Sex-limitation Models

Meike Bartels

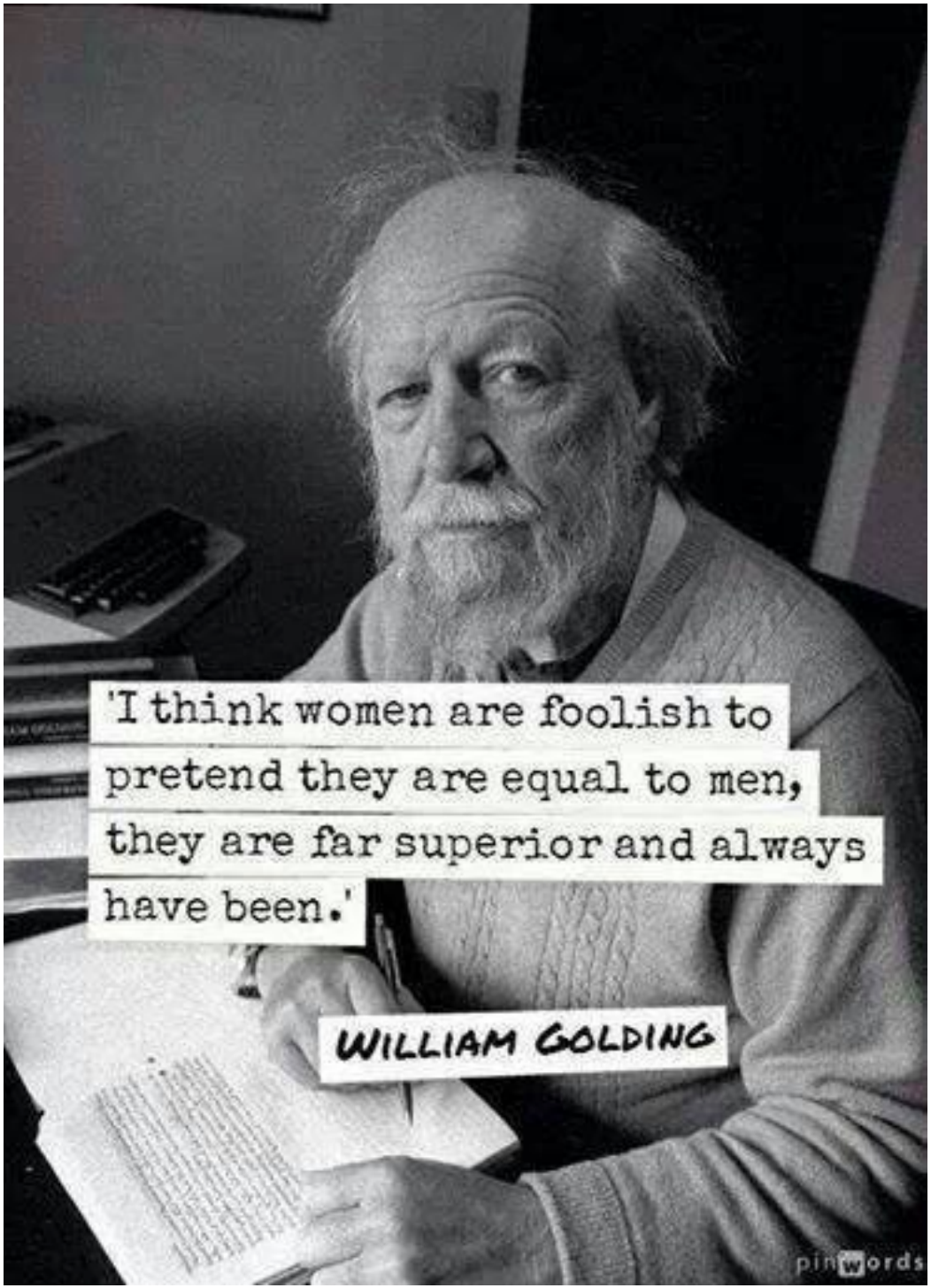
(Brad, Sarah, Hermine, Ben, Elizabeth, and most of the rest of the faculty that has contributed bits and pieces to various versions of this talk)

COPY FILES FROM:

Faculty/meike/2016/heterogeneity

single focus

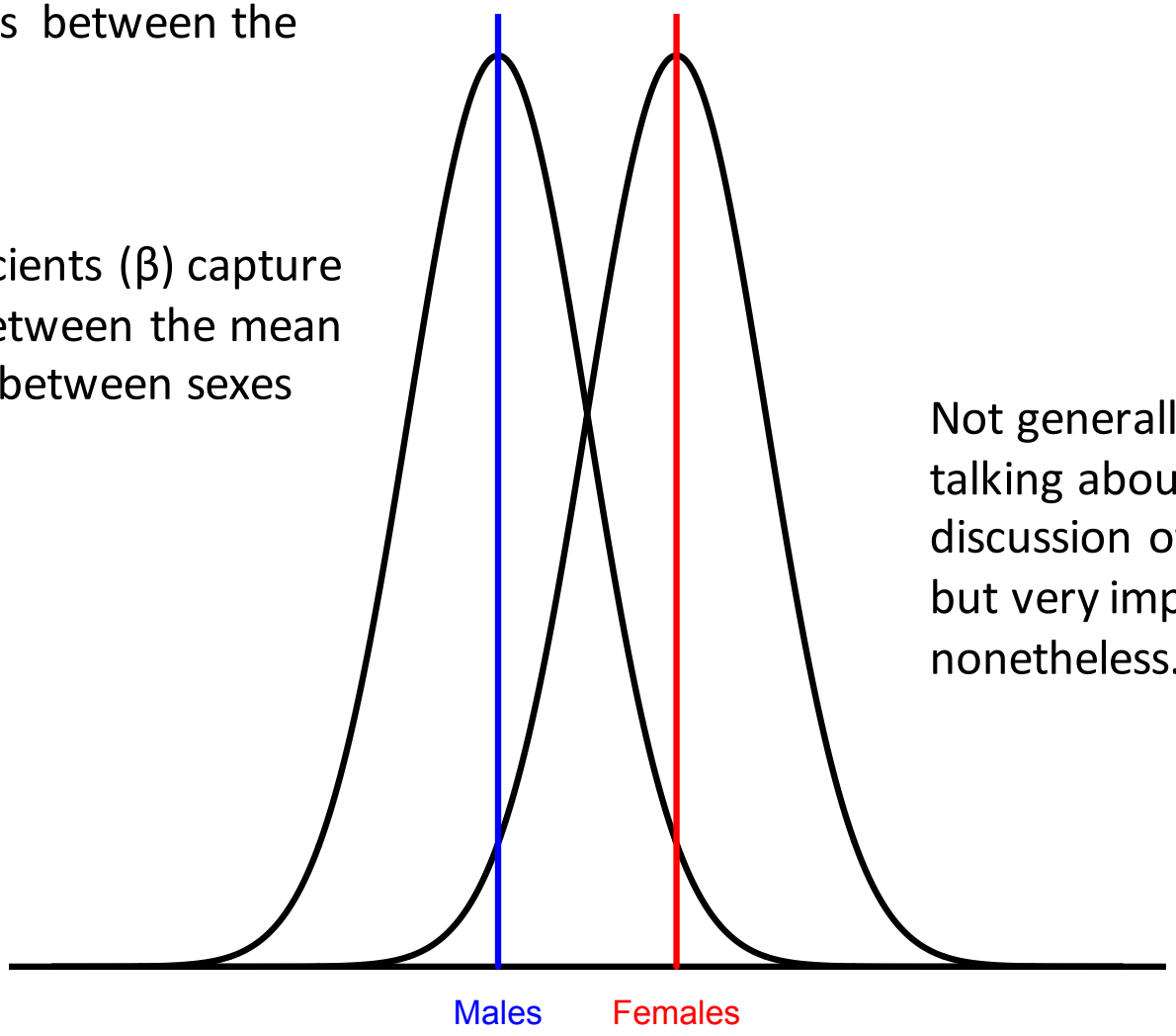
multitasking


'I think women are foolish to pretend they are equal to men, they are far superior and always have been.'
WILLIAM GOLDING
pinwords

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

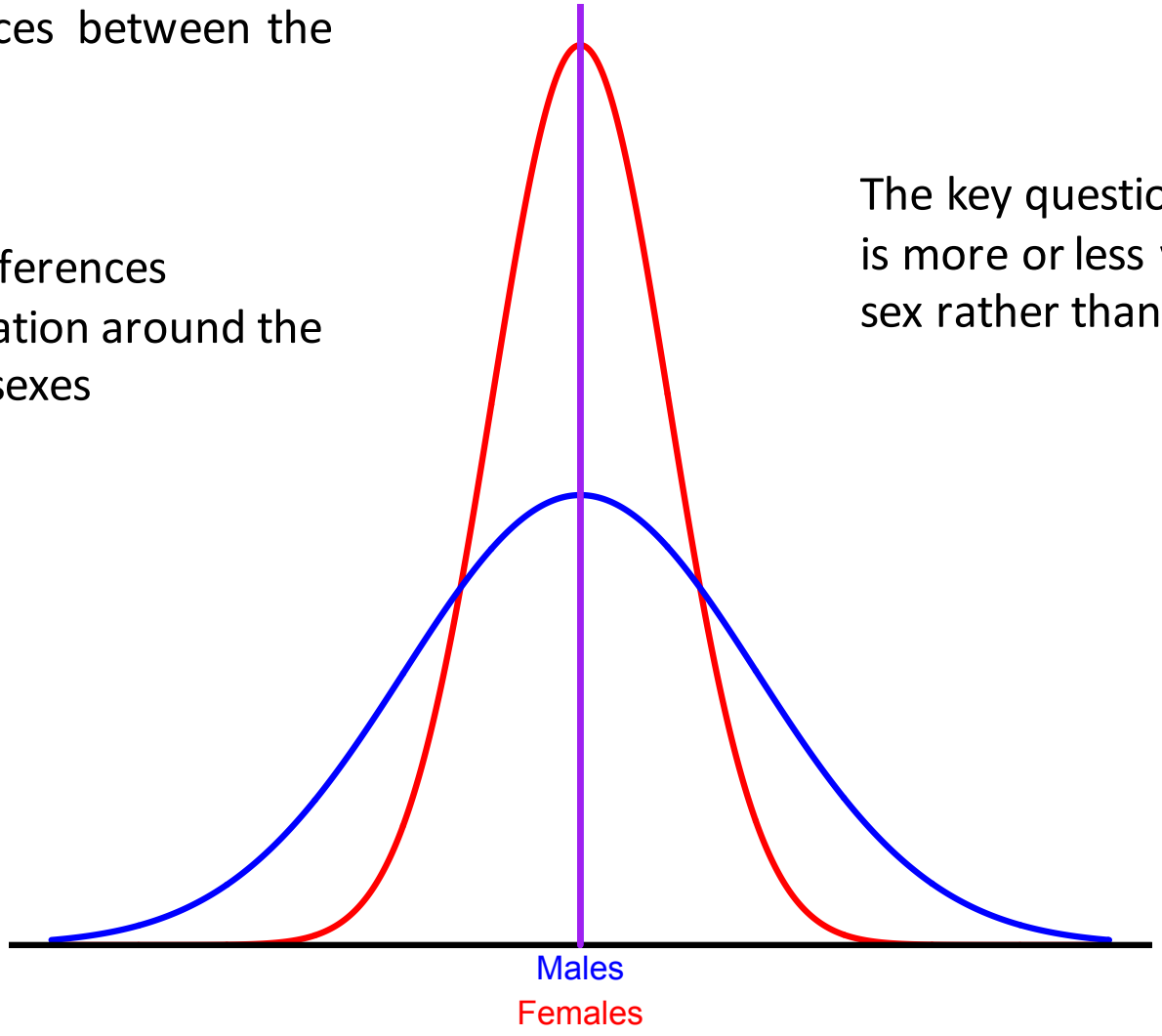


Not generally what we are talking about when discussion of Sex limitation, but very important nonetheless.

Two primary differences between Males and Females.

Variance Differences between the sexes

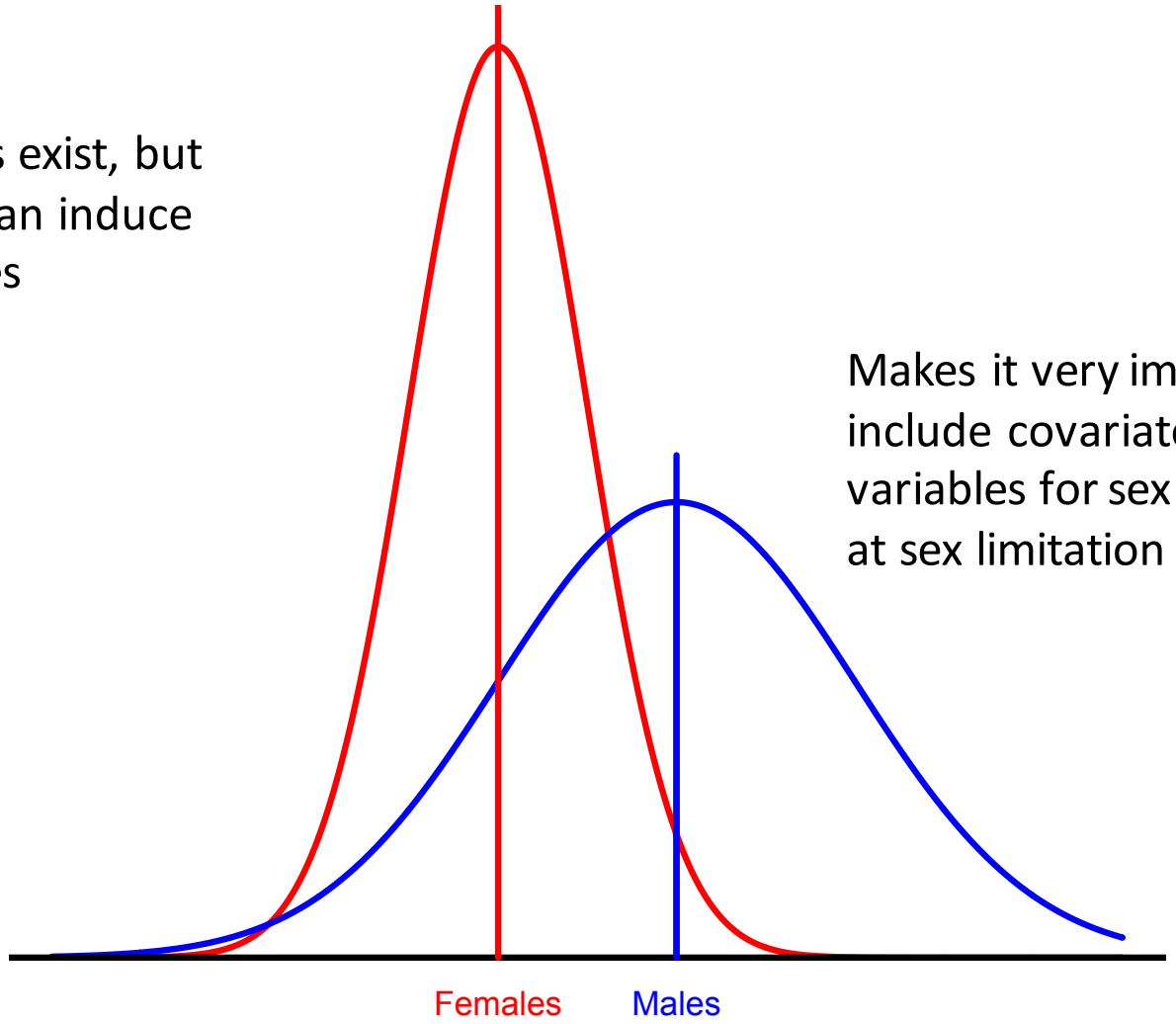
σ^2 capture the differences between the variation around the mean across the sexes



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

How can you have differences in variance?

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

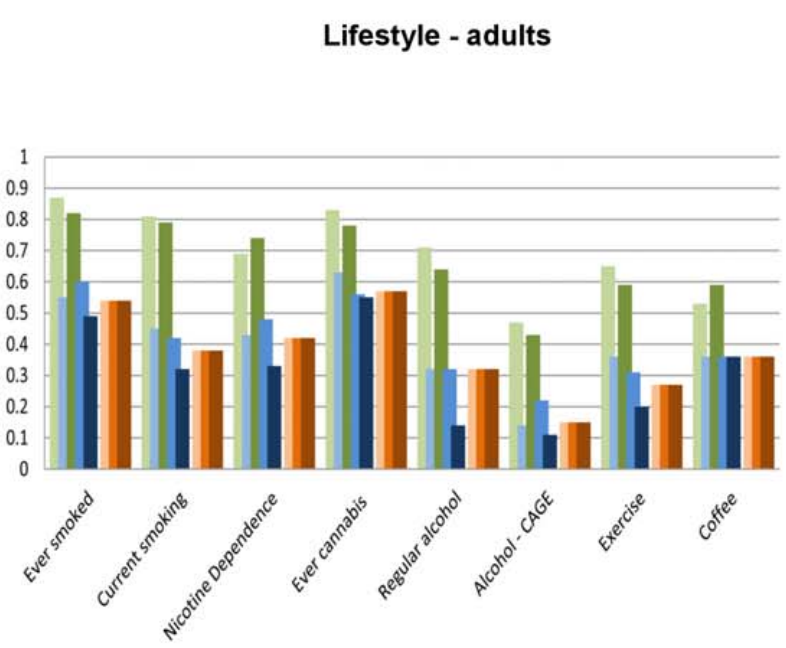
or

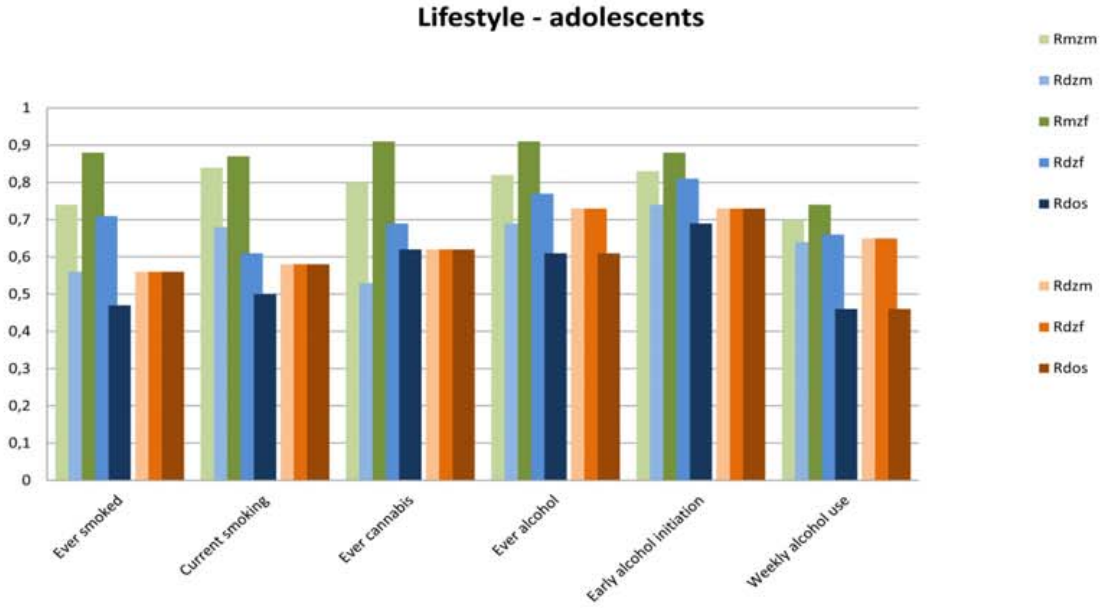
- Different independent variables can influence the trait in the different groups.

Sex Differences in Genetic Architecture of Complex Phenotypes?

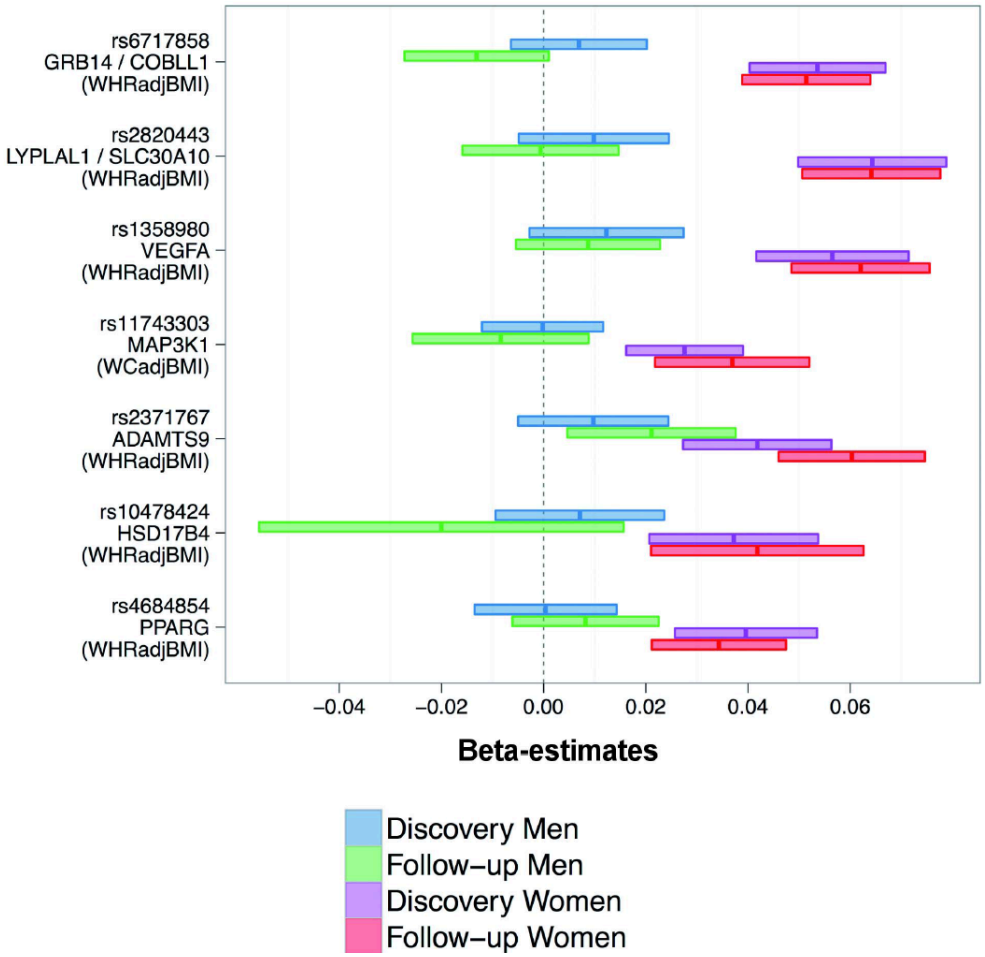
Jacqueline M. Vink*, Meike Bartels, Toos C. E. M. van Beijsterveldt, Jenny van Dongen, Jenny H. D. A. van Beek, Marijn A. Distel, Marleen H. M. de Moor, Dirk J. A. Smit, Camelia C. Minica, Lannie Ligthart, Lot M. Geels, Abdel Abdellaoui, Christel M. Middeldorp, Jouke Jan Hottenga, Gonneke Willemsen,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

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





www.tweelingenregister.org



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],

Genetic Associations with Subjective Well-Being Also Implicate Depression and Neuroticism

ABSTRACT: We conducted genome-wide association studies of three phenotypes: subjective well-being (SWB; *N* = 298,420), depressive symptoms (DS; *N* = 161,460), and neuroticism (*N* = 170,910). We identified three variants associated with SWB, two with DS, and eleven with neuroticism, including two inversion polymorphisms. The two DS loci replicate in an independent depression sample. Joint analyses that exploit the high genetic correlations between the phenotypes ($|\widehat{\rho}| \approx 0.8$) strengthen the overall credibility of the findings, and allow us to identify additional variants. Across our phenotypes, loci regulating expression in central nervous system and adrenal/pancreas tissues are strongly enriched for association.

Nature Genetics, accepted

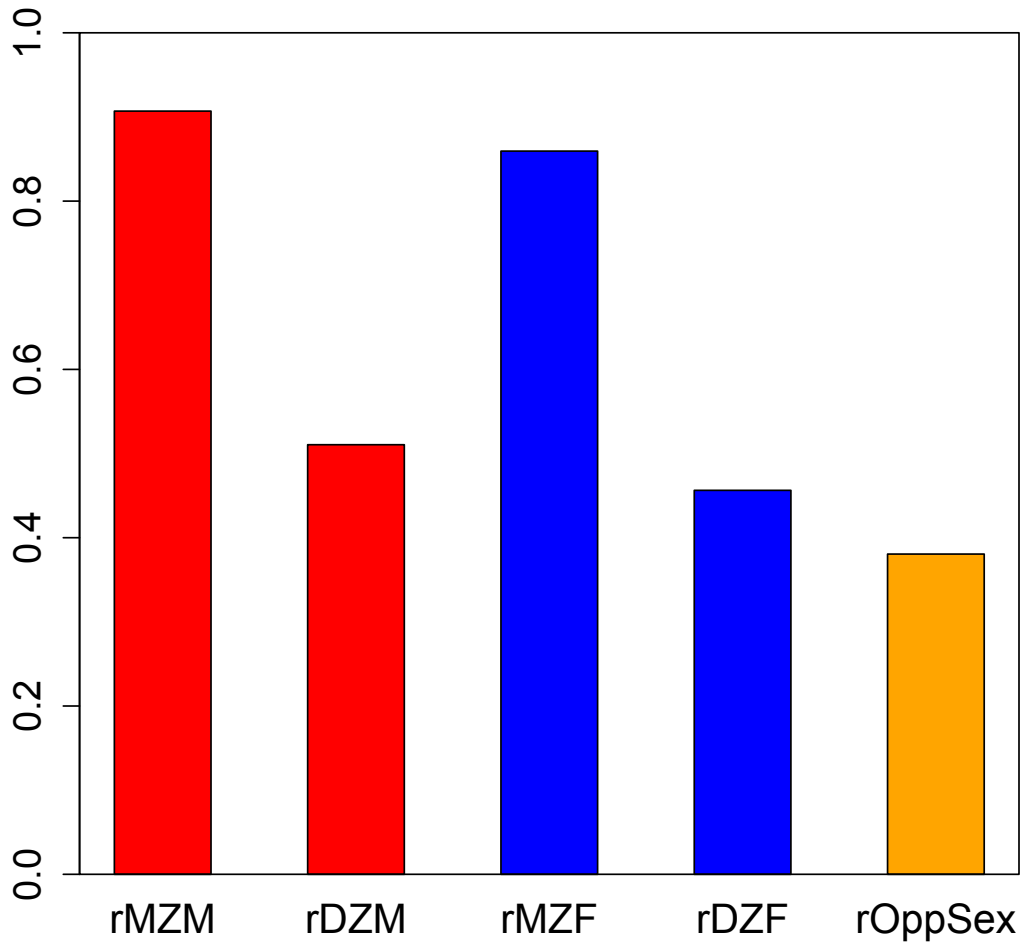
Heterogeneity Questions

- 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.?

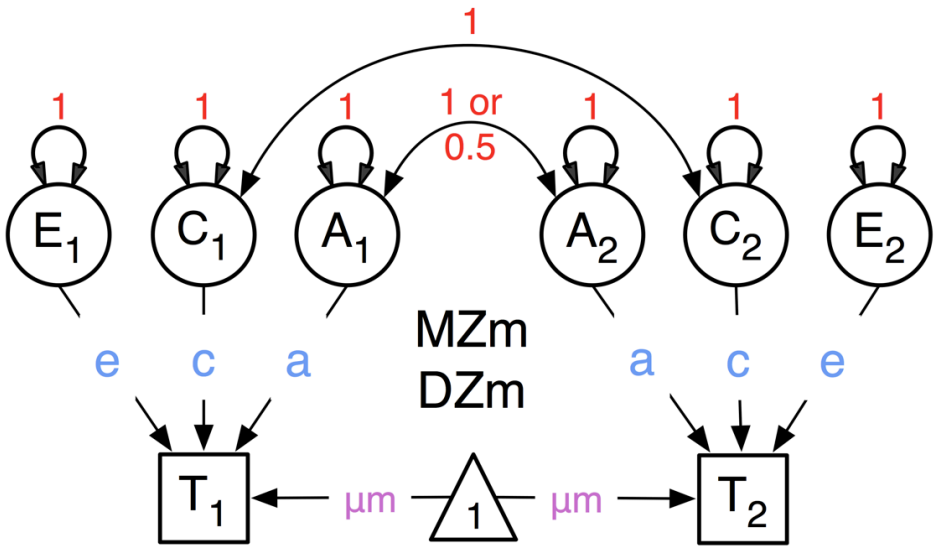
The language of heterogeneity

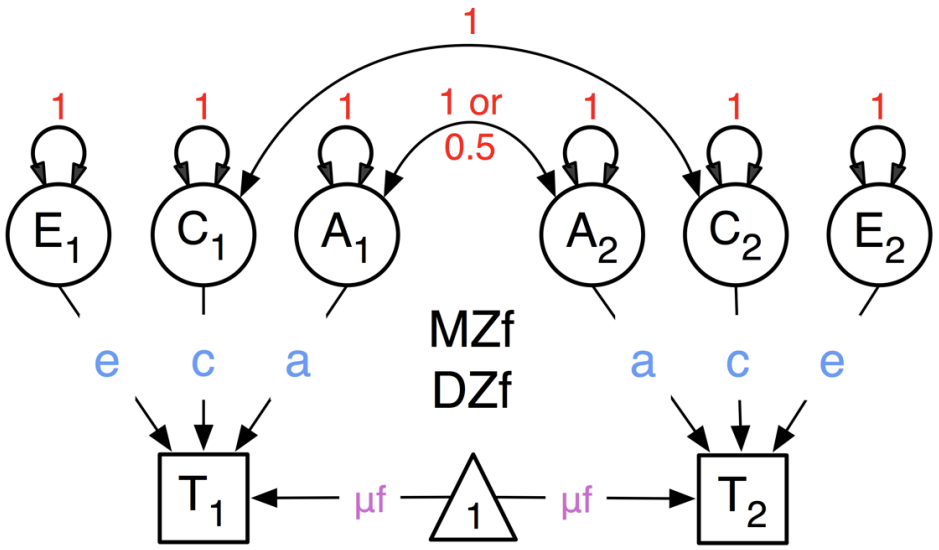
- Are these differences due to differences in the magnitude of the effects (quantitative)?
  - Is the contribution of genetic/environmental factors greater/smaller in males than in females?
- Are the differences due to differences in the nature of the effects (qualitative)?
  - Are there different genetic/environmental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

Look at the Correlations!



Homogeneity Model





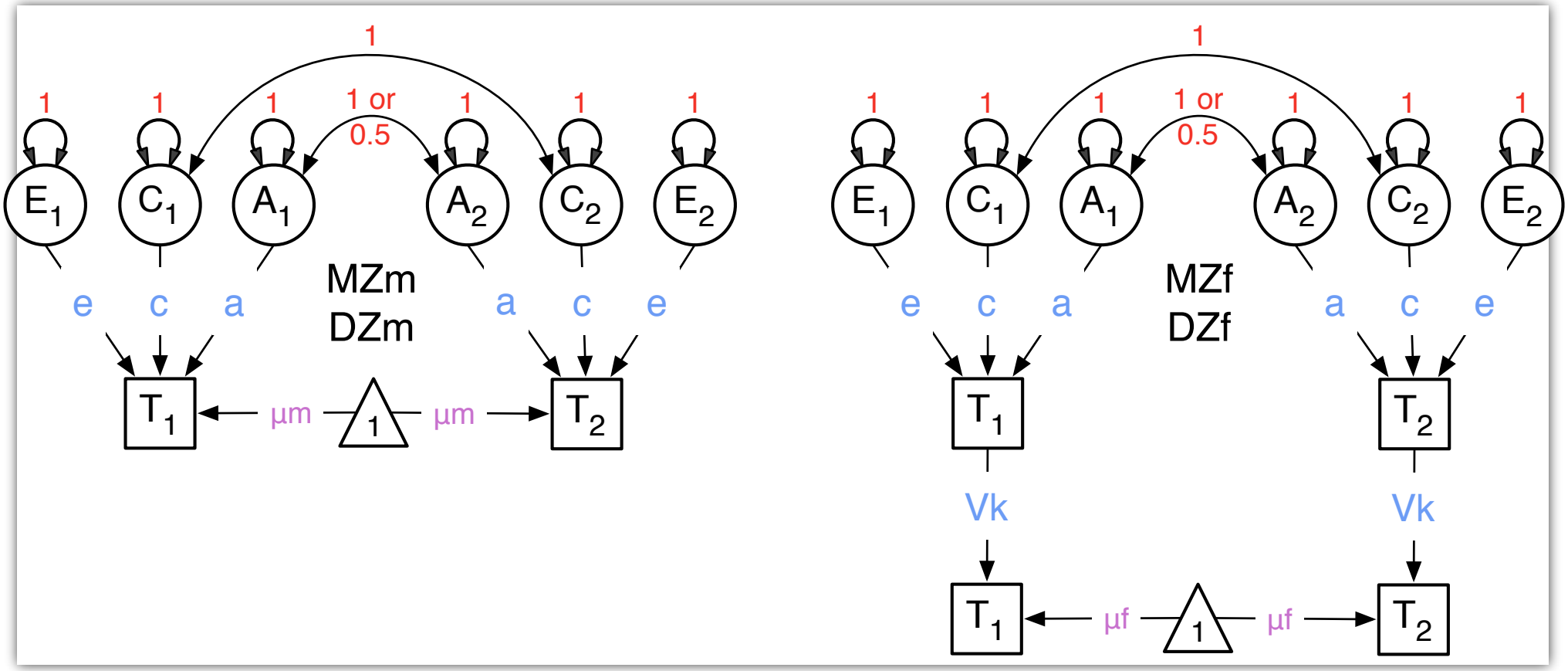
	Male	Male
Male	$a^2 + c^2 + e^2$	
Male	$.5a^2 + c^2$	$a^2 + c^2 + e^2$

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

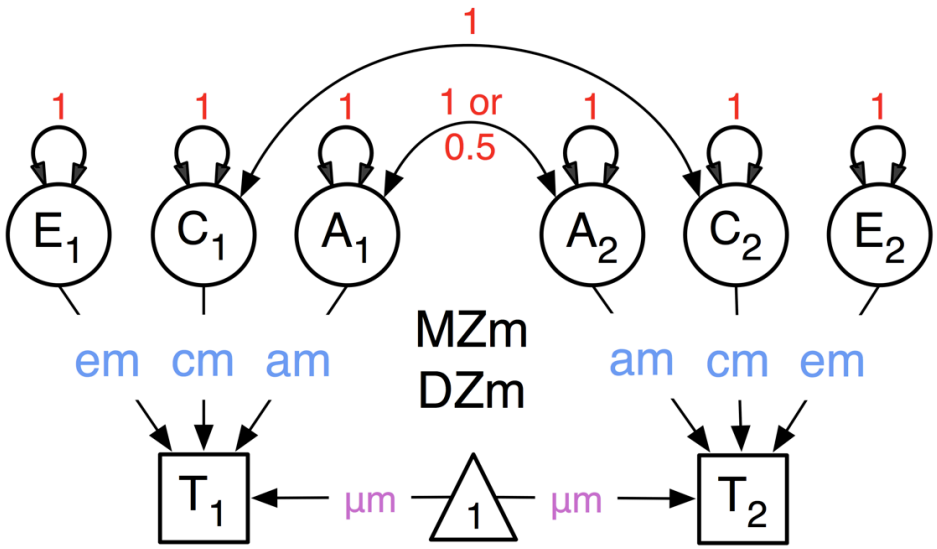
	Female	Female
Female	$k(a^2 + c^2 + e^2)$	$Vk(.5a^2 + c^2)$
Female	$Vk(.5a^2 + c^2)$	$k(a^2 + c^2 + e^2)$

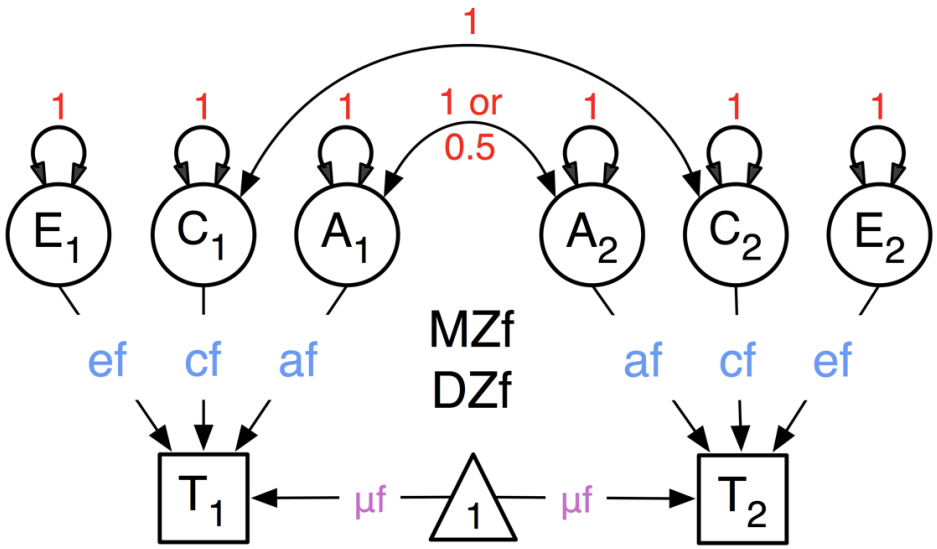
Scalar Heterogeneity

- 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





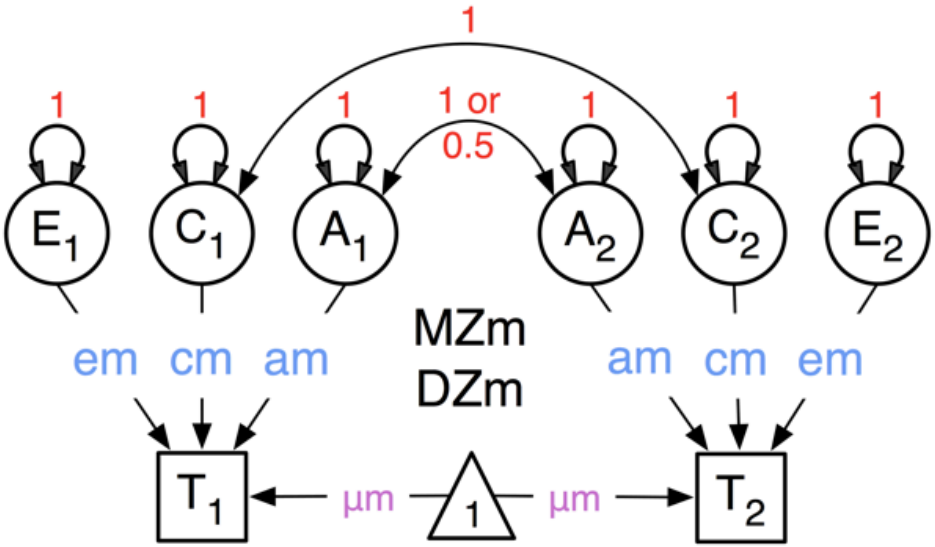
	Male	Male
Male	$a_m^2 + c_m^2 + e_m^2$	$.5a_m a'_m + c_m c'_m$
Male	$.5a_m a'_m + c_m c'_m$	$a_m^2 + c_m^2 + e_m^2$

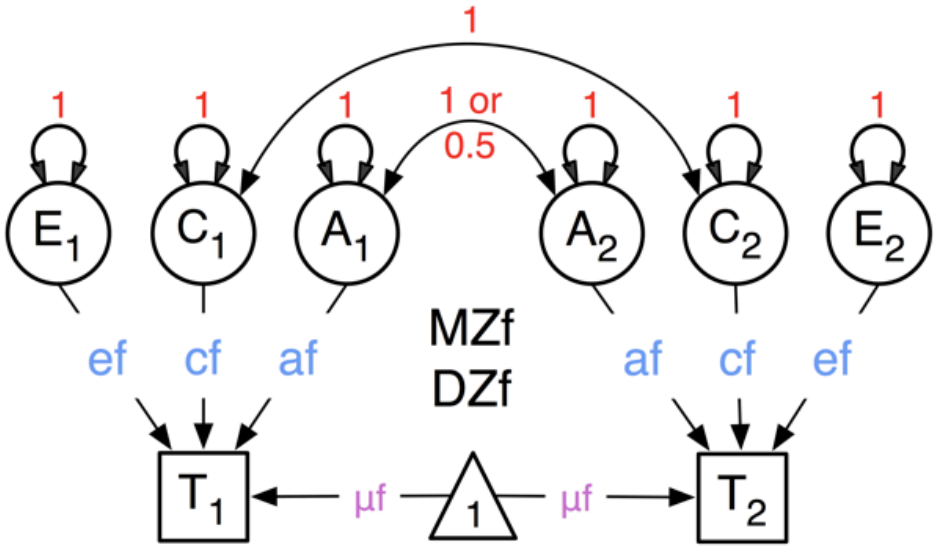
	Female	Female
Female	$a_f^2 + c_f^2 + e_f^2$	$.5a_f a'_f + c_f c'_f$
Female	$.5a_f a'_f + c_f c'_f$	$a_f^2 + c_f^2 + e_f^2$

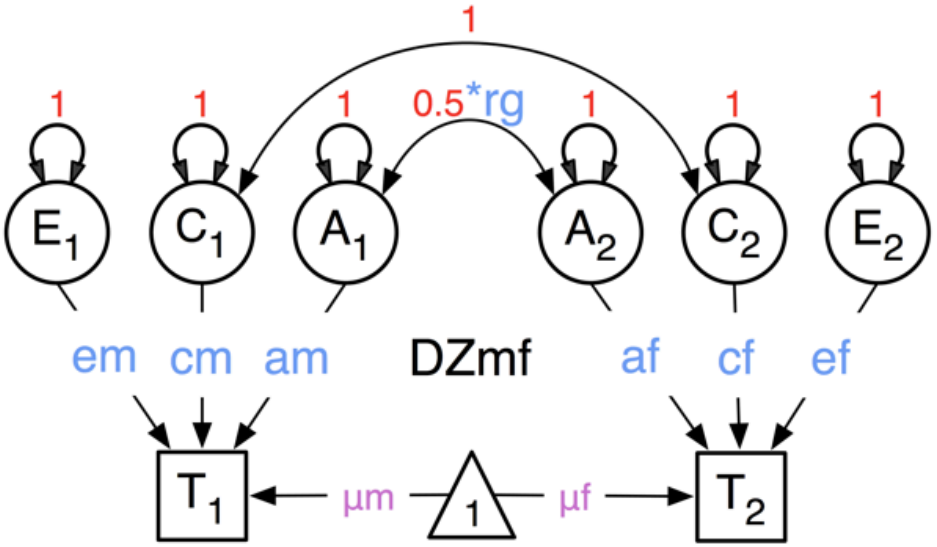
Non-Scalar Heterogeneity

- 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

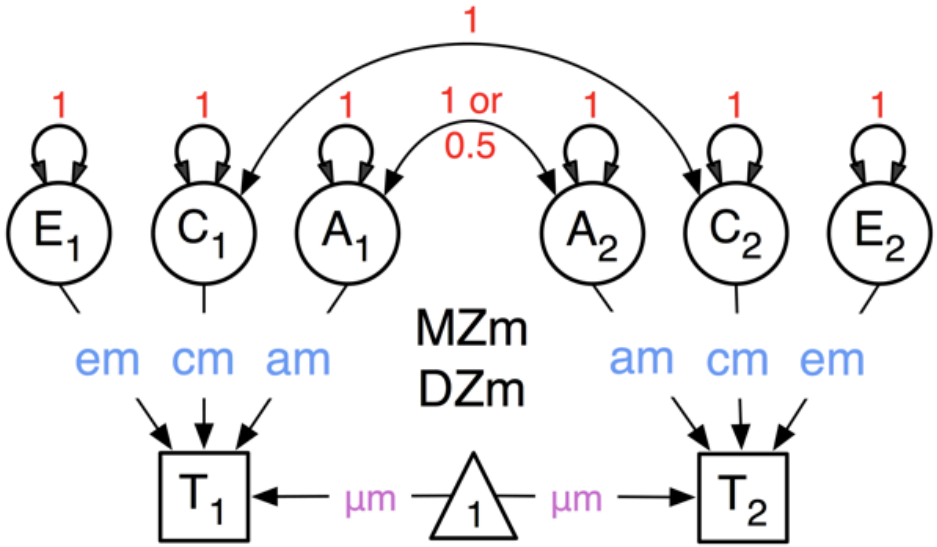
Parameters estimated separately

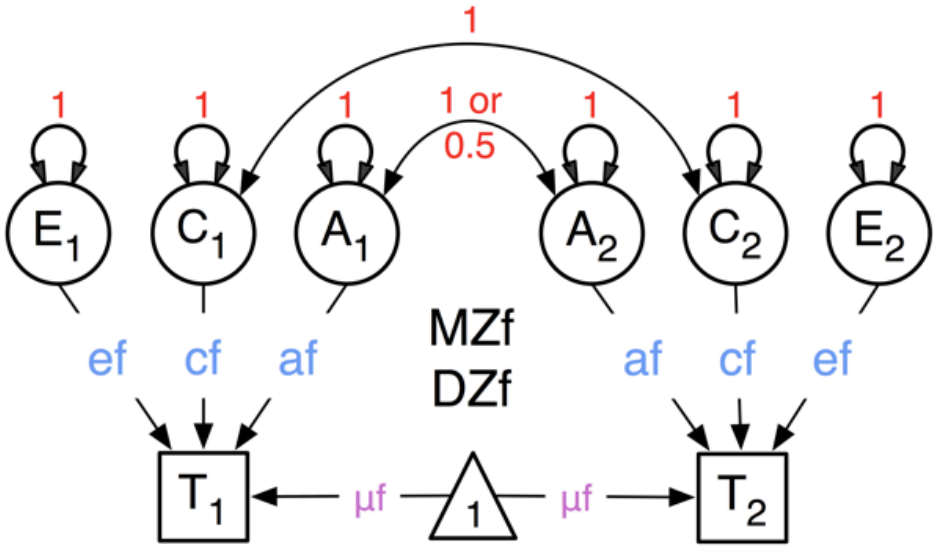


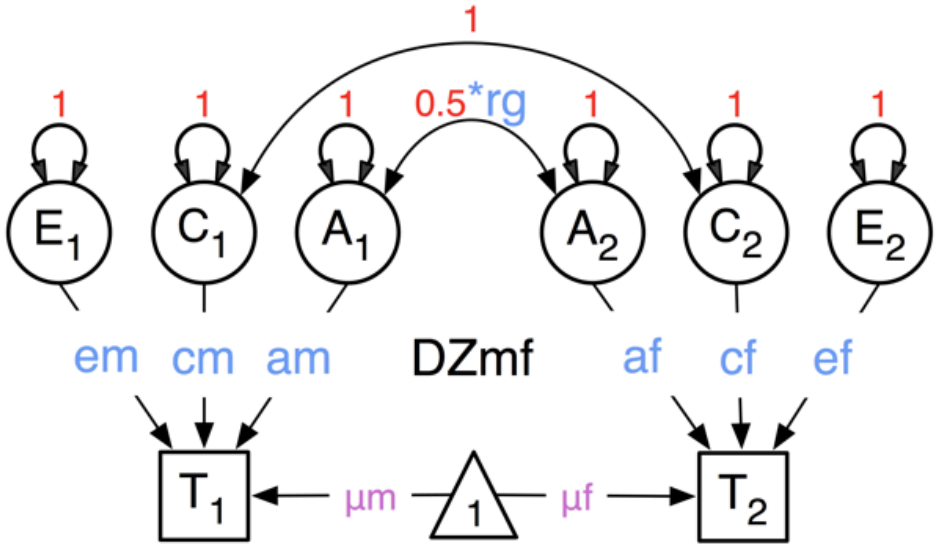




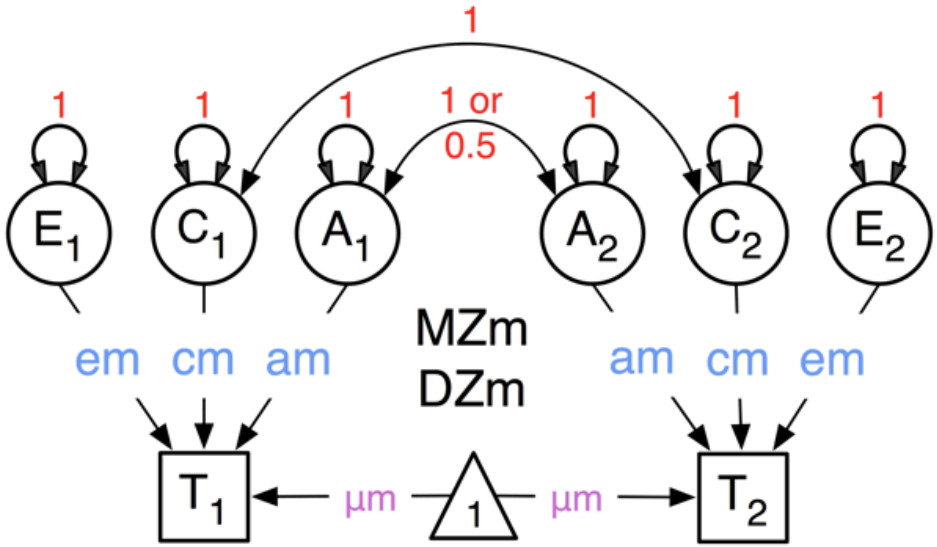
	Male	Male
Male	½ $a_m^2 + c_m^2 + e_m^2$	½ $a_m^2 + c_m^2$
Male	½ $a_m^2 + c_m^2$	½ $a_m^2 + c_m^2 + e_m^2$

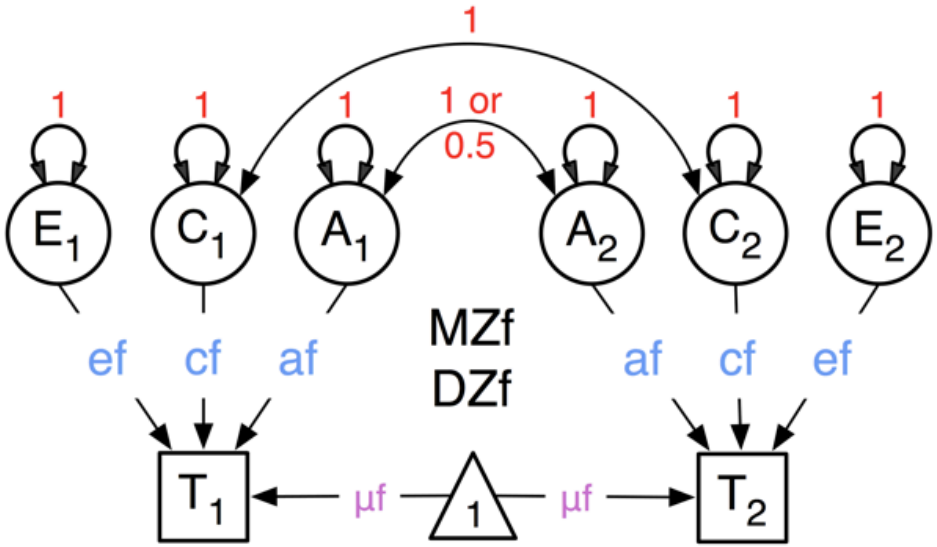


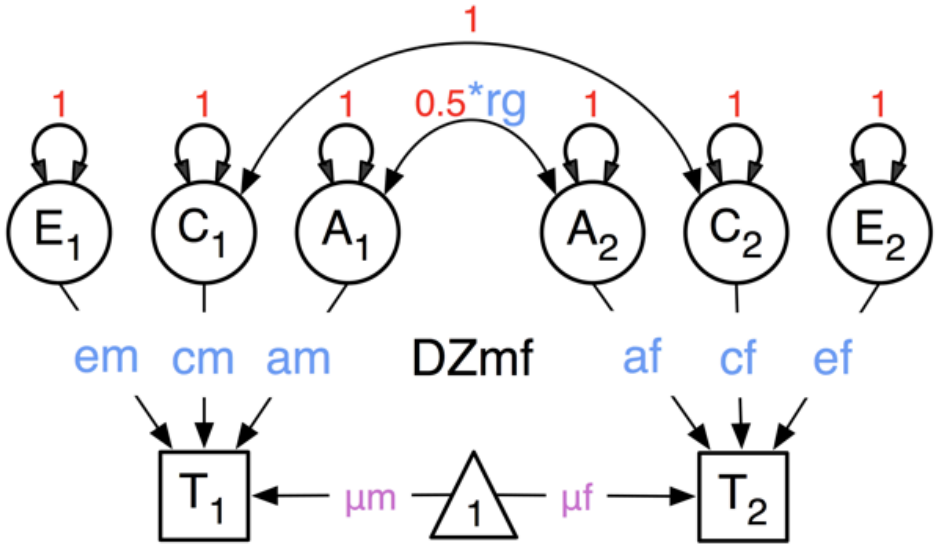




	Female	Female
Female	$a_f^2 + c_f^2 + e_f^2$	$.5a_fa'_f + c_fc'_f$
Female	$.5a_fa'_f + c_fc'_f$	$a_f^2 + c_f^2 + e_f^2$







	Male	Female
Male	$a_m^2 + c_m^2 + e_m^2$	$.5r_g a_m a'_f + c_m c'_f$
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

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

Practical

1. Open oneADE5ca_MB.R
2. Walk trough the first part of the script
3. Run it
4. Look at you estimates
5. Run submodels
6. Be sure that you know what you are doing

scriptsOpenMx.shtml

VCU		OpenMx Scripts				
2 groups	Continuous	Binary	Ordinal	Mean/Variance Ordinal	Joint	
Univariate Monophenotype	oneSATc oneACEc oneADEc	oneSATb oneACEb oneADEb	oneSATo oneACEo oneADEo	oneSATm oneACEm oneADEm		miFunctions
Bivariate DiPhenotype	twoSATc twoACEc twoADEc	twoSATb twoACEb twoADEb	twoSATo twoACEo twoADEo	twoSATm twoACEm twoADEm	twoSATj twoACEj twoADEj	
with Age Covariate	Continuous	Binary	Ordinal	Mean/Variance Ordinal	Joint	
Univariate Monophenotype	oneSATca oneACEca oneADEca	oneSATba oneACEba oneADEba	oneSAToa oneACEoa oneADEoa	oneSATma oneACEma oneADEma		
Bivariate DiPhenotype	twoSATca twoACEca twoADEca	twoSATba twoACEba twoADEba	twoSAToa twoACEoa twoADEoa	twoSATma twoACEma twoADEma	twoSATja twoACEja twoADEja	
5 groups	Continuous	Binary	Ordinal	Mean/Variance Ordinal	Joint	
Univariate Monophenotype	oneSAT5ca oneACE5ca oneADE5ca	oneSAT5ba oneACE5ba oneADE5ba	oneSAT5oa oneACE5oa oneADE5oa	oneSAT5ma oneACE5ma oneADE5ma		OpenMx Site hmaes@vcu.edu

MEAN DIFFERENCES

```
# Saturated Model
# Create Matrices for Covariates and linear Regression Coefficients
defAge    <- mxMatrix( type="Full", nrow=1, ncol=1, free=FALSE, labels=c("data.age"), name="Age" )
pathBf    <- mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, values=.01, label="bf11", name="bf" )
pathBm    <- mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, values=.01, label="bm11", name="bm" )

# Create Algebra for expected Mean Matrices
meanGf    <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svMe, labels=labMeZf, name="meanGf" )
meanGm    <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svMe, labels=labMeZm, name="meanGm" )
meanGo    <- mxMatrix( type="Full", nrow=1, ncol=ntv, free=TRUE, values=svMe, labels=labMeZo, name="meanGo" )
expMeanZf <- mxAlgebra( expression= meanGf + cbind(bf%*%Age,bf%*%Age), name="expMeanZf" )
expMeanZm <- mxAlgebra( expression= meanGm + cbind(bm%*%Age,bm%*%Age), name="expMeanZm" )
expMeanZo <- mxAlgebra( expression= meanGo + cbind(bf%*%Age,bm%*%Age), name="expMeanZo" )
```

Quantitative Sex-Differences

```
# Create Matrices for Path Coefficients
pathAf    <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=svPa, label="af11", lbound=lbPa, name="af" )
pathDf    <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=svPd, label="df11", lbound=lbPa, name="df" )
pathEf    <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=svPe, label="ef11", lbound=lbPa, name="ef" )
pathAm    <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=svPd, label="am11", lbound=lbPa, name="am" )
pathDm    <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=svPa, label="dm11", lbound=lbPa, name="dm" )
pathEm    <- mxMatrix( type="Lower", nrow=nv, ncol=nv, free=TRUE, values=svPe, label="em11", lbound=lbPa, name="em" )
pathRg    <- mxMatrix( type="Full", nrow=1, ncol=1, free=TRUE, values=1, label="rg11", lbound=0, ubound=1, name="rg" )

# Create Algebra for Variance Components
covAf     <- mxAlgebra( expression=af %*% t(af), name="Af" )
covDf     <- mxAlgebra( expression=df %*% t(df), name="Df" )
covEf     <- mxAlgebra( expression=ef %*% t(ef), name="Ef" )
covAm     <- mxAlgebra( expression=am %*% t(am), name="Am" )
covDm     <- mxAlgebra( expression=dm %*% t(dm), name="Dm" )
covEm     <- mxAlgebra( expression=em %*% t(em), name="Em" )
```

Quantitative Sex-Differences

```
# Create Algebra for expected Variance/Covariance Matrices in MZ & DZ twins
covPf     <- mxAlgebra( expression= Af+Df+Ef, name="Vf" )
covPm     <- mxAlgebra( expression= Am+Dm+Em, name="Vm" )
covMZf    <- mxAlgebra( expression= Af+Df, name="cMZf" )
covDZf    <- mxAlgebra( expression= 0.5%x%Af+ Df, name="cDZf" )
covMZm    <- mxAlgebra( expression= Am+Dm, name="cMZm" )
covDZm    <- mxAlgebra( expression= 0.5%x%Am+ Dm, name="cDZm" )
```

Qualitative Sex-Differences

```
covDZfm   <- mxAlgebra( expression= 0.5%*%rg%x%(af%*%t(am))+df%*%t(dm), name="covDZfm" )
covDZmf   <- mxAlgebra( expression= 0.5%*%rg%x%(am%*%t(af))+dm%*%t(df), name="covDZmf" )
expCovMZf <- mxAlgebra( expression= rbind( cbind(Vf, cMZf), cbind(t(cMZf), Vf)), name="expCovMZf" )
expCovDZf <- mxAlgebra( expression= rbind( cbind(Vf, cDZf), cbind(t(cDZf), Vf)), name="expCovDZf" )
expCovMZm <- mxAlgebra( expression= rbind( cbind(Vm, cMZm), cbind(t(cMZm), Vm)), name="expCovMZm" )
expCovDZm <- mxAlgebra( expression= rbind( cbind(Vm, cDZm), cbind(t(cDZm), Vm)), name="expCovDZm" )
expCovDZo <- mxAlgebra( expression= rbind( cbind(Vf, covDZfm), cbind(covDZmf, Vm)), name="expCovDZo" )
```

Full models and Submodels

	ep	-2LL	df	AIC	dif -2LL	dif df	p
oneADErq5ca	11	8229.5675	3643	943.56746			
testCov	9	8313.4336	3645	1023.4336	8.3866168e+01	2	6.1474203e-19
oneADEq5ca	10	8248.9231	3644	960.92309	1.9355627e+01	1	1.0849905e-05
oneADE5ca	7	8262.4116	3647	968.41157	3.2844108e+01	4	1.2855588e-06
oneAErq5ca	9	8229.5675	3645	939.56746	-1.3920853e-06	2	1.0000000e+00
oneErq5ca	6	8992.6761	3648	1696.6760	7.6310861e+02	5	1.1052891e-162
oneAE5ca	6	8265.9835	3648	969.98354	3.6416078e+01	5	7.8410016e-07
oneE5ca	5	9010.0485	3649	1712.0484	7.8048101e+02	6	2.5384122e-165