The Gloomy Prospect Wins: Statistical Significance and Population Stratification in Genome Wide Association Studies

Eric Turkheimer

University of Virginia

September 8, 2008

Turkheimer, 1998

Population-based behavioral genetics has demonstrated that genotype and behavior can be expected to covary. Although the epigenetic developmental pathways linking gene products to complex behavior will in general be almost unimaginably complex, modern molecular genetics has made it possible to detect small covariations between alleles and behavior that span the complexity of the causal network….. Such associations are real and potentially interesting, but they remain correlations—and small ones—not evidence of substantial causal pathways between individual alleles and complex behavior or evidence of genes for extroversion or intelligence or evidence that future scientific efforts will be most productively applied at a genetic level of analysis. If the history of empirical psychology has taught researchers anything, it is that correlations between causally distant variables cannot be counted on to lead to coherent etiological models.

Since 1998

- Linkage
  - Can search across genome, but limited statistical power and limited specificity
- Candidate Gene Association Studies
  - Limited to pre-identified candidates, but better statistical power
- Genome Wide Association Studies
  - Can search across genome, without candidates, and better statistical power

Height

News and Views

Nature Genetics 40, 489 - 490 (2008)
doi:10.1038/ng0508-489

Sizing up human height variation

Peter M Visscher[1]

Height as a Model Trait

- Essentially no environmental variability
- Zero cultural variation
- Near perfect measurement of phenotype
- No obvious GE correlation or interaction
- Should be unfolding of biological process

I. "Co-relations and their Measurement, chiefly from Anthropometric Data." By FRANCIS GALTON, F.R.S. Received December 5, 1888.

TABLE 1
Galton's correlation table

Height of the midparent in inches	Height of the adult child													Total no. of adult children
	<61.7	62.2	63.2	64.2	65.2	66.2	67.2	68.2	69.2	70.2	71.2	72.2	73.2	>73.7	
>73.0	—	—	—	—	—	—	—	—	—	—	—	1	3	—	4
72.5	—	—	—	—	—	—	—	1	2	1	2	7	2	4	19
71.5	—	—	—	—	1	3	4	3	5	10	4	9	2	2	43
70.5	1	—	1	—	1	1	3	12	18	14	7	4	3	3	68
69.5	—	—	1	16	4	17	27	20	33	25	20	11	4	5	183
68.5	1	—	7	11	16	25	31	34	48	21	18	4	3	—	219
67.5	—	3	5	14	15	36	38	28	38	19	11	4	—	—	211
66.5	—	3	3	5	2	17	17	14	13	4	—	—	—	—	78
65.5	1	—	9	5	7	11	11	7	7	5	2	1	—	—	66
64.5	1	1	4	4	1	5	5	—	2	—	—	—	—	—	23
<64.0	1	—	2	4	1	2	2	1	1	—	—	—	—	—	14
Totals	5	7	32	59	48	117	138	120	167	99	64	41	17	14	928

This cross-tabulation was compiled by Galton in 1885 and published in 1886 and again in 1889. It gives the heights of 928 adult children, classified by height of "midparents." All female heights were rescaled by multiplying by 1.08, and midparent heights were computed by averaging the height of the father and the rescaled height of the mother. For more information, see Stigler (1986, especially Table 8.1, page 286).

r .7

Population Genetics of Height

Estimates of Variance Components and Heritabilities for Height

	Men							Women						
	Model	Va	Vc	Ve	Vp	h^2	$\Delta\chi^2_1$	Model	Va	Vc	Ve	Vp	h^2	$\Delta\chi^2_1$
Australia	ACE	40.26	0.00	6.30	46.60	0.87	—	ACE	33.80	6.00	7.60	47.40	0.71	—
	AE	40.26		6.30	46.60	0.87	0.00	AE	39.27		7.47	46.74	0.84	4.86*
Denmark	ACE	37.20	1.90	5.00	44.20	0.84	—	ACE	29.50	6.60	4.20	40.30	0.73	—
	AE	38.80		5.00	43.80	0.89	0.55	AE	35.20		4.20	39.40	0.89	13.38***
Finland	ACE	34.28	6.98	3.77	45.03	0.76	—	ACE	24.30	6.10	4.30	34.70	0.70	—
	AE	40.10		3.71	43.81	0.89	3.51	AE	29.61		4.25	33.86	0.87	5.25*
Italy	ACE	37.48	12.90	3.29	53.67	0.70	—	ACE	25.57	4.39	2.31	32.27	0.79	—
	AE	48.31		3.25	51.56	0.94	2.60	AE	29.34		2.30	31.64	0.93	0.99
Netherlands	ACE	38.71	5.49	5.66	49.86	0.78	—	ACE	33.49	2.23	3.94	39.65	0.84	—
	AE	43.66		5.62	49.28	0.89	1.20	AE	35.50		3.92	39.42	0.90	0.58
Norway	ACE	33.32	4.47	5.47	43.26	0.77	—	ACE	30.00	3.34	4.28	37.66	0.79	—
	AE	37.17		5.40	42.57	0.87	2.47	AE	32.95		4.25	37.19	0.89	2.33
Sweden	ACE	29.80	4.10	5.00	38.90	0.77	—	ACE	25.94	1.08	3.48	30.50	0.85	—
	AE	33.32		4.94	38.26	0.87	14.44***	AE	26.90		3.50	30.40	0.89	1.87
UK	ACE							ACE	26.96	8.16	4.56	39.68	0.68	—
	AE							AE	33.89		4.34	38.23	0.89	8.21**

Note: Va = additive genetic variance, Vc = shared environmental variance, Ve = specific environmental variance, Vp = total phenotypic variance, h^2 = heritability estimate, $\Delta\chi^2$ = change in the χ^2-values between AE and ACE models

*$p < .05$, **$p < .01$, ***$p < .001$

Silventoinen et al (2003)

Methodology

- 63,000 individuals, in three papers each compiled from multiple studies
- GWAS with rigorous standards for Type I error rate
- Variants identified in initial screening genotyped in follow-up samples

Results

Study	X-Val Results	Indiv R2	Total R2
Weeden et al. 20 SNPs	.01-.3%	2.9%	
Lettre et al	10 SNPs	.1-.8%	2.0%
Gudbjartsson et al	21 SNPs		3.7%

- Variants appearing in at least two papers 8
- Variants appearing in all three papers 2

Conclusion

- Something like 90% of the variation in height is “ genetic” at the population level
- Intensive GWAS can account for 2-3%
- Response: Enthusiasm! Bigger studies!

Looking to the future

The main conclusion emerging from the current studies is that GWAS are able to robustly identify common variants that are associated with height but that the effect sizes of individual variants are small, so that very large sample sizes are needed to detect associations reliably. Single laboratories are unlikely to have sufficient sample sizes to do powerful studies on their own, and the trend in human complex trait mapping has been to create consortia of research groups and even consortia of consortia. It remains unclear at this stage how much genetic variation can be explained through the GWAS approach. However, if the samples in these three studies were combined together with other datasets that have been collected on height and genome-wide SNP data, then this question could be answered empirically. Genome-wide studies on, say, 100,000 individuals, unthinkable only a few years ago, will be soon be a reality. (Visscher, 2008)

Backing up

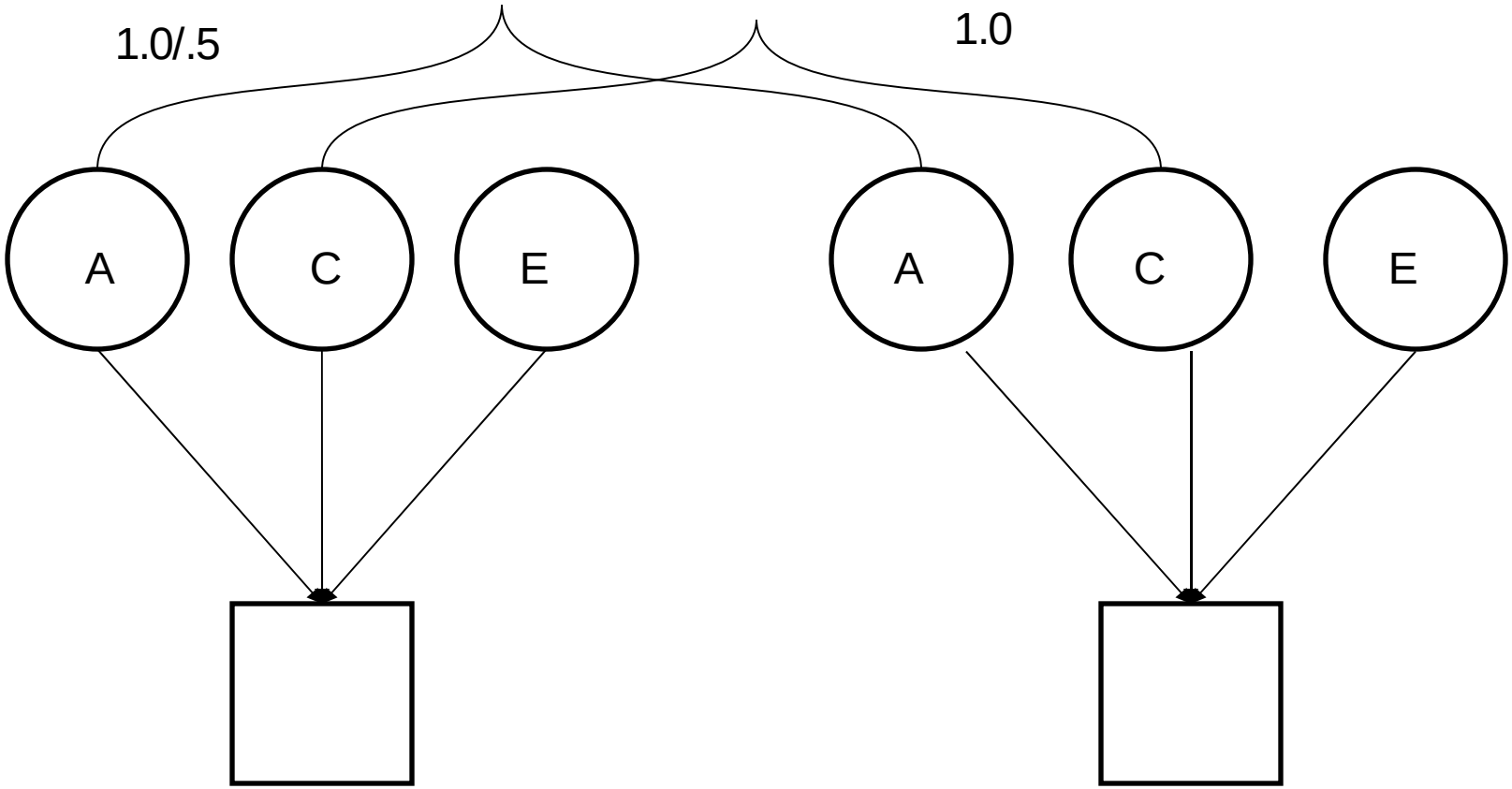
- Given a variance component that indisputably “ accounts for” a significant proportion of variance
  - Can we specify overall genetic effect in terms of the individual effects of its elements?
  - Can we identify causal consequences of individual predictors, independent of others?
- Look to environmental social science for answers

What is Social Science?

- A social scientist is a person who counts telephone poles. (Robert Hutchins)
- Social science is the attempt to explain the causes of complex human behavior when:
  - There are a large number of potential causes
  - The potential causes are non-independent
  - Randomized experimentation is not possible

Social Science I: The Nonshared Environment Project

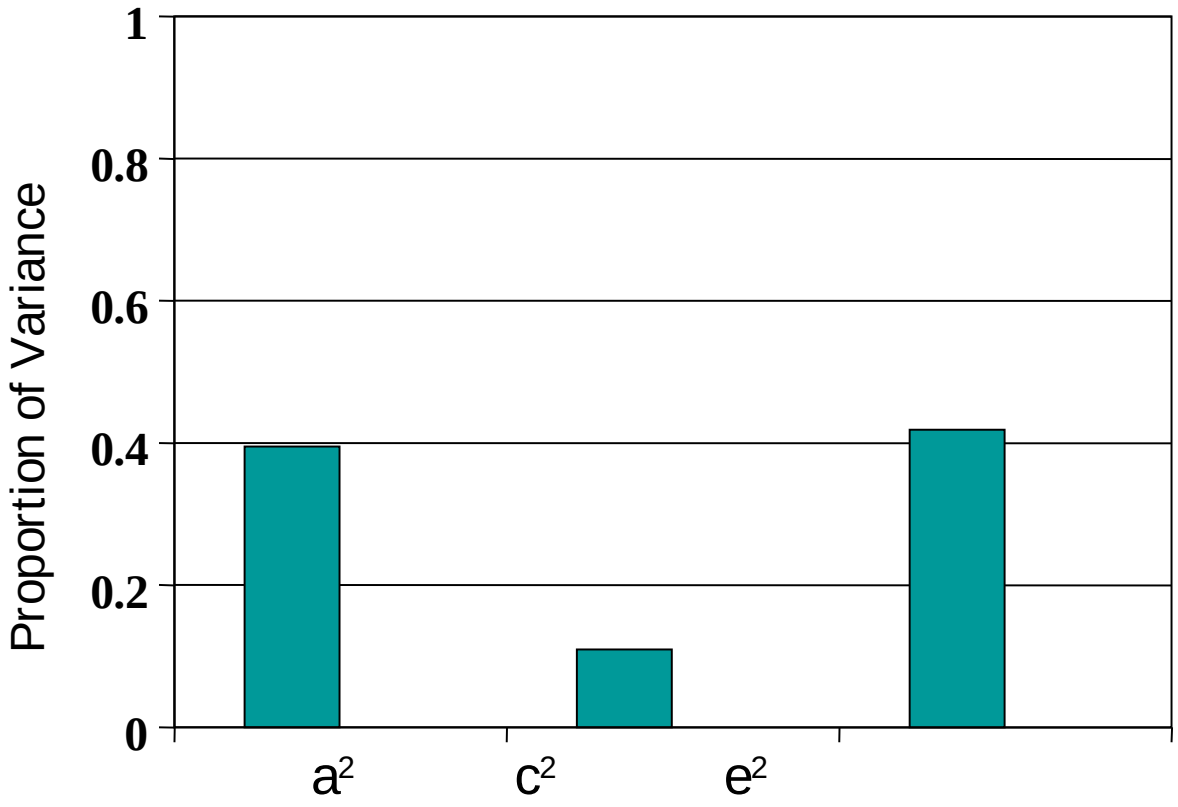
Basic ACE Model



Variance Components

All Studies, *N*=75

(Turkheimer and Waldron, 2001)



Plomin and Daniels' Conjecture

...one implication of our conclusion concerning the importance of nonshared environment is that *environmental factors shared by both children in a family are unlikely to be important sources of environmental influence* [italics added]... (p. 9, Plomin & Daniels, 1987).

Three step research program
(Plomin and Daniels)

1) Quantify Within Family Environment
2) Identify Specific Within Family Variables
3) Causal Associations between Within Family E and Behavior

Psychological Bulletin
2000, Vol. 126, No. 1, 78–108

0033-2909/00/$5.00 DOI: 10.1037//0033-2909.126.1.78

Nonshared Environment: A Theoretical, Methodological, and Quantitative Review

Eric Turkheimer and Mary Waldron
University of Virginia

Literature Search

Computerized PsycLit and Medline searches with keywords: *bivariate, multivariate,* or *cholesky* and *genetic*

Examination of reference lists of identified articles

Inclusion Criteria

Bivariate models only

Identified Studies Meeting Criteria *N*=75 (345 models)

Recorded Variables

Twin and Sibling Pair Characteristics

N, zygosity, age of pairs

Study Design

Cross-sectional v.s. longitudinal

Variables Examined

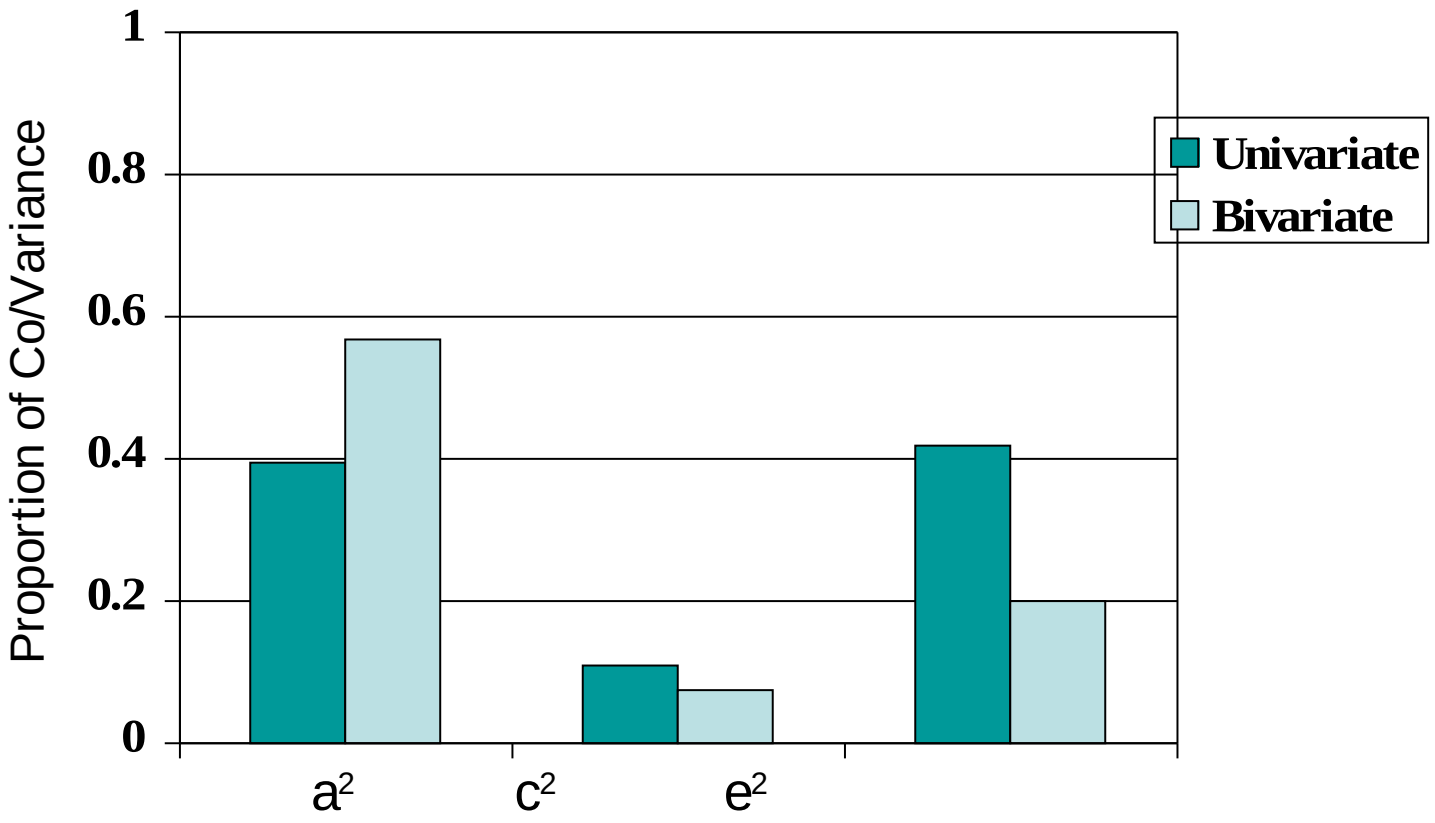
e.g., biomedical, cognitive, personality and temperament, adjustment and psychopathology, and environmental characteristics

Effect Sizes

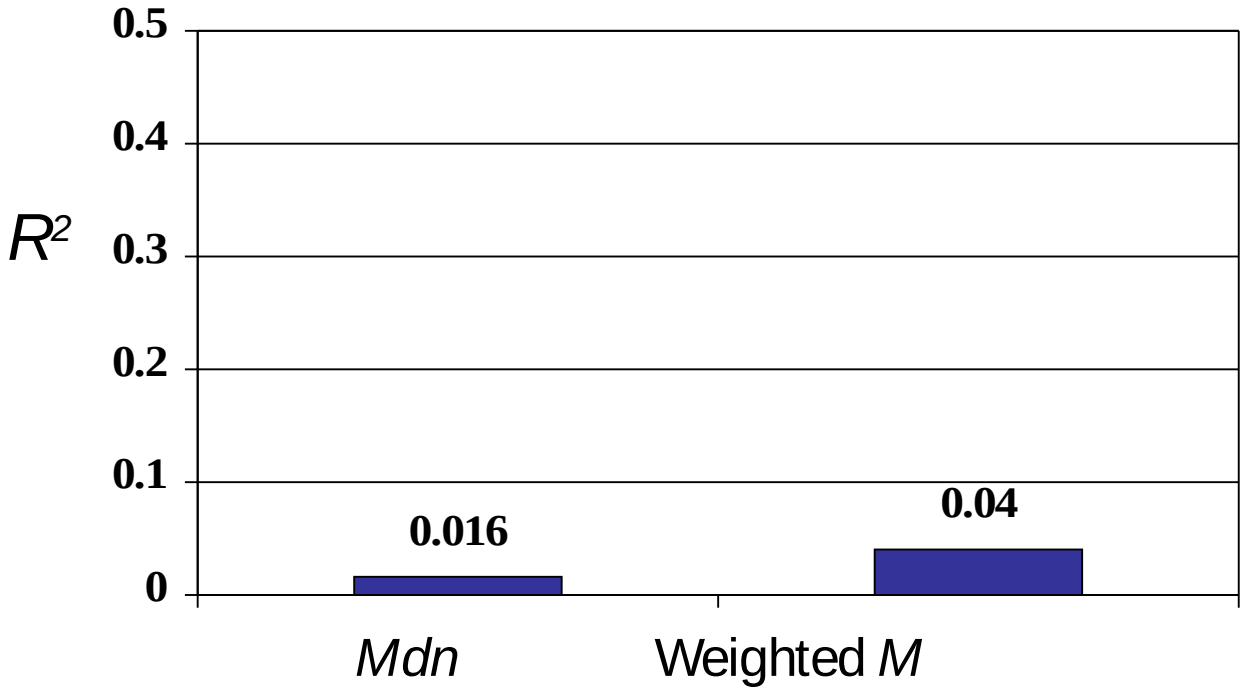
Bivariate a^2, c^2 and e^2 and the average univariate a^2, c^2 and e^2 of the two variables examined

Univariate and Bivariate Estimates

All Studies, *N*=75



Measured Within Family Environment



Average R^2 for Studies Relating Sibling Differences in Measured Environment to Sibling Outcome (*N*=43)

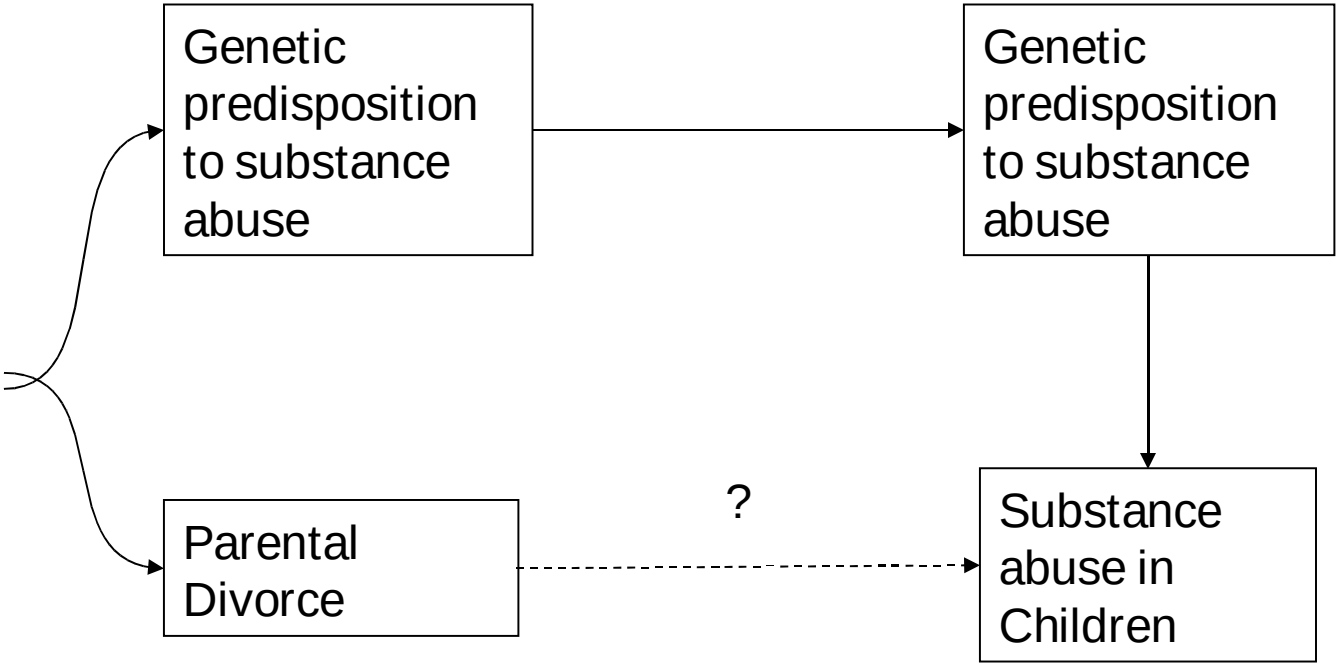
The Gloomy Prospect

One gloomy prospect is that the salient environment might be unsystematic, idiosyncratic, or serendipitous events such as accidents, illnesses, or other traumas... Such capricious events, however, are likely to prove a dead end for research. More interesting heuristically are possible systematic sources of differences between families. (Plomin and Daniels, p. 8)

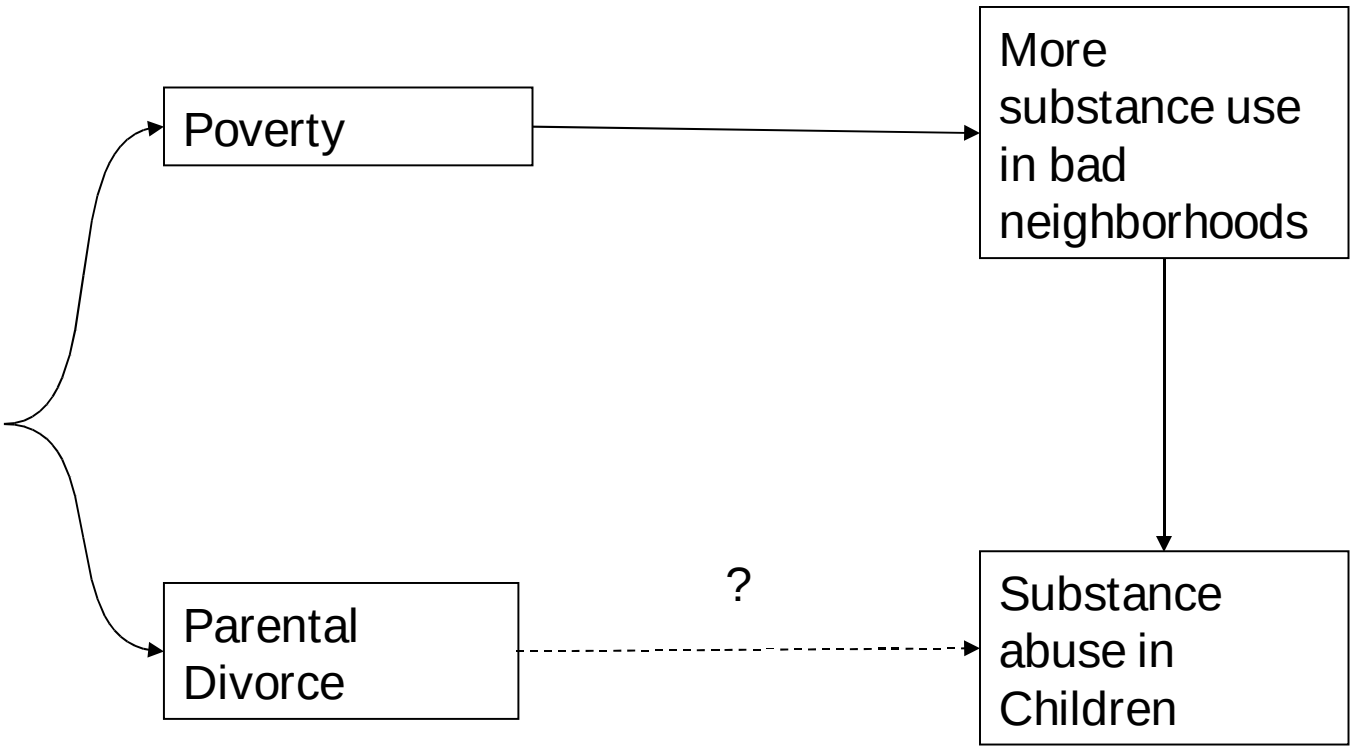
Social Science II: The consequences of divorce

- What are the effects of divorce on children?
- Old way: get divorced and non-divorced families, look for differences in their kids. Voila.
  - EWAS: Environment Wide Association Study
- But obviously this is lame, because
  - Children not randomly assigned to divorce
  - Many consequences of divorce (environmental pleitropy),
  - Many causes of problems in children (polyenvironmentalism)
  - Potential causes of problems in children are non-independent (environmental stratification)

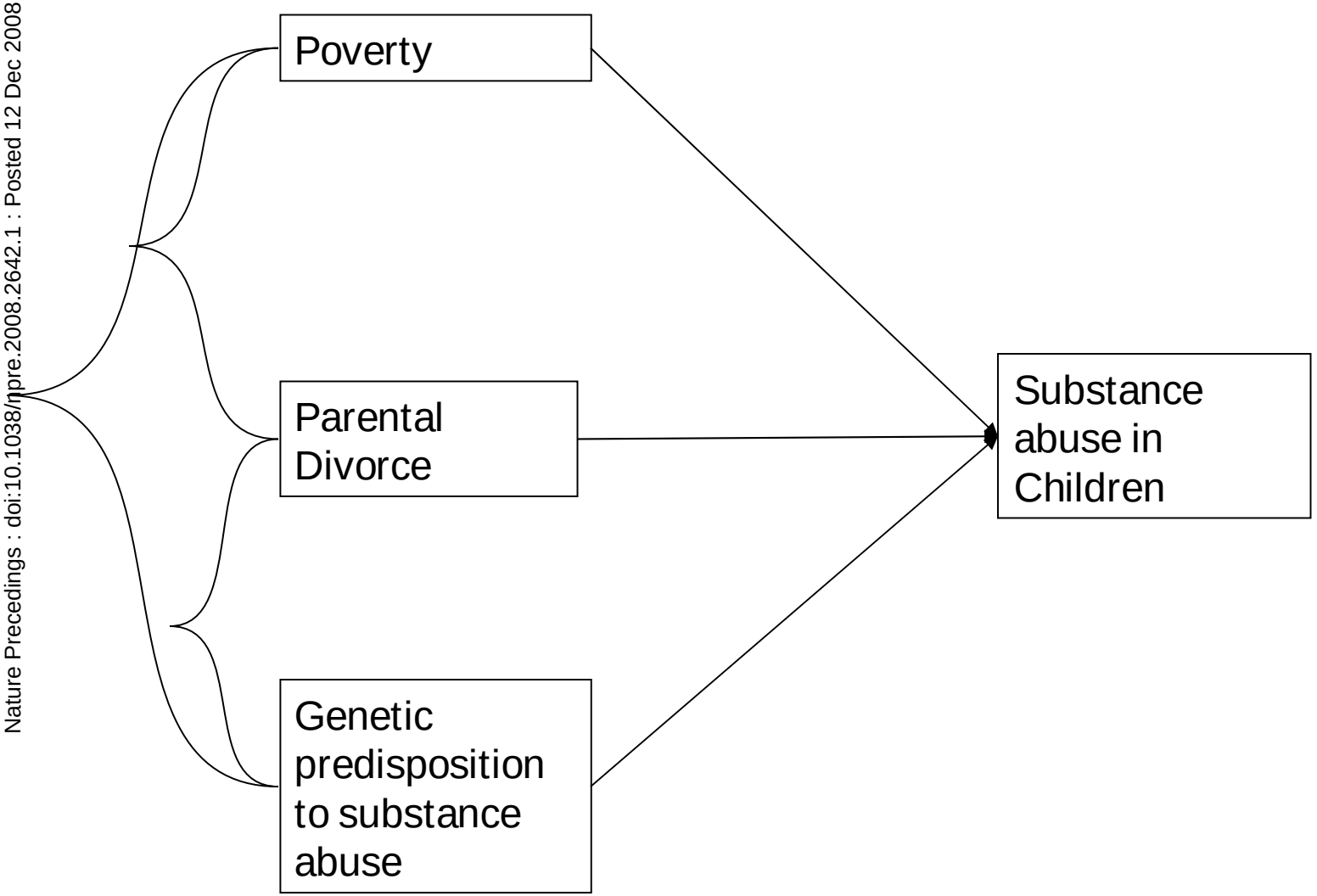
Genetic Confound of Causal Relationship



Environmental Confound of Causal Relationship



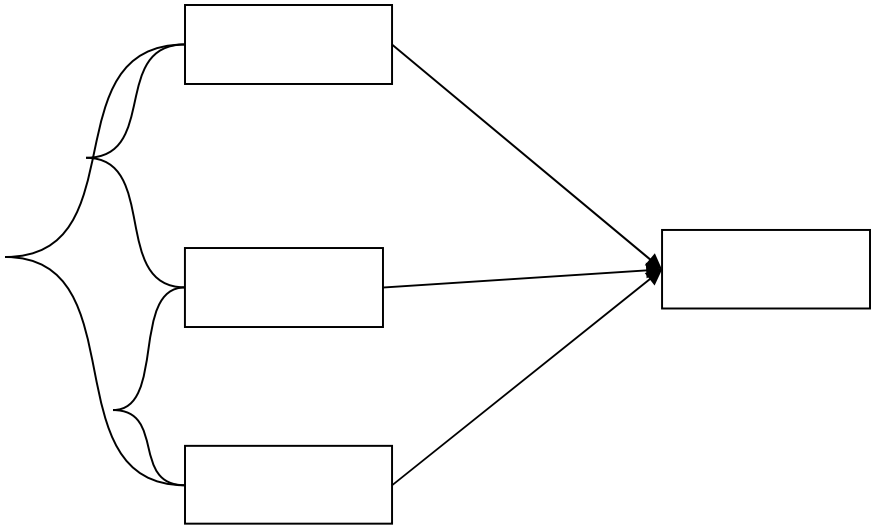
So Which Is It?



What is Social Science?

Social science is the attempt to explain the causes of complex human behavior when:

- There are a large number of potential causes
- The potential causes are non-independent
- Randomized experimentation is not possible



So What Do You Do?

- Statistical Significance
- Multiple Regression, Analysis of Covariance, etc
- Instrumental variable approaches
- Multivariate statistics, Principal Components Analysis
- Propensity Score Analysis

Statistical Significance

- Given null hypothesis of no association, what is probability of observing data?
  - If probability < α then decide null hypothesis must be false
- Problems:
  - Null hypothesis is always false
  - Ability to reject null hypothesis depends on n
  - Probability in null hypothesis is converse of what we want
  - Multiple hypothesis tests make α meaningless.

Finally

The Earth Is Round ($p < .05$)

Jacob Cohen

After 4 decades of severe criticism, the ritual of null hypothesis significance testing—mechanical dichotomous decisions around a sacred .05 criterion—still persists. This article reviews the problems with this practice, including its near-universal misinterpretation of p *as the probability that* H_0 *is false, the misinterpretation that its complement is the probability of successful replication, and the mistaken assumption that if one rejects* H_0 *one thereby affirms the theory that led to the test. Exploratory data analysis and the use of graphic methods, a steady improvement in and a movement toward standardization in measurement, an emphasis on estimating effect sizes using confidence intervals, and the informed use of available statistical methods is suggested. For generalization, psychologists must finally rely, as has been done in all the older sciences, on replication.*

In Summary

- NHST is a way of discriminating actual associations from those occurring because of sampling error
- NHST has nothing to do with causation
- NHST is not capable of distinguishing “ true” effect from “ spurious” ones.
- But NHST LIVES!

So How do we Discriminate “ Real” Causal Effects From Spurious Ones?

Multiple Regression, Analysis of Covariance

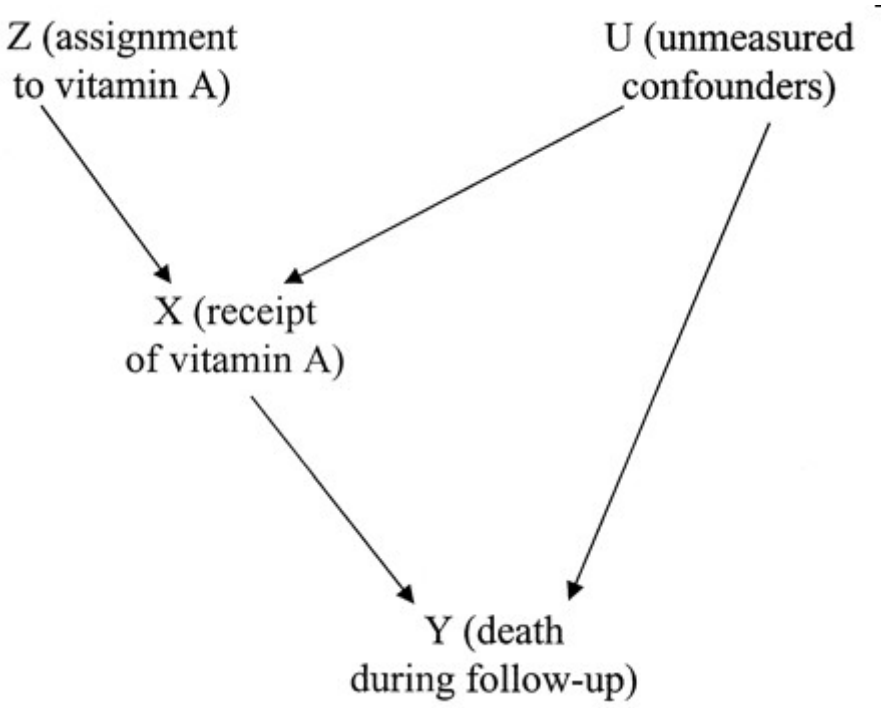
- Regress outcome on predictor while " controlling for" covariates.
- Assumes perfect measurement of covariates
- Assumes additivity of covariates and effect
- Assumes proper specification of covariates

Instrumental Variables

© International Epidemiological Association 2000 Printed in Great Britain International Journal of Epidemiology 2000;29:722–729

An introduction to instrumental variables for epidemiologists

Sander Greenland



- Z is independent of U
- Z is associated with X
- Z is independent of Y given X and U

Principal Components Analysis

- Given large numbers of correlated predictors
- Find weighted sums of predictors with greatest variance
- Interpret and use as covariates in regressions

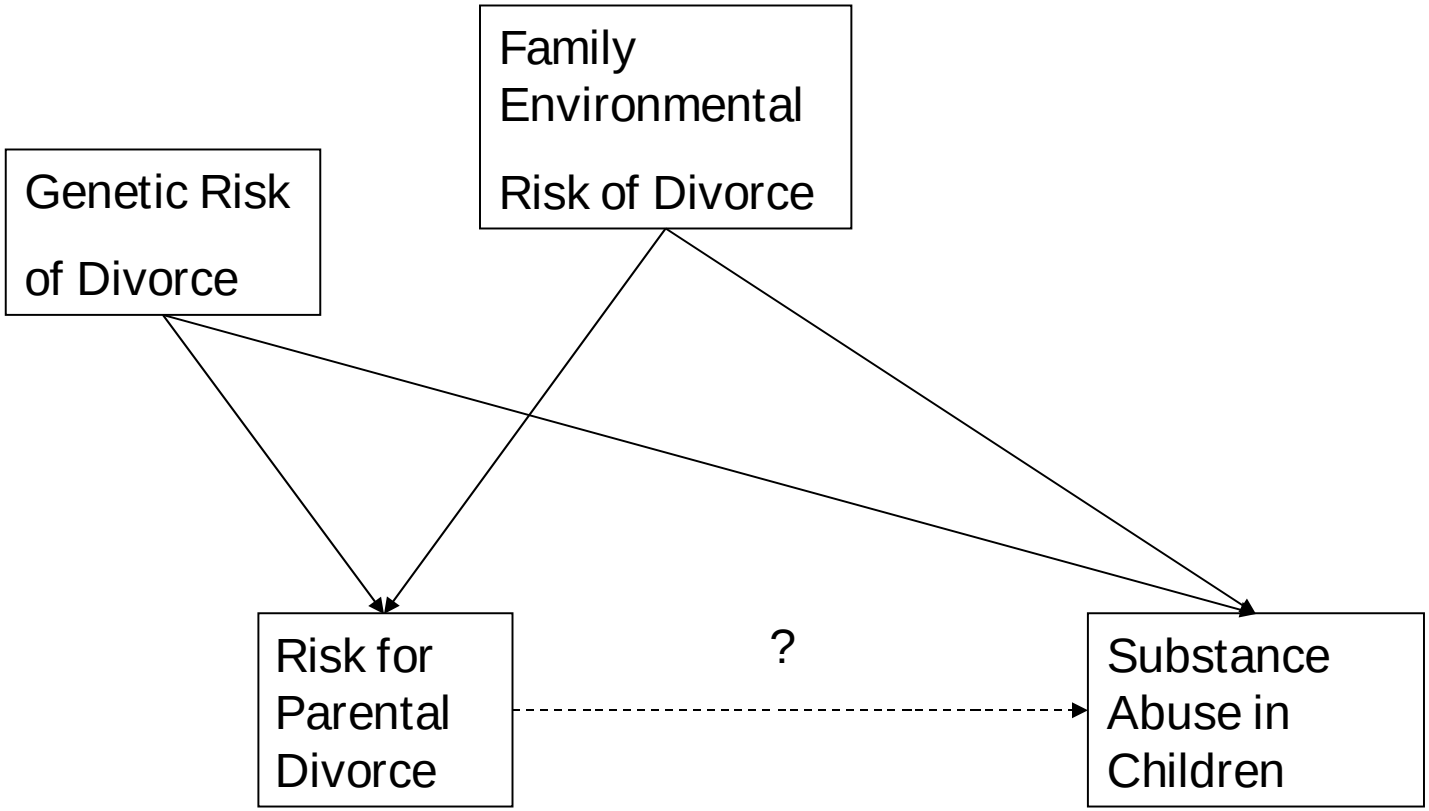
Propensity Scores

Reducing Bias in Observational Studies Using Subclassification on the Propensity Score

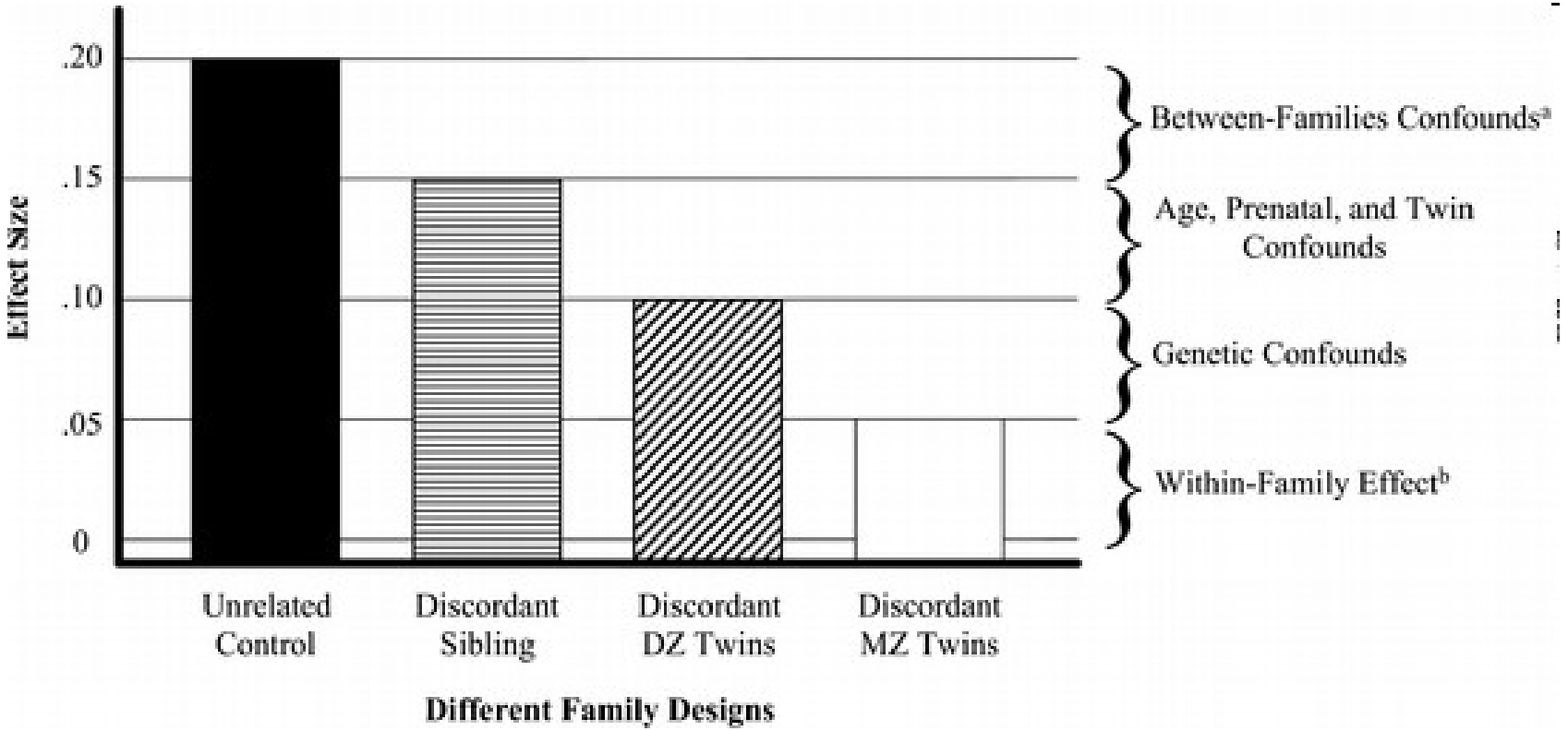
PAUL R. ROSENBAUM and DONALD B. RUBIN*

- Given non-random assignment to treatment
- Use all available of predictors of treatment in logistic regression
- Use composite predicted scores as covariate

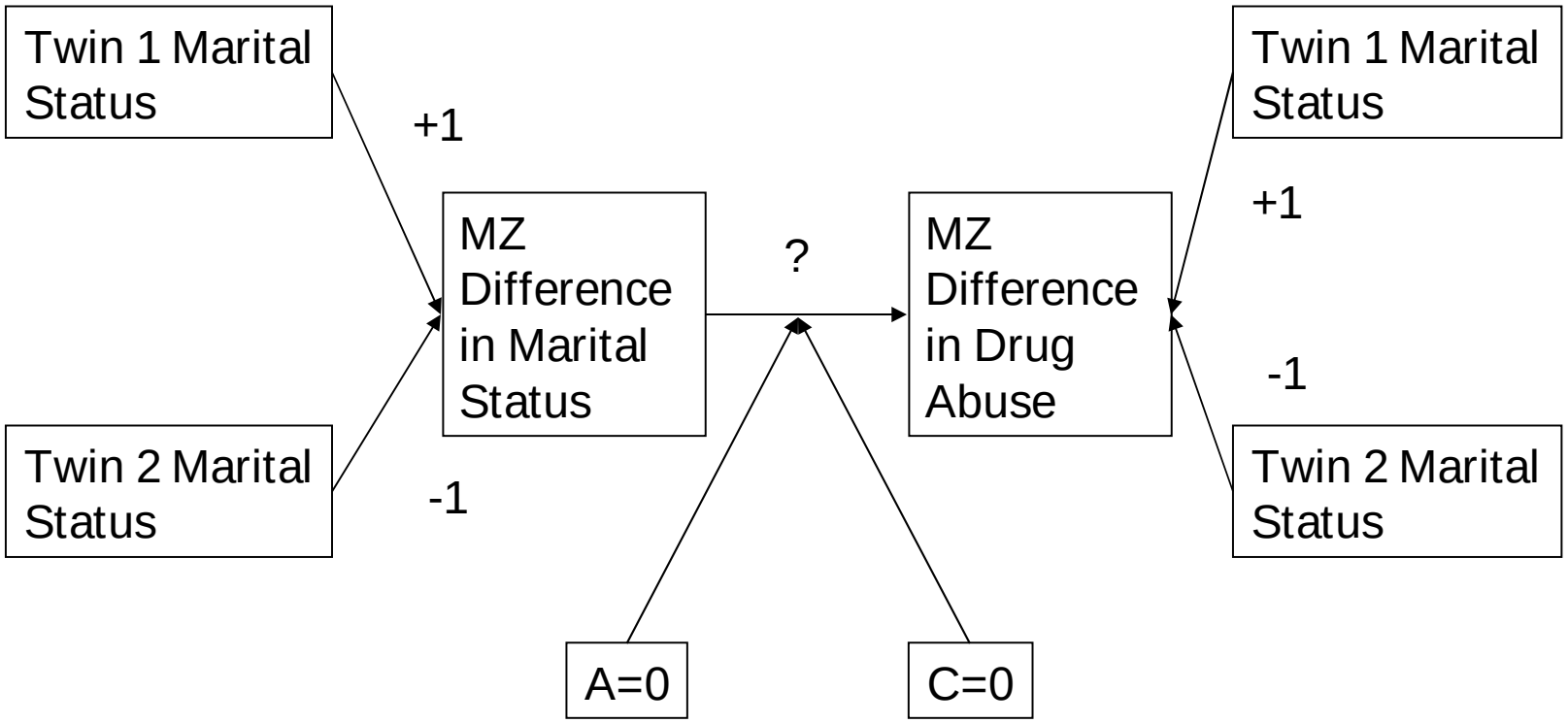
Within-Family Designs



Biometric Controls



MZ Twin Comparison



Journal of Child Psychology and Psychiatry 48:7 (2007), pp 667–675 doi:10.1111/j.1469-7610.2007.0174

A Children of Twins Study of parental divorce and offspring psychopathology

Brian M. D'Onofrio,[1] Eric Turkheimer,[2] Robert E. Emery,[2] Hermine H. Maes,[3] Judy Silberg,[3] and Lindon J. Eaves[3,1]

[1]Department of Psychological and Brain Sciences, Indiana University, USA; [2]Psychology Department, University of Virginia, USA; [3]Virginia Institute for Psychiatric and Behavior Genetics, Virginia Commonwealth University, USA

- Virginia 30,000
  - 14,763 twins and their families
  - 4,300 Offspring
- Marital status of twin parents
- Psychopathology in offspring

Journal of Child Psychology and Psychiatry 48:7 (2007), pp 667–675 doi:10.1111/j.1469-7610.2007.0174

A Children of Twins Study of parental divorce and offspring psychopathology

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	Lifetime alcohol problems[a]		Emotional problems[b]	
Family Structure	Risk	N	Risk	N
Unrelated offspring[c]				
Intact	1.0	1498	18.8	1769
Divorced	3.2	380	24.6	439
Offspring of discordant fraternal twins				
Intact	1.8	277	17.0	277
Divorced	3.1	225	25.7	222
Offspring of discordant identical twins				
Intact	1.4	341	24.5	338
Divorced	4.2	312	24.7	308

A Genetically Informed Study of Marital Instability and Its Association With Offspring Psychopathology

Brian M. D'Onofrio, Eric Turkheimer, and Robert E. Emery
University of Virginia

Wendy S. Slutske
University of Missouri

Andrew C. Heath and Pamela A. Madden
Washington University

Nicholas G. Martin
Queensland Institute of Medical Research

- 8,183 Twins from Australian Twin Registry
- 3,963 Offspring of Twins
- Marital Status in Parents
- In Offspring, Age at
  - ETOH
  - Cigarette
  - Marijuana
  - Depression
  - Suicidal Ideation

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Family structure	Drug and Alcohol[a]		Behavioral Problems		Internalizing[a]	
	M	*SD*	*M*	*SD*	*M*	*SD*
Dizygotic twin families						
Concordant–intact	−0.08	0.98	−0.07	0.97	−0.02	0.96
Discordant–parents married	0.00	0.96	−0.01	0.93	−0.08	0.96
Discordant–parents divorced	0.14	1.00	0.17	0.97	0.26	1.02
Concordant–divorced	0.40	1.13	0.15	1.07	0.28	0.99
Monozygotic twin families						
Concordant–intact	−0.04	0.93	−0.07	0.92	−0.11	0.96
Discordant–parents married	−0.12	0.88	−0.05	0.90	−0.04	0.90
Discordant–parents divorced	0.22	0.99	0.10	0.97	0.23	1.02
Concordant–divorced	0.38	1.02	0.32	0.92	0.19	0.98

So Where Are We?

- Traditional social science involves the search for cause under conditions of multiple correlated weak predictors and the absence of experimental control
  - This is a gloomy business
- Statistical significance has been discredited as a means for dealing with the situation
  - But it doesn’ t go away
- Statistical methods for coping with this situation are better than nothing and quantitatively interesting, but they don’ t work
- Family – based methods are better, but far from foolproof

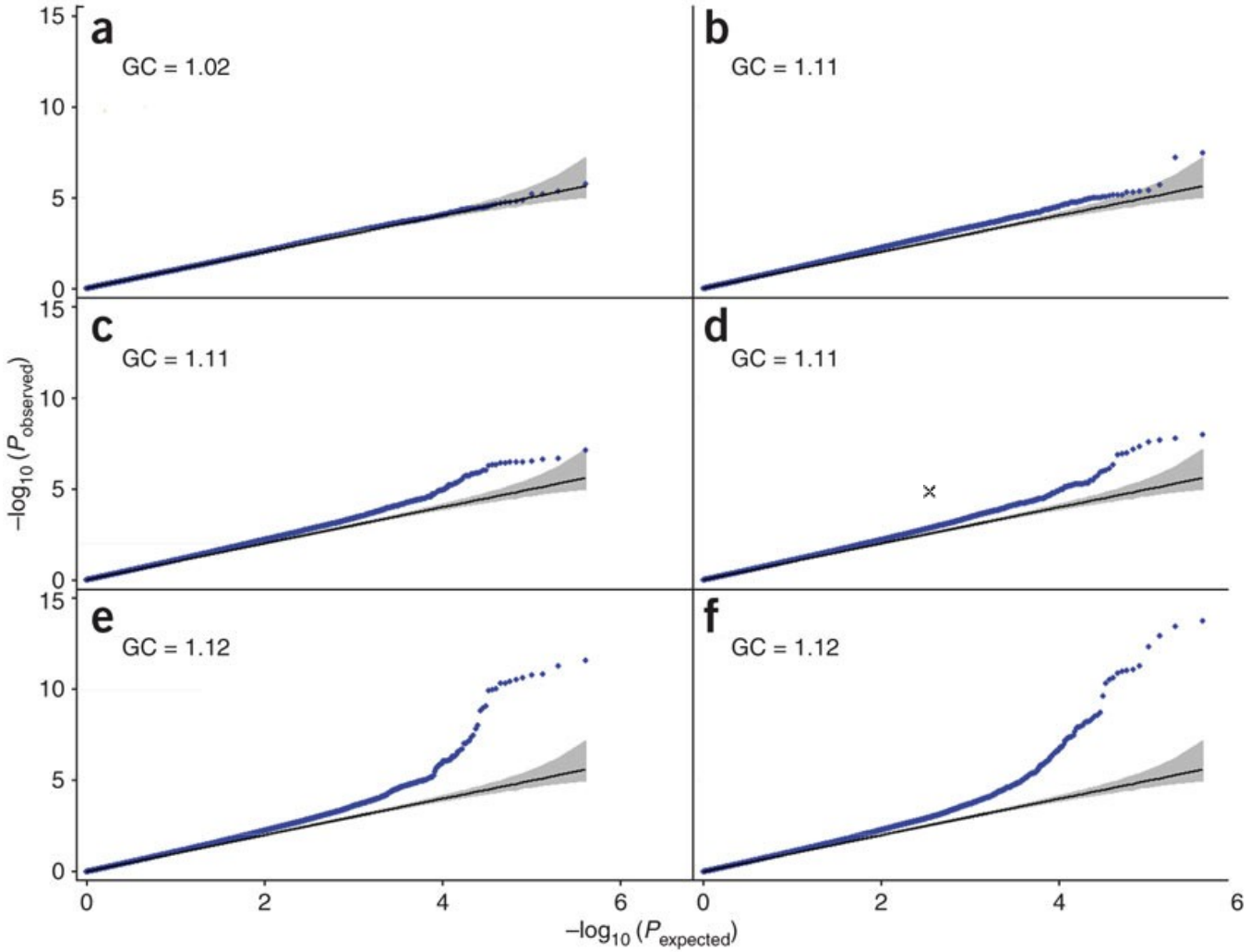
Back to Height

For the 20 SNPs, there was no evidence of heterogeneity across studies when taking into account the number of tests (all $P > 0.008$). In both joint and stage 2 only analyses, none of the WTCCC AIMs was associated with height, providing further evidence that population stratification is unlikely to have influenced the results (all $P > 0.01$). This means that the associations are likely to reflect ***true biological effects on height.*** Weedon (2008)

What is a “ True Biological Effect?”

- Many potential causes, all with low correlations with outcome.
- Potential causes are correlated with each other.
- How can we tell which are “ real?”
  - Statistical significance
  - Control for population stratification.

Weedon - Stage I



…there were many more significant associations than expected by chance. For example, we observed eight independent signals with a $P < 5 \times 10^{-7}$, where we would expect none under the null distribution, and 27 with a $P < 1 \times 10^{-5}$, where we would expect less than four. ***Approximately 23 of these loci are therefore likely to represent true positives***.

Weedon – Stage II

- In the stage 2 analyses, 20 of the 39 SNPs reached a $P < 0.005$ (with the same direction of effect as the GWA data), all of which reached a $P<5x10^{-7}$ in a joint analysis across GWA and stage 2 samples.

- What do we know?
  - At least 20 SNPs are related to height, and these relationships would be unlikely to occur on the basis of sampling error.

- What don't we know?
  - That these 20 associations occur because of a causal relationship between the SNP and human height.

What is the Null Hypothesis?

- H0 is that there is no association between variant and outcome, not
- That the association between sequence and y is a “ true biological process.”
- Of course there is an association between variant and y
- The problem is NOT sampling error

First Law of Behavior Genetics (Molecular Corollary)

- Everything is heritable
  - H2 is “ significantly” greater than 0!
  - At p<.000001 or whatever you want!
  - But heritability did not lead to genetic etiology
- Everything is associated with individual variants
  - What did you think?
  - Proving this again and again isn’ t getting us anywhere.

Population Stratification

News & Views

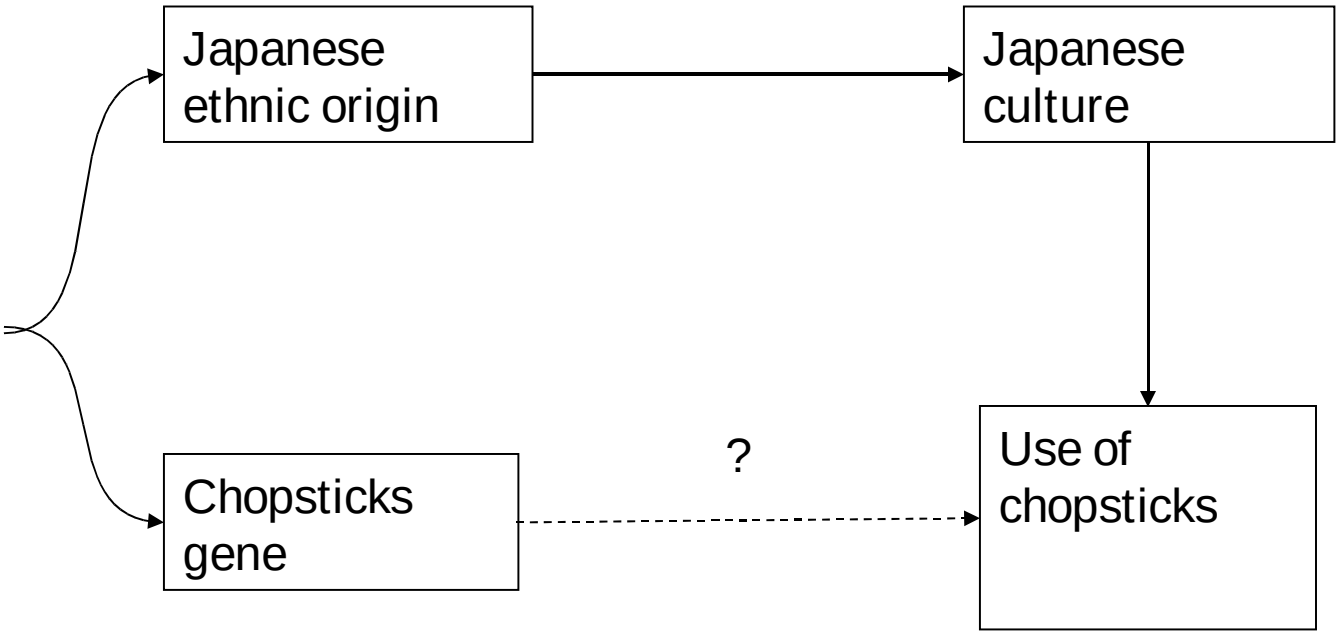
Beware the chopsticks gene

D Hamer and L Sirota

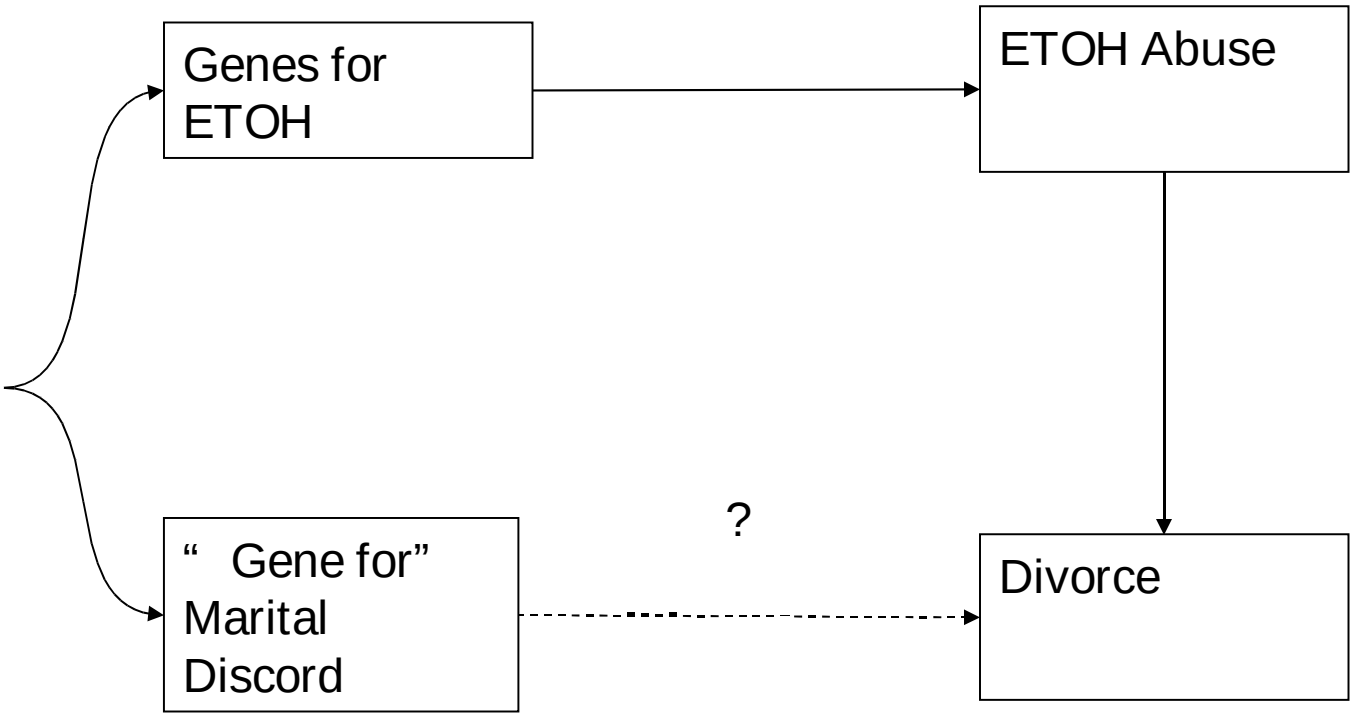
So long as these caveats are kept in mind, psychiatric geneticists should have no problem distinguishing 'chopsticks genes' from the real thing.

- What’ s the ‘ real thing’ ?
- Two approaches to population stratification
  - Statistical methods
  - Within-family designs

Cultural Confound of Causal Relationship



Genetic Confound of Causal Relationship



“ Controlling For” Population Stratification

ANCOVA etc.

Psychological Bulletin
2004, Vol. 130, No. 1, 66–79

0033-2909/04/$12.00 DOI: 10.1037/0033-2909.130.1.66

Population Stratification in the Candidate Gene Study: Fatal Threat or Red Herring?

Kent E. Hutchison, Michael Stallings, John McGeary, and Angela Bryan
University of Colorado at Boulder

Covariates for which *t* values exceed 1.5 at pretest or covariates that have previously been related to the outcome variable may subsequently be included as covariates in the analyses of the posttest scores (West et al., 2000). Most important, the proper adjustment for pretest differences across the groups can reasonably be expected to lead to a more accurate estimate of the effect of the genetic factor with respect to the experimental manipulation. Examples of this type of analysis include the analysis of covariance (ANCOVA), the ANCOVA with correction for unreliability, and a gain score analysis (Judd & Kenny, 1981; for an overview, see West et al., 2000).

Instrumental Variable Approaches

Am. J. Hum. Genet. 65:220–228, 1999

Use of Unlinked Genetic Markers to Detect Population Stratification in Association Studies

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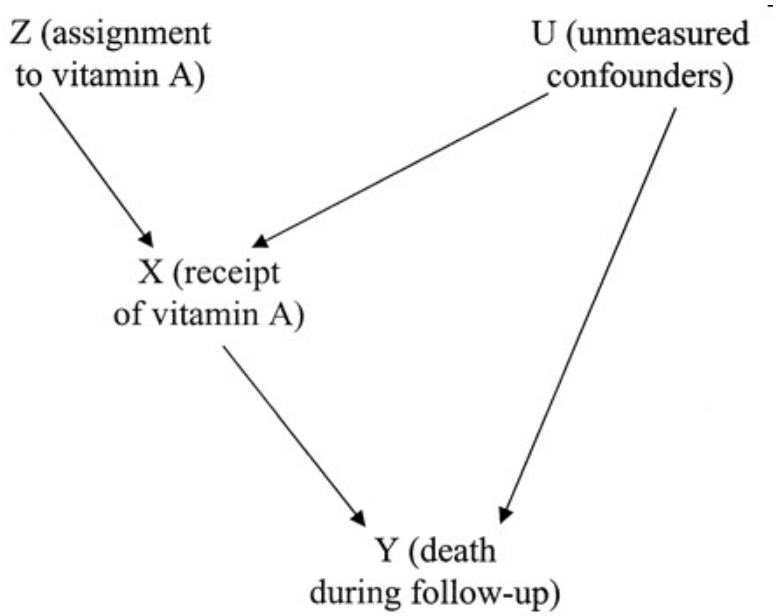

Principal Components Analysis

Principal components analysis corrects for stratification in genome-wide association studies

Alkes L Price[1,2], Nick J Patterson[2], Robert M Plenge[2,3], Michael E Weinblatt[3], Nancy A Shadick[3] & David Reich[1,2]

Propensity Scores

ARTICLE

A Simple and Improved Correction for Population Stratification in Case-Control Studies

Michael P. Epstein,* Andrew S. Allen,* and Glen A. Satten

Within-Family Designs

- Affected Sib-Pair Designs
- Transmission Disequilibrium Tests
- But they cost more!
- Instead of meaningful controls, bigger and bigger GWAS

It Gets Worse

Did you notice?

In Virginia,

No Causal Effect on Depression

	Emotional problems[b]	
	Risk	N
Unrelated	18.8	1769
	24.6	439
DZ	17.0	277
	25.7	222
MZ	24.5	338
	24.7	308

In Virginia,

Causal Effect on Depression

	Internalizing[a]	
	M	*SD*
DZ	−0.02	0.96
	−0.08	0.96
	0.26	1.02
	0.28	0.99
MZ	−0.11	0.96
	−0.04	0.90
	0.23	1.02
	0.19	0.98

Spinach and Ice Cream (Bateson)

- A mother rewards a child for eating his spinach by giving him a bowl of ice cream.
- When child grows up, does he:
  - Love or hate spinach?
  - Love or hate ice-cream?
  - Love or hate mother?

Maternal Behavior and Food Preference Research

- Correlations between maternal behavior and food preference outcome.
- But twin and adoption studies show that h^2=.4, c^2=.05, e^2=.55.
- Proceed to:
  - Nonshared E… It' s a non-starter.
  - Molecular G… ???

Spinach and Ice Cream Questions

- Prospective
  - What are the effects of parental divorce on children?
  - What are the effects of DRD4 on behavior
- Etiological
  - What are the causes of depression in adolescence?
  - What genes confer risk for depression in adolescence?

The Break Point of Non-Experimental Causal Models

- When there are many correlated, interacting causes the very notion of systematic “ risk factors” starts to break down.

> One understands fairly clearly what it means to conjecture that a "big-effect monogene" is the specific etiology of a disease..... But once we have excluded that simple situation, the very meaning of the phrase "specific etiology" begins to "fuzz up...." (Meehl, 1972, p. 376, italics in original).

The Price of Polygenics

....Monogenic theories suggest major biochemical pathways which can be uncovered, whereas polygenic models suggest a complexity of chemical interactions probably intractable to exact study. Thus if most behavior traits must be fit to polygenic models, we may be left only with statistical analyses of such problems as how many genes are involved and the specification of the almost infinite number of interactions between them. Such mathematical exercises seem to us to have only trivial importance and, furthermore, to be of small interest to most biologists and psychologists. (Fuller and Thompson, p. 438)

Conclusions

The Repressed Reason for Significance Testing

- Spinach and ice cream questions don’ t have answers
- Therefore most social science is spinning its wheels
- Significance testing allows us to believe the problem is sampling error
- Relief from gloom

Cancer Genetics and Heritability (Risch)

Just as heritability estimates from the MFT model applied to family and twin studies may not be the optimal measure of genetic impact when the MFT model does not apply, they should also not necessarily be viewed as a good predictor of the ease with which molecular genetic analysis can identify the actual susceptibility genes involved. In fact, looking historically, one would draw the conclusion that molecular genetic success is either independent of or negatively correlated with estimated heritability from twin studies.

The correct hypothesis

- Are there associations?
  - Of course there are
- There are no “ true positives,” “ biological effects,” “ spurious associations,” etc
- Absent other information there are no “ genes for” anything.

Back to Height

- Is height genetic?
  - Of course it is.
- Are there identifiable genetic mechanisms that regulate height?
  - Probably not

Study Links Gene Variant in Men to Marital Discord

By Shankar Vedantam
Washington Post Staff Writer
Tuesday, September 2, 2008; Page A02

Genetic variation in the vasopressin receptor 1a gene (*AVPR1A*) associates with pair-bonding behavior in humans

Hasse Walum*†‡, Lars Westberg†§, Susanne Henningsson§, Jenae M. Neiderhiser¶, David Reiss‖, Wilmar Igl*, Jody M. Ganiban**, Erica L. Spotts††, Nancy L. Pedersen*, Elias Eriksson§, and Paul Lichtenstein*

Turkheimer (2000)

The question is not whether there are correlations to be found between individual genes and complex behavior—of course there are—but instead whether there are domains of genetic causation in which the gloomy prospect does not prevail, allowing the little bits of correlational evidence to cohere into replicable and cumulative genetic models of development. My own prediction is that such domains will prove rare indeed, and that the likelihood of discovering them will be inversely related to the complexity of the behavior under study.