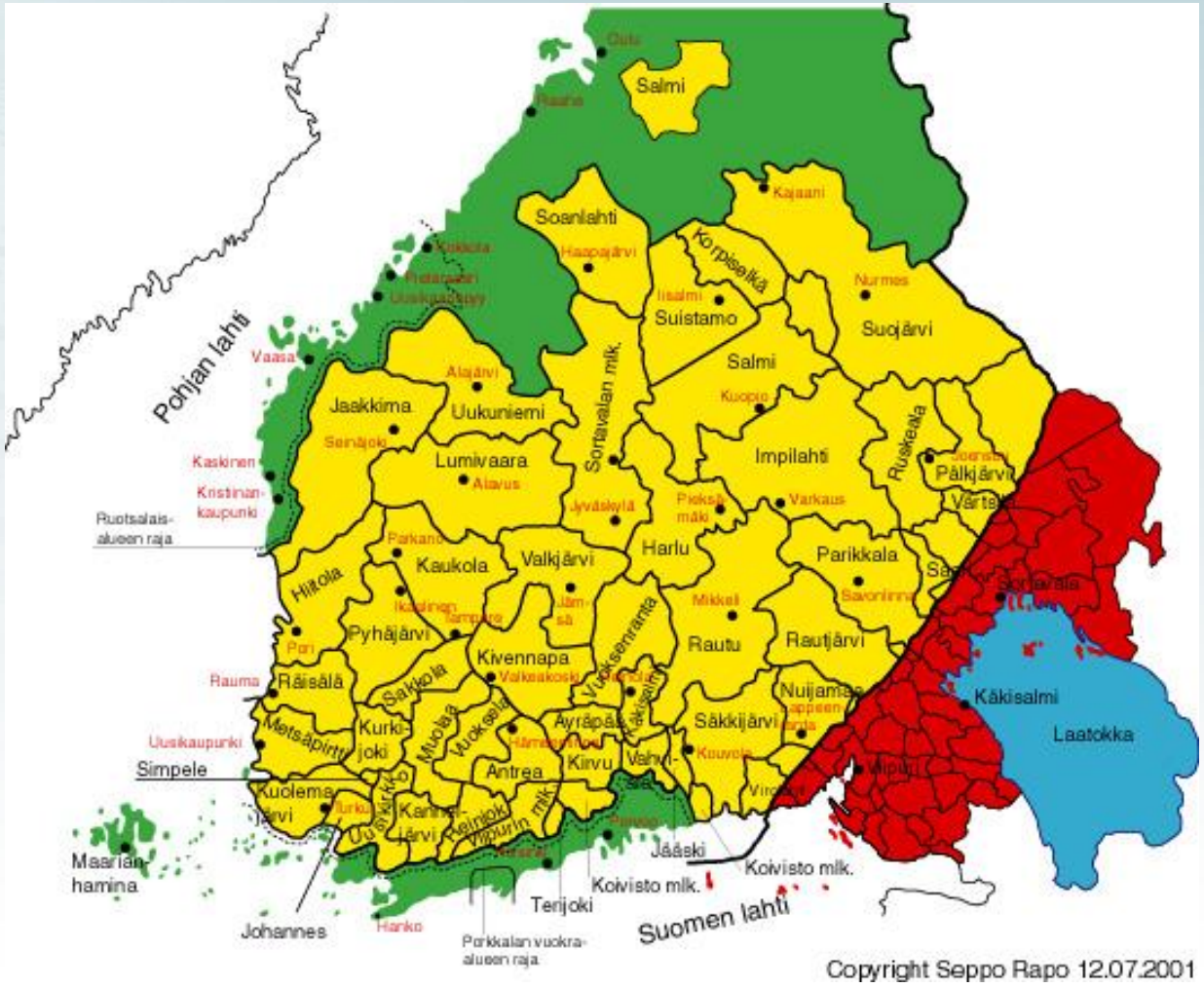
Effect of forced migration due to war on twin similarity

Migration and tobacco use

- Forced migration due to war and natural disasters has occurred throughout history and is common also at present
- Stressful life events associated with forced migration increase vulnerability for adverse health consequences
- Intermediate factors, such as smoking, can shed light on the mechanisms underlying this process
- Teasing out the causal contribution of migration is challenging due to selection effects and differences in social, cultural and biological characteristics between migrants and the host country population
- Using natural experiments such as migrations offer the opportunity to study the effects of stressful life events

Forced migration in Finland during and after World War II

- During WWII, Finland fought two wars (in 1939-1940 and 1941-1944) with the Soviet Union. In 1941 and in 1944, Finland ceded the areas of Karelia in South-East Finland as part of the peace agreement.
- Ceded Karelia formed 11% of the Finnish population at the time, 10% of the surface area and 10% of industrial production.
- All 410,000 inhabitants moved to Finland, virtually none stayed so there are no selection effects
- The migrants were settled after the war in the remaining parts of Finland, such that each community moved to a designated region (see map)



Aim of the study

We investigated if and how forced migration from Ceded Karelia due to World War II is associated with subsequent cigarette smoking within the nationwide Finnish Adult Twin Cohort

Materials and Methods

- Altogether 12933 twin individuals born before 1945 replied to a questionnaire in 1975 of the Finnish Twin Cohort (89% response rate) and included in the present analysis.
- The exposure (forced migration due to war, categorized as ‘no’, ‘once’,’ 2+’) used following measures: the municipality of birth and whether the respondent had moved municipality ever and if so, for what reason (10 options, including war).
- Of the respondents born in Ceded Karelia 83% replied that they had had to move due to war, with the corresponding percentages varying from 5% to 20% in other provinces. We grouped other provinces into those more affected by the war (border provinces and the capital region of Helsinki (bombed frequently) and others.
- Detailed smoking questions were used to create two smoking status variables: 1) ‘ever smoker’ versus ‘never smoker’ and 2) ‘current smoker’ versus ‘non-current smoker’. Logistic regression with correction for sampling of twins as twin pairs was used for analyses.

Results

Smoking status by experience of forced migration due to war

- Among men, 80.2% (352/439) were ever smokers in 1975 if they had experienced migration due to war , compared to 71.5% (3832/5358) of men with no such experience. The proportion was slightly smaller among men who had had to move two or more times (77.6%).
- Among women the corresponding proportions were 33.0% (149/452) and 24.2% (1351/5592).
- Overall, those who had experienced forced migration due to World War II showed higher likelihood of **being ever smoker** (age, sex, education, and birth area adjusted Odds Ratio =1.70, 95% Confidence Interval=1.43-2.02; p<0.001) than those without forced migration experience.
- For current smoking in 1975, the adjusted OR was 1.45 (95% CI 1.22 to 1.73).
- The duration of smoking did not differ in these groups, but men who experienced forced migration had more pack-years of smoking (20.5 vs 18.1, covariate adjusted p-value=0.054)

Effect of early traumatic experience on twin similarity

Men born before 1945	Ever smoker in 1975	No moves due to war	Pairs in which both twins have moved due to war
MZ	correlation	0.8353	
	se	0.0209	
	C-/D/C+ & (Total) pairs	274/192/696 (1162)	
DZ	correlation	0.5497	
	se	0.0256	
	C-/D/C+ & (Total)pairs	442/720/1478 (2640)	
Heritability	2*(rMZ-rDZ)	0.57	
Common env	2*rDZ-rMZ	0.26	

Effect of early traumatic experience on twin similarity

Men born before 1945	Ever smoker in 1975	No moves due to war	Pairs in which both twins have moved due to war
MZ	correlation	0.8353	**0.7053**
	se	0.0209	0.0922
	C-/D/C+ & (Total) pairs	274/192/696 (1162)	22/28/88 (138)
DZ	correlation	0.5497	**0.7857**
	se	0.0256	0.0530
	C-/D/C+ & (Total)pairs	442/720/1478 (2640)	44/48/214 (306)
Heritability	2*(rMZ-rDZ)	0.57	0
Common env	2*rDZ-rMZ	0.26	0.87

Thanks to our research group, my family and all the twins

Twins are a bridge between genes and environment

Thank you – Kiitos!