

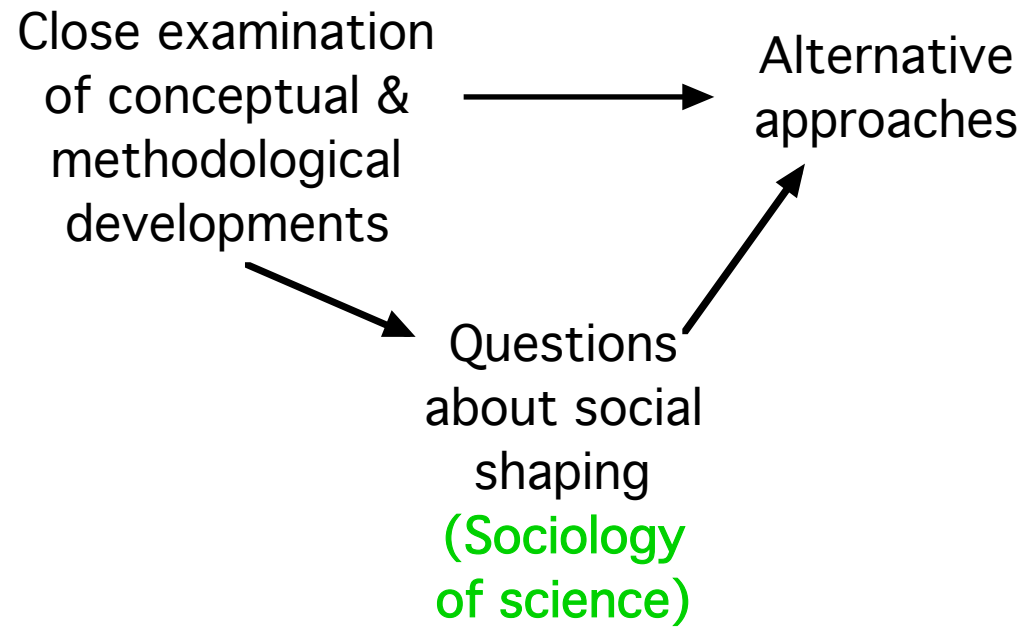
Troubled by Heterogeneity?

Questions for public health, heritability studies, and
personal genomics

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Sources & details at <http://bit.ly/IBMC12>

Sciences



research and application of resulting knowledge

not troubled by



pay more attention to

variation, particularity, heterogeneity

to the extent that

populations are well controlled



possibilities for participation

*established and
maintained through*

inviting more attention to

considerable effort or social infrastructure

heterogeneity

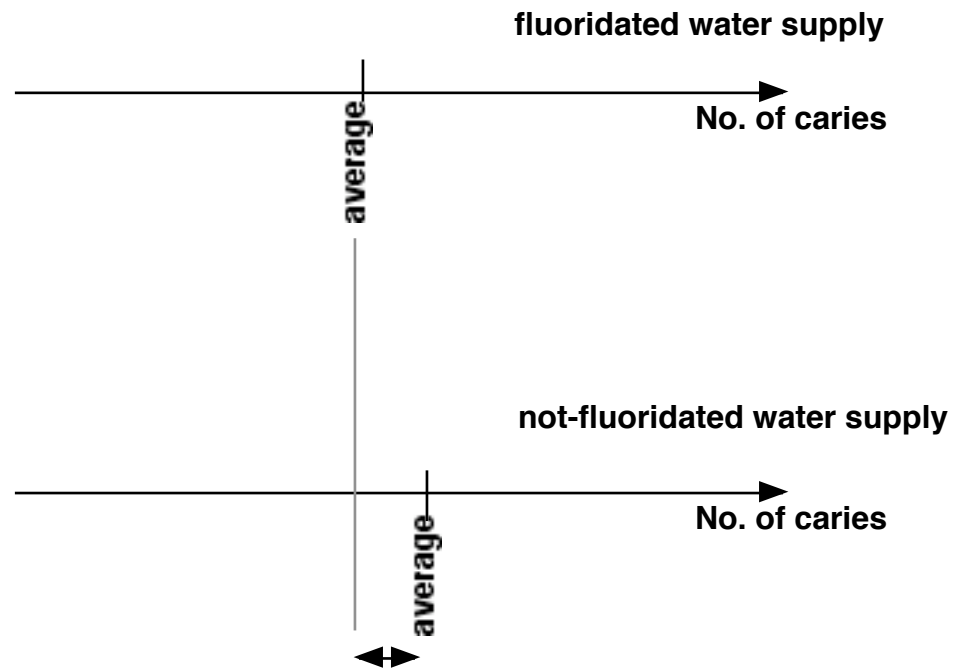
participation

control

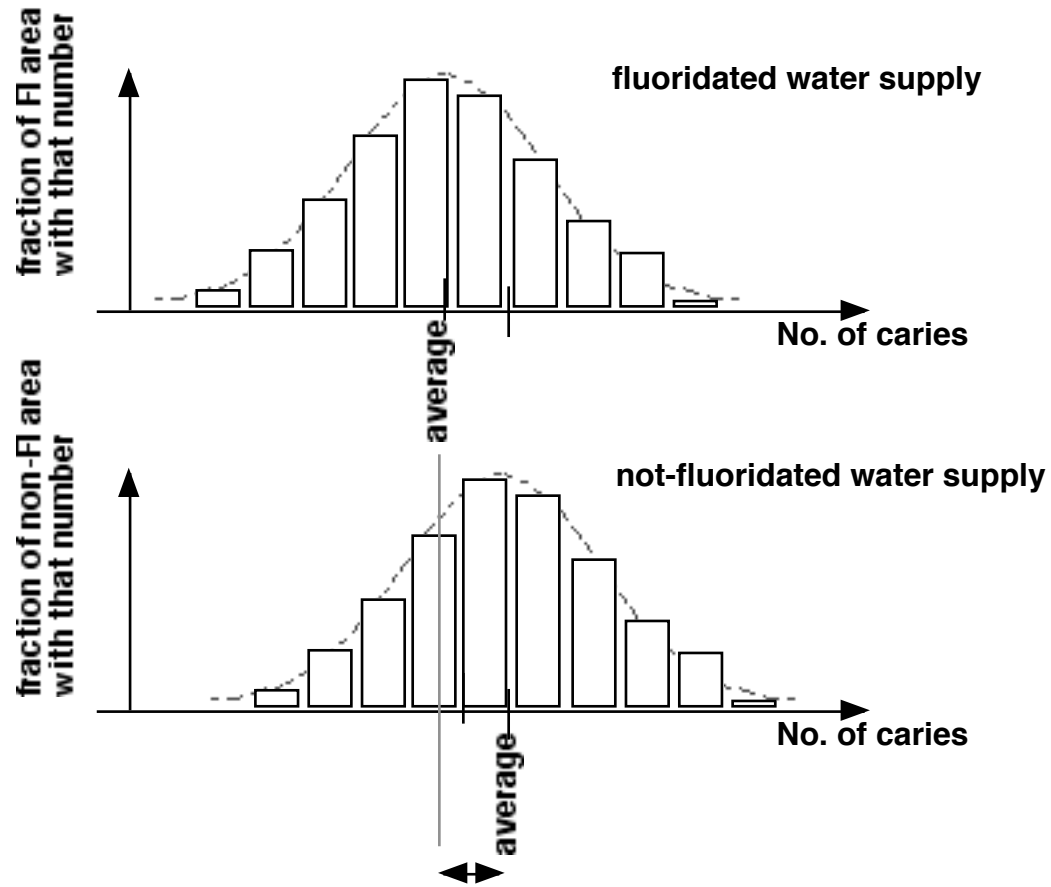
social infrastructure

Fluoridation in the U.S.A.

Fluoridation in the U.S.A.



Fluoridation in the U.S.A.





Prophylactic low-dose aspirin

Prophylactic low-dose aspirin

	Regular low-dose aspirin	Not
Over 50 years	Risk: stroke ↓ , GI bleeding ↑	Risk: stroke ↑ , GI bleeding –

Prophylactic low-dose aspirin

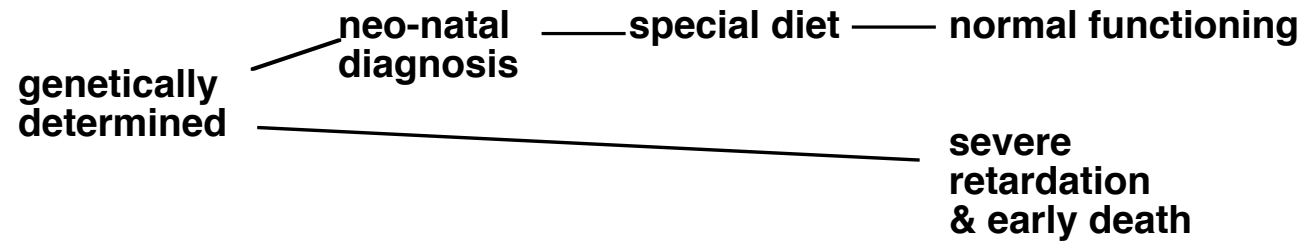
	Regular low-dose aspirin	Not
Over 50 years (aspirin-responsive)	Risk: stroke ↓ GI bleeding ↑	Risk: stroke ↑ GI bleeding –
Over 50 years (aspirin-resistant)	Risk: stroke – GI bleeding ↑	Risk: stroke – GI bleeding –

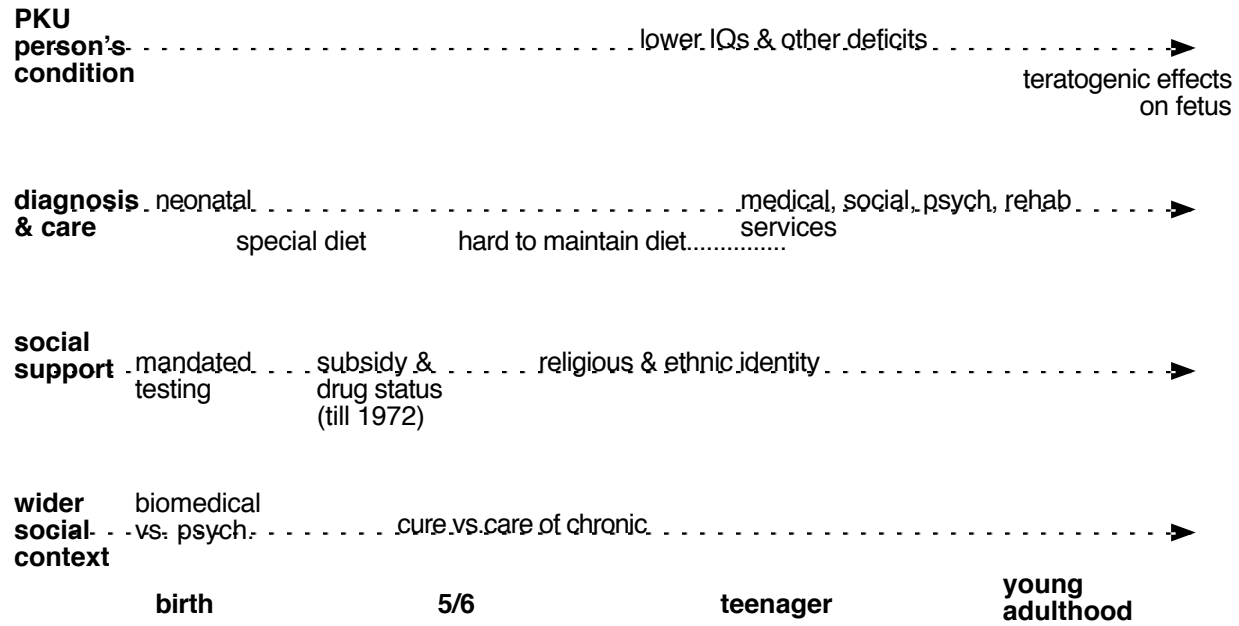
Medical promise of genomics

Medical promise of genomics

“..imagine a world where your physician has as part of your medical record your genetic code, which can be used to determine, for example, your risk profile for side effects from drugs or other medical treatments. These might be possible in a genomics-based medical system in the near future.” (Venter 2003)

PKU





“Missing” heritability

“Missing” heritability

The mystery of missing heritability: Genetic interactions create phantom heritability

Or Zuk^a, Eliana Hechter^a, Shamil R. Sunyaev^{a,b}, and Eric S. Lander^{a,1}

+ Author Affiliations

Contributed by Eric S. Lander, December 5, 2011 (sent for review October 9, 2011)

Abstract

Human genetics has been haunted by the mystery of “missing heritability” of common traits. Although studies have discovered >1,200 variants associated with common diseases and traits, these variants typically appear to explain only a minority of the heritability. The proportion of heritability explained by a set of variants is the ratio of (i) the heritability due to these variants (numerator), estimated directly from their observed effects, to (ii) the total heritability (denominator), inferred indirectly from population data. The prevailing view has been that the explanation for missing heritability lies in the numerator—that is, in as-yet undiscovered variants. While many variants surely remain to be found, we



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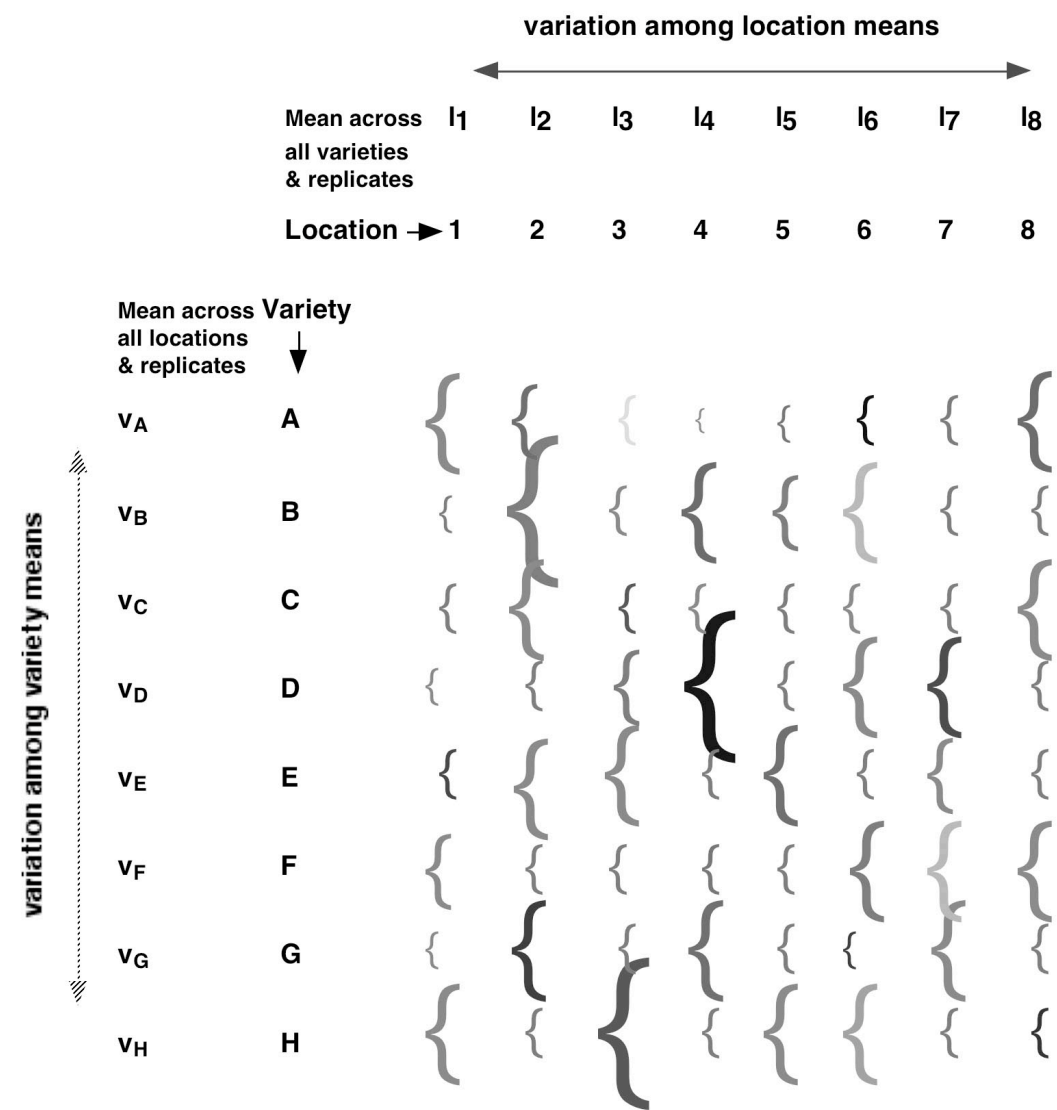
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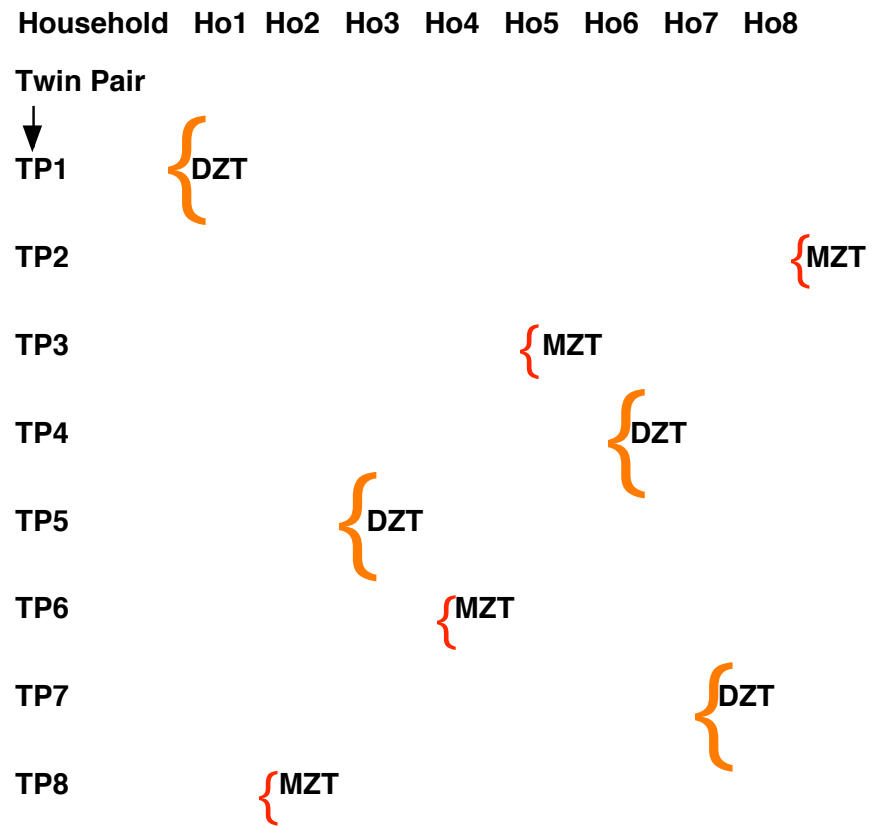
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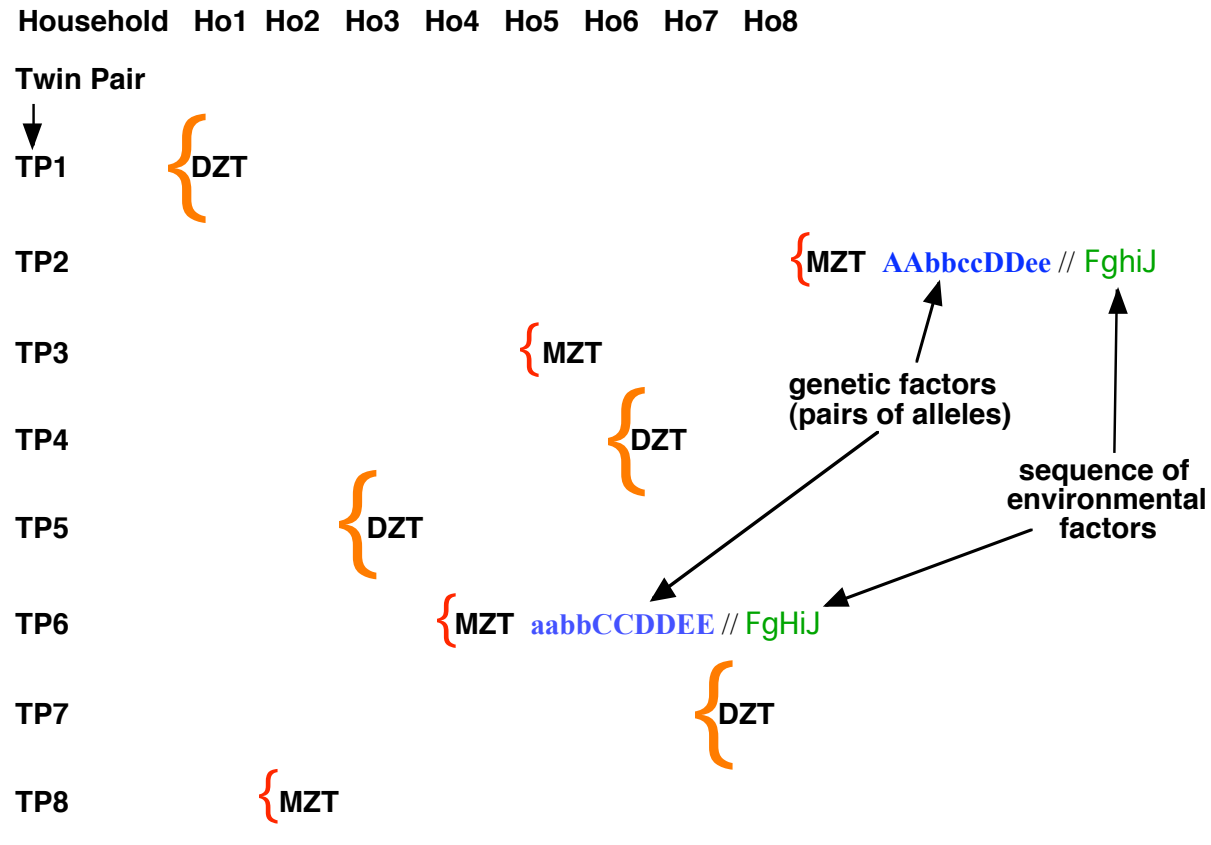
“Missing” heritability



“Missing” heritability



“Missing” heritability

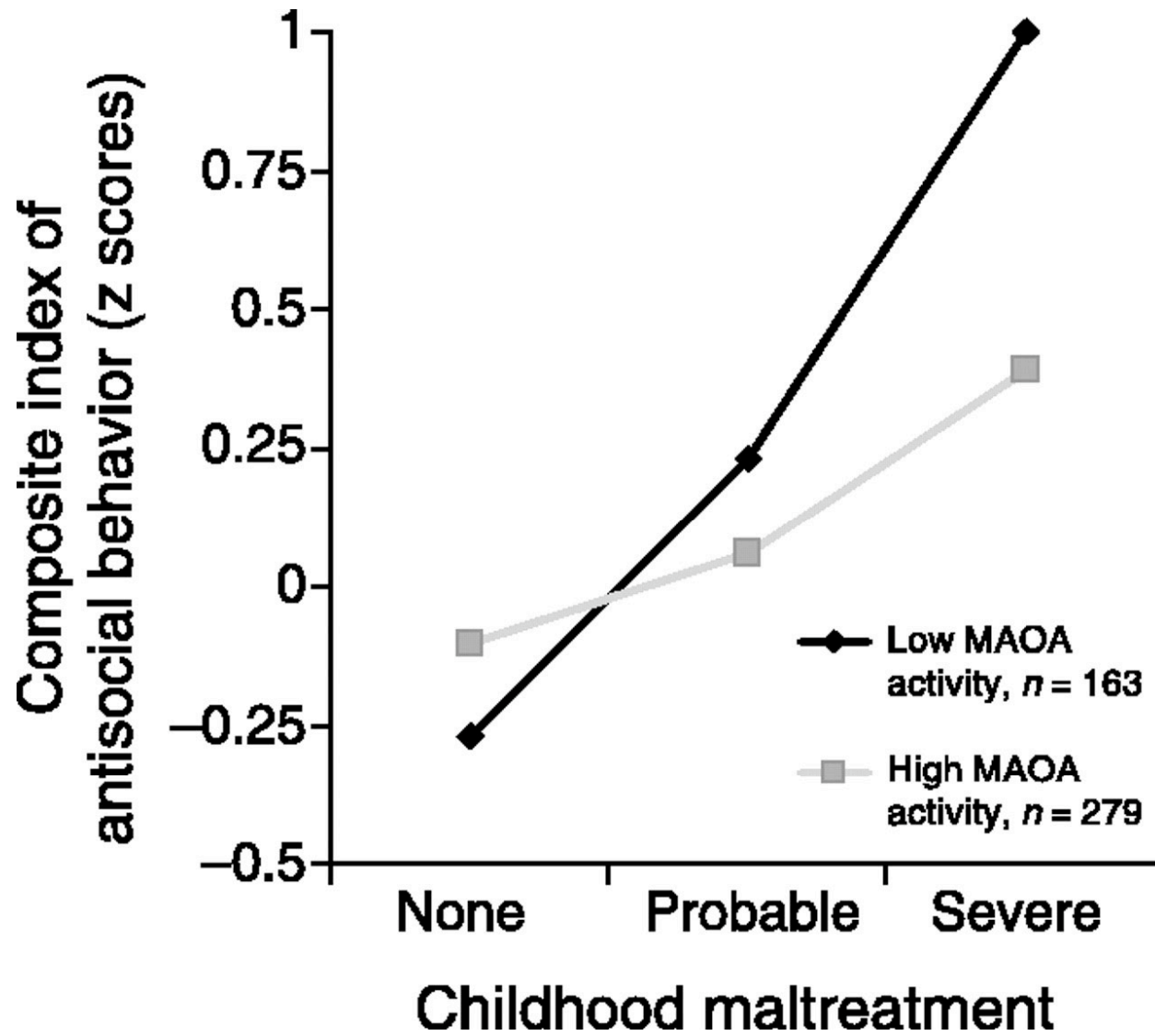


Given heterogeneity, heritability => ?

- Undertake *research* to identify the specific, measurable genetic and environmental factors *without reference to the trait's heritability* (or the other fractions of the total variance)
- Use high heritability to *guide molecular research* to identify the specific genetic factors involved
 - Restrict attention to *within a set of relatives*
 - Focus on *heritability as a fraction of the variation* among measurements
 - Reduce the possibility of underlying heterogeneity by *restricting the range of varieties or locations*

Gene by environment interaction in behaviour

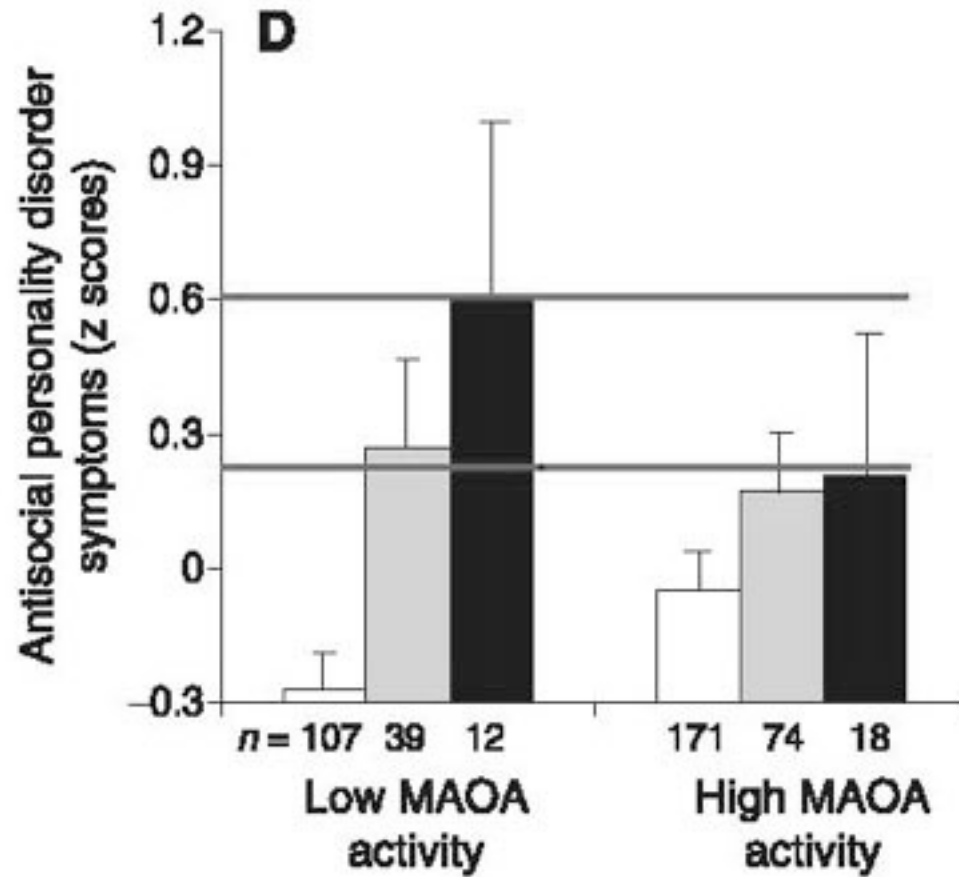
Gene by environment interaction in behaviour



Gene by environment interaction in behavior

Childhood maltreatment	MAOA	
	low	high
No or probable	Antisocial: low	Antisocial: low
Severe	Antisocial: HIGH	Antisocial: low

Gene by environment interaction in behaviour



Personalized medicine

Personalized medicine

investment in

pharmaceutical & sociological research, screening, & preventative treatment/monitoring

to address

the conjunction of

genetic & environmental factors involved?

1. identifiable classes

with significant treatment benefit on average...

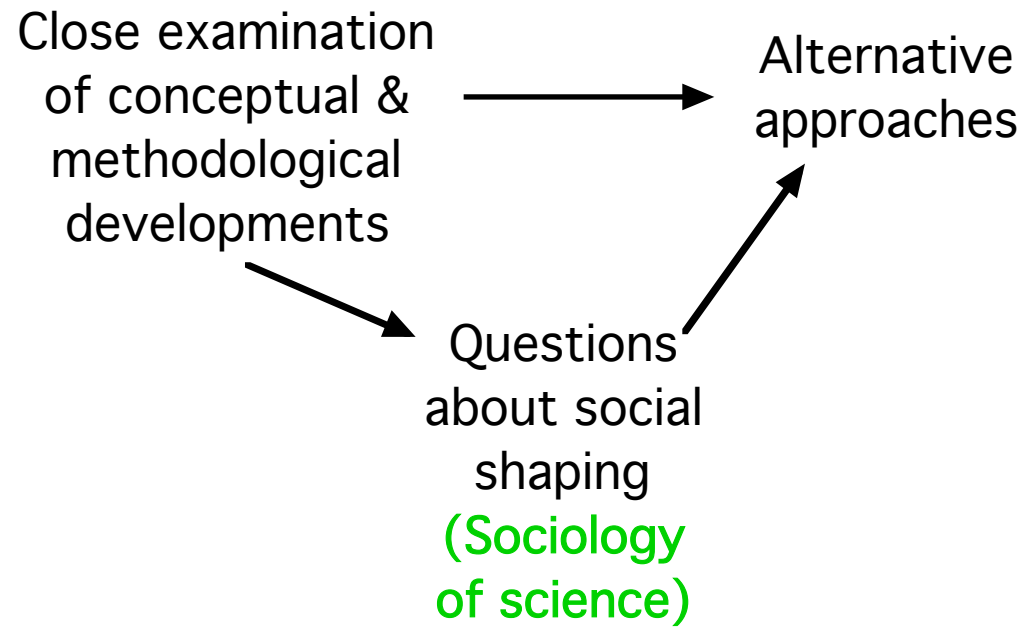
2. variation in benefit around average...

(incl. some who are harmed by treatment & some in non-treated classes who would benefit)

3. pressure on researchers to differentiate within classes...

4. customized treatment (“personalized medicine”)

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Participatory Warm-Up to Discussion

Guided freewriting (4-5 minutes)

Share a thought with a neighbor

Participatory Warm-Up to Discussion

Guided (topic-based) freewriting:

- clear mental and/or emotional space and
- allow ideas about an issue to begin to come to the surface
- before you simply push ahead.

In a freewriting exercise, you should not take your pen off the paper. Keep writing even if you find yourself stating over and over again, "I don't know what I'm expected to say." What you write will not be shown to anyone else, so do not go back to tidy up sentences, grammar, spelling. You will probably diverge from the topic, at least for a time while you acknowledge other preoccupations. That's OK- one of the purposes of the exercise is to express what is distracting you is. However, if you keep writing and do not stop, you should expose some thoughts about the topic that had been below the surface of your attention-that is another of the aims of the exercise.

Reference: Elbow, P. 1981. Writing with Power. New York: Oxford U. P.

Continue (in your preferred language) where this sentence leaves off:

"When I think about whether my research is—or could be—troubled by heterogeneity, the thoughts, experiences, feelings that arise include....."