Using Univariate Twin Models to Study Sex Differences: An Introduction

Elizabeth Prom-Wormley and Laura W. Wesseldijk

With Many Thanks to

Jose Morosoli, Hermine Maes and Sarah Medland

Files to Copy

If Using the Terminal, enter this and then open RStudio and make your working directory:

```
mkdir elizabeth
cd elizabeth
cp -R /faculty/elizabeth/2024/day2/* ./
```

If Using R Studio directly, enter this:

```
system("mkdir $HOME/elizabeth")
system("cp -R /faculty/elizabeth/2024/day2/* $HOME/elizabeth")
setwd("~/elizabeth")
```

Open Day2SexLimPrac.R
Click on Link to Qualtrics Survey

https://qimr.az1.qualtrics.com/jfe/form/SV_eXmQtPdjWv4yO9g

Where We've Been and Where We're Going

Heritability, baby!

Heritability Estimation Using

Twin Study- Hermine/Sarah/Liz/Laura
Molecular data- Sarah/Ben/Madhur

Related Individuals (twins + relatives)
Katrina/Baptiste

Heritability Considerations

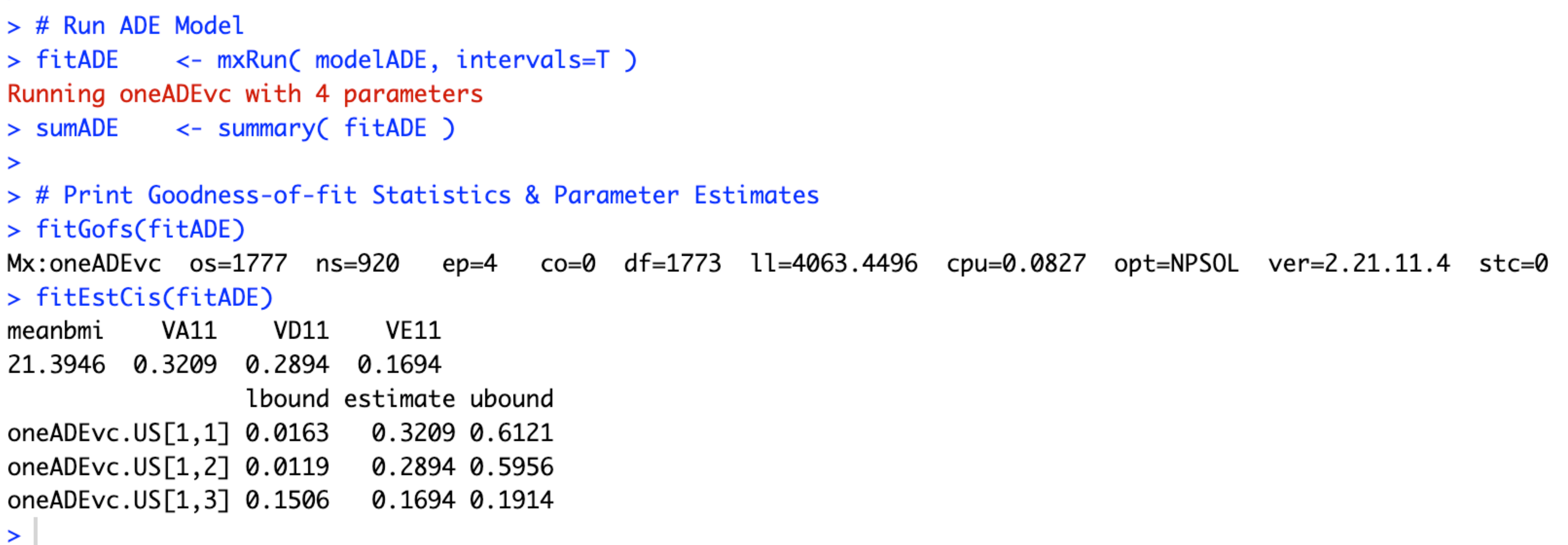
Twin Study Assumptions- Ben and Matt

Foundational Knowledge Common to Twin and Molecular Analyses for Modeling and Discussing Heritability

- Biometrical genetics- Abdel
- SEM basics (and implementing in OpenMx)- Mike Hunter
- Likelihood, the foundational workhorse underlying models estimating heritability- Baptiste

Results from Yesterday’s Univariate ADE Model

- Research Question - To what degree does variance from genetic (additive and dominance) and environmental influences contribute to the total phenotypic variance of a trait?



```
> # Run ADE Model
> fitADE     <- mxRun( modelADE, intervals=T )
Running oneADEvc with 4 parameters
> sumADE     <- summary( fitADE )
>
> # Print Goodness-of-fit Statistics & Parameter Estimates
> fitGofs(fitADE)
Mx:oneADEvc  os=1777  ns=920   ep=4   co=0  df=1773  ll=4063.4496  cpu=0.0827  opt=NPSOL  ver=2.21.11.4  stc=0
> fitEstCis(fitADE)
meanbmi    VA11    VD11    VE11
21.3946  0.3209  0.2894  0.1694
                 lbound estimate ubound
oneADEvc.US[1,1] 0.0163   0.3209 0.6121
oneADEvc.US[1,2] 0.0119   0.2894 0.5956
oneADEvc.US[1,3] 0.1506   0.1694 0.1914
>
```

VA = 0.32

VD = 0.29

VE = 0.17

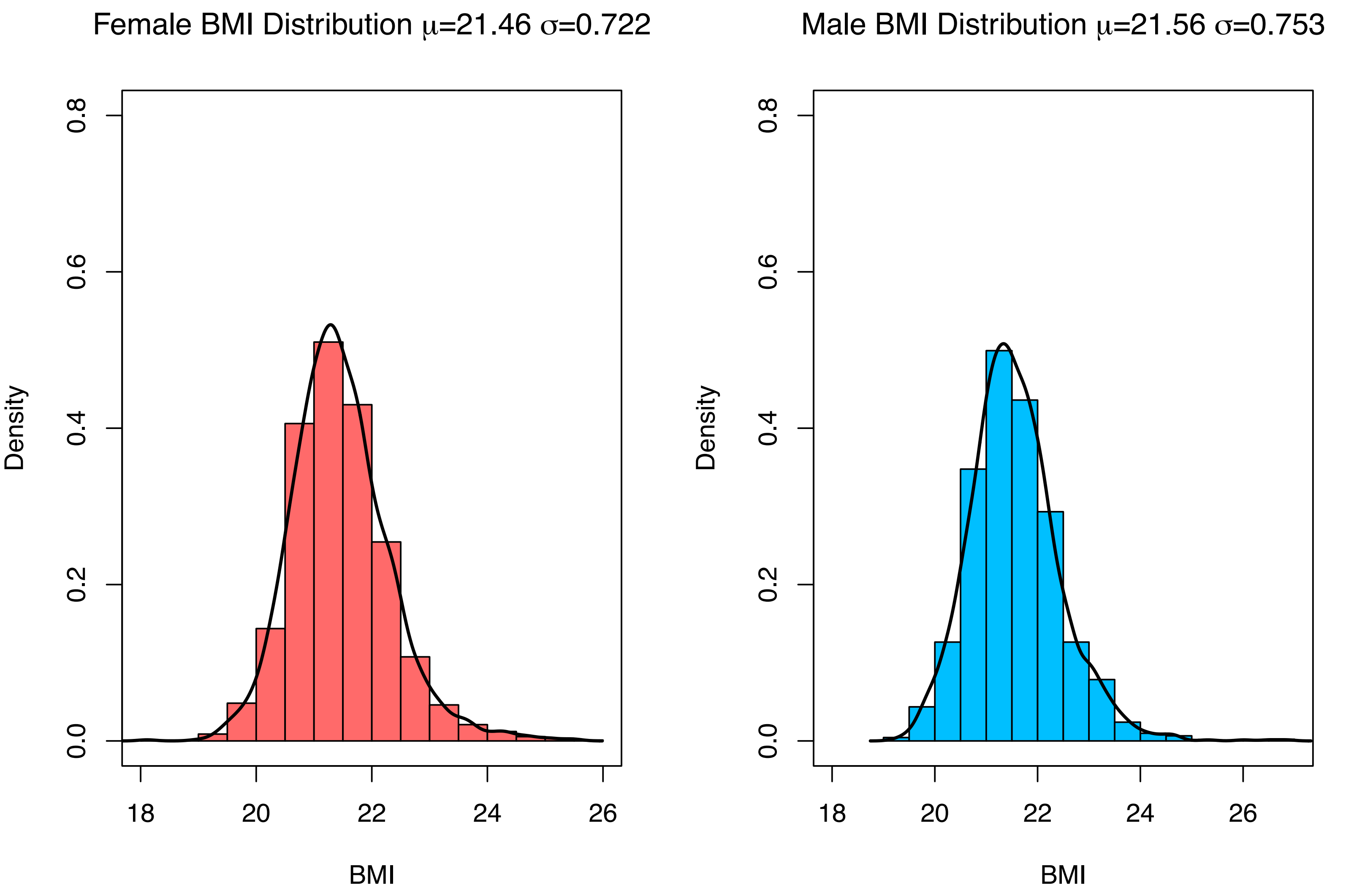
By the End of this Session You Should be Able to

- Use twin correlations and models to estimate and assess quantitative sex differences on genetic and environmental variance components estimates.

- Conduct basic interpretations of results from twin models of quantitative sex limitation

- Summarize issues of only using same sex pairs to study sex limitation.

New Challenge- Understanding Sex Differences



How do sex differences in genetic and environmental influences contribute to the variance in BMI?

We could study by evaluating sex limitation on BMI

Sex Limitation Defined

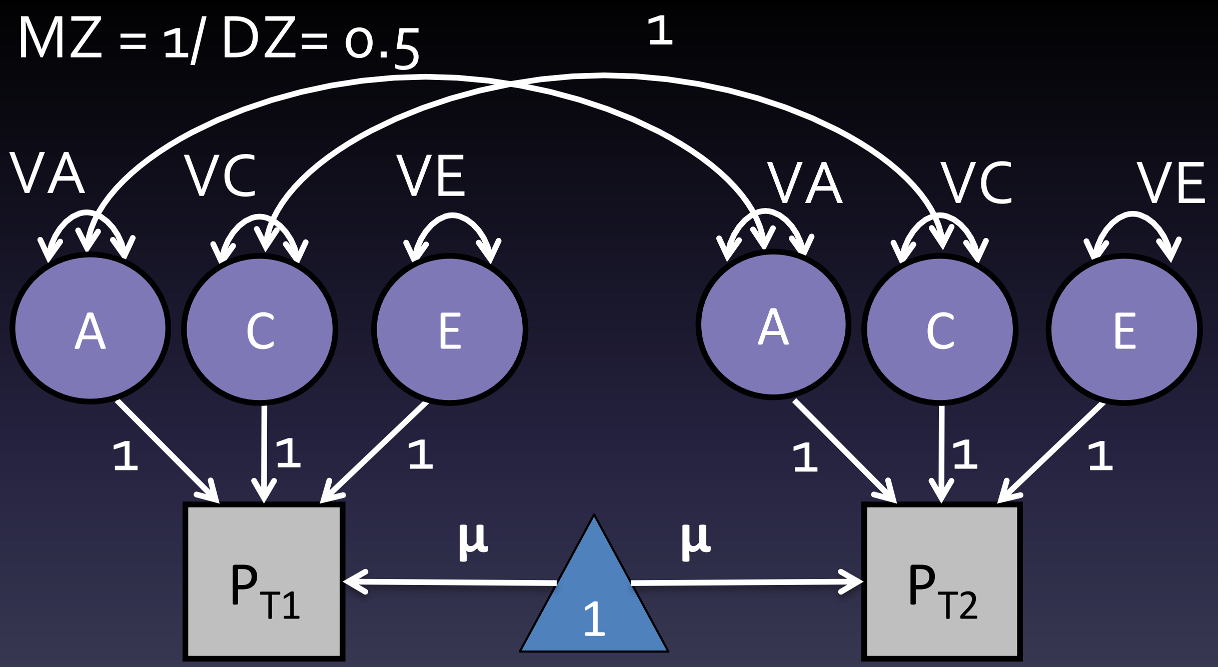
- Sex limitation occurs when the effects of genetic or environmental factors differ between males and females.
- Sex differences (e.g., mean differences, differences in prevalence by sex, variance differences) may arise as a result of sex limitation.
- Tests of sex limitation can help understand the role of genetic and environmental factors on sex differences.

Research Questions Using Twin Models to Discuss the Role of Sex Limitation on Sex Differences

- Are there different sets of genetic (or environmental) factors in males and females that contribute to a phenotype?
  Quantitative + Qualitative Sex Limitation

- Are there differences in the magnitude of genetic and environmental sources of variance between males and females that influence a phenotype?
  Quantitative Sex Limitation

Classical Twin Model



Parameters Estimated

1- Mean

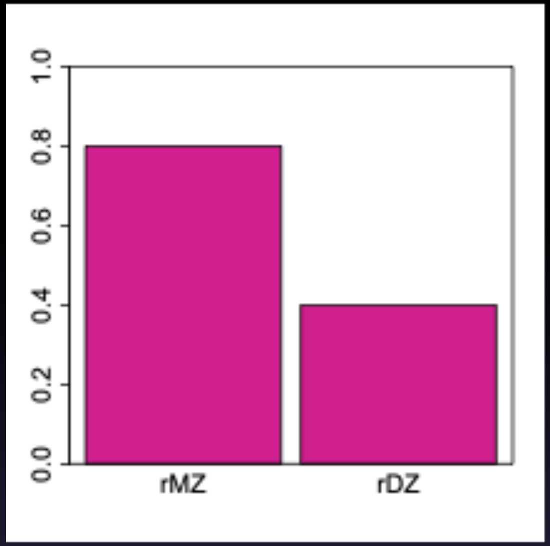
2- Variance due to A

3- Variance due to C

4- Variance due to E

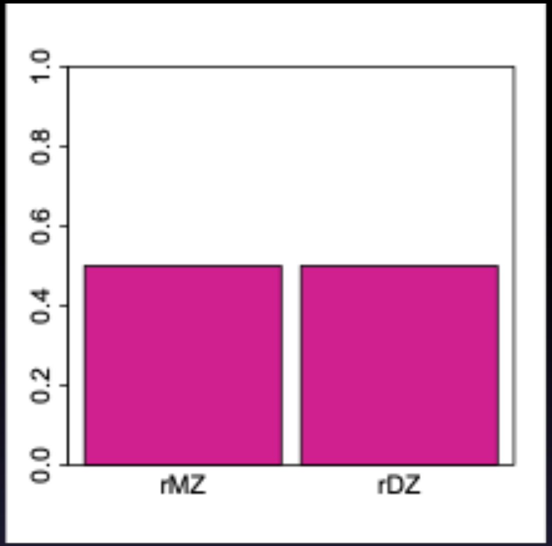
4 Total Parameters

Patterns of Twin Correlation

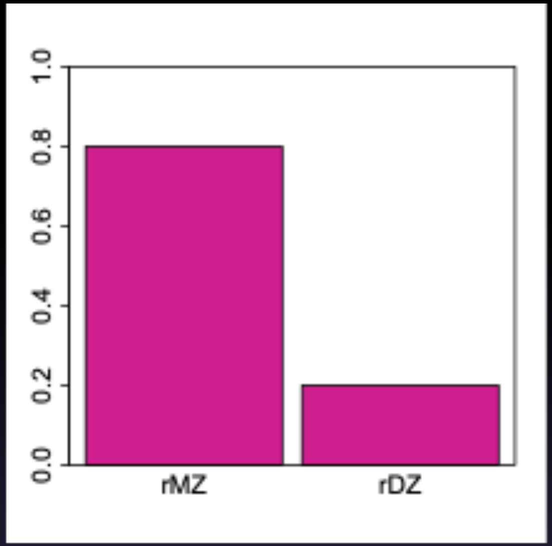


rMZ = 2rDZ
Additive

DZ twins on average share 50% of additive effects

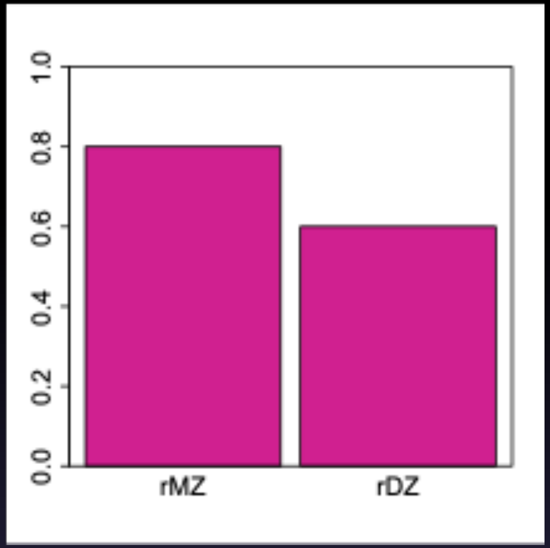


rMZ = rDZ
Shared Environment



rMZ > 2rDZ
Additive &
Dominance

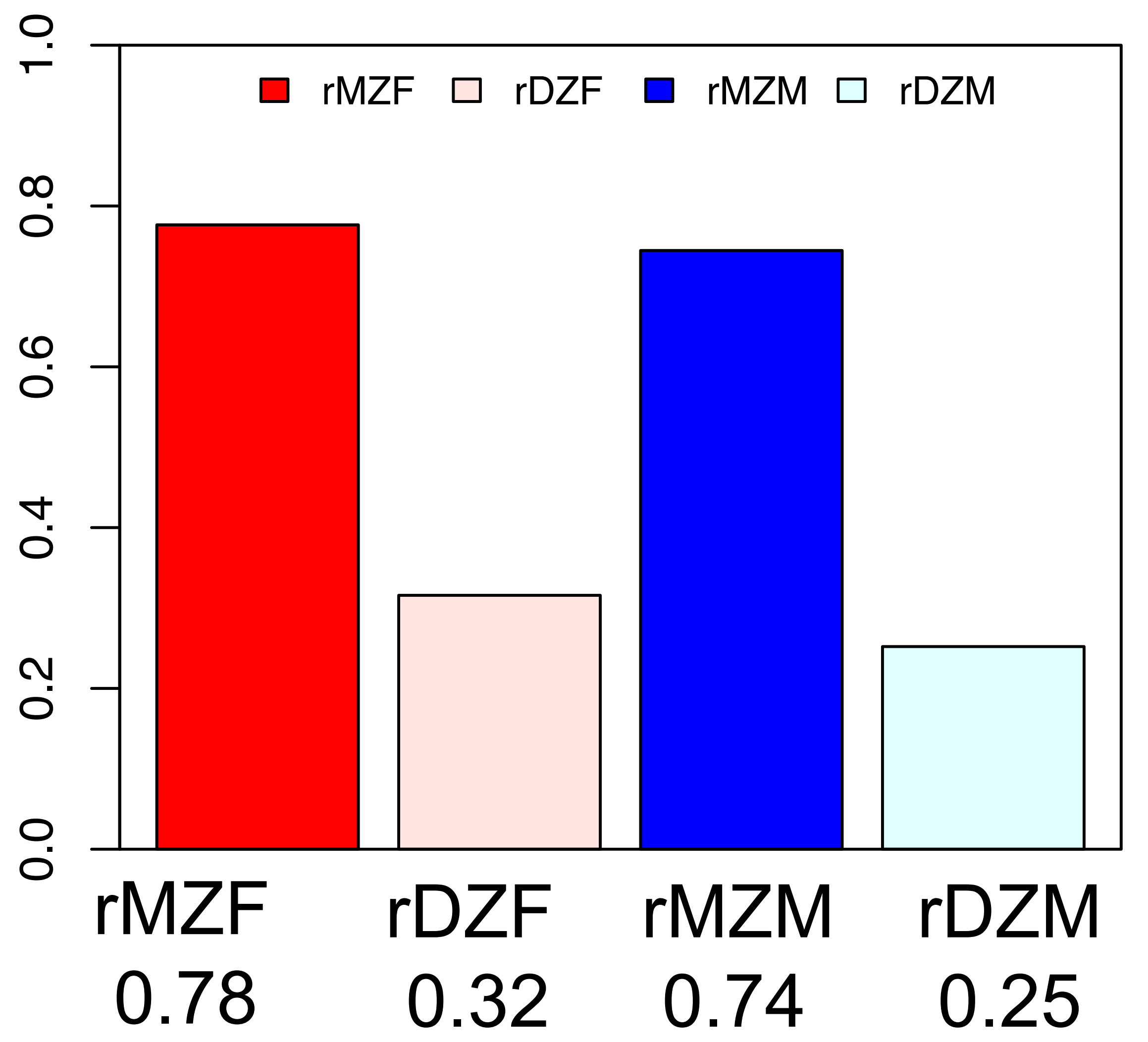
DZ twins on average share 25% of dominance effects



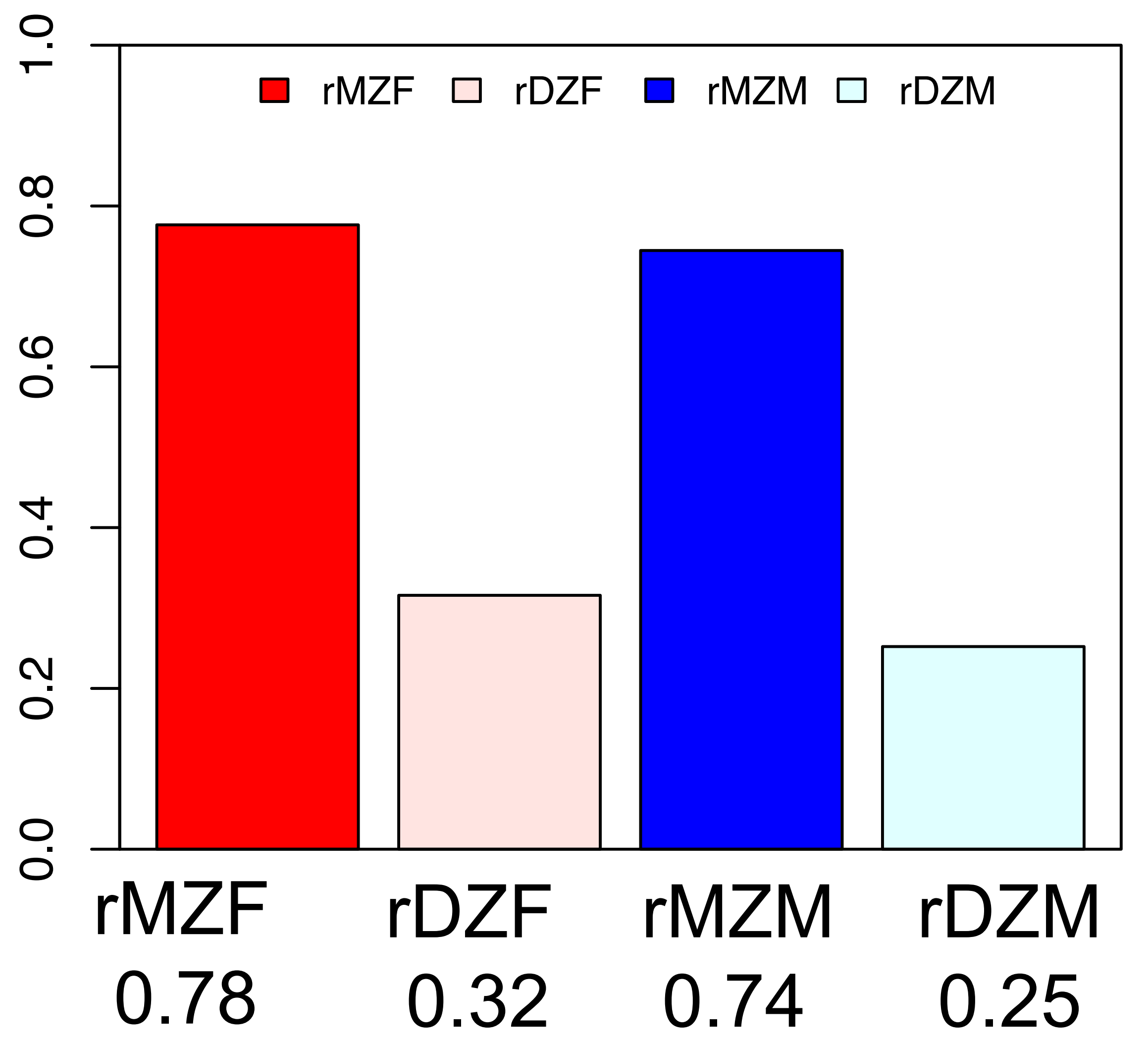
???
Additive &
“Shared Environment”

A = 2(rMZ-rDZ)
C = 2rDZ - rMZ
E = 1- rMZ

Am = 2(rMZ-rDZ)
Cm= 2rDZ - rMZ
Em = 1- rMZ



Af = 2(rMZ-rDZ)
Cf= 2rDZ - rMZ
Ef = 1- rMZ



$Am = 2(rMZ-rDZ)$

$Cm= 2rDZ - rMZ$

$Em = 1- rMZ$

$Am- 2*(rMZM-rDZM) = 2*(0.74-0.25) = 0.98$

Cm (or Dm)- $2rDZM-rMZM = 2*0.25-0.74 = -0.24$

$Em- 1-rMZM = 1-0.74 = 0.26$

$Af = 2(rMZ-rDZ)$

$Cf= 2rDZ - rMZ$

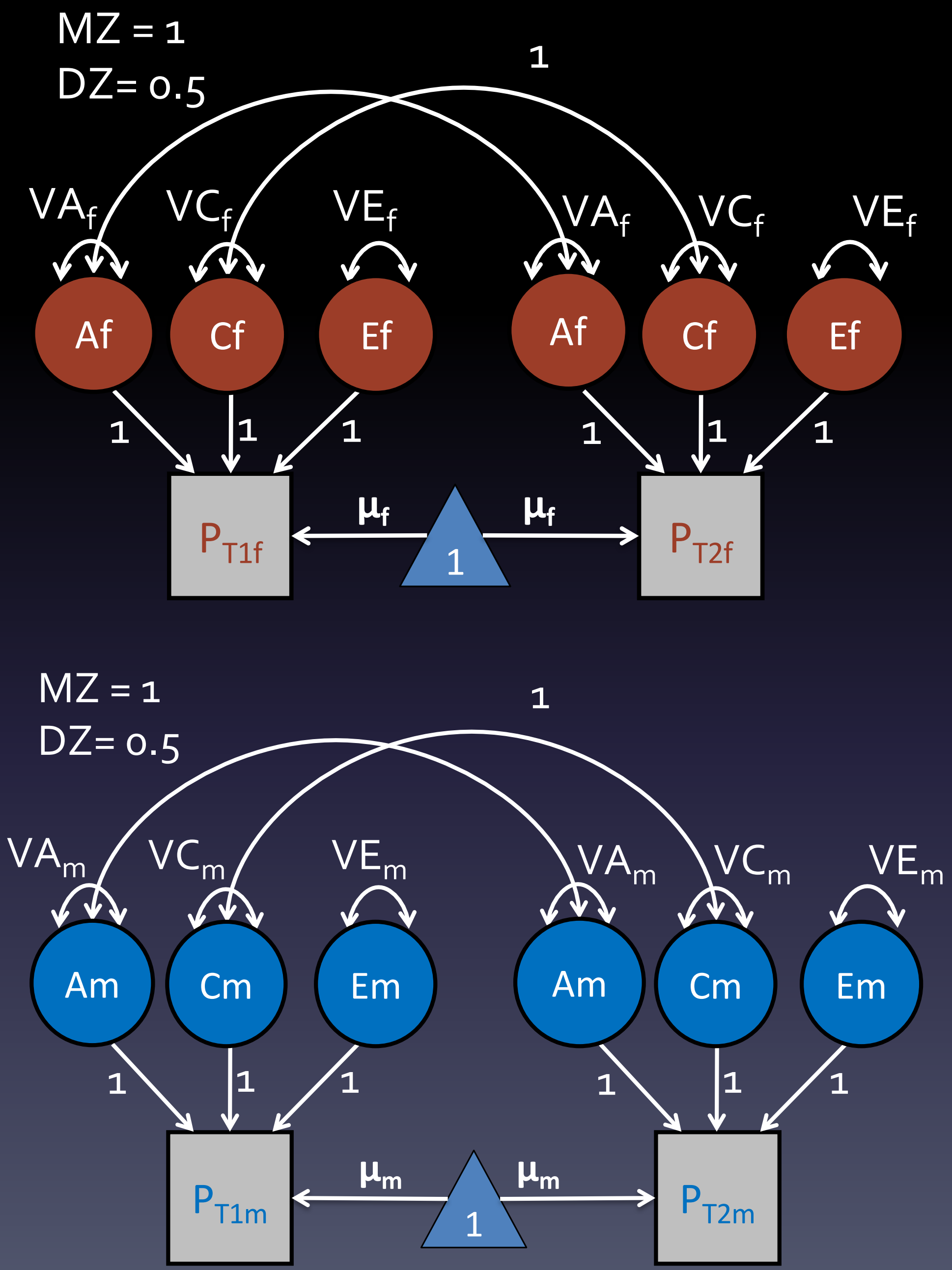
$Ef = 1- rMZ$

$Af- 2*(rMZF-rDZF) = 2*(0.78-0.32) = 0.92$

Cf (or Df)- $2rDZF-rMZF = 2*0.32-0.78 = -0.14$

$Ef- 1-rMZF = 1-0.78 = 0.22$

Quantitative Sex Limitation

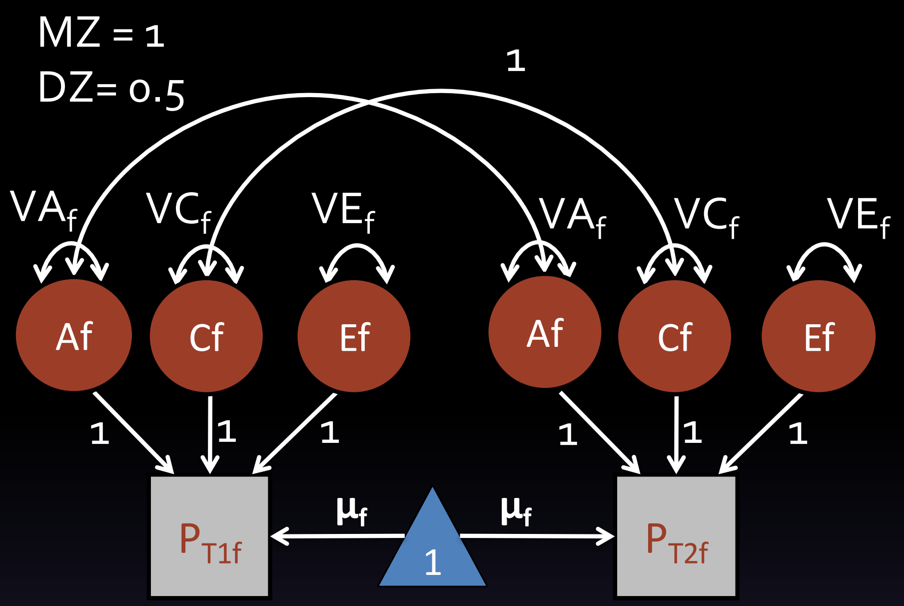


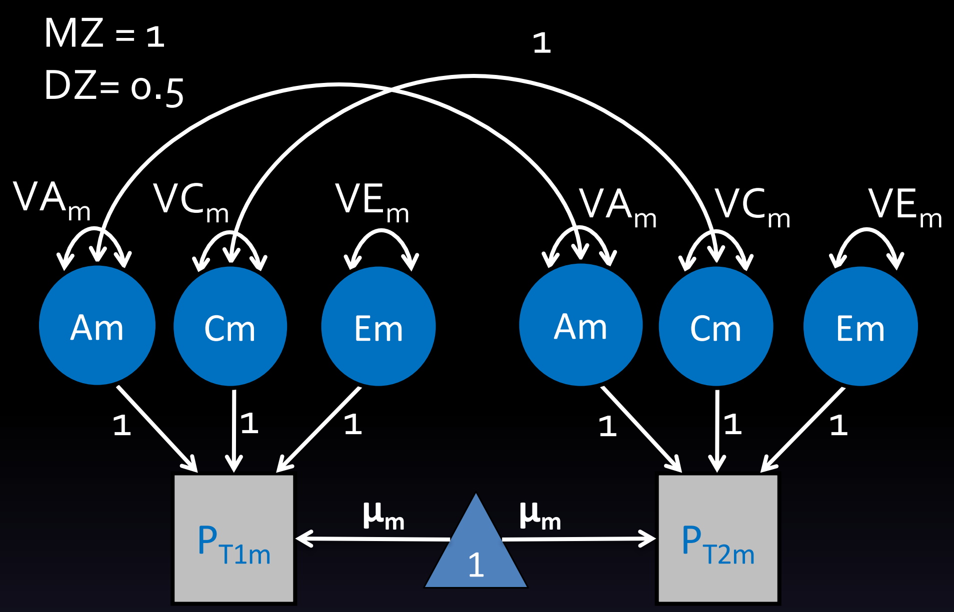
Parameters Estimated

1- Mean (females)
2- Variance due to Af
3- Variance due to Cf
4- Variance due to Ef

5- Mean (males)
6- Variance due to Am
7- Variance due to Cm
8- Variance due to Em

8 Total Parameters





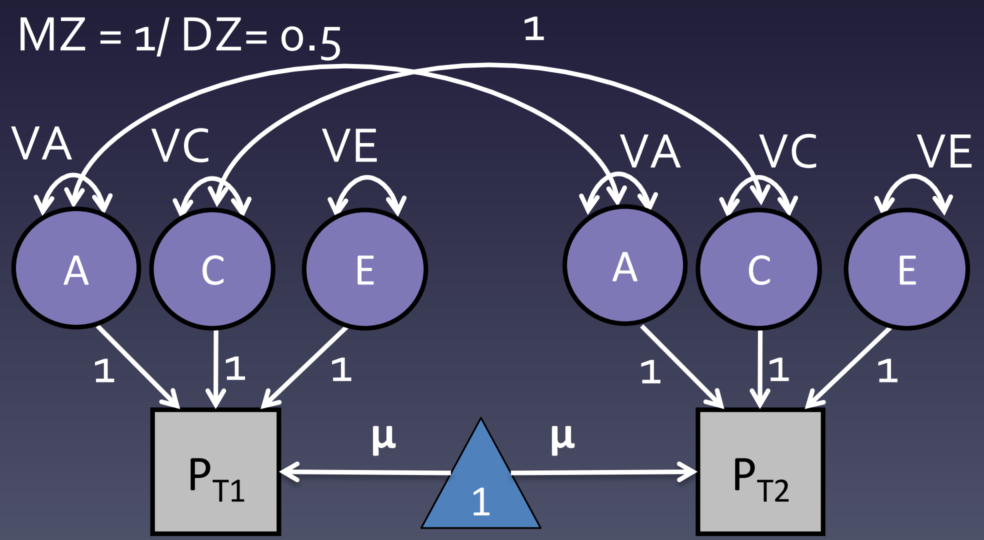
Quantitative Sex Limitation

VAf ≠ VAm

VCf ≠ VCm

VEf ≠ Vem

varF ≠ varM



No Sex Limitation

VAf = VAm

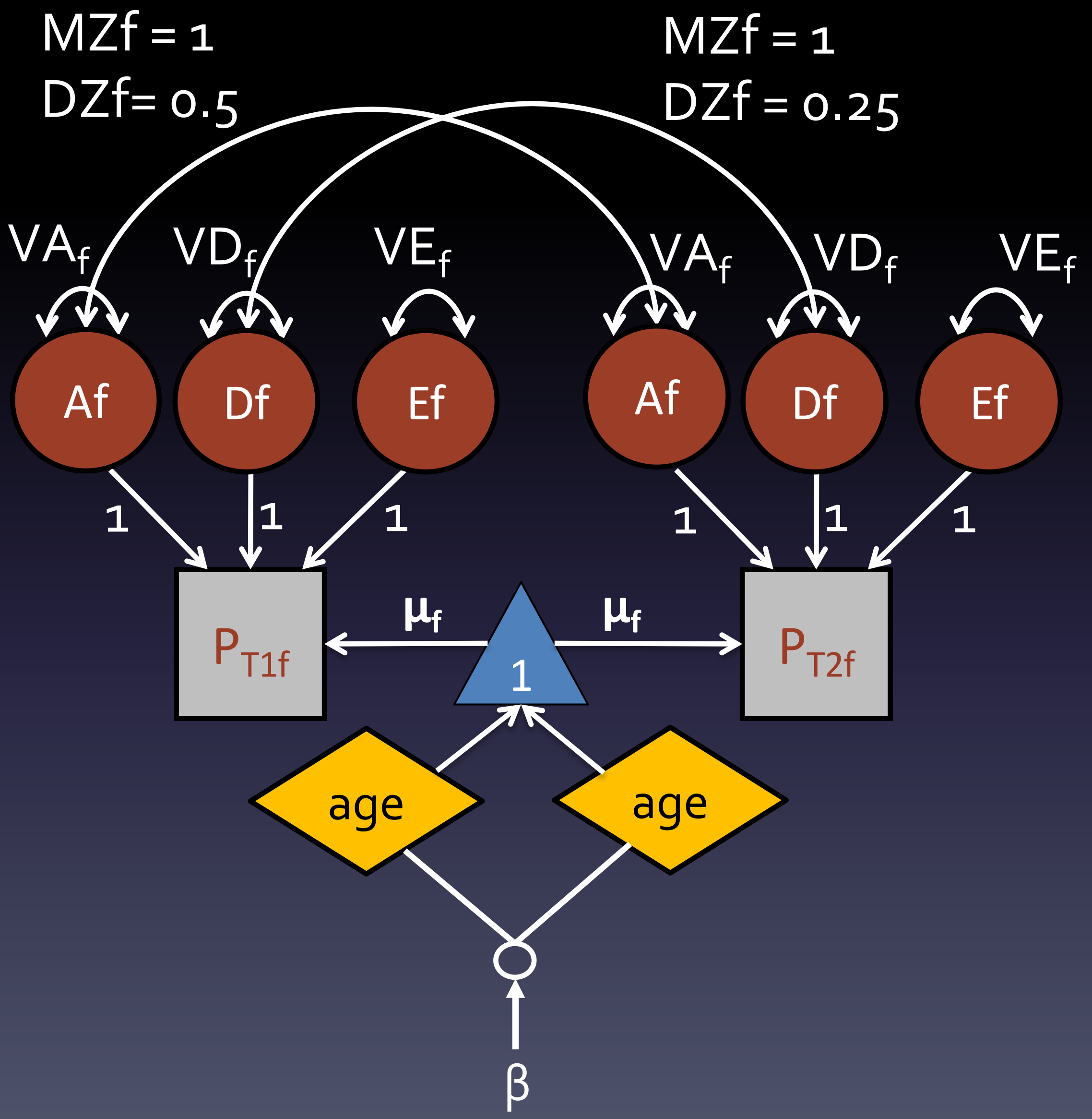
VCf = VCm

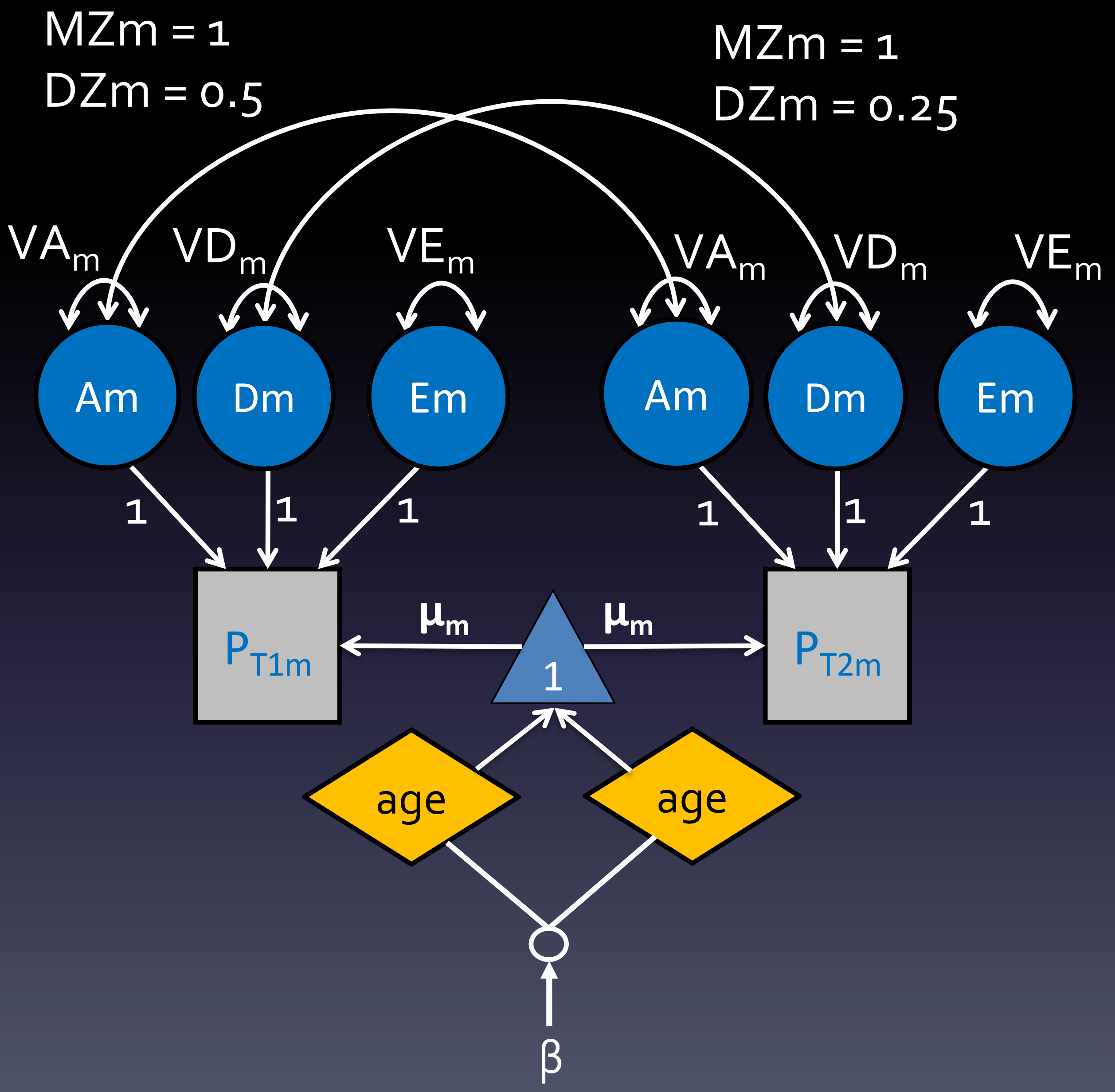
VEf = Vem

varF = varM

Implementing a Quantitative Sex Limitation Model in OpenMx

Open Day2SexLimPrac.R


MZf = 1
DZf= 0.5
MZf = 1
DZf = 0.25
VA_f
VD_f
VE_f
VA_f
VD_f
VE_f
Af
Df
Ef
Af
Df
Ef
1
1
1
1
1
1
P_{T1f}
μ_f
1
μ_f
P_{T2f}
age
age
β


MZm = 1
DZm = 0.5
MZm = 1
DZm = 0.25
VA_m
VD_m
VE_m
VA_m
VD_m
VE_m
Am
Dm
Em
Am
Dm
Em
1
1
1
1
1
1
P_{T1m}
μ_m
1
μ_m
P_{T2m}
age
age
β

Quantitative Sex Limitation Deconstructed Means and Covariate (using Definition Variable)

```
defL     <- mxMatrix( type="Full",
nrow=1, ncol=1, free=FALSE,
labels=c("data.age"), name="defL" )
```

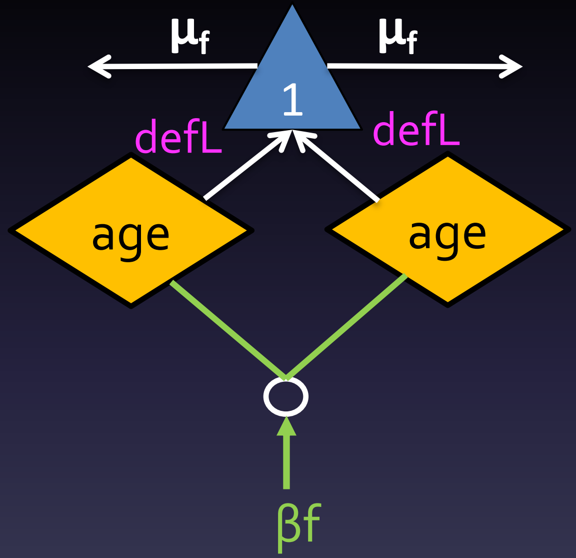
```
pathBf   <- mxMatrix( type="Full",
nrow=1, ncol=1, free=TRUE,
values=svBe, label="bf11", name="bf" )
```

Quantitative Sex Limitation Deconstructed Means and Covariate (using Definition Variable)

Data. age

1x1 matrix

```
defL     <- mxMatrix( type="Full",
nrow=1, ncol=1, free=FALSE,
labels=c("data.age"), name="defL" )
```



bf11

1x1 matrix

```
pathBf   <- mxMatrix( type="Full",
nrow=1, ncol=1, free=TRUE,
values=svBe, label="bf11", name="bf" )
```

Quantitative Sex Limitation Deconstructed Variance Components

```
covAf    <- mxMatrix( type="Symm",
nrow=nv, ncol=nv, free=TRUE,
values=svPa, label="VAf11", name="VAf" )
```

```
covDf    <- mxMatrix( type="Symm",
nrow=nv, ncol=nv, free=TRUE,
values=svPa, label="VDf11", name="VDf" )
```

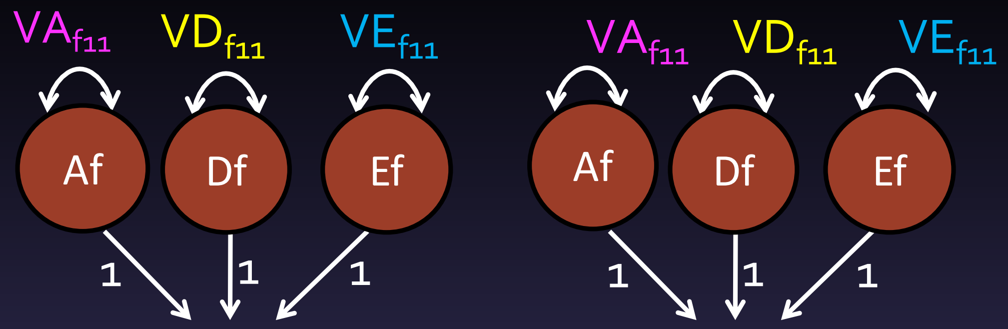
```
covEf    <- mxMatrix( type="Symm",
nrow=nv, ncol=nv, free=TRUE,
values=svPe, label="VEf11", name="VEf" )
```

Quantitative Sex Limitation Deconstructed Variance Components

VAf11

1x1 matrix

```
covAf    <- mxMatrix( type="Symm",
nrow=nv, ncol=nv, free=TRUE,
values=svPa, label="VAf11", name="VAf" )
```



VDf11

1x1 matrix

```
covDf    <- mxMatrix( type="Symm",
nrow=nv, ncol=nv, free=TRUE,
values=svPa, label="VDf11", name="VDf" )
```

VEf11

1x1 matrix

```
covEf    <- mxMatrix( type="Symm",
nrow=nv, ncol=nv, free=TRUE,
values=svPe, label="VEf11", name="VEf" )
```

Quantitative Sex Limitation Deconstructed Variance/Covariance Matrix

```
covPf <- mxAlgebra( expression=
VAf+VDf+VEf, name="Vf" )
```

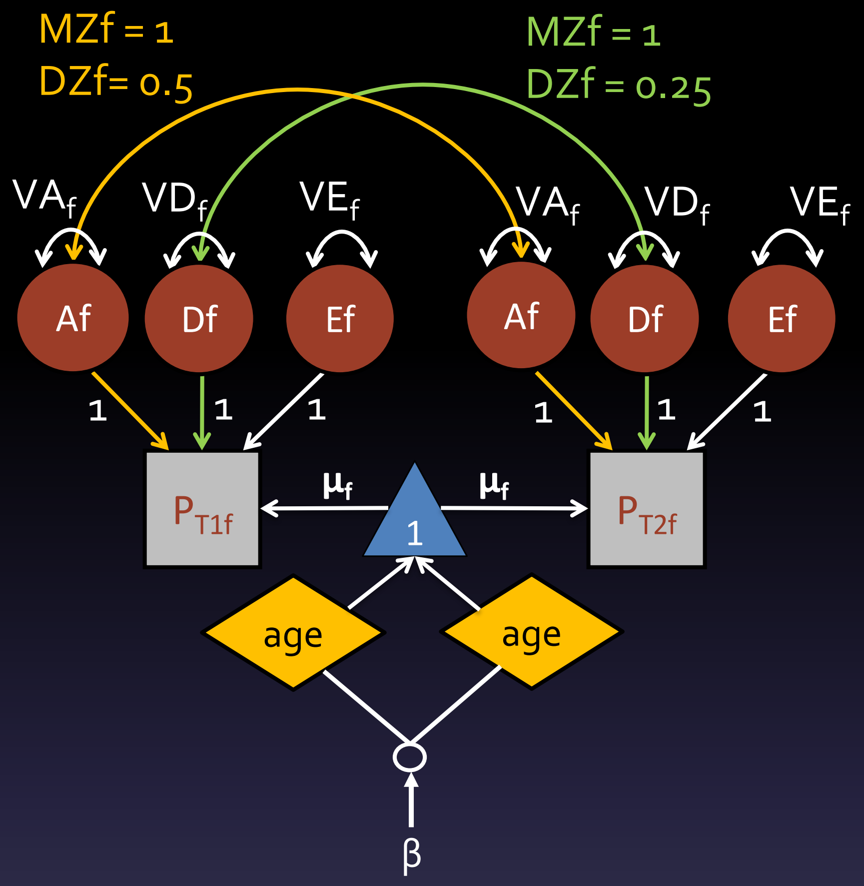
```
covMZf <- mxAlgebra( expression= VAf+VDf,
name="cMZf" )
```

```
covDZf <- mxAlgebra( expression=
0.5%x%VAf+ 0.25%x%VDf, name="cDZf" )
```

```
covPf <- mxAlgebra( expression=
VAf+VDf+VEf, name="Vf" )
```

```
covMZf <- mxAlgebra( expression= VAf+VDf,
name="cMZf" )
```

```
covDZf <- mxAlgebra( expression=
0.5%x%VAf+ 0.25%x%VDf, name="cDZf" )
```



	T1	T2
T1	**VAf+VDf+VEf**	**VAf+VDf**
T2	VAf+VDf	VAf+VDf+VEf

MZ Variance/Covariance Matrix

	T1	T2
T1	**VAf+VDf+VEf**	**VAf+VDf**
T2	0.5%x%VAf+ 0.25%x%VDf	VAf+VDf+VEf

DZ Variance/Covariance Matrix

Sex Limitation – A Roadmap (Part 1)

- Step 1- Data Check
  - Same sex only?
  - Same sex + DZO? If DZO, is sex ordered consistently? For DZO twin pairs- All twin 1s are the same sex and twin 2s are the same sex (e.g., all twin 1s are male and twin 2s are female)
- Step 2- Test basic assumptions inherent to ACE (ADE) models
  - Saturated Models to estimate/review means, variances, covariances, correlations for each zygosity group and establish expectations. Submodels to evaluate assumptions

Sex Limitation – A Roadmap (Part 2)

- Step 3- Estimate sex limitation models
  - ADE or ACE Models with sex limitation

- Step 4- Test sex limitation submodels
  - Quantitative
    - Equating variance components to be equal between sexes
    - Testing significance of variance components

Sex Limitation – A Roadmap (Part 3)

- Step 3- Estimate sex limitation models
  - ADE or ACE Models with sex limitation

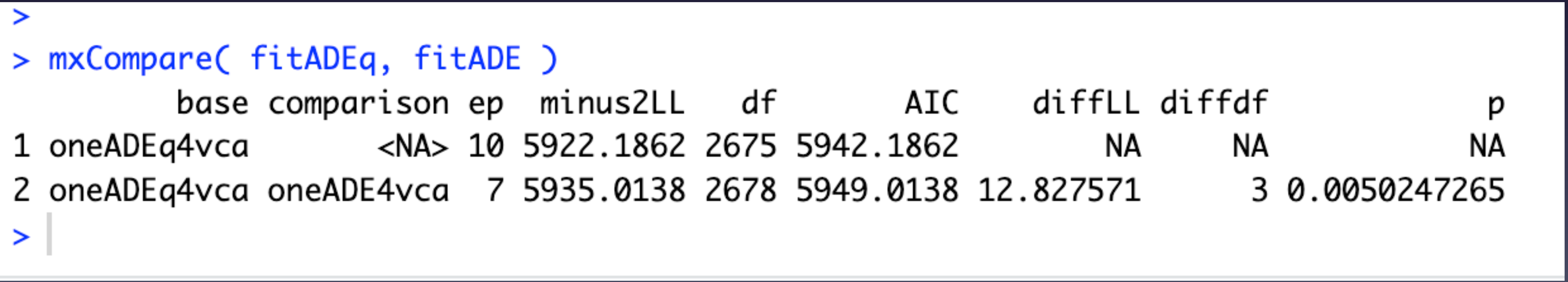
- Step 4- Test sex limitation submodels
  - Quantitative + Qualitative-
    - Submodel 1- Equating genetic or environmental correlations to be equal to 1 as a test of qualitative sex limitation (option 1)
    - Submodel 2- Equating variance components to be equal between sexes as a test of quantitative sex differences.
    - Testing significance of variance components

Time to Play!

Run Qualtrics and Day2SexLimPrac.R

Take Home Points

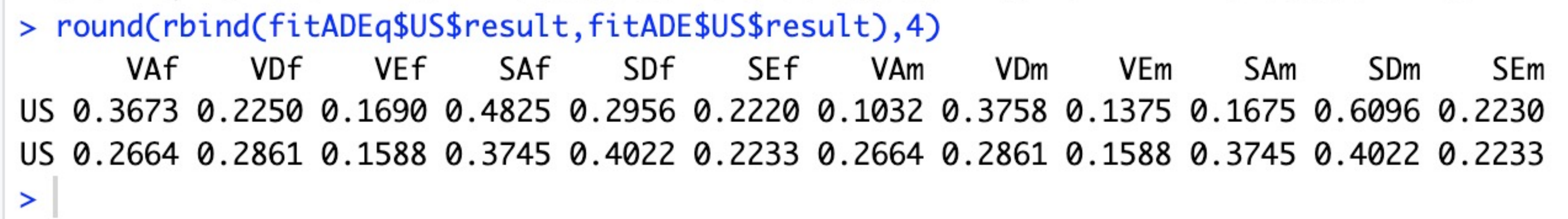
- A model equating variance component estimates between males and females does not improve model fit compared to one that allows variance components between males and females to be estimated. Evidence for quantitative sex limitation



```
>
> mxCompare( fitADEq, fitADE )
         base comparison ep  minus2LL   df       AIC    diffLL diffdf            p
1 oneADEq4vca       <NA> 10 5922.1862 2675 5942.1862        NA     NA           NA
2 oneADEq4vca oneADE4vca  7 5935.0138 2678 5949.0138 12.827571      3 0.0050247265
>
```

Take Home Points

Estimates for males and females. It can be helpful to inspect Unstandardized (e.g., VAf) and Standardized (e.g., SAf) estimates to interpret results.



```
> round(rbind(fitADEq$US$result,fitADE$US$result),4)
      VAf    VDf    VEf    SAf    SDf    SEf    VAm    VDm    VEm    SAm    SDm    SEm
US 0.3673 0.2250 0.1690 0.4825 0.2956 0.2220 0.1032 0.3758 0.1375 0.1675 0.6096 0.2230
US 0.2664 0.2861 0.1588 0.3745 0.4022 0.2233 0.2664 0.2861 0.1588 0.3745 0.4022 0.2233
> 
```

From these results:

The magnitude of VAf is larger than VDm

The magnitude of VDf is larger than VDm

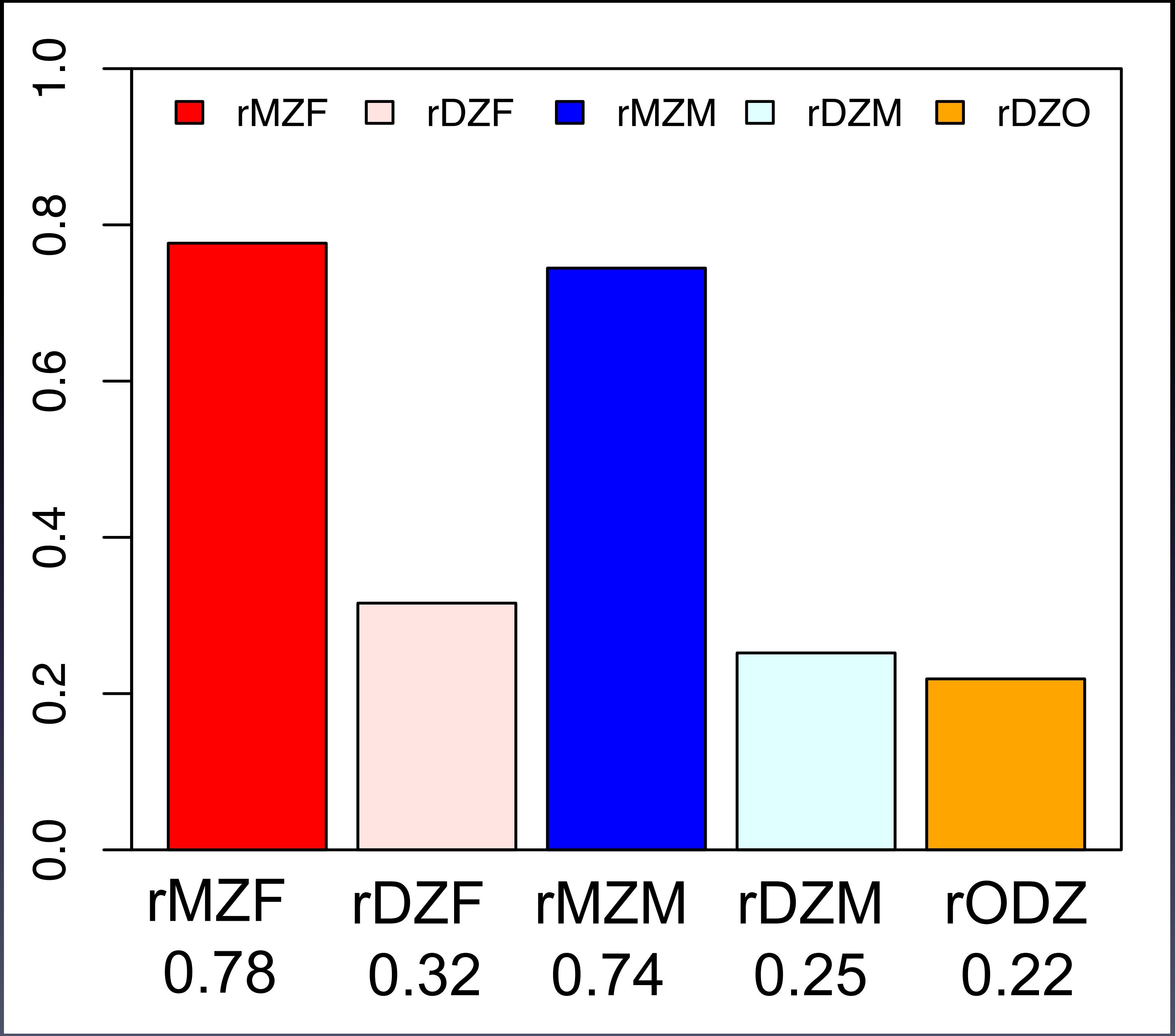
Practical Take Home Points

The estimates and 95% CI of ADE in males and females?

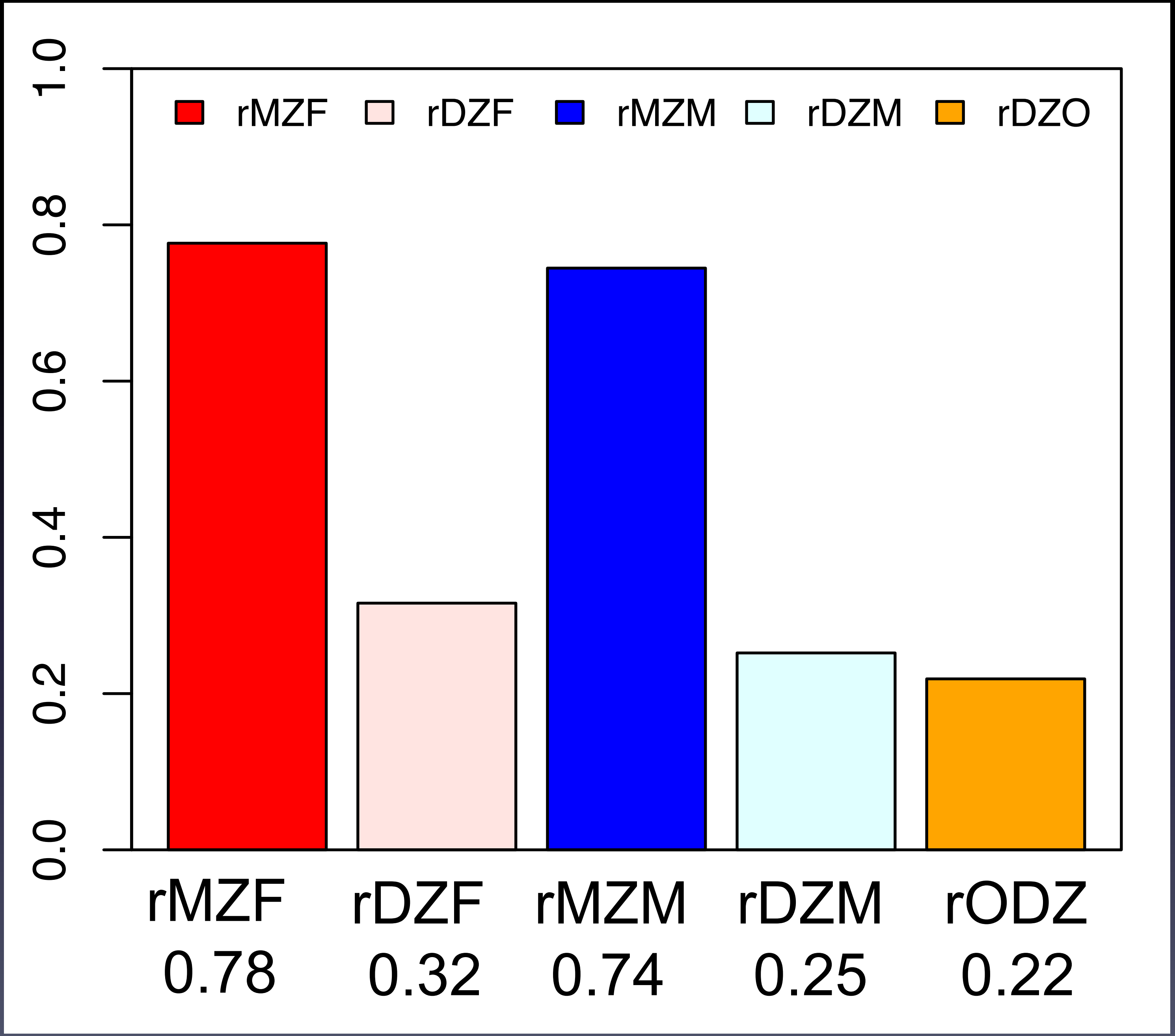
	lbound	estimate	ubound
oneADEq4vca.US[1,1]	0.0681	0.3674	0.6530
oneADEq4vca.US[1,2]	-0.0459	0.2250	0.5244
oneADEq4vca.US[1,3]	0.1503	0.1690	0.1910
oneADEq4vca.US[1,7]	-0.2054	0.1032	0.3965
oneADEq4vca.US[1,8]	0.0929	0.3758	0.6960
oneADEq4vca.US[1,9]	0.1157	0.1375	0.1650

But What about Opposite Sex Twin Pairs?

Opposite sex twin pairs provide an additional statistic (the covariance between ODZ pairs) to allow estimation on the nature of genetic and environmental factors between males and females. If you have them, use them.



What are the patterns you see?



What are the patterns you see?

When rODZ is much lower than same sex correlations, this suggests the role of quantitative sex limitation

Sex Limitation Cheat Sheet

Sex Limitation Type	NO SEX LIMITATION	QUANTITATIVE			QUANTITATIVE + QUALITATIVE	
Research Question	*To what extend do genetic and enviornmental factors influence the variance of a trait?*	*Are there significant differences in the magnitude (quantity) o variance components estimates between males & females?*			*Are there different sets of genetic (or environmental) factors between males and females in addition to differences in the magnitude of variance components estimates?*	
Model Name(s)	No Sex Limitation	Scalar Limitation	Non-Scalar Sex Limitation	Non-Scalar Sex Limitation or Common Effects Sex Limitation	General Non-Scalar Sex-Limitation or Full Sex-Limitation (Two Options for Modeling, Results are Equivalent)	
Model Notes	Total variance between males and females is equal. Same proportion of variance due to due to A, C, E in males and females.	Total variances for males and females are not the same and differ by a scaled value. Proportion of variance due to A,C,E are not equal between males and females.	Total variance is not equal between males and females. The variance components also varies between males and females.	Total variance is not equal between males and females. The variance components also varies between males and females.	Option 1- Estimate genetic or environmental correlation between males and females in ODZ pairs. Estimate proportions for variance component to vary between males and females.	Option 2- Estimate specific genetic or specific common environmental effects in males or females. Estimate proportions for variance component to vary between males and females.
Parameters of Interest	Vam = Vaf	k*Vam, VAf	VAm, VAf	VAm, VAf	VAm, VAf	VAm, VAf
	VCm = VCf	k*VCm, VCf	VCm, VCf	VCm, VCf	VCm, VCf	VCm, VCf
	Vem = Vef	k*VEm , VEf	VEm, VEf	VEm, VEf	VEm, VEf	VEm, VEf
	varm = varf	varm, varf	varm, varf	varm, varf	varm, varf	varm, varf
			meanm, meanf	meanm, meanf	meanm, meanf	meanm, meanf
		Note: Vam = Vaf, Vcm = Vcf, Vem = Vef		For ODZ pairs, the following are set in the model: r(Vaf, Vam) = 0.5 r(VCf, VCm) = 1 r(Vef, VEm) = 0	One correlation between males and females (r(Af, Am) or r(Cf, Cm)) is estimated in ODZ group to allow estimation of correlation between sexes. This represents a set of genetic or environmental factors that may be shared between males and females. ACE model.	Variance specific to one sex group (Vspecific) in the ODZ group to allow genetic or env factors to be estimated. This represents a set of genetic or environmental factors that may specifically influence males or females.
					Alternatively r(Df, Dm) and r(Af, Am) are estimated for an ADE model	
Data	Same Sex Only or Same Sex + ODZ	Same Sex Only or Same Sex + ODZ	Same Sex Only or Same Sex + ODZ	Same Sex + Opposite Sex DZ	Same Sex + Opposite Sex DZ	Same Sex + Opposite Sex DZ (can easily be extended to siblings/family)

Note: Tests of all submodels should also be considered

Sex Limitation Cheat Sheet

Sex Limitation Type	**NO SEX LIMITATION**	**QUANTITATIVE**			**QUANTITATIVE + QUALITATIVE**	
Research Question	*To what extend do genetic and envionmental factors influence the variance of a trait?*	*Are there significant differences in the magnitude (quantity) of variance components estimates between males & females?*			*Are there different sets of genetic (or environmental) factors between males and females in addition to differences in the magnitude of variance components estimates?*	
Model Name(s)	No Sex Limitation	Scalar Limitation	Non-Scalar Sex Limitation	Non-Scalar Sex Limitation or Common Effects Sex Limitation	General Non-Scalar Sex-Limitation or Full Sex-Limitation (Two Options for Modeling, Results are Equivalent)	
Model Notes	Total variance between males and females is equal. Same proportion of variance due to due to A, C, E in males and females.	Total variances for males and females are not the same and differ by a scaled value. Proportion of variance due to A,C,E are not equal between males and females.	Total variance is not equal between males and females The variance components also varies between males and females.	Total variance is not equal between males and females. The variance components also varies between males and females.	Option 1- Estimate genetic or environmental correlation between males and females in ODZ pairs. Estimate proportions for variance component to vary between males and females.	Option 2- Estimate specific genetic or specific common environmental effects in males or females. Estimate proportions for variance component to vary between males and females.
Parameters of Interest	Vam = Vaf	k*Vam, VAf	VAm, VAf	VAm, VAf	VAm, VAf	VAm, VAf
	VCm = VCf	k*VCm, VCf	VCm, VCf	VCm, VCf	VCm, VCf	VCm, VCf
	Vem = Vef	k*VEm , VEf	VEm, VEf	VEm, VEf	VEm, VEf	VEm, VEf
	varm = varf	varm, varf	varm, varf	varm, varf	varm, varf	varm, varf
			meanm, meanf	meanm, meanf	meanm, meanf	meanm, meanf
		Note: Vam = Vaf, Vcm = Vcf, Vem = Vef		For ODZ pairs, the following are set in the model: r(Vaf, Vam) = 0.5 r(VCf, VCm) = 1 r(Vef, VEm) = 0	One correlation between males and females (r(Af, Am) or r(Cf, Cm)) is estimated in ODZ group to allow estimation of correlation between sexes. This represents a set of genetic or environmental factors that may be shared between males and females. ACE model.	Variance specific to one sex group (Vspecific) in the ODZ group to allow genetic or env factors to be estimated. This represents a set of genetic or environmental factors that may specifically influence males or females.
					Alternatively r(Df, Dm) and r(Af, Am) are estimated for an ADE model	
Data	Same Sex Only or Same Sex + ODZ	Same Sex Only or Same Sex + ODZ	Same Sex Only or Same Sex + ODZ	Same Sex + Opposite Sex DZ	Same Sex + Opposite Sex DZ	Same Sex + Opposite Sex DZ (can easily be extended to siblings/family)

Note: Tests of all submodels should also be considered

References

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