Supplementary Note 1: Example script for running computational speed up in mother-offspring pairs

```
######################
## Eigen decomposition ##
######################

## read in genetic relationship matrix (matrix A) and phenotype files
load("GRMoffspring_MotherOffspringPairs_fullmatrix.RData")
pheno<- read.table("mother_offspring _phenotypes.txt", header=TRUE)

## Setting parameters
y = pheno$SBP_adj_o                 # Outcome phenotype (here systolic blood pressure)
ms = pheno$full_unweightedGRS_m     # Maternal genetic risk score
cs = pheno$full_unweightedGRS_o     # Offspring genetic risk scoer
a = pheno$Age_o                     # Offspring age
s = pheno$Sex_o                     # Offspring sex
p = pheno$ParticipationRound_o      # Participation round of offspring

x <- cbind(ms,cs,a,s,p)



#Select only rows and columns from matrix to remove NA values in phenotype
```

```
select <- !is.na(y)
y_new <- y[select]
x_new <- x[select]

Anew <- A[select, select]

Eigen <- eigen(Anew) #<--New eigen decomposition of the GRM
save(Eigen_new, file = "SBP_eigenA_mother_offspring_pairs.Rdata")

################################################
## SBP analysis with Age, Sex and Participation Round  ##
##                    Mother-Offspring pars                          ##
################################################

rm(list=ls())
library("OpenMx")

## read in eigen file and phenotype file
load("SBP_eigenA_mother_offspring_pairs.Rdata")
pheno<- read.table("mother_offspring _phenotypes.txt ", header=TRUE)

#remove  NAs in phenotype to match eigen file
pheno_2 <- subset(pheno, !is.na(SBP_adj_o))
```

#Analysis : Maternal GRS - adjusted for Offspring SNPS + age +sex + participation period. All autosomal birthweight SNPs

#Generate starting values for mean of systolic blood pressure

```
Ybar<-mean(pheno_2$SBP_adj_o)

## Setting parameters
y = pheno$SBP_adj_o                 # Outcome phenotype (here systolic blood pressure)
ms = pheno$full_unweightedGRS_m     # Maternal genetic risk score
cs = pheno$full_unweightedGRS_o     # Offspring genetic risk scoer
a = pheno$Age_o                     # Offspring age
s = pheno$Sex_o                     # Offspring sex
p = pheno$ParticipationRound_o      # Participation round of offspring

#eigenvectors of the GRM:
yrot <- t(Eigen_new$vectors) %*% y                  #x is a column vector of the dependent variable
xrot <- t(Eigen_new$vectors) %*% cbind(1,ms,cs,a,s,p)   #x: dataframe containing a column of ones and then columns of the independent variables
datrot <- cbind(yrot,xrot,Eigen_new$values)
colnames(datrot) <- c("y","x0","ms","cs","a","s","p","eva")

# Fitting full model
TIME1<-proc.time()
```

```
MxTest_full <-mxModel("GCTA_diag",
        mxData(observed=datrot, type="raw"),            #The Yobs dataset from earlier
        mxMatrix(type="Full",nrow=1,ncol=1,free=TRUE,values=0.5,name="G"), #SNP Variance component
        mxMatrix(type="Full",nrow=1,ncol=1,free=TRUE,values=0.5,name="E"),  #Residual Variance component
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE,values=Ybar,name="mu"), #Intercept in fixed effects part of model
        mxMatrix(type="Full",nrow=1,ncol=7, free=FALSE, labels=c("data.x0","data.ms","data.cs","data.a","data.s","data.p","data.eva"), name="defVars"),
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.02, labels = "beta1", name = "b1"), #Regression coefficient
       mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = -0.02, labels = "beta2", name = "b2"), #Regression coefficient for child genetic score
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.1, labels = "beta3", name = "b3"), #Regression coefficient for age
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.1, labels = "beta4", name = "b4"), #Regression coefficient for sex
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.1, labels = "beta5", name = "b5"), #Regression coefficient for participation round
        mxAlgebra(defVars[1,1]*mu + defVars[1,2]*b1 + defVars[1,3]*b2 + defVars[1,4]*b3 + defVars[1,5]*b4 + defVars[1,6]*b5, name="Ey"),
                mxAlgebra(defVars[1,7]*G + E, name="ESigma"),
                mxExpectationNormal(covariance="ESigma", means="Ey",dimnames=c("y")),
                mxFitFunctionML(rowwiseParallel=T)
)

Results<-mxRun(MxTest_full,unsafe=TRUE) #Run Model
summary(Results) #Summarize results

MxTest_sub<-mxModel("GCTA_diag_dropM",
            mxData(observed=datrot, type="raw"),        #The Yobs dataset from earlier
            mxMatrix(type="Full",nrow=1,ncol=1,free=TRUE,values=0.5,name="G"), #SNP Variance component
            mxMatrix(type="Full",nrow=1,ncol=1,free=TRUE,values=0.5,name="E"),  #Residual Variance component
```

```
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE,values=Ybar,name="mu"), #Intercept in fixed effects part of model
        mxMatrix(type="Full",nrow=1,ncol=7, free=FALSE, labels=c("data.x0","data.ms","data.cs","data.a","data.s","data.p","data.eva"), name="defVars"),
        mxMatrix(type="Full",nrow=1,ncol=1, free=FALSE, values = 0, labels = "beta1", name = "b1"), #Regression coefficient
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.1, labels = "beta2", name = "b2"), #Regression coefficient for child genetic score
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.1, labels = "beta3", name = "b3"), #Regression coefficient for age
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.1, labels = "beta4", name = "b4"), #Regression coefficient for sex
        mxMatrix(type="Full",nrow=1,ncol=1, free=TRUE, values = 0.1, labels = "beta5", name = "b5"), #Regression coefficient for participation round
        mxAlgebra(defVars[1,1]*mu + defVars[1,2]*b1 + defVars[1,3]*b2 + defVars[1,4]*b3 + defVars[1,5]*b4 + defVars[1,6]*b5, name="Ey"),
        mxAlgebra(defVars[1,7]*G + E, name="ESigma"),
        mxExpectationNormal(covariance="ESigma", means="Ey",dimnames=c("y")),
        mxFitFunctionML(rowwiseParallel=T)
)
Results_dropM<-mxRun(MxTest_sub,unsafe=TRUE) #Run Model
summary(Results_dropM) #Summarize results
## Setting up to compare the two models (minus two log likelihood):

#Full model:
minus2ll <- mxAlgebra(expression=GCTA_diag.fitfunction, name="minus2loglikelihood")
obj <- mxFitFunctionAlgebra("minus2loglikelihood")
model <- mxModel(model="MxTest", MxTest_full, minus2ll, obj)

base <- mxRun(model,unsafe=TRUE)
Zscore_base <- summary(base)$parameters[,5]/summary(base)$parameters[,6]
```

```
Pval_base <- 2*(1-pnorm(abs(Zscore_base),0,1))

Full <- data.frame()
Full <- rbind(Full, c(summary(base)$parameters[4,5], summary(base)$parameters[4,6], Pval_base[4]))
names(Full) <- c("Beta_cov_c", "SE_cov_c", "P_wald_cov_c")

#Model where maternal effect is constrained to zero:
minus2ll_dropM <- mxAlgebra(expression=GCTA_diag_dropM.fitfunction, name="minus2loglikelihood")
obj_dropM <- mxFitFunctionAlgebra("minus2loglikelihood")
model_dropM <- mxModel(model="MxTest", MxTest_sub, minus2ll_dropM, obj_dropM)

base_dropM <- mxRun(model_dropM,unsafe=TRUE)
Zscore_base_dropM <- summary(base_dropM)$parameters[,5]/summary(base_dropM)$parameters[,6]
Pval_base_dropM <- 2*(1-pnorm(abs(Zscore_base_dropM),0,1))

dropM <- data.frame()
dropM <- rbind(dropM, c(summary(base_dropM)$parameters[4,5], summary(base_dropM)$parameters[4,6], Pval_base_dropM[4]))
names(dropM) <- c("Beta_cov_c", "SE_cov_c", "P_wald_cov_c")

#Comparing the two models to obtain p-value:
compare <- (mxCompare(base, base_dropM))
```

Supplementary Note 2: Details of Computational Speed Up

Under the linear mixed model,

$$\mathbf{y} = \mathbf{Xb} + \mathbf{Wu} + \mathbf{e} \qquad (1)$$

, where

$\mathbf{y}$ is an $n \times 1$ vector of phenotype scores,

$\mathbf{X}$ is the $n \times k$ design matrix for the fixed effects (covariates),

$\mathbf{b}$ is the $k \times 1$ vector of regression coefficients,

$\mathbf{W}$ is the $n \times m$ design matrix for the random effects of m genetic markers,

$\mathbf{u}$ is an $m \times 1$ vector of normal i.i.d. genetic random effects, with expectation zero, and variance σ_u^2 i.e. $\mathbf{u} \sim \mathrm{N}(0, \mathbf{I}\sigma_u^2)$, and

$\mathbf{e}$ is an $n \times 1$ vector of i.i.d. residuals.

The residuals are assumed to be normally distributed, with expectation zero. Define the genomic-relatedness matrix $\mathbf{A}$ as

$$\mathbf{A} = \frac{\mathbf{WW}^T}{m} \qquad (2)$$

. Conditional on $\mathbf{X}$, the variance of $\mathbf{y}$ is

$$\mathrm{var}(\mathbf{y} \mid \mathbf{X}) = \mathbf{WW}^T\sigma_u^2 + \mathbf{I}\sigma_e^2 = \mathbf{A}\sigma_g^2 + \mathbf{I}\sigma_e^2 \qquad (3)$$

, where

$\sigma_g^2 = m\sigma_u^2$ is the additive-genetic variance component,

σ_e^2 is the nonshared-environmental (residual) variance component, and

$\mathbf{I}$ is an $n \times n$ identity matrix.

Consider now the eigen decomposition of $\mathbf{A}$,

$$\mathbf{A} = \mathbf{Q}\boldsymbol{\Lambda}\mathbf{Q}^T \tag{4}$$

, where

$\mathbf{Q}$ is an $n \times n$ matrix, the columns of which are the orthonormal eigenvectors of $\mathbf{A}$, and

$\boldsymbol{\Lambda}$ is an $n \times n$ diagonal matrix, the diagonal elements of which are the corresponding eigenvalues of $\mathbf{A}$.

Suppose we premultiply both sides of (1) by $\mathbf{Q}^T$:

$$\mathbf{Q}^T\mathbf{y} = \mathbf{Q}^T\mathbf{X}\mathbf{b} + \mathbf{Q}^T\mathbf{W}\mathbf{u} + \mathbf{Q}^T\mathbf{e} \tag{5}$$

. Then, conditional on $\mathbf{Q}^T\mathbf{X}$, the variance of $\mathbf{Q}^T\mathbf{y}$ is

$$\begin{aligned}
\mathrm{var}(\mathbf{Q}^T\mathbf{y} \mid \mathbf{Q}^T\mathbf{X}) &= \mathbf{Q}^T\mathbf{W}\mathbf{W}^T\mathbf{Q}\sigma_u^2 + \mathbf{Q}^T\mathbf{Q}\sigma_e^2 \\
&= \mathbf{Q}^T\mathbf{A}\mathbf{Q}\sigma_g^2 + \mathbf{I}\sigma_e^2 \\
&= \mathbf{Q}^T\mathbf{Q}\boldsymbol{\Lambda}\mathbf{Q}^T\mathbf{Q}\sigma_g^2 + \mathbf{I}\sigma_e^2 \\
&= \boldsymbol{\Lambda}\sigma_g^2 + \mathbf{I}\sigma_e^2
\end{aligned} \tag{6}$$

Thus, the premultiplication by $\mathbf{Q}^T$has "rotated away" the dependence among the elements of $\mathbf{y}$, leaving the random effects uncorrelated. Since the random effects are assumed to be normally distributed, their lack of correlation implies their stochastic independence. Now, evaluating the likelihood of one n-dimensional datum has been broken up into the evaluation of n 1-dimensional data, which greatly reduces the computational burden.

Supplementary Tables 1-3:

Supplementary Table 1: Results from the analysis of offspring birthweight regressed on maternal GRS*/paternal GRS* and offspring GRS. Mother-offspring pairs (*N*=7,825) and Father-offspring pairs (*N*=6,875)

			Autosomal SNPs (204 SNPs)			**Autosomal SNPs with maternal effect (71 SNPs)**			**Autosomal SNPs with maternal effect only (31 SNPs)**		
Outcome	Analysis sample	Exposure	Effect estimate	SE	p-value	Effect estimate	SE	p-value	Effect estimate	SE	p-value
Offspring Birthweight (kg)	Mother-Offspring pairs	Maternal GRS	0.0926	0.0114	2.51E-16	0.0943	0.0114	1.55E-16	0.0804	0.0115	2.58E-12
	Mother-Offspring pairs	Maternal GRS - adjusted for Offspring GRS	0.0778	0.0130	2.13E-09	0.0730	0.0131	2.80E-08	0.0743	0.0131	1.51E-08
	Mother-Offspring pairs	Offspring GRS	0.0685	0.0112	8.02E-10	0.0773	0.0111	4.23E-12	0.0474	0.0112	2.40E-05
	Mother-Offspring pairs	Offspring GRS - adjusted for Maternal GRS	0.0321	0.0127	0.0111	0.0419	0.0128	1.04E-03	0.0121	0.0128	0.3409
	Father-Offspring pairs	Paternal GRS	0.0183	0.0123	0.1367	0.0369	0.0122	0.0026	0.0187	0.0122	0.1265
	Father-Offspring pairs	Paternal GRS - adjusted for Offspring GRS	-0.0236	0.0139	0.1014	0.0003	0.0138	0.9762	-0.0061	0.0139	0.6665
	Father-Offspring pairs	Offspring GRS	0.0753	0.0119	2.62E-10	0.0770	0.0119	1.13E-10	0.0478	0.0120	0.0001
	Father-Offspring pairs	Offspring GRS - adjusted for Paternal GRS	0.0857	0.0135	2.05E-10	0.0767	0.0135	1.21E-08	0.0506	0.0136	0.0002

The regression coefficients give the estimated expected change in offspring birthweight, per one unit (i.e. allele) increase in maternal/paternal (or offspring) genetic risk score, with or without conditioning on offspring (or maternal/paternal) genetic risk score. All analyses are adjusted for sex and measurement occasion of the offspring. Effect estimates and standard errors are standardized. P-values reflect minus two log-likelihood chi-square tests between the full model and a sub-model where the relevant parameter is fixed to zero. All p-values are two sided uncorrected for multiple testing. SNP: Single Nucleotide Polymorphism, N: number of individuals, SE: Standard Error; GRS: Genetic risk score.

*Maternal, paternal and offspring GRS were coded so that increasing dosages reflected maternal alleles associated with increased offspring birthweight based on conditional GWAS results previously published

Supplementary Table 2: Results from analyses stratifying mother-offspring and father-offspring pairs into two age strata

Young < 40 years Old Offspring *N*=12,037 (Mother-Offspring pairs; *N*=10,393 Father-Offspring pairs)											
			Autosomal SNPs (204 SNPs)			Autosomal SNPs with maternal effect (71 SNPs)			Autosomal SNPs with only maternal effect (31 SNPs)		
Outcome	Analysis sample	Exposure	Effect estimate	SE	p-value	Effect estimate	SE	p-value	Effect estimate	SE	p-value
Offspring SBP (mmHg)	Mother-Offspring pairs	Maternal GRS	-0.0171	0.0083	0.0389	-0.0162	0.0083	0.0515	-0.0236	0.0083	0.0044
	Mother-Offspring pairs	Maternal GRS - adjusted for Offspring GRS	-0.0155	0.0095	0.1035	-0.0046	0.0095	0.6277	-0.0092	0.0095	0.3349
	Mother-Offspring pairs	Offspring GRS	-0.0108	0.0082	0.1877	-0.0253	0.0082	0.0020	-0.0332	0.0082	0.0001
	Mother-Offspring pairs	Offspring GRS - adjusted for Maternal GRS	-0.0033	0.0094	0.7285	-0.0230	0.0094	0.0143	-0.0286	0.0094	0.0025
	Father-Offspring pairs	Paternal GRS	-0.0122	0.0090	0.1750	-0.0202	0.0089	0.0244	-0.0137	0.0089	0.1272
	Father-Offspring pairs	Paternal GRS - adjusted for Offspring GRS	-0.0080	0.0102	0.4352	-0.0126	0.0101	0.2142	-0.0025	0.0102	0.8108
	Father-Offspring pairs	Offspring GRS	-0.0123	0.0088	0.1634	-0.0215	0.0088	0.0146	-0.0237	0.0089	0.0073
	Father-Offspring pairs	Offspring GRS - adjusted for Paternal GRS	-0.0085	0.0101	0.3988	-0.0156	0.0100	0.1185	-0.0226	0.0101	0.0265
Mid 40-60 Years Old Offspring (*N*=11,849 Mother-Offspring pairs; *N*=8,402 Father-Offspring pairs)											
			Autosomal SNPs (204 SNPs)			Autosomal SNPs with maternal effect (71 SNPs)			Autosomal SNPs with only maternal effect (31 SNPs)		
Outcome	Analysis sample	Exposure	Effect estimate	SE	p-value	Effect estimate	SE	p-value	Effect estimate	SE	p-value
Offspring SBP (mmHg)	Mother-Offspring pairs	Maternal GRS	-0.0135	0.0092	0.1405	0.0006	0.0091	0.9427	-0.0077	0.0092	0.4019
	Mother-Offspring pairs	Maternal GRS - adjusted for Offspring GRS	-0.0059	0.0105	0.5739	-0.0061	0.0087	0.6549	0.0011	0.0103	0.9125
	Mother-Offspring pairs	Offspring GRS	-0.0182	0.0088	0.0399	-0.0061	0.0088	0.4868	-0.0179	0.0089	0.0435
	Mother-Offspring pairs	Offspring GRS - adjusted for Maternal GRS	-0.0156	0.0101	0.1241	-0.0082	0.0100	0.4101	-0.0184	0.0099	0.0657
	Father-Offspring pairs	Paternal GRS	-0.0159	0.0109	0.1455	0.0032	0.0109	0.7689	0.0058	0.0109	0.5926
	Father-Offspring pairs	Paternal GRS - adjusted for Offspring GRS	-0.0079	0.0124	0.5228	0.0085	0.0123	0.4691	0.0179	0.0122	0.1475
	Father-Offspring pairs	Offspring GRS	-0.0200	0.0105	0.0579	-0.0071	0.0105	0.5017	-0.0166	0.0105	0.1163
	Father-Offspring pairs	Offspring GRS - adjusted for Paternal GRS	-0.0164	0.0120	0.1696	-0.0109	0.0119	0.3602	-0.0248	0.0118	0.0386

The regression coefficients give the estimated expected change in offspring SBP (mmHg), per one unit (i.e. allele) increase in maternal/paternal (or offspring) genetic risk score, with or without conditioning on offspring (or maternal/paternal) genetic risk score. All analyses are adjusted for age, sex and measurement occasion of the offspring. Effect estimates and standard errors are standardized. P-values reflect minus two log-likelihood chi-square tests between the full model and a sub-model where the relevant parameter is fixed to zero. All p-values are two sided uncorrected for multiple testing. SNP: Single Nucleotide Polymorphism, N: number of individuals, SE: Standard Error; GRS: Genetic Risk Score; SBP: Systolic Blood Pressure.

NB. Maternal, paternal and offspring GRS were coded so that increasing dosages reflected maternal alleles associated with increased offspring birthweight based on conditional GWAS results previously published

Supplementary Table 3: Overview of numbers of offspring per parent in the analysis

	Total number of offspring	**Number of unique parents**	**Number of offspring in the analysis**							
			1	2	3	4	5	6	7	8
Mothers	26057	15261	8096	4623	1748	581	148	50	13	2
Fathers	19792	11867	6486	3543	1317	380	105	29	6	1