Sex-limitation Models

Brad Verhulst, Elizabeth Prom-Wormley
(Sarah, Hermine, and most of the rest of the faculty that has contributed bits and pieces to various versions of this talk)

The language of heterogeneity

- Sex differences = Sex limitation

1948

ON SEX LIMITATION IN HUMAN GENETICS*

By H. HARRIS, M.B., B.Chir.(Camb.)

IT is well known that in many instances of hereditary disease the condition is observed to occur more frequently in one

cases, the sons never inherit the peculiarity directly from their fathers, but the daughters, and the daughters alone, transmit the latent tendency, so that the sons of the daughters

1840

L'HÉRÉDITÉ DANS LES MALADIES,

PAR P. A. PIORRY,

Docteur en médecine, Chevalier de la Légion-d'Honneur, Médecin de l'Hôpital de la Pitié, Agrégé à la Faculté de Médecine de Paris, Professeur de Clinique et de Pathologie interne, Membre de l'Académie Royale de Médecine, des Sociétés médicales de Tours, de Boulogne, de Goettingue, de l'Académie Royale de Médecine de Madrid, etc.

1861

THE

BRITISH AND FOREIGN

MEDICO-CHIRURGICAL

REVIEW

OR

QUARTERLY JOURNAL

OF

PRACTICAL MEDICINE AND SURGERY.

VOL. XXVII.

JANUARY — APRIL, 1861.

ART. III.

On Sexual Limitation in Hereditary Disease. By WILLIAM SEDGWICK.

(*Concluded from our last.*)

FROM hereditary diseases of the organ of vision, the transition is easy to those affecting the organ of hearing, for there are some defects which these organs seem, as it were, to share in common. This connexion has been already referred to by some writers, amongst whom Mr. White Cooper* states that imperfection of the two senses (of sight and hearing) not infrequently co-exist, especially in the curious class of cases we have just been considering, where the inability to distinguish colours is often associated with a corresponding inability to distinguish musical sounds. Dr. Earle relates, in his case of colour-blindness, that "the whole family, of which the chart has been exhibited, is probably no less generally characterized by a defective musical ear than an imperfect appreciation of colours. Several of the individuals comprised in it are utterly incapable of distinguishing one tune from another."†

* Cyclopædia of Anatomy and Physiology, art. "Vision," p. 1453.
† American Journal of Medical Science, vol. xxxv. p. 347. 1845.

Terminology

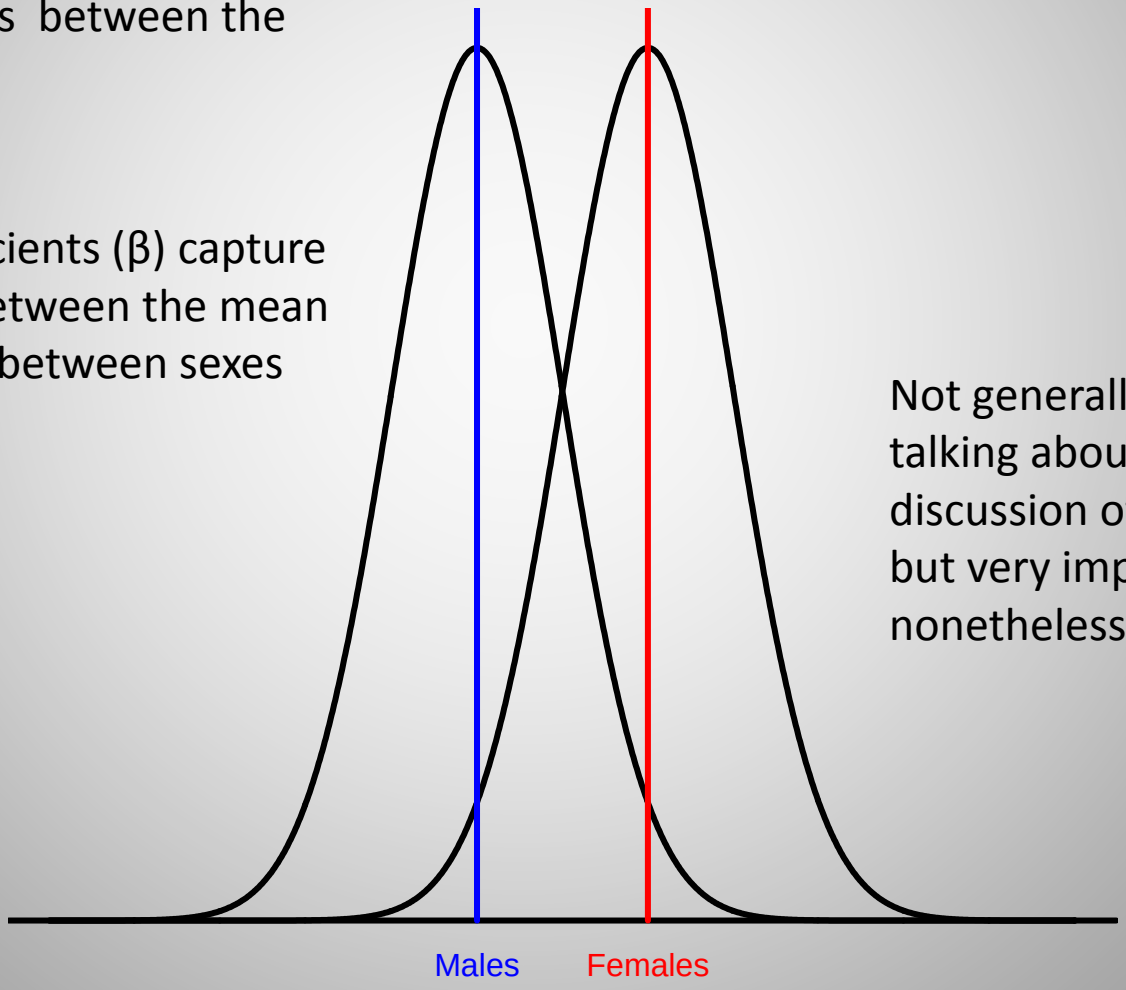
- Serious issue with Sex-Limitation Models:
  - The terminology is fungible and can (often) be reversed (Moderation, confounding, GxE)

- Solution: Be very, very, very clear about what you are testing.

Two primary differences between Males and Females.

Means Differences between the sexes

Regression coefficients (β) capture the differences between the mean levels of the trait between sexes



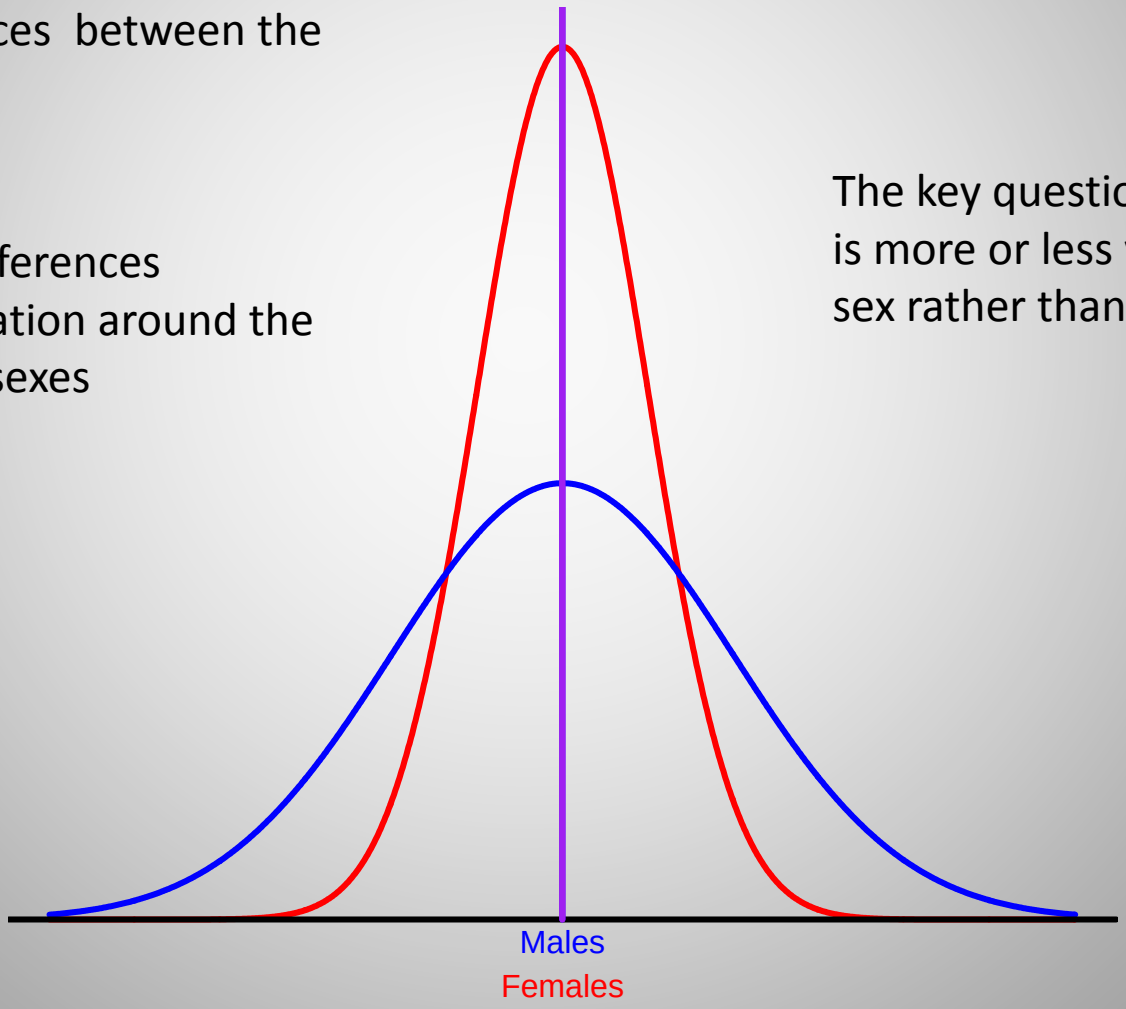
Not generally what we are talking about when discussion of Sex limitation, but very important nonetheless.

Two primary differences between Males and Females.

Variance Differences between the sexes

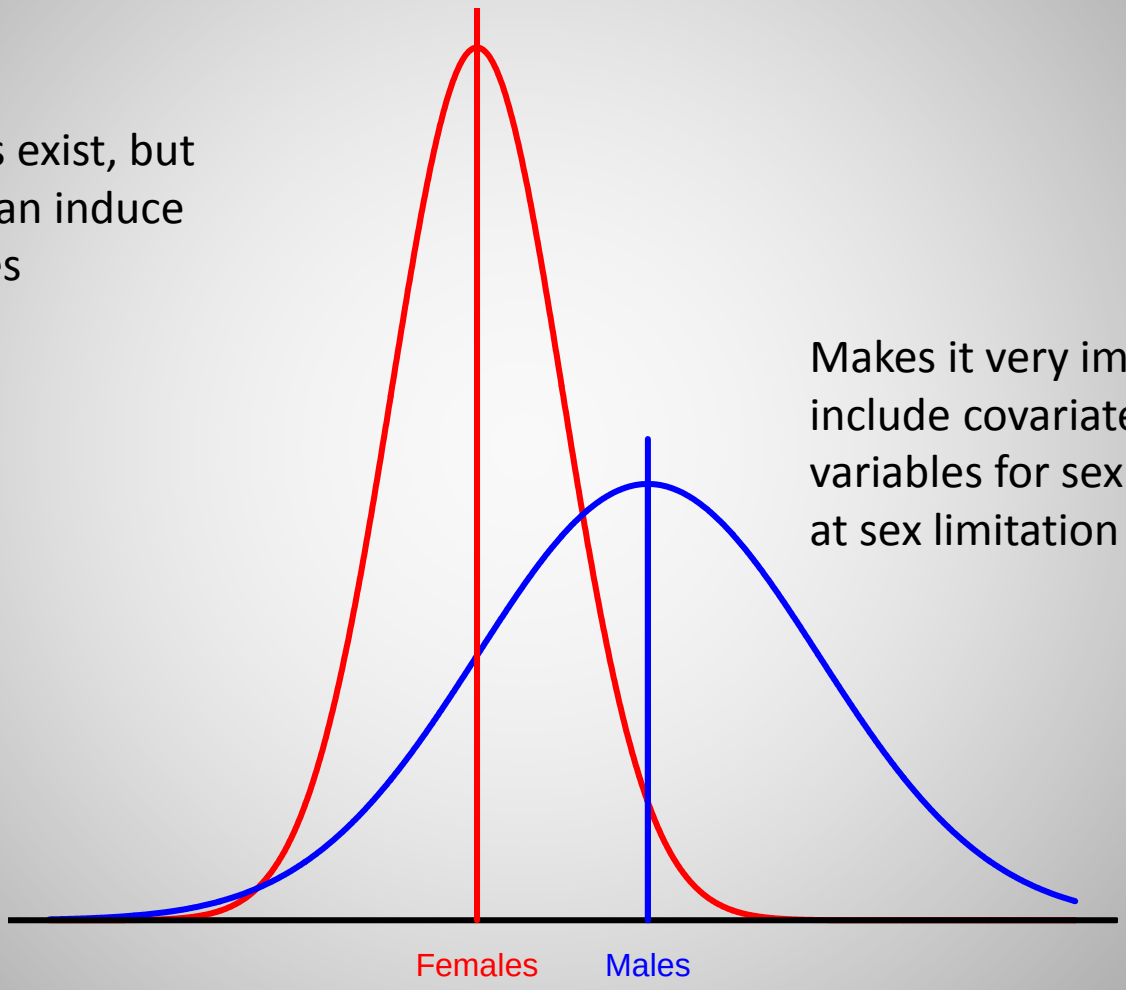
σ^2 capture the differences between the variation around the mean across the sexes

The key question is why there is more or less variation in one sex rather than the other



Both Mean and Variance Differences

If mean differences exist, but are ignored, they can induce variance differences



Makes it very important to include covariates/definition variables for sex when looking at sex limitation models

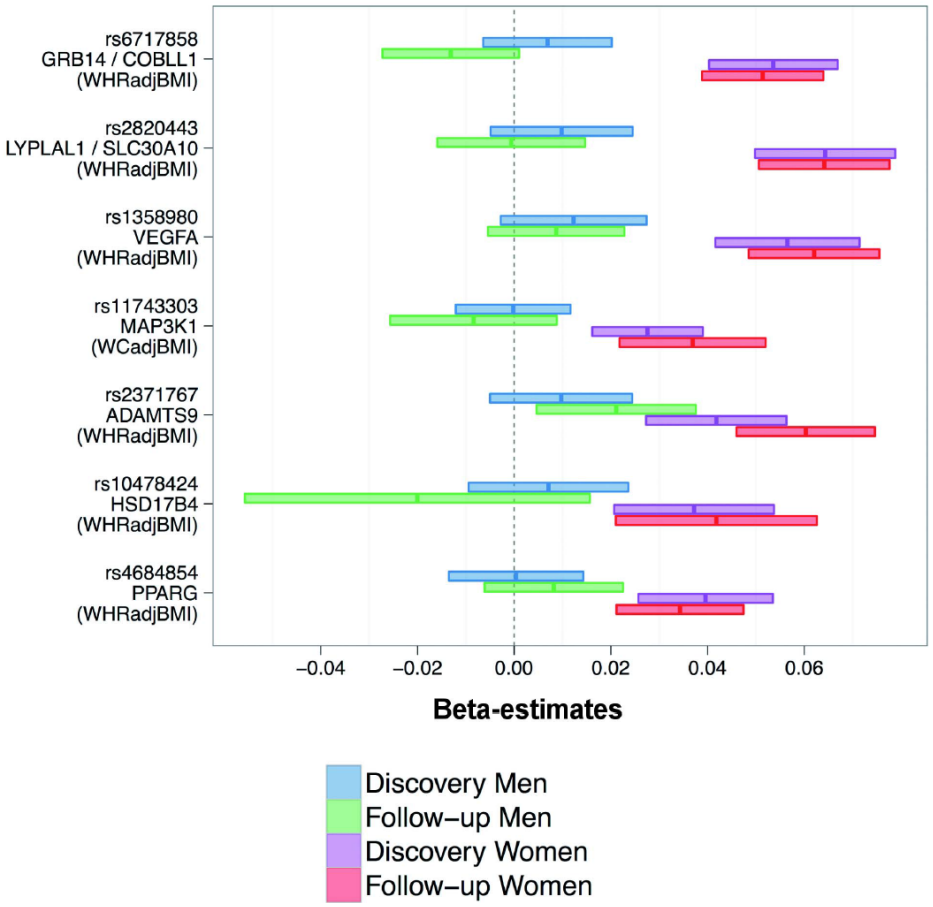
Including mean effects is analogous to including constituent terms in an interaction model

How can you have differences is variance?

- Independent variables (millions of them) can influence the trait to different extents in different groups

or

- Different independent variables can influence the trait in the different groups.



On all of the SNPs presented, women are affected by the polymorphism, while men are not.

Ergo, different genes "cause" the trait in males and females!
Or
Molecular evidence of qualitative sex limitation

OPEN ACCESS Freely available online

PLOS | GENETICS

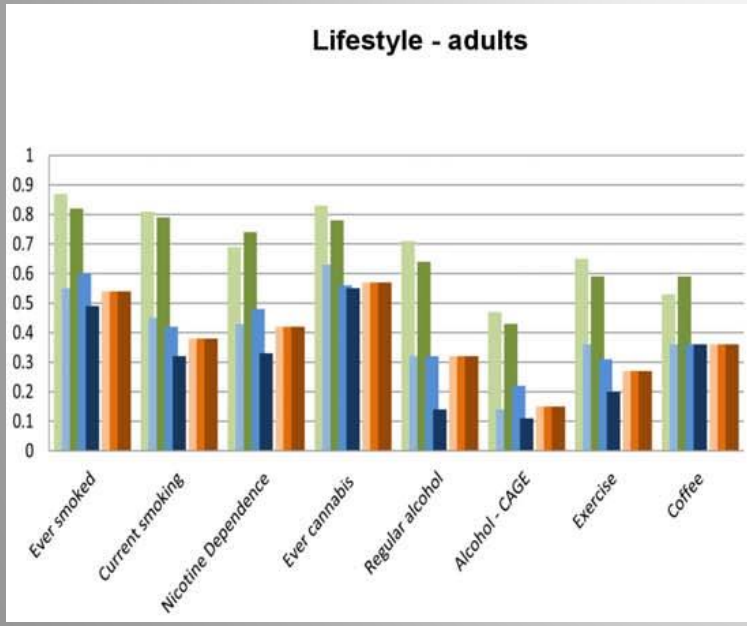
Sex-stratified Genome-wide Association Studies Including 270,000 Individuals Show Sexual Dimorphism in Genetic Loci for Anthropometric Traits

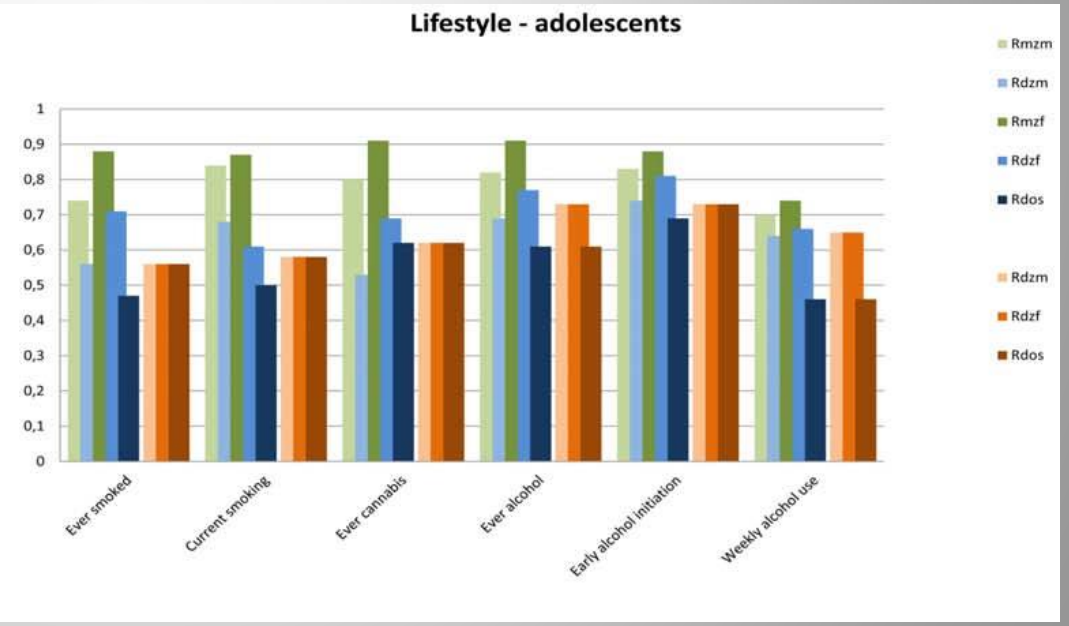
Joshua C. Randall[1,2☯], Thomas W. Winkler[3☯], Zoltán Kutalik[4,5☯], Sonja I. Berndt[6☯], Anne U. Jackson[7], Keri L. Monda[8], Tuomas O. Kilpeläinen[9], Tõnu Esko[10,11], Reedik Mägi[2,10], Shengxu Li[9,12], Tsegaselassie Workalemahu[13], Mary F. Feitosa[14], Damien C. Croteau-Chonka[15], Felix R. Day[9],

Sex Differences in Genetic Architecture of Complex Phenotypes?

Jacqueline M. Vink*, Meike Bartels, Toos C. E. M. van Beijsterveldt, Jenny van Dongen, Jenny H. D. A. van Beek, Marijn A. Distel, Marleen H. M. de Moor, Dirk J. A. Smit, Camelia C. Minica, Lannie Ligthart, Lot M. Geels, Abdel Abdellaoui, Christel M. Middeldorp, Jouke Jan Hottenga, Gonneke Willemsen, Eco J. C. de Geus, Dorret I. Boomsma

Netherlands Twin Register, Department of Biological Psychology, VU University Amsterdam, Amsterdam, The Netherlands





Heterogeneity Questions

- Univariate Analysis:
  - What are the contributions of additive genetic, dominance/shared environmental and unique environmental factors to the variance?
- Heterogeneity:
  - Are the contributions of genetic and environmental factors equal for different groups,
  - sex, race, ethnicity, SES, environmental exposure, etc.?

The language of heterogeneity

- Are these differences due to differences in the magnitude of the effects (quantitative)?
  - Is the contribution of genetic/environmental factors greater/smaller in males than in females?
- Are the differences due to differences in the nature of the effects (qualitative)?
  - Are there different genetic/environmental factors influencing the trait in males and females?

The language of heterogeneity

Quantitative

- differences in the magnitude of the effects

Models

- Scalar
- Non-scalar with OS twins

Qualitative

- differences in the source/nature of the effects

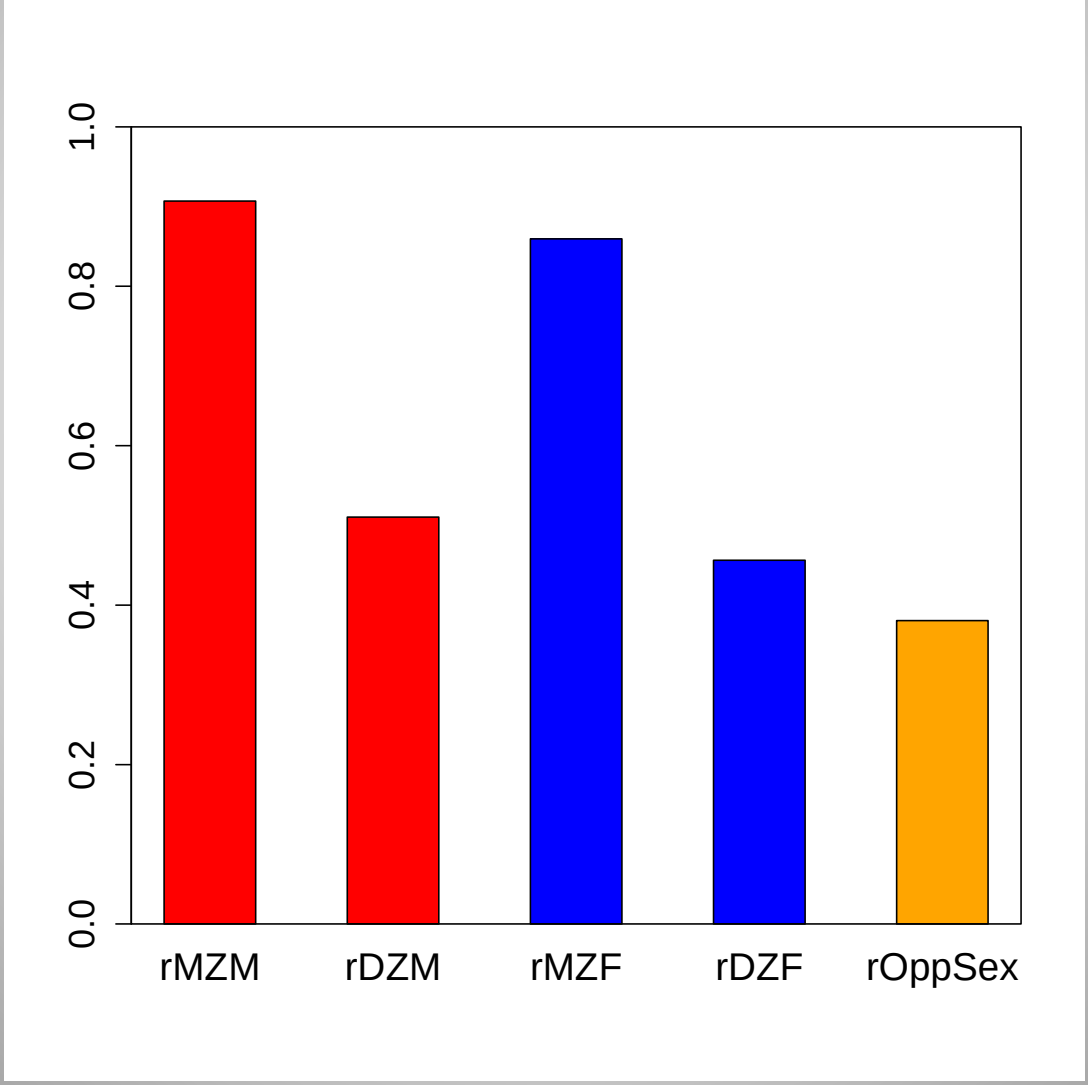
Models

- Non-scalar without OS twins
- General Non-scalar

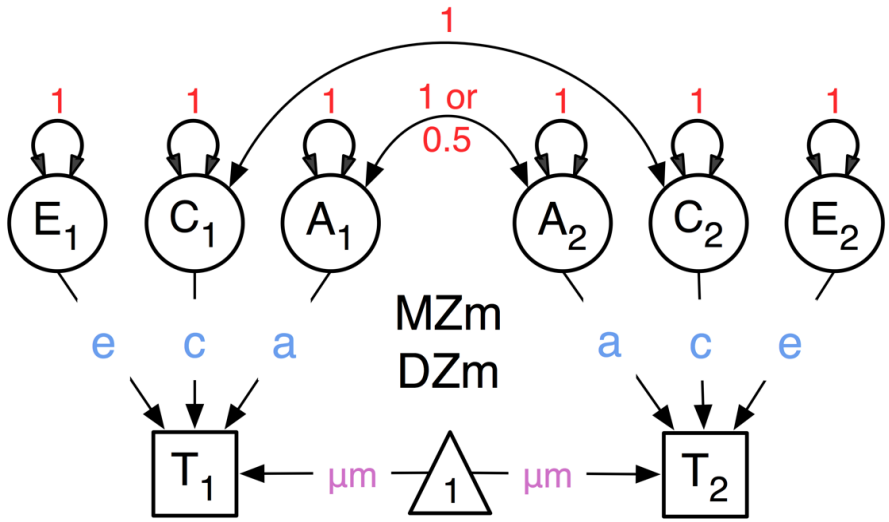
Potential (Genetic) Groups

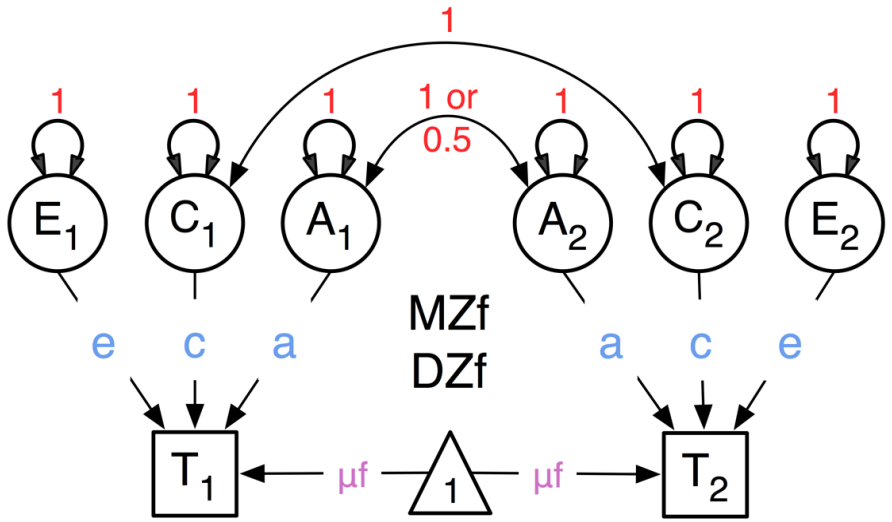
Comparison	Concordant for group membership	Discordant for group membership
Sex	MZ & DZ: MM & FF pairs	DZ: opposite sex pairs
Age	MZ & DZ: young & old pairs	
Nationality	MZ & DZ: OZ & US pairs	
Environment	MZ & DZ: urban & rural pairs	MZ & DZ: urban & rural pairs

Look at the Bloody Correlations!



Homogeneity Model





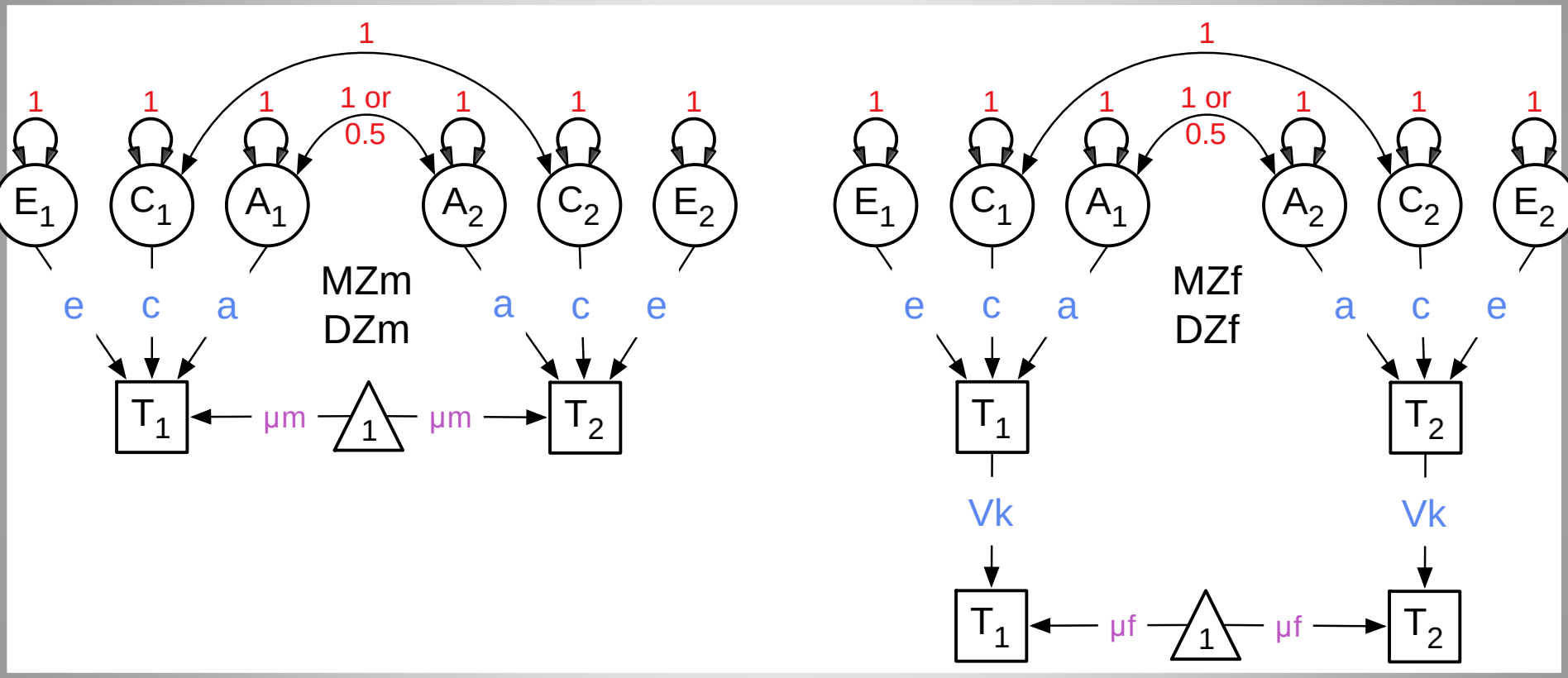
	Male	Male
Male	$a^2 + c^2 + e^2$	
Male	$.5a^2 + c^2$	$a^2 + c^2 + e^2$

	Female	Female
Female	$a^2 + c^2 + e^2$	
Female	$.5a^2 + c^2$	$a^2 + c^2 + e^2$

Homogeneity

- No heterogeneity
- The same proportion (%) of variance due to A, C, E equal between groups
- Total variance equal between groups
  - $V_m = V_f$
- Variance Components are equal between groups
  - $A_m = A_f$
  - $C_m = C_f$
  - $E_m = E_f$

Scalar Heterogeneity Model



	Male	Male
Male	$a^2 + c^2 + e^2$	
Male	$.5a^2 + c^2$	$a^2 + c^2 + e^2$

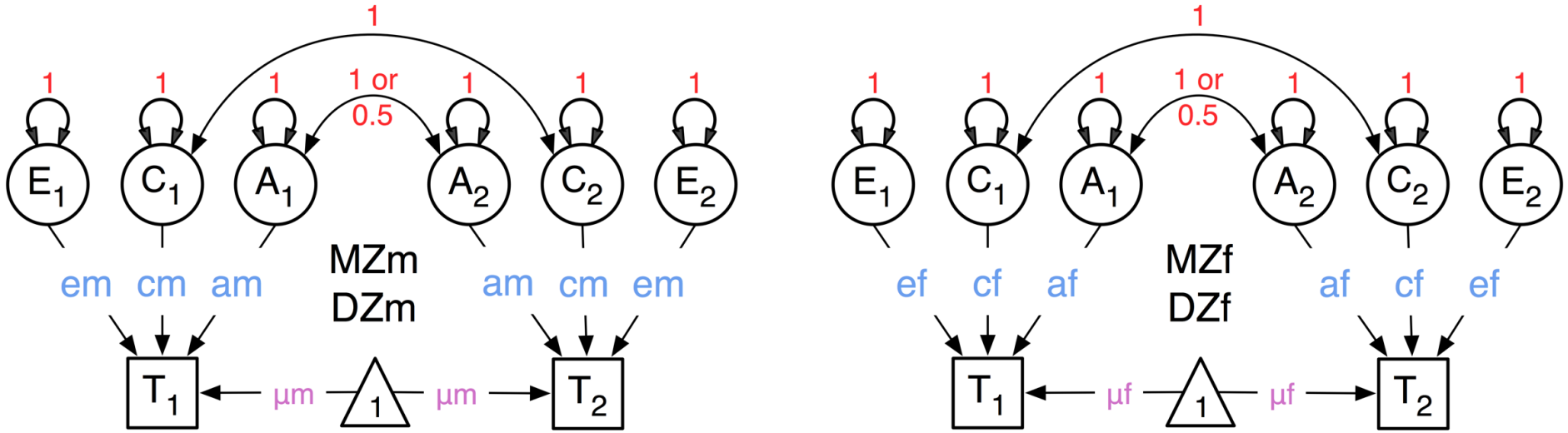
	Female	Female
Female	$k(a^2 + c^2 + e^2)$	$Vk(.5a^2 + c^2)$
Female	$Vk(.5a^2 + c^2)$	$k(a^2 + c^2 + e^2)$

Scalar Heterogeneity

- Scalar sex-limitation (Quantitative)
- The proportion (%) of variance due to A, C, E alters by a scalar (single value
- total variance not equal between groups
  - Vm = k* Vf
  - Am = k* Af
  - Cm = k* Cf
  - Em = k* Ef

k is scalar

Heterogeneity Model



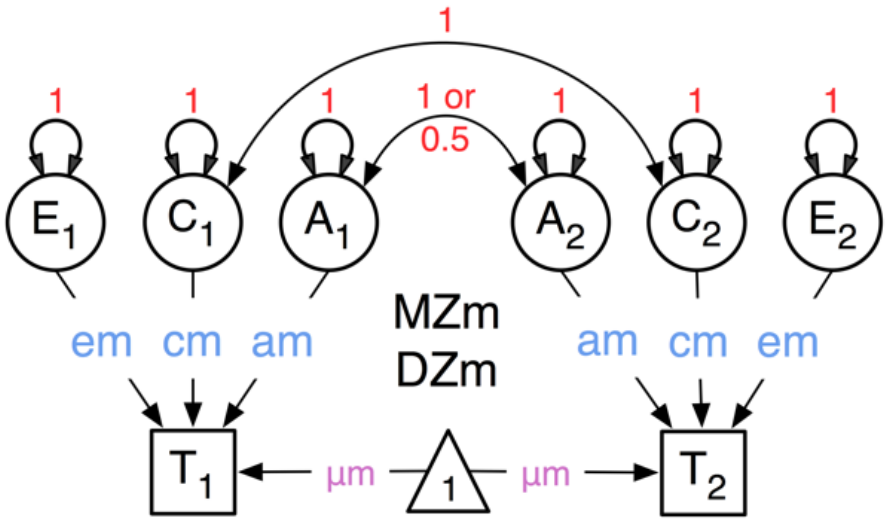
	Male	Male
Male	$a_m^2 + c_m^2 + e_m^2$	$.5a_m a'_m + c_m c'_m$
Male	$.5a_m a'_m + c_m c'_m$	$a_m^2 + c_m^2 + e_m^2$

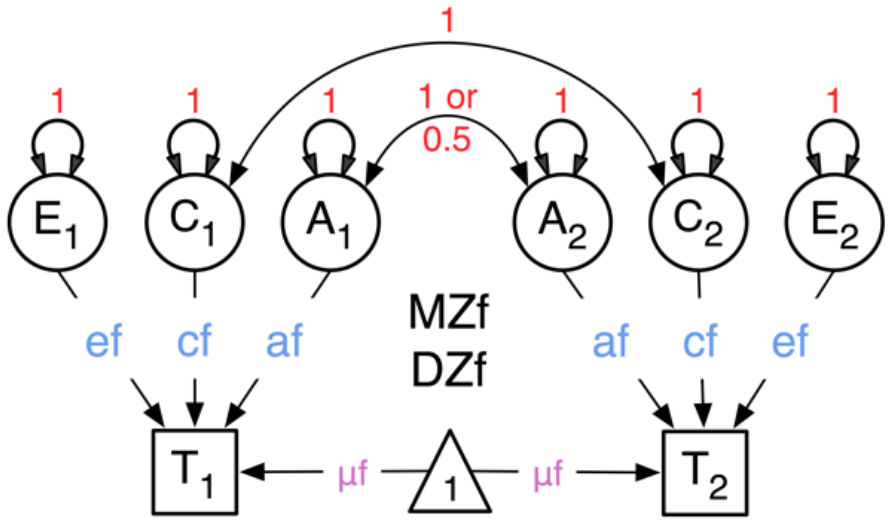
	Female	Female
Female	$a_f^2 + c_f^2 + e_f^2$	$.5a_f a'_f + c_f c'_f$
Female	$.5a_f a'_f + c_f c'_f$	$a_f^2 + c_f^2 + e_f^2$

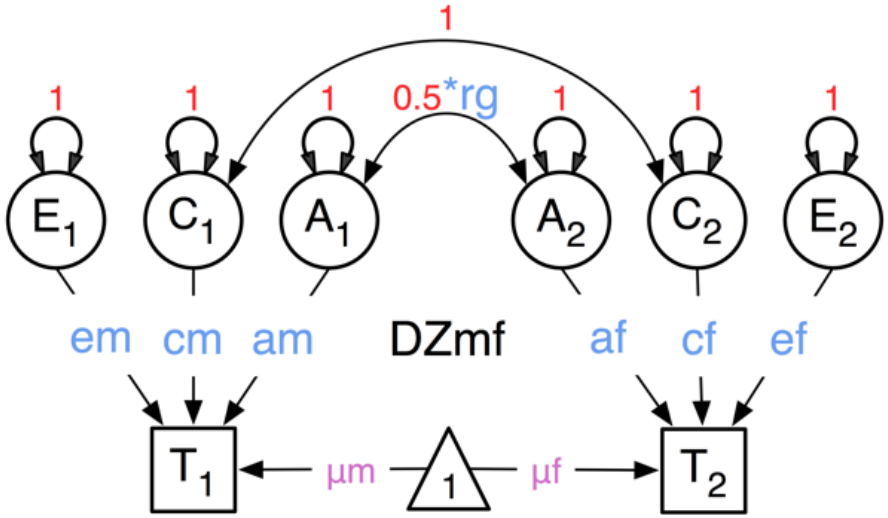
Non-Scalar Heterogeneity

- Non-Scalar sex-limitation, can be estimated without opposite sex pairs (Quantitative/Qualitative), but…
  - Reduced power
- The total variance and proportion (%) of variance due to A, C, E not equal between groups
  - Vm ≠ Vf
  - Am ≠ Af
  - Cm ≠ Cf
  - Em ≠ Ef

Parameters estimated separately







	M			Male	Female
Male	½	Female	Male	$a_m^2 + c_m^2 + e_m^2$	$.5r_g a_m a'_f + c_m c'_f$
Male	½	Female	Female	$.5r_g a_f a'_m + c_f c'_m$	$a_f^2 + c_f^2 + e_f^2$

General Heterogeneity

- Non-Scalar sex-limitation with opposite sex pairs (Quantitative & Qualitative)
- The total variance and proportion (%) of variance due to A, C, E is not equal between groups
  - Vm ≠ Vf
  - Am ≠ Af
  - Cm ≠ Cf
  - Em ≠ Ef

Parameters estimated jointly, linked via opposite sex correlations
r(Am,Af)=.5; r(Cm,Cf)=1, r(Em,Ef)=0

What twin groups are needed for each Sex Limitation Model

Model Type	Data Requirements
Classical Twin Design	MZ & DZ Twins (Sex doesn't matter)
Scalar Sex Limitation Model (Quantitative/Qualitative)	MZm, MZf, DZm & DZf Twins
General Sex Limitation Model (Qualitative & Quantitative)	MZm, MZf, DZm, DZf & DZo Twins

Qualitative Sex Limitation: Notes of Caution and Friendly Suggestions

- Collect data of Opposite Sex Twins.
  - The power to detect qualitative sex differences is relatively low, but it might be important for your trait
- If you find qualitative sex differences, STOP!
  - It is incredibly difficult to make heads or tails of quantitative sex differences in the presence of qualitative sex differences