Supplementary for
"Testing the moderation of quantitative gene by environment interactions in unrelated individuals"

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1 Statistical analysis

In the subsequent subsections, the GxE models on unrelated individuals using 5 different models will be presented and their power and type I error will be calculated. To do this, let

$$z_{ik} = (x_{ik} - 2p_k)/\sqrt{2p_k q_k}, \tag{1}$$

be the standardized genotype for individual i and variant k, where $x_{ik} \in \{0, 1, 2\}$ and p_k is the allele frequency for the kth variant. Denote by V_P the phenotypic variance component and V_E non-genetic variance component, such that $V_P = V_A + V_E$.

1.1 Model 1 – V_A and V_E as a function of moderator

The gene by environment interaction model can be written as

$$y_i = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i + (a + a' M_i) g_i + (e + e' M_i)\epsilon_i, \tag{2}$$

where β_l's are some coefficients, w_{il}'s are covariates, M_i is the standardized moderator (i.e., with mean zero and variance one), $g_i = \sum_{k=1}^{m} z_{ik}\alpha_k$, and the coefficients α_k's are some random numbers from a normal distribution with mean zero and variance $1/m$, and $a, a', e, e' \in \mathbb{R}$ are four arbitrary numbers, and ϵ_i's are assumed to be random numbers from a standard normal distribution and independent from α_k. In Appendix, we show that for individuals i and j

$$\text{cov}[y_i, y_j | Z, M_i, M_j] = (a + a' M_i)(a + a' M_j)\frac{1}{m}\sum_{k=1}^{m} z_{ik} z_{jk} + (e + e' M_i)(e + e' M_j)\mathbb{1}_{\{i=j\}}, \tag{3}$$

where $\mathbb{1}_{\{i=j\}} = 1$ if $i = j$ and 0 otherwise, or in the matrix format

$$\text{cov}[Y | Z, M] = \frac{1}{m} T \circ ZZ' + K \circ I_n, \tag{4}$$

where $Y = [y_1, \ldots, y_n]'$ is the column vector of phenotypes and I_n is the identity matrix of size n, $Z = [z_{ik}]$ is the standardized genotype matrix, $T = [(a+a'M_i)(a+a'M_j)]$, $K = [(e+e'M_i)(e+e'M_j)]$, and the operator $\circ$ is Hadamard (Schur) product (or matrix element–wise product).

Equation (4) can be written as

$$\mathrm{cov}[y|Z, M] = a^2 ZZ'/m + aa'\mathbf{\Lambda} \circ ZZ'/m + a'^2\mathbf{\Gamma} \circ ZZ'/m + K \circ I_n, \tag{5}$$

where $\mathbf{\Gamma} = [M_iM_j]$ and $\mathbf{\Lambda} = [M_i + M_j]$. This representation shows that the REML method (implemented by GCTA) can not solve this type of equations, because it is a constrained optimization problem. In fact, the coefficient in the second term (aa') is a function of of the coefficients of the first and third terms.

1.2 Model 2 – V_A constant but V_E as a function of moderator

This model can be written as

$$y_i = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i + ag_i + (e + e'M_i)\epsilon_i, \tag{6}$$

The covariance matrix for this model is

$$\mathrm{cov}[Y|Z, M] = a^2 \frac{1}{m} ZZ' + K \circ I_n, \tag{7}$$

where $K = [(e + e'M_i)(e + e'M_j)]$.

1.3 Model 3 – V_A as a function of moderator but V_E constant

This model can be written as

$$y_i = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i + (a + a'M_i)g_i + e\epsilon_i, \tag{8}$$

The covariance matrix for this model is

$$\mathrm{cov}[Y|Z, M] = \frac{1}{m} T \circ ZZ' + e^2 I_n, \tag{9}$$

where $T = [(a + a'M_i)(a + a'M_j)]$.

1.4 Model 4 – V_A and V_E constant

This model can be written as

$$y_i = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i + ag_i + e\epsilon_i, \tag{10}$$

The covariance matrix for this model is

$$\mathrm{cov}[Y|Z, M] = a^2 \frac{1}{m} ZZ' + e^2 I_n. \tag{11}$$

1.5 Model 5 – V_A and V_E as a function of moderator, but h^2 constant

This model can be written as

$$y_i = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i + (a + a'M_i)g_i + (e + ea'/aM_i)\epsilon_i, \tag{12}$$

This model, which will be used to test if h^2 is constant, is special case of Model 1 with $e' = ea'/a$. In this case,

$$V_E = (e + ea'/aM)^2 = e^2/a^2(a + a'M)^2 = e^2/a^2 V_A$$

is proportional to V_A for all M's, and

$$h^2 = \frac{V_A}{V_A + V_E} = \frac{(a + a'M)^2}{(a + a'M)^2 + e^2/a^2(a + a'M)^2} = \frac{a^2}{a^2 + e^2},$$

is not a function of M.

2 Parameter estimation

Assuming the column vector of phenotypes, $Y = [y_1, \ldots, y_n]'$, follows a normal distribution, then each model follows a multivariate normal distribution with mean $\beta_0 + \sum_l \beta_l w_{il} + \lambda M_i$ and the covariance matrix presented in Subsections 1.1–1.5. We used the maximum likelihood (ML) method to estimate the parameters. Since ML estimations are computationally extensive and need huge RAM, so we used XSEDE computing facilities [12] for part of these simulations.

Finding the initial value for all the numerical optimization methods is crucial and can dramatically decrease computational time. Starting from a random initial value can lead to finding a local optimal point, and as a result the estimated parameters could be unbiased. In many cases, the optimization algorithm will not converge, if we start from a bad initial value. In the following subsections, we use moment matching method for finding the initial values for Models 1 and 3. The method for finding the initial values for model 2 is similar to Model 3, and for model 4 the Haseman-Elston (HE) regression, which is the moment matching method, will be used.

2.1 Initial values for the parameters of Model 1

We can rewrite equation (4) as

$$\text{cov}[y|Z, M] = a^2 ZZ'/m + aa'\mathbf{\Lambda} \circ ZZ'/m + a'^2\mathbf{\Gamma} \circ ZZ'/m + e^2 I_n + ee'\mathbf{\Lambda} \circ I_n + e'^2\mathbf{\Gamma} \circ I_n,$$

where $\mathbf{\Gamma} = [M_i M_j]$ and $\mathbf{\Lambda} = [M_i + M_j]$. Using moment matching method, we can estimate initial values for a and a', denoted by $\tilde{a}$ and $\tilde{a}'$, by fitting the non-linear model $\vec{\Psi} \sim a^2\vec{A}_1 + aa'\vec{A}_2 + a'^2\vec{A}_3$, where $\vec{X}$ denotes the vector created by the off diagonal elements of matrix X (for elements x_{ij} with $i < j$). Ψ is a matrix with elements $\Psi_{ij} = (y_i - \bar{y})(y_j - \bar{y})$, $A_1 = 1/mZZ'$, $A_2 = \mathbf{\Lambda} \circ ZZ'/m$, and $A_3 = \mathbf{\Gamma} \circ ZZ'/m$. Solving this non-linear model is fast, because there is no need to take inversion of any matrix.

The parameters e and e' then can be initially estimated by fitting the non-linear model $\text{diag}(\Psi_2) \sim e^2\text{diag}(I_n) + ee'\text{diag}(\mathbf{\Lambda}) + e'^2\text{diag}(\mathbf{\Gamma})$, where the matrix $\Psi_2 = \Psi - \tilde{a}^2\text{diag}(A_1) - \tilde{a}\tilde{a}'\text{diag}(A_2) - \tilde{a}'^2\text{diag}(A_3)$, where $\text{diag}(X)$ denotes the diagonal elements of matrix X.

2.2 Initial values for the parameters of Model 3

We can rewrite equation (9) as

$$\text{cov}[y|Z,M] = a^2 ZZ'/m + aa'\mathbf{\Lambda} \circ ZZ'/m + a'^2\mathbf{\Gamma} \circ ZZ'/m + e^2 I_n,$$

where $\mathbf{\Gamma} = [M_i M_j]$ and $\mathbf{\Lambda} = [M_i + M_j]$.

Using moment matching method, we can estimate initial values for a and a', denoted by $\tilde{a}$ and $\tilde{a}'$, by fitting the non-linear model $\vec{\Psi} \sim a^2\vec{A_1} + aa'\vec{A_2} + a'^2\vec{A_3}$. Ψ is a matrix with elements $\Psi_{ij} = (y_i - \bar{y})(y_j - \bar{y})$, $A_1 = 1/mZZ'$, $A_2 = \mathbf{\Lambda} \circ ZZ'/m$, and $A_3 = \mathbf{\Gamma} \circ ZZ'/m$. Solving this non-linear model is fast, because there is no need to take inversion of any matrix.

The parameter e then can be initially estimated via the mean of vector $\eta = \text{diag}(\Psi) - \tilde{a}^2\text{diag}(A_1) - \tilde{a}\tilde{a}'\text{diag}(A_2) - \tilde{a}'^2\text{diag}(A_3)$, i.e. $\tilde{e} = \bar{\eta}$.

3 Simulation results

For this study, we simulated several populations with sizes $N \in \{500, 1000, 2000, 4000, 8000\}$ for different sets of parameters $\theta = (a, a', e, e')$. These values for θ are shown in Table 2. For θ_6 with $(a, a') = (0.6325, 0.0384)$, the genotypic variance is $V_A = a^2 = .4$ for $M = 0$ and is $(a + a'\,M)^2 = .45$ for $M = 1$, i.e., increasing one standard unit of the moderator, leads to increase of 0.05 units of V_A. Similarly, for $(e, e') = (0.7746, 0.0316)$, the non-genotypic variance is $V_E = E^2 = .6$ for $M = 0$ and is $(e + e'\,M)^2 = .65$ for $M = 1$.

The genotypes were from UK Biobank and phenotypes were simulated using modes 1–5. The cleaning data process for UK Biobank is discussed in the Method section of the paper. For each set of the parameters, we simulated $r = 200$ replications (for $N = 8000$, $r = 100$) with different set of individuals and different set of casual variants (CVs), where the number of CVs is set to be 1000.

3.1 Bias and variance of the estimated parameters

To check the accuracy of the proposed method, we estimated the parameters for each replication and computed the bias and variance as

$$\text{bias}(\hat{\theta}) = \frac{1}{r}\sum_r \left(\hat{\theta}_r - \theta\right),$$

$$\text{var}(\hat{\theta}) = \frac{1}{r}\sum_r \left(\hat{\theta}_r - \mathbb{E}(\hat{\theta})\right)^2,$$

for $\theta \in \{a, a', e, e'\}$, where $\mathbb{E}(\hat{\theta}) = 1/r\sum_r \hat{\theta}_r$, in Tables 4–6. As can be seen, the proposed method is unbiased and can accurately estimate the parameters, especially when the sample size increases.

In order to have a better sense of biasness for the estimated parameters, the results for the simulated data from model 1 with 8000 individuals are plotted in Figure 2 of the main paper. In that figure, we drew the box-plot for the estimated parameters form each of the 5 models. The true values were shown with a horizontal red line. The blue vertical lines were the %95 confidence intervals. The confidence intervals were constructed after removing the outliers. There was also a red star above each box-plot to show that if the difference between the true value and its estimated value is meaningful at $\alpha = 0.05$ level. Figures 18–21 also have the same format when the data are simulated form models 2 to 5, respectively. Based on these plots, we can see the estimated parameters from each of proposed models are unbiased with the minimum variance.

3.2 Power and Type-I calculations

In order to investigate the power, we simulated r data sets with sizes $N \in \{500, 1000, 2000, 4000, 8000\}$ from the model defined by the alternative model (the null and alternative could be any model of 1 to 5, depending on which parameter(s) is(are) going to be tested, e.g., in order to calculate power for testing $a' = 0$ in model 1, the null and alternative are models 2 and 1, respectively, where data are simulated form the alternative model). Then, we computed the maximum value of the log-likelihood for both the null and alternative models. These log-likelihood values are denoted by $\ell(\Theta_0)$ and $\ell(\Theta_1)$, respectively. The test statistics is $\chi^2 = -2(\ell(\Theta_0) - \ell(\Theta_1))$ and will be compared with the critical value $Q_{1-\alpha}$, which can be obtained from the central chi-square distribution with df degrees of freedom, where df is the difference between the number of free parameters of models alternative and null. Finally, the power is computed as

$$\text{Power} = \frac{1}{r}\sum_{i=1}^{r} \mathbb{1}[\chi_i^2 > Q_{1-\alpha}],$$

where we set $\alpha = 0.05$ with $r = 200$ replications (For $N = 8000$, we used $r = 100$).

Similarly, we computed the type I error by simulating r data sets from the null distribution, and then calculating the ratio of rejected test, i.e.,

$$\text{Type I Error} = \frac{1}{r}\sum_{i=1}^{r} \mathbb{1}[\chi_i^2 > Q_{1-\alpha}].$$

As an example, type I error for testing $a' = 0$ in model 1 is computed when the null and alternative are models 2 and 1, respectively, and the data are simulated form the null model.

Tables 7–12 compare the power for testing different parameters in different models and report type I error. According to each model, the true parameters for simulations are chosen from θ_i, presented above each table. For example, in Table 7, the true parameter is θ_1. So $(a, a', e, e') = (0.6325, 0.1151, 0.7746, 0.0949)$ is used for model 1, $(a, e, e') = (0.6325, 0.7746, 0.0949)$ is used for model 2, $(a, a', e) = (0.6325, 0.1151, 0.7746)$ is used for model 3, and so on.

The power and type I error plots for different tests are shown in Figures 10–17 and 1–9, respectively.

3.3 Sensitivity analysis

In this section, the uncertainty in model selection is studied. More precisely, data are simulated from one model and the parameters will be estimated from another model to see how biased are the estimated parameters. Tables 13–20 show the estimated biases and variances.

In general, the bias and variance of estimated parameters increase when the parameters are estimated using a different model rather than the model which the data were simulated. In some cases these differences are big, but in some cases it is negligible. One can get more insight by comparing Tables 4–6 with Tables 13–20. We also plotted these comparisons in Figures 18–21.

4 Results for UK Biobank data

The mean for standardized fluid intelligence score in male and female are statistically different (significant at 0.001). It is .046 in males and -.042 in females. The sample age is in range $[40, 79]$.

The standardized fluid intelligence score decreases slightly as age increases with the slope -0.0092 (p-value ~ 0 and adjusted R-squared $= 0.0057$). The mean for standardized TDI are -0.0028 and -0.0025 in males and females, respectively (p-value$= 0.596$). In this paper, we use the negative of TDI as a measure for SES.

After fitting the covariates in the models 1–5 and estimating the residuals, the parameters (a, a', e and e' – depending on the model) can be estimated using maximum likelihood approach with the appropriate covariance matrix presented in Section 1, assuming that the vector of observations, Y, follows a multivariate normal distribution.

The estimated parameters are presented in the main paper (Table 1). We also calculated the %95 confidence interval (CI) for the each parameter. The p-values are also showed in brackets. Figures 3.a and 3.b in the main paper show the $V_A = (a + a'TDI)^2$, V_E and $V_P = V_A + V_E$ as a function of TDI with a %95 confidence interval for models 3 and 5.

5 Qualitative GxE

This model can be presented as

$$y_{i(k)} = \sigma_g \sum_{j=1}^{m} x_{ij}\alpha_j + \tau_k \sum_{j=1}^{m} x_{ij}\beta_j + \epsilon_i,$$

where $\alpha_j \sim N(0, 1/m)$, $\beta_j \sim N(0, 1/m)$, $\tau_k \sim N(0, \sigma_E^2)$ and $\epsilon_i \sim N(0, \sigma_e^2)$. For this model

$$\text{cov}[Y|X] = \sigma_g^2 A + \sigma_E^2 D \circ A + \sigma_e^2 I,$$

where $D = TT'$ is a $n \times n$ matrix with $D_{ij} = 1$ if individuals i and j have the same environment, and $D_{ij} = 0$ otherwise. In other words, T is a $n \times k$ design matrix with $T_{ik} = 1$ if individual i belongs to environment k and 0 otherwise. GCTA can solve this problem using `--gxe` option.

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Appendix

Here, we just estimate the covariance matrix for models 1 and 3. The proofs for the other models are similar.

Let

$$z_{ik} = (x_{ik} - 2p_k)/\sqrt{2p_k q_k}, \tag{13}$$

be the standardized genotype for individual i and variant k, where $x_{ik} \in \{0,1,2\}$ and p_k is the allele frequency for the kth variant.

Define $g_i = \sum_{k=1}^{m} z_{ik}\alpha_k$. Clearly,

$$\mathbb{E}[g_i|Z] = 0, \tag{14}$$

$$\text{var}[g_i|Z] = \text{var}[\sum_{k=1}^{m} z_{ik}\alpha_k] = \sum_{k=1}^{m} z_{ik}^2 \text{var}[\alpha_k] = \frac{1}{m}\sum_{k=1}^{m} z_{ik}^2, \tag{15}$$

$$\begin{aligned}\text{cov}[g_i, g_j|Z] =& \text{cov}[\sum_{k=1}^{m} z_{ik}\alpha_k, \sum_{k=1}^{m} z_{jk}\alpha_k] \\ =& \sum_{k=1}^{m} z_{ik}z_{jk}\text{cov}[\alpha_k, \alpha_k] = \frac{1}{m}\sum_{k=1}^{m} z_{ik}z_{jk}.\end{aligned} \tag{16}$$

Model 1 – V_A and V_E are a function of moderator

We can write the gene by environment interaction model as

$$y_i = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i + (a + a'M_i)g_i + (e + e'M_i)\epsilon_i, \tag{17}$$

where $g_i = \sum_{k=1}^{m} z_{ik}\alpha_k$.

For this model, the mean, variance and covariance are

$$\mathbb{E}[y_i|Z, M_i] = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i, \tag{18}$$

$$\begin{aligned}\text{var}[y_i|Z, M_i] =& \text{var}[(a + a'M_i)g_i + (e + e'M_i)\epsilon_i|Z, M_i] \\ =& (a + a'M_i)^2 \text{var}[g_i|Z] + (e + e'M_i)^2 \text{var}[\epsilon_i] \\ =& (a + a'M_i)^2 \frac{1}{m}\sum_{k=1}^{m} z_{ik}^2 + (e + e'M_i)^2\end{aligned} \tag{19}$$

and

$$\begin{aligned}\text{cov}[y_i, y_j|Z, M_i, M_j] =& \text{cov}[(a + a'M_i)g_i + (e + e'M_i)\epsilon_i, (a + a'M_j)g_j + (e + e'M_j)E_j|Z, M_i, M_j] \\ =& (a + a'M_i)(a + a'M_j)\text{cov}[g_i, g_j|Z] + (e + e'M_i)(e + e'M_j)\mathbb{1}_{\{i=j\}} \\ =& (a + a'M_i)(a + a'M_j)\frac{1}{m}\sum_{k=1}^{m} z_{ik}z_{jk} + (e + e'M_i)(e + e'M_j)\mathbb{1}_{\{i=j\}}.\end{aligned} \tag{20}$$

And in the matrix format

$$\text{cov}[Y|Z, T] = \frac{1}{m} T \circ ZZ' + K \circ I_n, \tag{21}$$

where $T = [(a + a'M_i)(a + a'M_j)]$, $K = [(e + e'M_i)(e + e'M_j)]$, and the operator $\circ$ is Hadamard (Schur) product (or matrix element–wise product).

Model 3 – V_A as a function of moderator, but V_E constant

We can write the gene by environment interaction model as

$$y_i = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i + (a + a' M_i) g_i + e\epsilon_i, \tag{22}$$

The mean, variance and covariance are

$$\mathbb{E}[y_i|Z, M_i] = \beta_0 + \sum_l \beta_l w_{il} + \lambda M_i, \tag{23}$$

$$\begin{aligned} \text{var}[y_i|Z, M_i] =& \text{var}[(a + a' M_i) g_i + e\epsilon_i|Z, M_i] \\ =& (a + a' M_i)^2 \text{var}[g_i|Z] + e^2 \text{var}[\epsilon_i] \\ =& (a + a' M_i)^2 \frac{1}{m} \sum_{k=1}^{m} z_{ik}^2 + e^2 \end{aligned} \tag{24}$$

and

$$\begin{aligned} \text{cov}[y_i, y_j|Z, M_i, M_j] =& \text{cov}[(a + a' M_i) g_i + e\epsilon_i, (a + a' M_j) g_j + eE_j|Z, M_i, M_j] \\ =& (a + a' M_i)(a + a' M_j) \text{cov}[g_i, g_j|Z] + e^2 \mathbb{1}_{\{i=j\}} \\ =& (a + a' M_i)(a + a' M_j) \frac{1}{m} \sum_{k=1}^{m} z_{ik} z_{jk} + e^2 \mathbb{1}_{\{i=j\}}. \end{aligned} \tag{25}$$

And in the matrix format

$$\text{cov}[Y|Z, T] = \frac{1}{m} T \circ ZZ' + e^2 I_n, \tag{26}$$

where $T = [(a + a' M_i)(a + a' M_j)]$, and the operator $\circ$ is Hadamard (Schur) product (or matrix element–wise product).

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Supplementary Table 1: Recent GxE studies on twins

Ref	Study	Twin pairs	Country	Phase of life	SES measure	IQ measure	Result
[13]	Meta analysis	24926	US,EU	CO	SES	Intelligence and academic achievement	For US, V_A increasing, V_E decreasing; reverse for Europe
[2]	Twins of the Brisbane Adolescent Twin Study	2307	AU	AD	Australian Socioeconomic Index 2006 (AUSEI06)	five IQ subtests of the Multidimensional Aptitude Battery	V_A constant, V_E increasing
[8]	Minnesota Twin Family Study (MTFS)	2494	US	AD	Parental occupational, educational and annual household income.	FSIQ	V_A and V_E increasing
[10]	GHCA-database	10897	US,UK, AU,NE	CO	unmeasured environmental factor that is uncorrelated in family members	IQ scores	–
[3]	Midlife in the United States (MIDUS)	851	US	MC	Duncan Socioeconomic Index	five cognitive-ability tests	V_A and V_E increasing
[6]	Twins Early Development Study (TEDS)	8716	EN	CH,AD	parental education, occupation, and family income	verbal and nonverbal cognitive tests	h^2 increasing
[14]	National Merit Twin Study	777	US	AD	NMSQT (English Usage, Mathematics Usage, Social Science Reading, Natural Science Reading, and Word Usage.)	Intellectual Efficiency scale of the California Psychological Inventory	V_A increasing, V_E decreasing
[11]	Early Childhood Longitudinal Study-Birth Cohort (ECLS-B)	700	US	EC	paternal and maternal education, paternal and maternal occupation, and family income	Bayley Short Form-Research Edition (BSF-R)	V_A increasing, V_E decreasing
[15]	Early Childhood Longitudinal Study-Birth Cohort (ECLS-B)	750	US	EC	paternal and maternal education, paternal and maternal occupation, and family income	Bayley Short Form test of infant mental ability	V_A increasing, V_E decreasing
[5, 9]	Vietnam Era Twin Registry (VET)	3203	US	EA,MA	Parental education	Armed Forces Qualification Test (AFQT)	h^2 decreasing
[17]	Netherlands Twin Register–Adult (NTR-A)	314	NE	EA,MA	parental and partner educational level, as well as urbanization level and mean real estate price of the participants' residential area.	Full scale IQ scores (FSIQ)	V_A constant, V_E increasing
[7]	National Merit Scholastic Qualifying Test	839	US	AD	Parental income and education	English Usage, Mathematics Usage, Social Science Reading, Natural Science Reading, and Word Usage-Vocabulary	V_A increasing, V_E constant
[1]	Twins Early Development Study (TEDS)	8716	EN	CH,AD	parental education, occupation, and family income	verbal and nonverbal cognitive tests	h^2 decreases for verbal ability and increase for nonverbal ability
[16]	National Collaborative Perinatal Project (NCPP)	319	US	EC	parental education, occupational status, and income	Wechsler Intelligence Scale for Children (WISC)	V_A increasing, V_E decreasing
[4]	Swedish Twin Registry	215	SW	MC	parental occupation and family income	verbal test, an inductive test, and a clerical speed test	–

Australia (AU) , The Netherlands (NE), England (EN), Sweden (SW) — Adolescent (AD), Childhood (CH), Middle childhood (MC), Early Childhood (EC), Early adulthood (EA), Middle adulthood (MA), Combined (CO)

Supplementary Table 2: Different sets of values for $\theta = (a, a', e, e')$ used for simulations.

Set 1	$\theta_1 = (0.6325, 0.1151, 0.7746, 0.0949)$
Set 2	$\theta_2 = (0.6325, 0.0767, 0.7746, 0.0949)$
Set 3	$\theta_3 = (0.6325, 0.0767, 0.7746, 0.0633)$
Set 4	$\theta_4 = (0.6325, 0.0767, 0.7746, 0.0316)$
Set 5	$\theta_5 = (0.6325, 0.0384, 0.7746, 0.0633)$
Set 6	$\theta_6 = (0.6325, 0.0384, 0.7746, 0.0316)$

Supplementary Table 3: Simulation results for model 1 with different set of parameters and different sample sizes, N. Columns are bias and standard deviation of the estimation for different sets of true parameters, θ_i, presented in Table 2.

θ	N	$\hat{a}$		$\hat{a}'$		$\hat{e}$		$\hat{e}'$	
		bias	sd	bias	sd	bias	sd	bias	sd
θ_1	500	−0.0579	0.3737	0.0052	0.0865	−0.1505	0.3642	−0.0148	0.1116
	1000	−0.0217	0.2386	0.0137	0.0763	−0.0485	0.1840	−0.0058	0.0765
	2000	−0.0092	0.1128	0.0030	0.0726	−0.0091	0.0877	0.0033	0.0609
	4000	−0.0046	0.0593	−0.0019	0.0509	−0.0008	0.0451	0.0037	0.0403
	8000	0.0004	0.0349	0.0038	0.0331	0.0000	0.0254	−0.0016	0.0265
θ_2	500	−0.0472	0.3127	0.0056	0.1083	−0.0955	0.2746	−0.0075	0.0930
	1000	0.0005	0.1961	0.0037	0.0833	−0.0595	0.1861	−0.0014	0.0752
	2000	−0.0154	0.1096	−0.0006	0.0753	−0.0110	0.0897	−0.0037	0.0578
	4000	−0.0029	0.0575	−0.0014	0.0570	−0.0052	0.0465	0.0028	0.0456
	8000	−0.0009	0.0303	−0.0012	0.0340	−0.0031	0.0219	0.0006	0.0267
θ_3	500	−0.0617	0.3670	0.0140	0.0978	−0.1249	0.3200	−0.0200	0.1124
	1000	−0.0595	0.2569	0.0073	0.0834	−0.0298	0.1970	−0.0020	0.0796
	2000	−0.0039	0.1051	0.0000	0.0730	−0.0139	0.0840	0.0019	0.0589
	4000	−0.0031	0.0519	0.0027	0.0598	−0.0024	0.0399	0.0009	0.0472
	8000	0.0005	0.0327	0.0079	0.0345	−0.0018	0.0245	−0.0060	0.0267
θ_4	500	−0.0662	0.3710	−0.0022	0.0957	−0.1303	0.3362	0.0016	0.0974
	1000	−0.0391	0.2421	−0.0024	0.0823	−0.0465	0.2191	0.0001	0.0841
	2000	−0.0008	0.1148	−0.0055	0.0801	−0.0191	0.0903	0.0043	0.0660
	4000	0.0013	0.0539	−0.0096	0.0560	−0.0072	0.0418	0.0074	0.0466
	8000	0.0026	0.0312	−0.0016	0.0373	−0.0039	0.0217	0.0018	0.0292
θ_5	500	−0.0687	0.3476	−0.0047	0.1025	−0.1213	0.3447	0.0017	0.0887
	1000	−0.0161	0.2173	0.0099	0.0861	−0.0603	0.2169	−0.0026	0.0778
	2000	−0.0122	0.1251	−0.0043	0.0755	−0.0108	0.0895	0.0037	0.0583
	4000	−0.0026	0.0622	0.0041	0.0610	−0.0061	0.0479	−0.0029	0.0492
	8000	−0.0008	0.0346	0.0031	0.0383	−0.0029	0.0259	−0.0018	0.0300
θ_6	500	−0.0860	0.3615	0.0025	0.1059	−0.1025	0.3133	−0.0033	0.0947
	1000	−0.0205	0.2312	0.0087	0.0909	−0.0482	0.1746	−0.0013	0.0835
	2000	−0.0220	0.1173	−0.0042	0.0771	0.0001	0.0815	0.0043	0.0617
	4000	−0.0059	0.0585	−0.0048	0.0646	−0.0023	0.0470	0.0047	0.0531
	8000	0.0001	0.0338	0.0039	0.0348	−0.0018	0.0238	−0.0034	0.0273

Supplementary Table 4: Simulation results for model 2 with different set of parameters and different sample sizes, N. Columns are bias and standard deviation for different sets of true parameters, θ_i, presented in Table 2. Model 2 has no a' in either simulation or estimation.

θ	N	$\hat{a}$		$\hat{e}$		$\hat{e}'$	
		bias	sd	bias	sd	bias	sd
	500	−0.0954	0.3467	−0.0506	0.2502	0.0215	0.0731
	1000	−0.0355	0.2281	−0.0248	0.1713	0.0113	0.0480
θ_1	2000	−0.0086	0.1254	−0.0063	0.0927	0.0039	0.0251
	4000	0.0009	0.0584	−0.0032	0.0461	0.0019	0.0171
	8000	0.0003	0.0334	0.0012	0.0237	0.0004	0.0103
	500	−0.1353	0.3440	−0.0220	0.2436	0.0163	0.0651
	1000	−0.0493	0.2219	−0.0090	0.1604	0.0024	0.0425
θ_2	2000	−0.0071	0.1112	−0.0104	0.0983	0.0030	0.0308
	4000	−0.0079	0.0546	0.0017	0.0430	−0.0003	0.0148
	8000	−0.0005	0.0299	−0.0021	0.0221	−0.0015	0.0091
	500	−0.0824	0.3486	−0.0734	0.2768	0.0330	0.0930
	1000	−0.0393	0.2554	−0.0347	0.1891	0.0108	0.0479
θ_3	2000	−0.0163	0.1095	0.0044	0.0843	0.0026	0.0233
	4000	0.0027	0.0575	−0.0041	0.0460	0.0002	0.0153
	8000	−0.0007	0.0314	0.0007	0.0237	−0.0007	0.0105
	500	−0.1079	0.3685	−0.0765	0.2980	0.0125	0.0845
	1000	−0.0622	0.2618	−0.0246	0.1991	0.0055	0.0393
θ_4	2000	−0.0076	0.1247	−0.0098	0.0874	0.0010	0.0201
	4000	0.0040	0.0573	−0.0061	0.0451	0.0014	0.0141
	8000	0.0028	0.0313	−0.0029	0.0214	0.0005	0.0102
	500	−0.1169	0.3491	−0.0418	0.2653	0.0233	0.0736
	1000	−0.0527	0.2569	−0.0288	0.1892	0.0104	0.0486
θ_5	2000	−0.0219	0.1238	−0.0013	0.0882	0.0008	0.0229
	4000	−0.0033	0.0603	−0.0029	0.0455	0.0017	0.0158
	8000	−0.0015	0.0339	−0.0012	0.0249	0.0002	0.0101
	500	−0.0997	0.3737	−0.0806	0.3034	0.0193	0.0860
	1000	−0.0601	0.2539	−0.0159	0.1716	0.0048	0.0339
θ_6	2000	0.0186	0.1164	−0.0329	0.1074	−0.0008	0.0247
	4000	−0.0032	0.0595	−0.0022	0.0457	0.0002	0.0142
	8000	−0.0003	0.0338	−0.0002	0.0238	−0.0006	0.0090

Supplementary Table 5: Simulation results for model 3 with different set of parameters and different sample sizes, N. Columns are bias and standard deviation for different sets of true parameters, θ_i, presented in Table 2. Model 3 has no e' in either simulation or estimation.

θ	N	$\hat{a}$		$\hat{a}'$		$\hat{e}$	
		bias	sd	bias	sd	bias	sd
θ_1	500	0.0113	0.2690	0.0166	0.0860	−0.1373	0.3222
	1000	0.0002	0.1660	0.0071	0.0535	−0.0378	0.1560
	2000	−0.0062	0.1052	0.0070	0.0357	−0.0084	0.0842
	4000	0.0026	0.0589	−0.0002	0.0211	−0.0025	0.0451
	8000	0.0004	0.0324	0.0018	0.0135	0.0011	0.0224
θ_2	500	−0.0418	0.2857	0.0217	0.0867	−0.0835	0.2922
	1000	−0.0227	0.1968	0.0155	0.0584	−0.0306	0.1680
	2000	−0.0093	0.1121	0.0026	0.0277	−0.0046	0.0836
	4000	−0.0013	0.0610	−0.0004	0.0194	−0.0026	0.0469
	8000	−0.0008	0.0302	−0.0011	0.0123	−0.0020	0.0216
θ_3	500	−0.0278	0.2826	0.0291	0.0917	−0.1115	0.3169
	1000	−0.0305	0.2104	0.0174	0.0598	−0.0238	0.1690
	2000	−0.0161	0.1212	0.0083	0.0340	−0.0016	0.0853
	4000	−0.0003	0.0581	0.0028	0.0196	−0.0012	0.0425
	8000	−0.0013	0.0321	0.0007	0.0137	0.0010	0.0237
θ_4	500	−0.0409	0.3028	0.0203	0.0973	−0.1124	0.3275
	1000	−0.0251	0.2151	0.0170	0.0608	−0.0376	0.1982
	2000	−0.0038	0.1356	0.0070	0.0357	−0.0175	0.0988
	4000	0.0004	0.0540	0.0023	0.0205	−0.0043	0.0407
	8000	0.0032	0.0310	0.0005	0.0136	−0.0032	0.0208
θ_5	500	−0.0055	0.3042	0.0093	0.0906	−0.1497	0.3410
	1000	−0.0641	0.2221	0.0103	0.0614	−0.0024	0.1612
	2000	0.0038	0.1121	0.0032	0.0302	−0.0188	0.0888
	4000	−0.0067	0.0578	−0.0001	0.0184	0.0003	0.0435
	8000	−0.0012	0.0346	−0.0001	0.0132	−0.0014	0.0252
θ_6	500	−0.0442	0.3212	0.0053	0.1097	−0.1084	0.3236
	1000	−0.0401	0.2238	0.0115	0.0628	−0.0238	0.1693
	2000	−0.0152	0.1128	0.0065	0.0291	0.0006	0.0854
	4000	−0.0006	0.0607	0.0011	0.0162	−0.0029	0.0453
	8000	−0.0002	0.0336	−0.0005	0.0112	−0.0002	0.0236

Supplementary Table 6: Simulation results for model 4 with different set of parameters and different sample sizes, N. Columns are bias and standard deviation for different sets of true parameters, θ_i, presented in Table 2. Model 4 has no a', e' in either simulation or estimation.

θ	N	$\hat{a}$		$\hat{e}$	
		bias	sd	bias	sd
θ_1	500	−0.0681	0.3553	−0.0967	0.3205
	1000	−0.0391	0.2498	−0.0365	0.2121
	2000	−0.0218	0.1407	0.0000	0.0942
	4000	0.0055	0.0546	−0.0054	0.0425
	8000	0.0007	0.0339	0.0010	0.0238

Supplementary Table 7: Power for testing different parameters to check if they are zero or not. The numbers in parentheses are the type I error. The true parameters for simulations belong to θ_1, according to the null and alternative models.

	N				
H_0 test	500	1000	2000	4000	8000
a' in model 1	0.03 (0.03)	0.05 (0.02)	0.16 (0.06)	0.5 (0.09)	0.97 (0.01)
e' in model 1	0.05 (0.01)	0.12 (0.02)	0.34 (0.02)	0.8 (0.08)	0.96 (0.11)
(a', e') in model 1	0.99 (0.04)	1 (0.01)	1 (0.02)	1 (0.03)	1 (0.09)
(a, a', e') in model 1	0.98 (0.02)	1 (0.04)	1 (0.04)	1 (0.03)	1 (0.05)
e' in model 2	0.65 (0.06)	0.92 (0.04)	1 (0.02)	1 (0.04)	1 (0.05)
(a, e') in model 2	0.61 (0.04)	0.92 (0.04)	1 (0.04)	1 (0.04)	1 (0.06)
a' in model 3	0.6 (0.07)	0.88 (0.05)	1 (0.02)	1 (0.04)	1 (0.06)
(a, a') in model 3	0.58 (0.05)	0.88 (0.06)	1 (0.05)	1 (0.05)	1 (0.09)
a in model 4	0.13 (0.02)	0.36 (0.02)	0.8 (0.04)	1 (0.04)	1 (0.05)

Supplementary Table 8: Power for testing different parameters to check if they are zero or not. The numbers in parentheses are the type I error. The true parameters for simulations belong to θ_2, according to the null and alternative models.

	N				
H_0 test	500	1000	2000	4000	8000
a' in model 1	0.02 (0.01)	0.04 (0.06)	0.1 (0.05)	0.28 (0.07)	0.65 (0.02)
e' in model 1	0.02 (0.01)	0.04 (0.01)	0.24 (0.04)	0.72 (0.06)	0.97 (0.06)
(a', e') in model 1	0.94 (0.03)	1 (0.04)	1 (0.06)	1 (0.04)	1 (0.04)
(a, a', e') in model 1	0.91 (0.02)	1 (0.01)	1 (0.02)	1 (0.03)	1 (0.01)
e' in model 2	0.63 (0.06)	0.88 (0.06)	1 (0.04)	1 (0.04)	1 (0.02)
(a, e') in model 2	0.55 (0.02)	0.9 (0.02)	1 (0.03)	1 (0.03)	1 (0.03)
a' in model 3	0.34 (0.06)	0.57 (0.06)	0.87 (0.04)	0.98 (0.04)	1 (0.03)
(a, a') in model 3	0.3 (0.02)	0.7 (0.02)	0.96 (0.03)	1 (0.03)	1 (0.03)
a in model 4	0.15 (0.02)	0.3 (0.02)	0.87 (0.04)	1 (0.01)	1 (0.02)

Supplementary Table 9: Power for testing different parameters to check if they are zero or not. The numbers in parentheses are the type I error. The true parameters for simulations belong to θ_3, according to the null and alternative models.

	N				
H_0 test	500	1000	2000	4000	8000
a' in model 1	0 (0.02)	0.03 (0.02)	0.04 (0.06)	0.24 (0.05)	0.69 (0.05)
e' in model 1	0.01 (0)	0.04 (0.02)	0.09 (0.05)	0.32 (0.08)	0.65 (0.07)
(a', e') in model 1	0.72 (0.06)	0.96 (0.05)	1 (0.05)	1 (0.05)	1 (0.04)
(a, a', e') in model 1	0.71 (0.02)	0.96 (0.02)	1 (0.03)	1 (0.03)	1 (0.03)
e' in model 2	0.39 (0.1)	0.62 (0.08)	0.91 (0.04)	0.99 (0.06)	1 (0.03)
(a, e') in model 2	0.36 (0.03)	0.7 (0.04)	0.98 (0.05)	1 (0.02)	1 (0.05)
a' in model 3	0.38 (0.08)	0.57 (0.08)	0.9 (0.05)	0.98 (0.05)	1 (0.05)
(a, a') in model 3	0.34 (0.02)	0.64 (0.05)	0.98 (0.05)	1 (0.02)	1 (0.05)
a in model 4	0.1 (0.01)	0.38 (0.03)	0.86 (0.05)	1 (0.01)	1 (0.01)

Supplementary Table 10: Power for testing different parameters to check if they are zero or not. The numbers in parentheses are the type I error. The true parameters for simulations belong to θ_4, according to the null and alternative models.

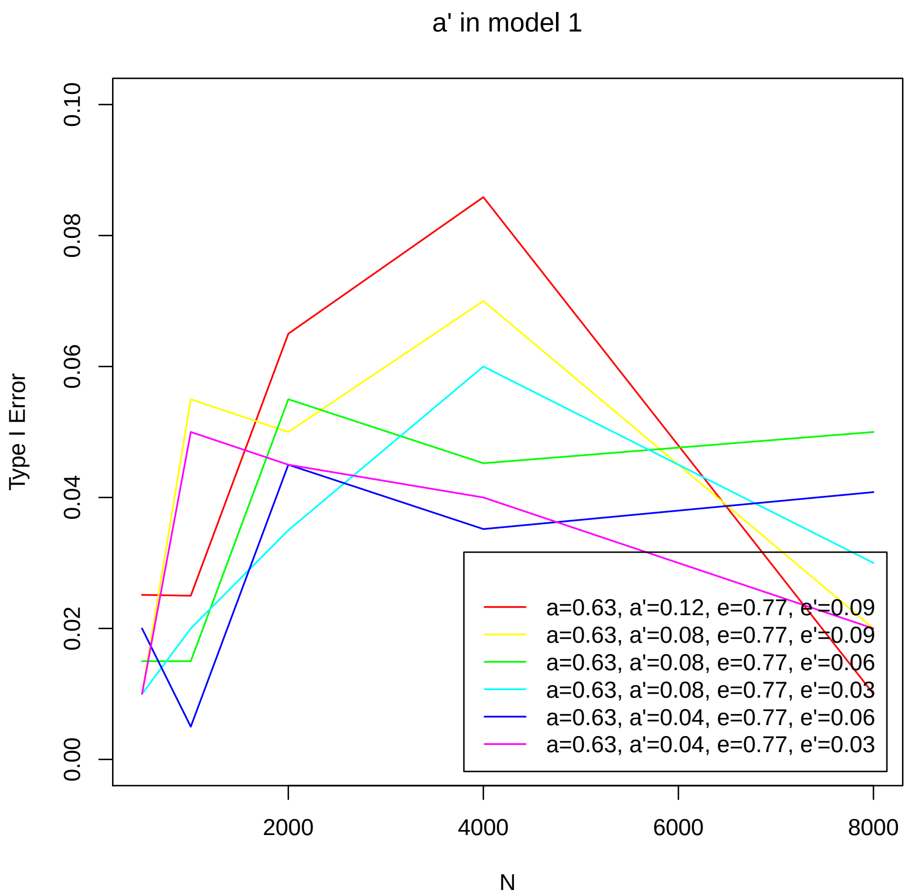
	N				
H_0 test	500	1000	2000	4000	8000
a' in model 1	0.02 (0.01)	0.01 (0.02)	0.08 (0.04)	0.18 (0.06)	0.5 (0.03)
e' in model 1	0 (0)	0.02 (0.02)	0.04 (0.04)	0.1 (0.06)	0.24 (0.06)
(a', e') in model 1	0.49 (0.04)	0.8 (0.04)	0.98 (0.04)	1 (0.04)	1 (0.06)
(a, a', e') in model 1	0.48 (0.01)	0.88 (0.03)	1 (0.04)	1 (0.03)	1 (0.05)
e' in model 2	0.1 (0.05)	0.14 (0.06)	0.36 (0.04)	0.62 (0.07)	0.89 (0.05)
(a, e') in model 2	0.2 (0.02)	0.38 (0.02)	0.9 (0.03)	1 (0.04)	1 (0.03)
a' in model 3	0.32 (0.08)	0.53 (0.1)	0.86 (0.04)	0.98 (0.06)	1 (0.07)
(a, a') in model 3	0.31 (0.03)	0.63 (0.03)	0.96 (0.06)	1 (0.04)	1 (0.06)
a in model 4	0.12 (0)	0.34 (0)	0.86 (0.02)	1 (0.03)	1 (0.06)

Supplementary Table 11: Power for testing different parameters to check if they are zero or not. The numbers in parentheses are the type I error. The true parameters for simulations belong to θ_5, according to the null and alternative models.

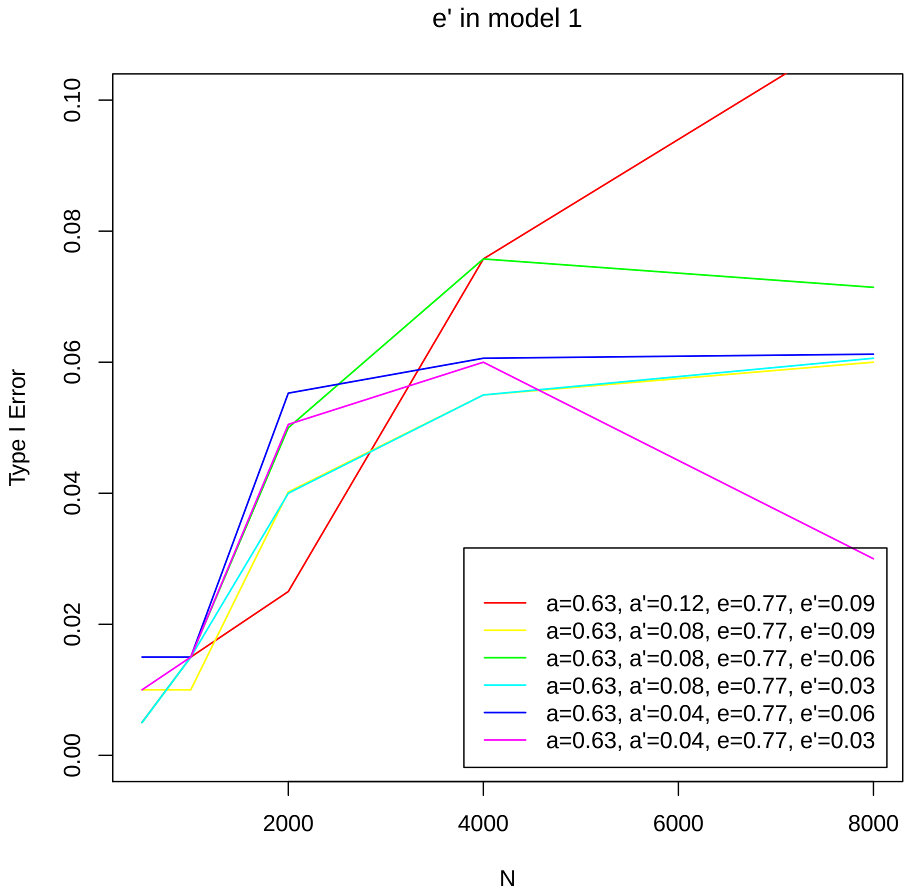
	N				
H_0 test	500	1000	2000	4000	8000
a' in model 1	0.01 (0.02)	0.02 (0)	0.04 (0.04)	0.1 (0.04)	0.2 (0.04)
e' in model 1	0.02 (0.02)	0.02 (0.02)	0.08 (0.06)	0.25 (0.06)	0.6 (0.06)
(a', e') in model 1	0.5 (0.05)	0.81 (0.02)	0.98 (0.06)	1 (0.05)	1 (0.06)
(a, a', e') in model 1	0.45 (0.01)	0.81 (0.01)	1 (0.03)	1 (0.03)	1 (0.03)
e' in model 2	0.38 (0.07)	0.62 (0.04)	0.86 (0.09)	0.99 (0.06)	1 (0.04)
(a, e') in model 2	0.34 (0.02)	0.7 (0.02)	0.97 (0.03)	1 (0.06)	1 (0.03)
a' in model 3	0.17 (0.08)	0.18 (0.04)	0.37 (0.07)	0.56 (0.08)	0.89 (0.08)
(a, a') in model 3	0.2 (0)	0.32 (0.02)	0.92 (0.03)	1 (0.05)	1 (0.02)
a in model 4	0.14 (0.02)	0.4 (0.03)	0.85 (0.04)	1 (0.05)	1 (0)

Supplementary Table 12: Power for testing different parameters to check if they are zero or not. The numbers in parentheses are the type I error. The true parameters for simulations belong to θ_6, according to the null and alternative models.

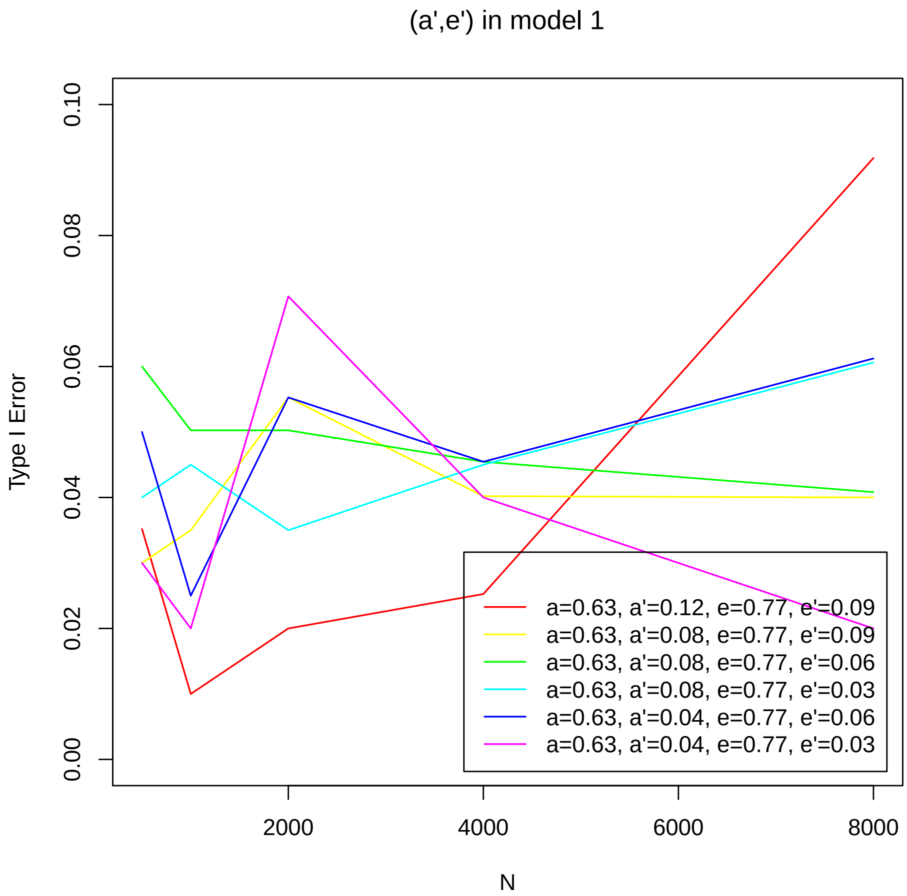
	N				
H_0 test	500	1000	2000	4000	8000
a' in model 1	0 (0.01)	0.02 (0.05)	0.04 (0.04)	0.08 (0.04)	0.18 (0.02)
e' in model 1	0.01 (0.01)	0.02 (0.02)	0.02 (0.05)	0.14 (0.06)	0.15 (0.03)
(a', e') in model 1	0.18 (0.03)	0.49 (0.02)	0.74 (0.07)	0.98 (0.04)	1 (0.02)
(a, a', e') in model 1	0.18 (0.04)	0.62 (0.04)	0.98 (0.03)	1 (0.03)	1 (0.05)
e' in model 2	0.13 (0.04)	0.25 (0.04)	0.33 (0.06)	0.58 (0.02)	0.89 (0.02)
(a, e') in model 2	0.18 (0.04)	0.36 (0.03)	0.9 (0.06)	1 (0.02)	1 (0.03)
a' in model 3	0.14 (0.06)	0.2 (0.02)	0.31 (0.08)	0.62 (0.02)	0.88 (0.03)
(a, a') in model 3	0.15 (0.05)	0.33 (0.04)	0.89 (0.06)	1 (0.02)	1 (0.05)
a in model 4	0.13 (0.02)	0.34 (0.02)	0.91 (0.03)	1 (0)	1 (0.03)



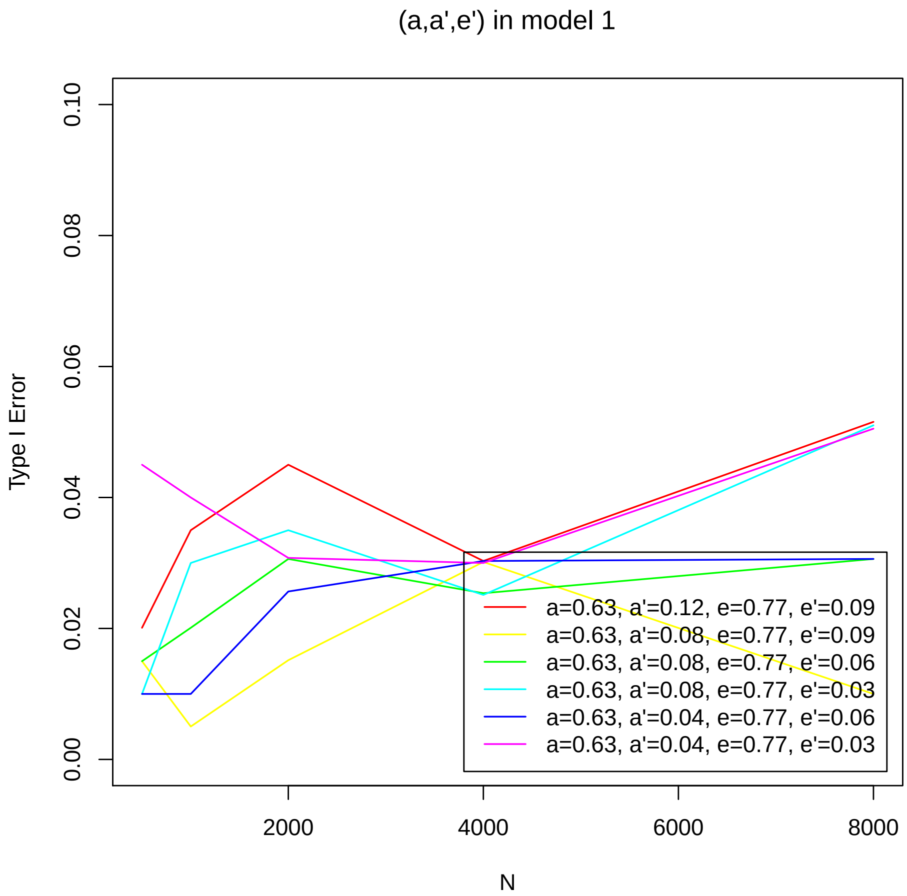
Supplementary Figure 1: Type I error.



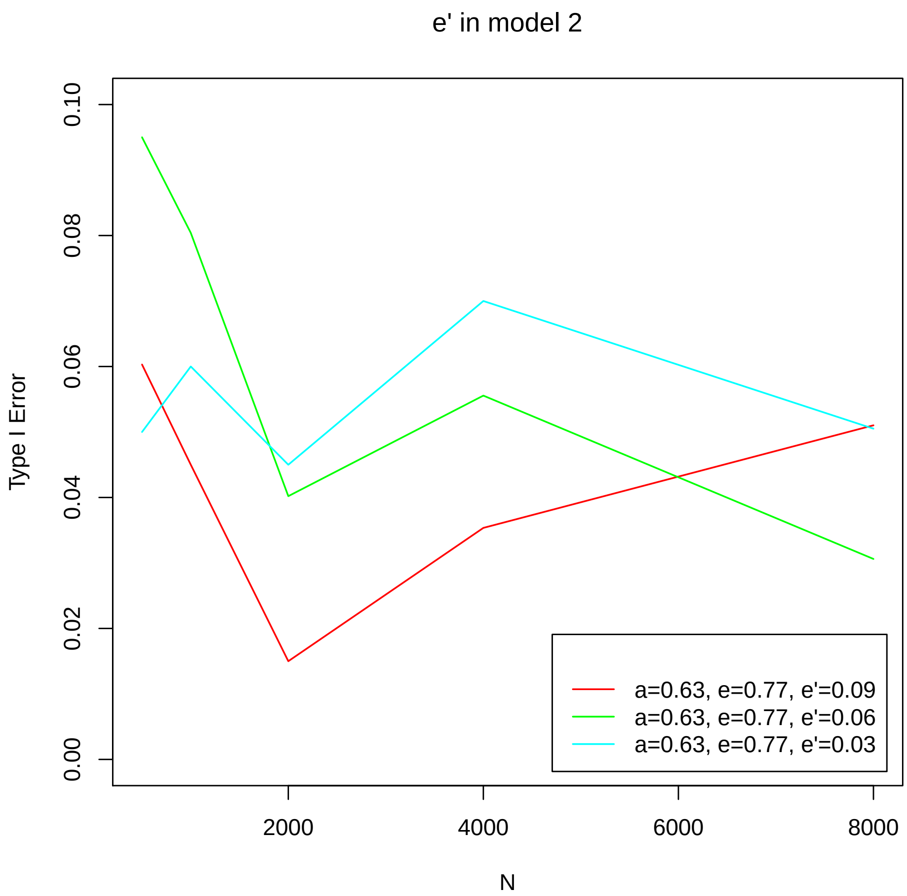
Supplementary Figure 2: Type I error.



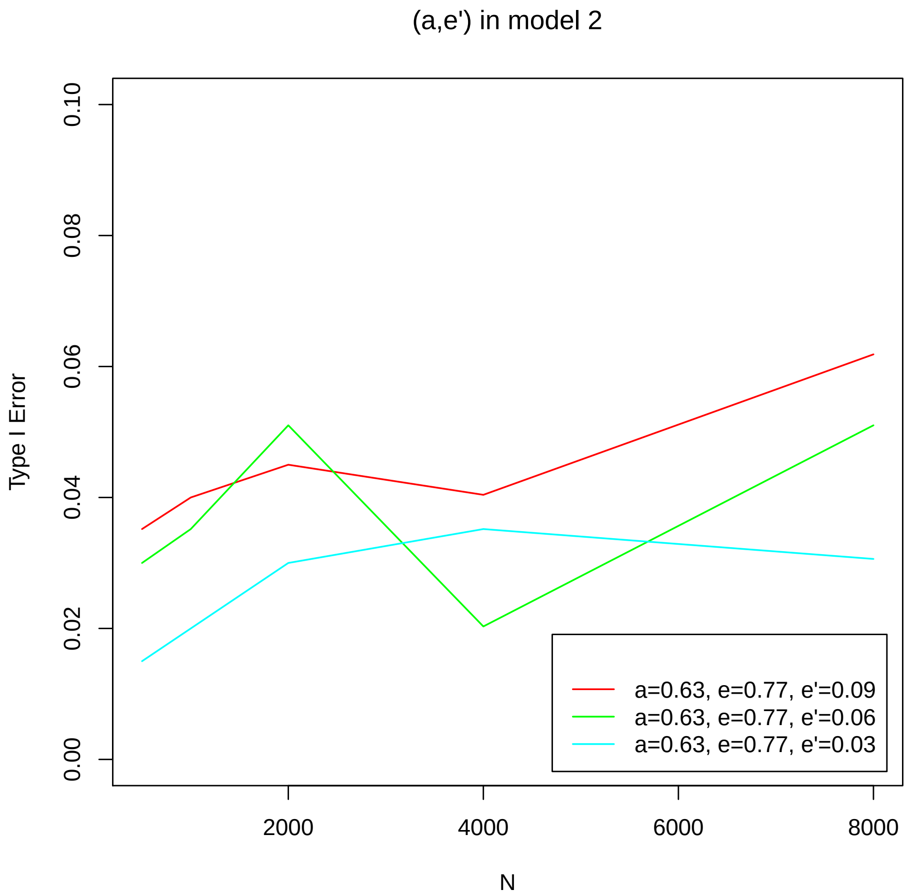
Supplementary Figure 3: Type I error.



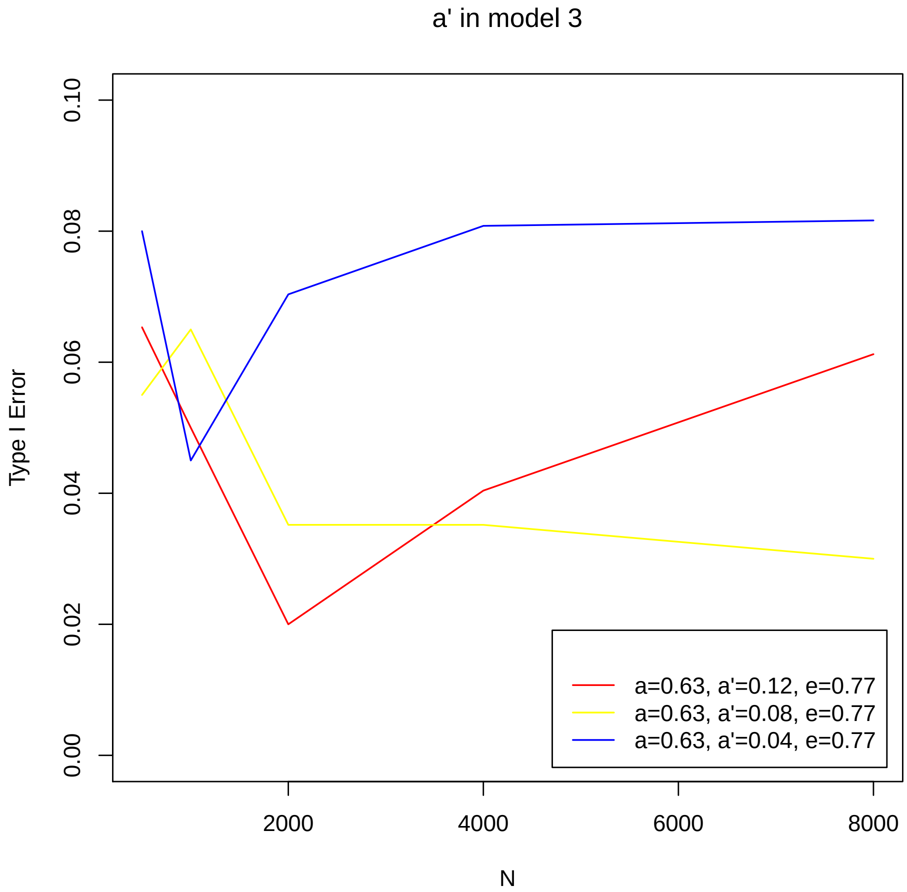
Supplementary Figure 4: Type I error.



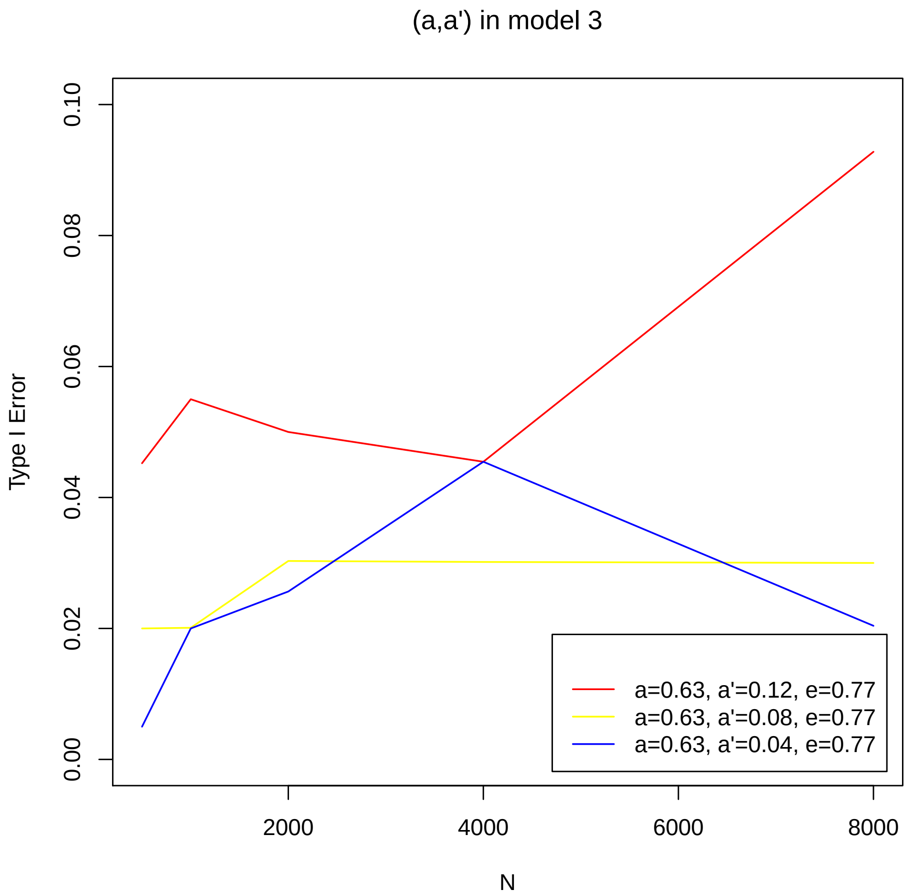
Supplementary Figure 5: Type I error.



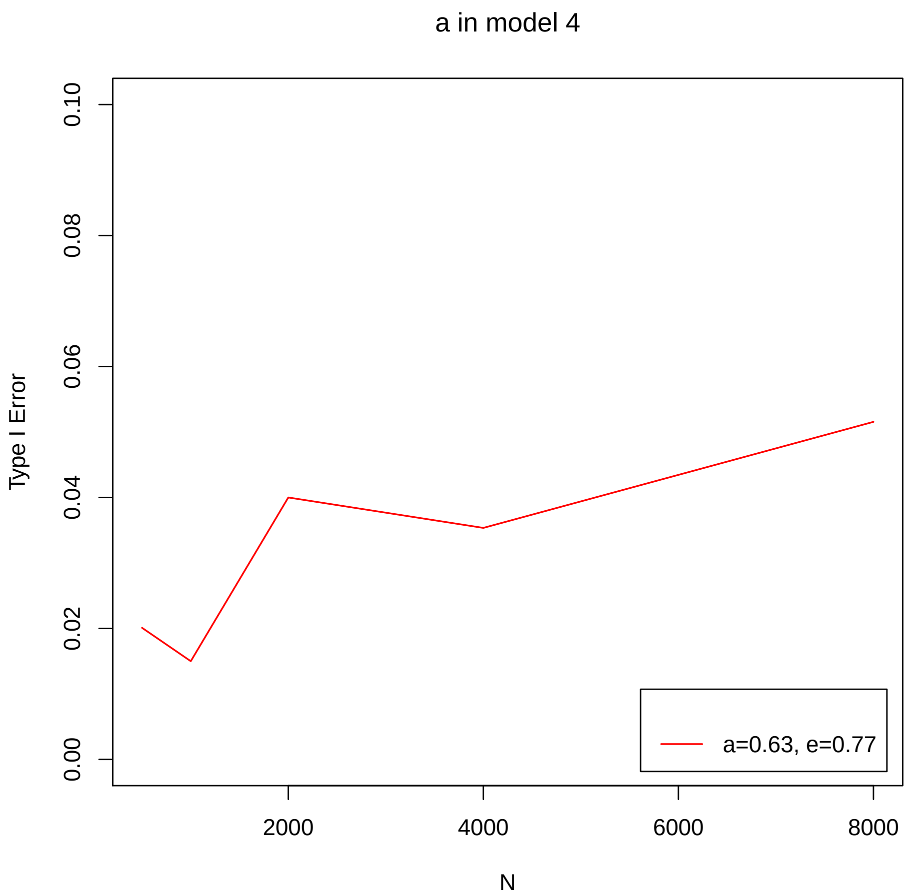
Supplementary Figure 6: Type I error.



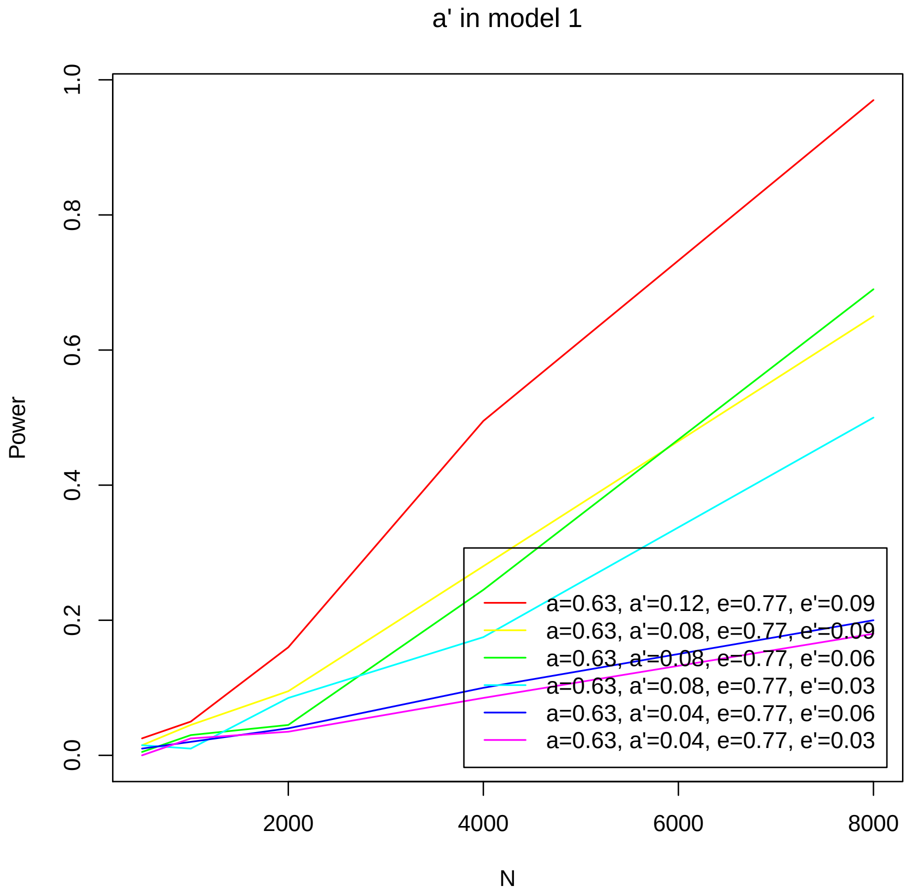
Supplementary Figure 7: Type I error.



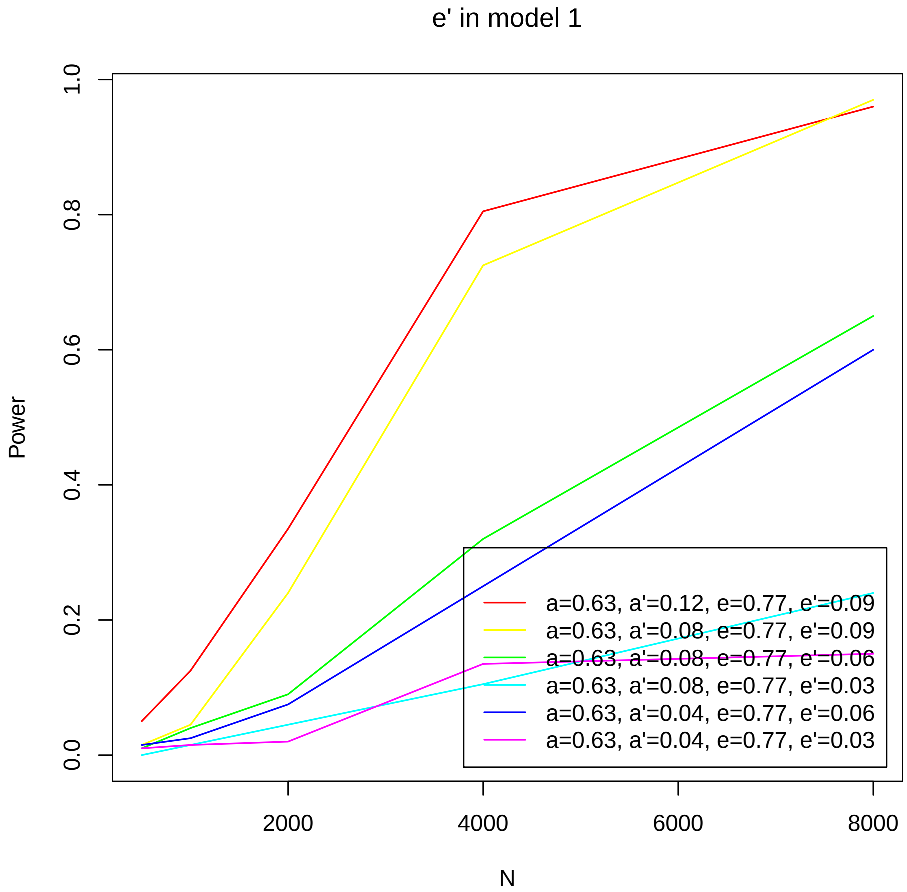
Supplementary Figure 8: Type I error.



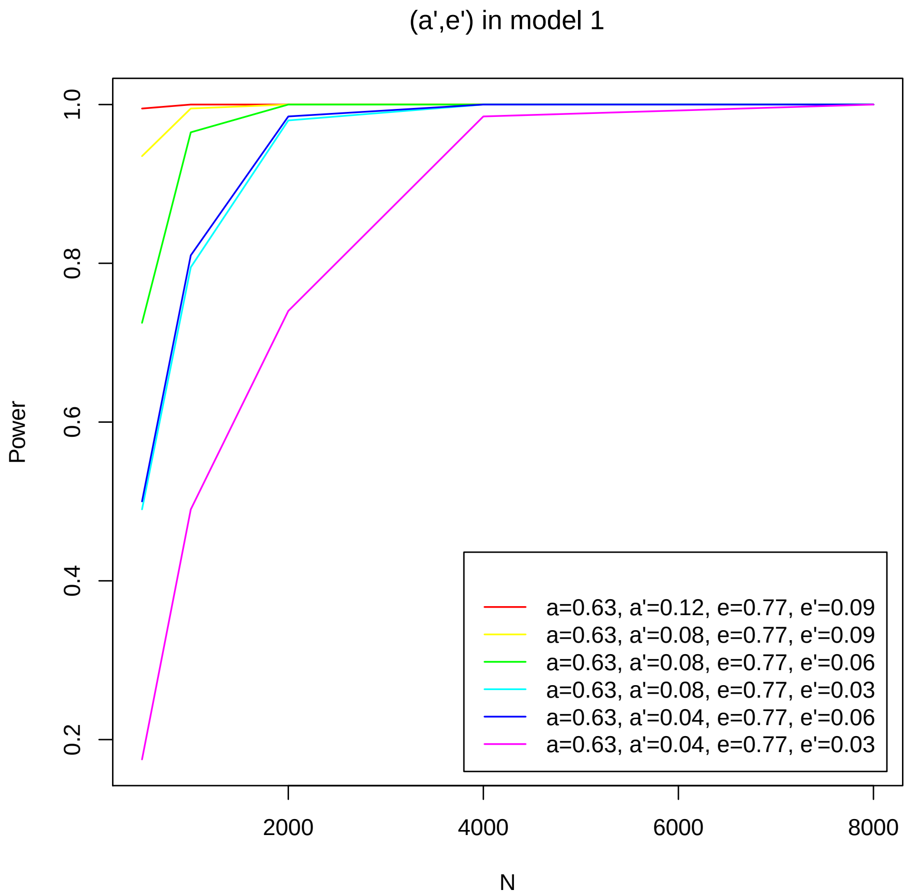
Supplementary Figure 9: Type I error.



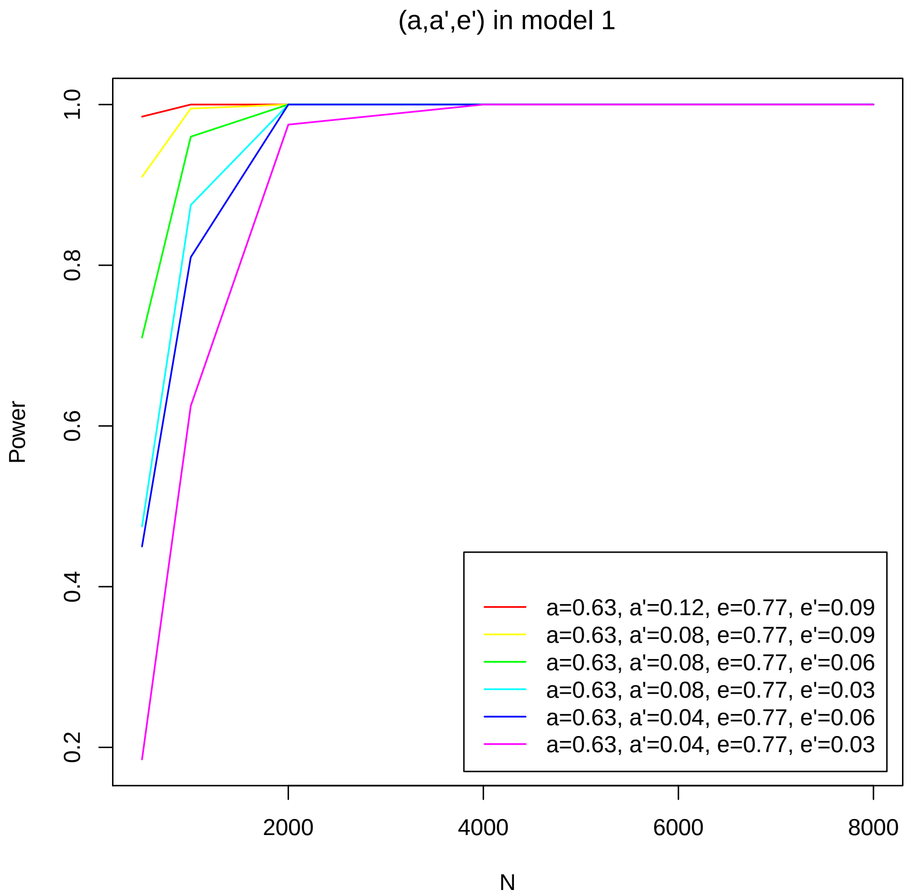
Supplementary Figure 10: Power plot.



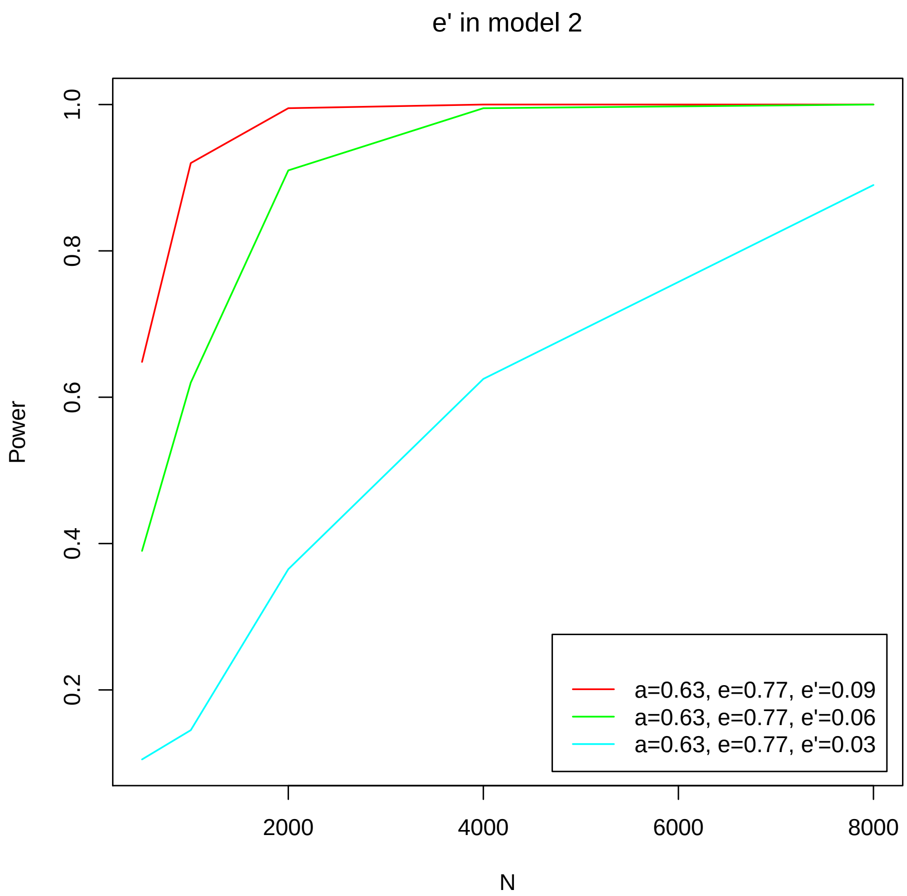
Supplementary Figure 11: Power plot.



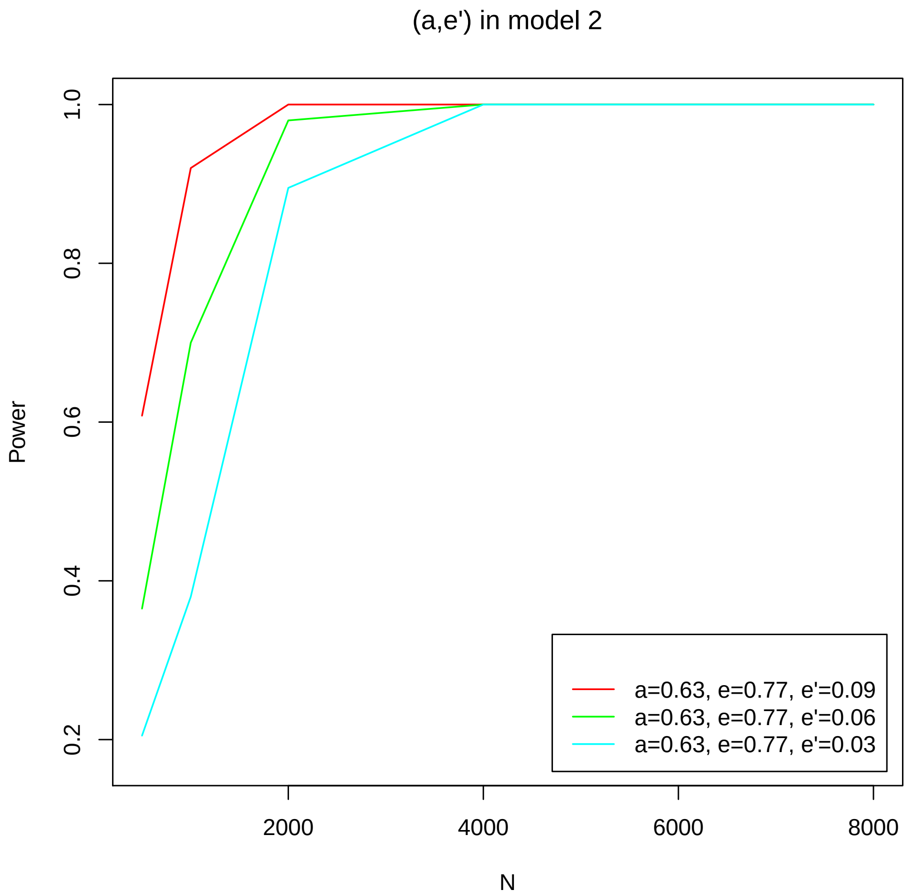
Supplementary Figure 12: Power plot.



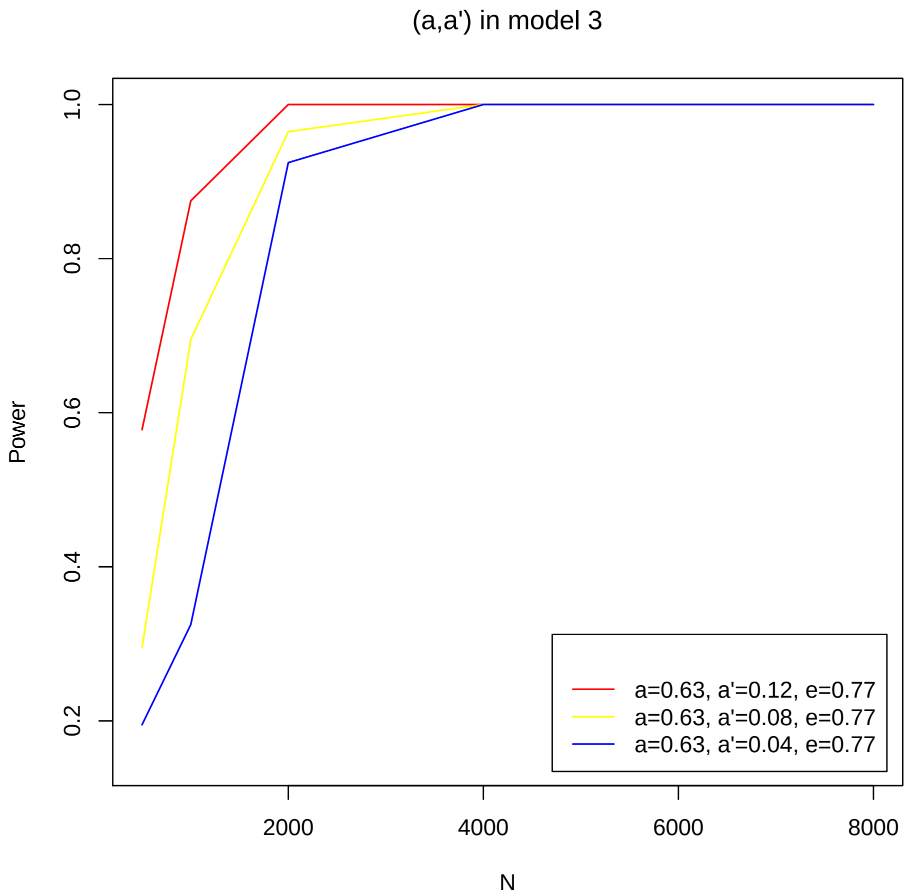
Supplementary Figure 13: Power plot.



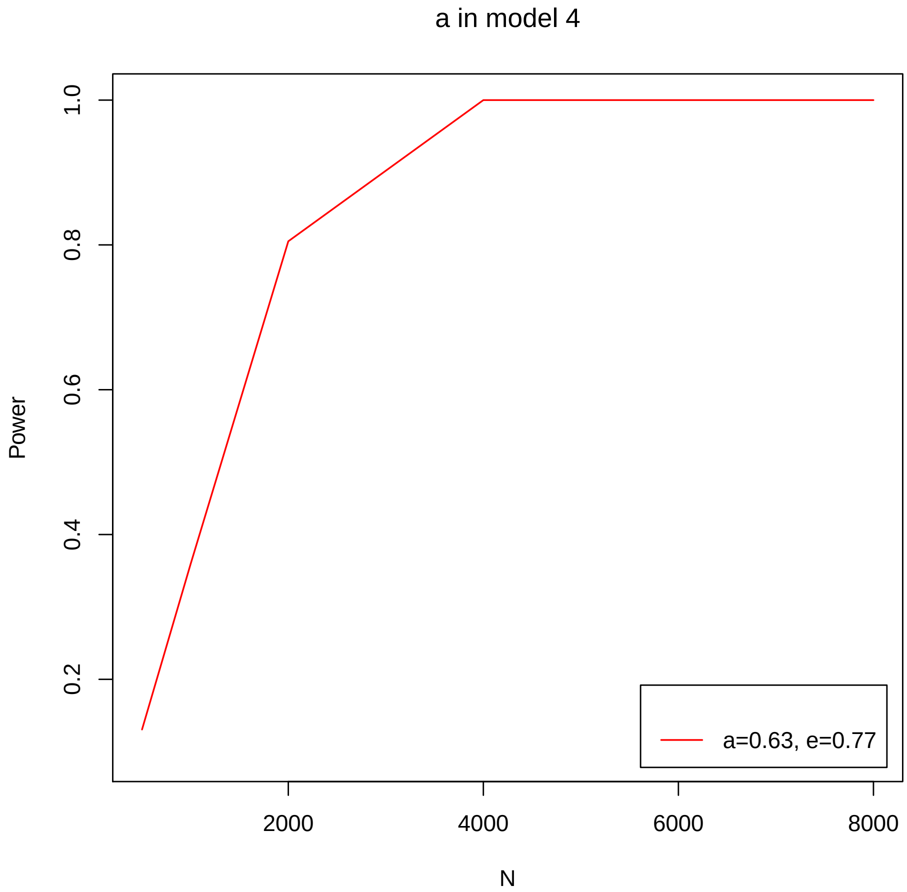
Supplementary Figure 14: Power plot.



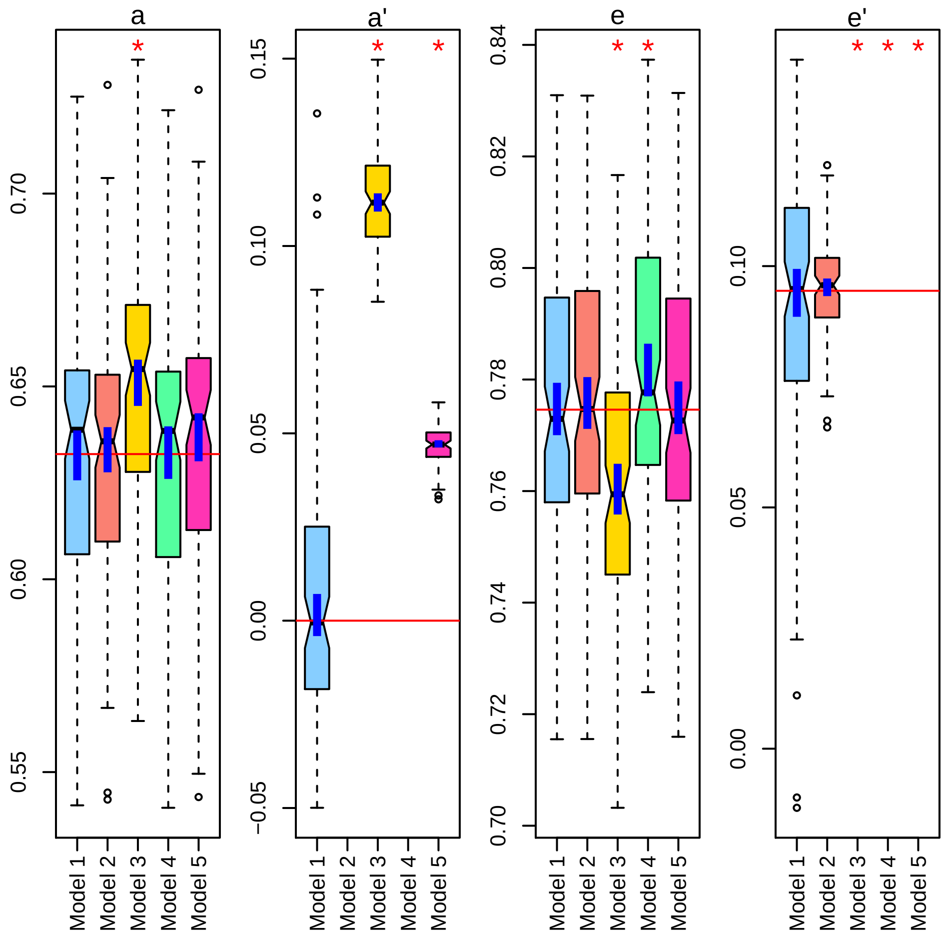
Supplementary Figure 15: Power plot.



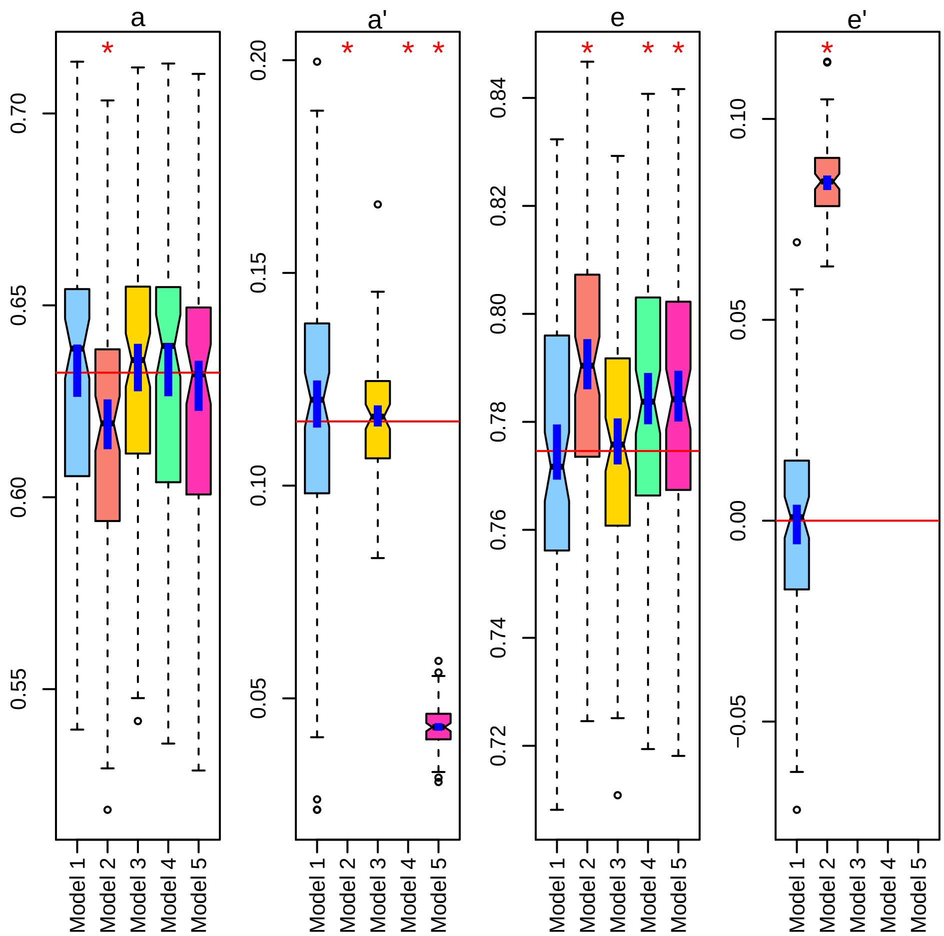
Supplementary Figure 16: Power plot.



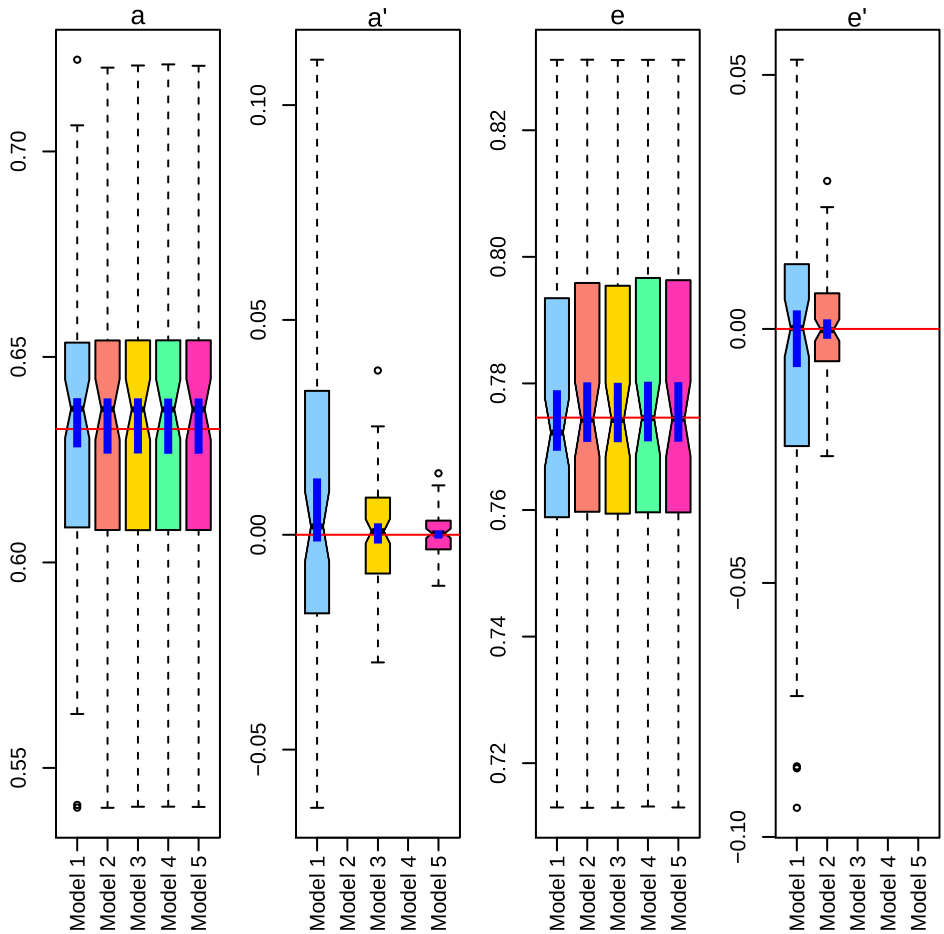
Supplementary Figure 17: Power plot.



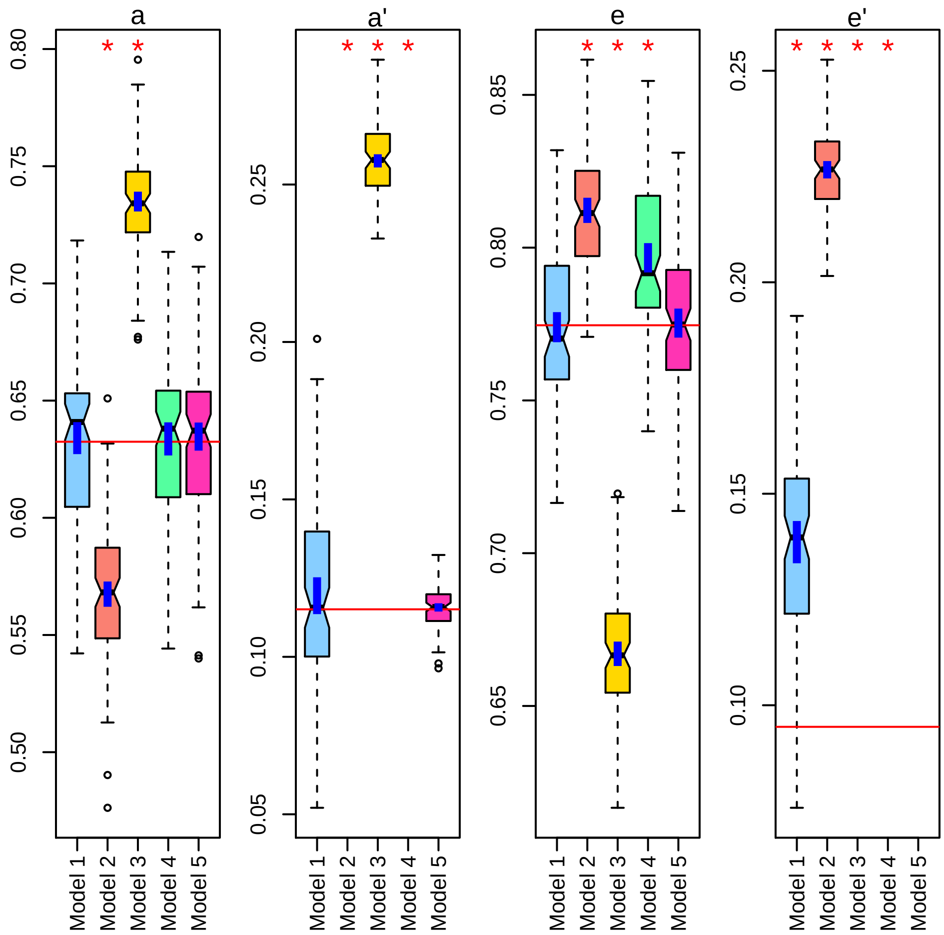
Supplementary Figure 18: Data are simulated form model 2 with $N = 8000$.



Supplementary Figure 19: Data are simulated form model 3 with $N = 8000$.



Supplementary Figure 20: Data are simulated form model 4 with $N = 8000$.



Supplementary Figure 21: Data are simulated form model 5 with $N = 8000$.

Supplementary Table 13: Phenotypes are simulated from model 1, and the parameters are estimated from model 2.

		$\hat{a}$		$\hat{e}$		$\hat{e}'$	
N	θ	bias	var	bias	var	bias	var
500	θ_1	−0.1497	0.0860	0.0215	0.0281	0.1054	0.0037
	θ_2	−0.1526	0.0864	0.0211	0.0303	0.0689	0.0034
	θ_3	−0.1667	0.1147	0.0040	0.0476	0.0782	0.0051
	θ_4	−0.1363	0.1254	−0.0221	0.0608	0.0750	0.0050
	θ_5	−0.1169	0.1110	−0.0255	0.0513	0.0501	0.0042
	θ_6	−0.1238	0.1250	−0.0453	0.0744	0.0489	0.0049
1000	θ_1	−0.1181	0.0426	0.0445	0.0125	0.0927	0.0017
	θ_2	−0.1031	0.0470	0.0310	0.0159	0.0630	0.0014
	θ_3	−0.0790	0.0519	0.0085	0.0214	0.0663	0.0018
	θ_4	−0.0341	0.0503	−0.0267	0.0262	0.0695	0.0020
	θ_5	−0.0429	0.0552	−0.0239	0.0279	0.0432	0.0024
	θ_6	−0.0754	0.0567	0.0003	0.0268	0.0371	0.0018
2000	θ_1	−0.0801	0.0131	0.0412	0.0055	0.0895	0.0007
	θ_2	−0.0473	0.0128	0.0179	0.0067	0.0634	0.0006
	θ_3	−0.0401	0.0125	0.0157	0.0063	0.0633	0.0006
	θ_4	−0.0130	0.0122	−0.0062	0.0071	0.0616	0.0006
	θ_5	−0.0230	0.0139	0.0030	0.0084	0.0344	0.0008
	θ_6	−0.0289	0.0138	0.0063	0.0080	0.0358	0.0005
4000	θ_1	−0.0528	0.0028	0.0318	0.0017	0.0886	0.0003
	θ_2	−0.0236	0.0034	0.0089	0.0020	0.0611	0.0003
	θ_3	−0.0155	0.0035	0.0076	0.0019	0.0609	0.0003
	θ_4	−0.0097	0.0039	0.0034	0.0023	0.0596	0.0003
	θ_5	−0.0015	0.0037	−0.0019	0.0021	0.0342	0.0002
	θ_6	−0.0117	0.0034	0.0038	0.0020	0.0297	0.0002

Supplementary Table 14: Phenotypes are simulated from model 1, and the parameters are estimated from model 3.

		$\hat{a}$		$\hat{a}'$		$\hat{e}$	
N	θ	bias	var	bias	var	bias	var
500	θ_1	0.1821	0.0247	0.0803	0.0036	−0.3092	0.0806
	θ_2	0.1320	0.0342	0.0956	0.0035	−0.2420	0.0774
	θ_3	0.0652	0.0493	0.0798	0.0052	−0.1782	0.0905
	θ_4	0.0041	0.0711	0.0547	0.0065	−0.1336	0.1048
	θ_5	0.0146	0.0682	0.0993	0.0057	−0.1447	0.0988
	θ_6	−0.0274	0.0847	0.0579	0.0066	−0.1097	0.0932
1000	θ_1	0.1403	0.0142	0.0846	0.0015	−0.1831	0.0291
	θ_2	0.1046	0.0160	0.0976	0.0017	−0.1411	0.0288
	θ_3	0.0488	0.0205	0.0710	0.0019	−0.0794	0.0210
	θ_4	0.0264	0.0307	0.0409	0.0027	−0.0711	0.0307
	θ_5	0.0136	0.0323	0.0863	0.0030	−0.0667	0.0391
	θ_6	−0.0457	0.0414	0.0596	0.0042	−0.0168	0.0274
2000	θ_1	0.0937	0.0044	0.0936	0.0007	−0.1046	0.0042
	θ_2	0.0718	0.0048	0.1025	0.0008	−0.0815	0.0047
	θ_3	0.0312	0.0072	0.0752	0.0008	−0.0424	0.0051
	θ_4	0.0136	0.0107	0.0382	0.0012	−0.0299	0.0066
	θ_5	0.0086	0.0090	0.0803	0.0010	−0.0208	0.0059
	θ_6	−0.0134	0.0131	0.0493	0.0009	−0.0075	0.0078
4000	θ_1	0.0712	0.0018	0.0996	0.0004	−0.0769	0.0015
	θ_2	0.0587	0.0023	0.1020	0.0003	−0.0638	0.0017
	θ_3	0.0315	0.0028	0.0726	0.0004	−0.0342	0.0017
	θ_4	0.0111	0.0035	0.0361	0.0004	−0.0156	0.0021
	θ_5	0.0197	0.0035	0.0787	0.0004	−0.0214	0.0020
	θ_6	−0.0028	0.0034	0.0395	0.0003	−0.0045	0.0020

Supplementary Table 15: Phenotypes are simulated from model 1, and the parameters are estimated from model 4.

		$\hat{a}$		$\hat{e}$	
N	θ	bias	var	bias	var
500	θ_1	−0.0421	0.1344	−0.1291	0.1224
	θ_2	−0.0652	0.1289	−0.0976	0.1016
	θ_3	−0.1134	0.1416	−0.0765	0.1118
	θ_4	−0.1043	0.1413	−0.0848	0.1200
	θ_5	−0.0881	0.1386	−0.0977	0.1138
	θ_6	−0.1067	0.1374	−0.0822	0.1080
1000	θ_1	−0.0229	0.0610	−0.0307	0.0423
	θ_2	−0.0392	0.0605	−0.0216	0.0394
	θ_3	−0.0538	0.0638	−0.0113	0.0306
	θ_4	−0.0181	0.0536	−0.0384	0.0330
	θ_5	−0.0353	0.0593	−0.0313	0.0397
	θ_6	−0.0662	0.0572	−0.0050	0.0304
2000	θ_1	−0.0172	0.0157	0.0096	0.0151
	θ_2	−0.0107	0.0152	0.0043	0.0083
	θ_3	−0.0166	0.0123	0.0084	0.0066
	θ_4	0.0001	0.0122	−0.0110	0.0076
	θ_5	−0.0194	0.0140	0.0073	0.0073
	θ_6	−0.0214	0.0141	0.0032	0.0083
4000	θ_1	−0.0018	0.0036	0.0146	0.0022
	θ_2	0.0047	0.0039	0.0022	0.0024
	θ_3	0.0042	0.0038	0.0018	0.0021
	θ_4	0.0000	0.0040	0.0015	0.0023
	θ_5	0.0045	0.0040	−0.0006	0.0022
	θ_6	−0.0070	0.0035	0.0026	0.0021

Supplementary Table 16: Phenotypes are simulated from model 2, and the parameters are estimated from model 1.

		$\hat{a}$		$\hat{a}'$		$\hat{e}$		$\hat{e'}$	
N	θ	bias	var	bias	var	bias	var	bias	var
500	θ_1	−0.0732	0.1280	−0.0344	0.0095	−0.1013	0.0967	−0.0619	0.0107
	θ_2	−0.0545	0.1027	−0.0296	0.0116	−0.0873	0.0783	−0.0372	0.0100
	θ_3	−0.0693	0.1201	−0.0211	0.0103	−0.1079	0.0997	−0.0385	0.0105
	θ_4	−0.1058	0.1472	−0.0238	0.0107	−0.0968	0.0927	−0.0236	0.0087
	θ_5	−0.0553	0.1114	−0.0200	0.0148	−0.1210	0.1094	−0.0043	0.0126
	θ_6	−0.0528	0.1115	−0.0108	0.0123	−0.1285	0.1118	−0.0246	0.0099
1000	θ_1	−0.0643	0.0737	−0.0469	0.0098	−0.0260	0.0333	−0.0510	0.0084
	θ_2	−0.0155	0.0471	−0.0400	0.0091	−0.0438	0.0277	−0.0282	0.0065
	θ_3	−0.0140	0.0580	−0.0318	0.0081	−0.0576	0.0394	−0.0297	0.0058
	θ_4	−0.0318	0.0602	−0.0374	0.0064	−0.0487	0.0409	−0.0327	0.0057
	θ_5	−0.0266	0.0489	−0.0189	0.0089	−0.0361	0.0296	−0.0048	0.0067
	θ_6	−0.0404	0.0566	−0.0214	0.0091	−0.0435	0.0373	−0.0101	0.0081
2000	θ_1	−0.0026	0.0113	−0.0814	0.0073	−0.0143	0.0076	−0.0253	0.0044
	θ_2	0.0006	0.0131	−0.0592	0.0059	−0.0198	0.0079	−0.0091	0.0045
	θ_3	−0.0067	0.0159	−0.0447	0.0064	−0.0142	0.0090	−0.0240	0.0041
	θ_4	−0.0056	0.0159	−0.0576	0.0065	−0.0209	0.0073	−0.0172	0.0053
	θ_5	−0.0129	0.0184	−0.0288	0.0065	−0.0108	0.0092	−0.0015	0.0045
	θ_6	−0.0261	0.0158	−0.0292	0.0062	−0.0030	0.0082	−0.0071	0.0039
4000	θ_1	−0.0003	0.0030	−0.1033	0.0033	−0.0042	0.0019	−0.0084	0.0024
	θ_2	−0.0016	0.0035	−0.0628	0.0029	−0.0045	0.0021	−0.0106	0.0021
	θ_3	−0.0018	0.0029	−0.0599	0.0034	−0.0010	0.0018	−0.0117	0.0022
	θ_4	−0.0001	0.0034	−0.0677	0.0042	−0.0081	0.0018	−0.0092	0.0028
	θ_5	−0.0001	0.0035	−0.0306	0.0045	−0.0046	0.0018	−0.0041	0.0033
	θ_6	−0.0108	0.0032	−0.0372	0.0035	0.0003	0.0016	−0.0018	0.0022

Supplementary Table 17: Phenotypes are simulated from model 2, and the parameters are estimated from model 3.

		$\hat{a}$		$\hat{a}'$		$\hat{e}$	
N	θ	bias	var	bias	var	bias	var
500	θ_1	0.0394	0.0578	0.0118	0.0059	−0.1429	0.0880
	θ_2	0.0326	0.0609	0.0524	0.0048	−0.1369	0.0833
	θ_3	−0.0042	0.0788	0.0203	0.0072	−0.1306	0.1009
	θ_4	−0.0454	0.0912	−0.0187	0.0099	−0.1030	0.0987
	θ_5	−0.0046	0.0872	0.0654	0.0079	−0.1430	0.1133
	θ_6	−0.0331	0.1041	0.0151	0.0099	−0.1347	0.1142
1000	θ_1	−0.0149	0.0357	0.0148	0.0040	−0.0318	0.0252
	θ_2	0.0252	0.0306	0.0382	0.0028	−0.0644	0.0274
	θ_3	0.0149	0.0398	0.0136	0.0032	−0.0668	0.0397
	θ_4	−0.0137	0.0450	−0.0319	0.0028	−0.0480	0.0417
	θ_5	−0.0015	0.0375	0.0564	0.0035	−0.0464	0.0319
	θ_6	−0.0381	0.0560	0.0087	0.0044	−0.0387	0.0393
2000	θ_1	0.0188	0.0097	0.0007	0.0011	−0.0285	0.0069
	θ_2	0.0267	0.0103	0.0387	0.0010	−0.0373	0.0074
	θ_3	0.0039	0.0132	0.0039	0.0013	−0.0173	0.0083
	θ_4	−0.0002	0.0116	−0.0405	0.0008	−0.0156	0.0071
	θ_5	−0.0011	0.0157	0.0473	0.0013	−0.0142	0.0089
	θ_6	−0.0252	0.0160	0.0046	0.0010	0.0014	0.0082
4000	θ_1	0.0190	0.0027	−0.0026	0.0003	−0.0193	0.0018
	θ_2	0.0182	0.0031	0.0342	0.0004	−0.0204	0.0020
	θ_3	0.0061	0.0029	0.0005	0.0003	−0.0058	0.0018
	θ_4	0.0016	0.0033	−0.0408	0.0004	−0.0056	0.0017
	θ_5	0.0071	0.0034	0.0408	0.0004	−0.0073	0.0017
	θ_6	−0.0089	0.0032	0.0003	0.0003	0.0019	0.0016

Supplementary Table 18: Phenotypes are simulated from model 2, and the parameters are estimated from model 4.

		$\hat{a}$		$\hat{e}$	
N	θ	bias	var	bias	var
500	θ_1	−0.0740	0.1282	−0.0853	0.1029
	θ_2	−0.0758	0.1299	−0.0798	0.0918
	θ_3	−0.0728	0.1292	−0.0987	0.1067
	θ_4	−0.0900	0.1285	−0.0847	0.0994
	θ_5	−0.0835	0.1393	−0.1108	0.1300
	θ_6	−0.0607	0.1269	−0.1213	0.1184
1000	θ_1	−0.0624	0.0627	−0.0018	0.0302
	θ_2	−0.0238	0.0512	−0.0302	0.0346
	θ_3	−0.0193	0.0617	−0.0519	0.0506
	θ_4	−0.0343	0.0616	−0.0451	0.0510
	θ_5	−0.0347	0.0544	−0.0231	0.0332
	θ_6	−0.0547	0.0678	−0.0301	0.0408
2000	θ_1	−0.0071	0.0121	0.0000	0.0078
	θ_2	−0.0035	0.0137	−0.0052	0.0081
	θ_3	−0.0088	0.0166	−0.0044	0.0089
	θ_4	−0.0036	0.0120	−0.0120	0.0072
	θ_5	−0.0148	0.0196	−0.0003	0.0091
	θ_6	−0.0287	0.0167	0.0052	0.0084
4000	θ_1	−0.0064	0.0090	0.0053	0.0018
	θ_2	−0.0029	0.0036	0.0043	0.0022
	θ_3	−0.0025	0.0030	0.0049	0.0018
	θ_4	−0.0002	0.0034	−0.0031	0.0018
	θ_5	−0.0001	0.0035	0.0026	0.0018
	θ_6	−0.0112	0.0032	0.0048	0.0016

Supplementary Table 19: Phenotypes are simulated from model 3, and the parameters are estimated from model 1.

		$\hat{a}$		$\hat{a}'$		$\hat{e}$		$\hat{e'}$	
N	θ	bias	var	bias	var	bias	var	bias	var
500	θ_1	-0.0865	0.1334	-0.0271	0.0104	-0.1067	0.1178	-0.0819	0.0125
	θ_2	-0.1105	0.1257	-0.0492	0.0117	-0.0852	0.1017	-0.0623	0.0107
	θ_3	-0.0968	0.1305	-0.0348	0.0136	-0.0876	0.0940	-0.0297	0.0099
	θ_4	-0.1008	0.1514	-0.0053	0.0106	-0.1181	0.1195	-0.0268	0.0102
	θ_5	-0.0749	0.1252	-0.0385	0.0131	-0.1082	0.1040	-0.0256	0.0125
	θ_6	-0.0759	0.1184	-0.0015	0.0128	-0.0974	0.0965	-0.0325	0.0095
1000	θ_1	-0.0265	0.0514	-0.0284	0.0086	-0.0470	0.0402	-0.0753	0.0082
	θ_2	-0.0337	0.0589	-0.0405	0.0073	-0.0393	0.0336	-0.0606	0.0058
	θ_3	-0.0150	0.0568	-0.0144	0.0084	-0.0558	0.0365	-0.0572	0.0076
	θ_4	-0.0393	0.0533	-0.0140	0.0094	-0.0389	0.0416	-0.0266	0.0068
	θ_5	-0.0315	0.0547	-0.0326	0.0120	-0.0377	0.0284	-0.0383	0.0091
	θ_6	-0.0569	0.0635	-0.0028	0.0081	-0.0373	0.0442	-0.0254	0.0060
2000	θ_1	-0.0056	0.0116	-0.0276	0.0075	-0.0097	0.0069	-0.0705	0.0055
	θ_2	-0.0005	0.0120	-0.0248	0.0064	-0.0183	0.0081	-0.0786	0.0043
	θ_3	-0.0043	0.0133	-0.0135	0.0069	-0.0150	0.0107	-0.0521	0.0049
	θ_4	-0.0026	0.0095	-0.0148	0.0061	-0.0143	0.0060	-0.0188	0.0041
	θ_5	-0.0050	0.0129	-0.0147	0.0079	-0.0161	0.0086	-0.0460	0.0063
	θ_6	-0.0068	0.0128	-0.0044	0.0064	-0.0152	0.0085	-0.0290	0.0051
4000	θ_1	0.0011	0.0033	-0.0082	0.0032	-0.0056	0.0022	-0.0861	0.0021
	θ_2	0.0012	0.0035	-0.0113	0.0032	-0.0079	0.0021	-0.0855	0.0022
	θ_3	-0.0050	0.0033	-0.0121	0.0034	0.0008	0.0019	-0.0531	0.0022
	θ_4	-0.0030	0.0024	-0.0132	0.0038	-0.0042	0.0015	-0.0222	0.0024
	θ_5	0.0078	0.0036	-0.0080	0.0038	-0.0100	0.0022	-0.0554	0.0029
	θ_6	-0.0087	0.0037	-0.0067	0.0041	-0.0020	0.0021	-0.0237	0.0027

Supplementary Table 20: Phenotypes are simulated from model 3, and the parameters are estimated from model 2.

		$\hat{a}$		$\hat{e}$		$\hat{e'}$	
N	θ	bias	var	bias	var	bias	var
500	θ_1	−0.1277	0.1181	−0.0149	0.0570	0.0144	0.0057
	θ_2	−0.1533	0.1438	−0.0497	0.0868	−0.0126	0.0065
	θ_3	−0.1101	0.1176	−0.0417	0.0691	0.0179	0.0057
	θ_4	−0.0976	0.1240	−0.0595	0.0764	0.0469	0.0059
	θ_5	−0.0923	0.1376	−0.0857	0.0944	−0.0002	0.0088
	θ_6	−0.1050	0.1347	−0.0737	0.0941	0.0074	0.0068
1000	θ_1	−0.0465	0.0532	−0.0183	0.0301	0.0079	0.0031
	θ_2	−0.0506	0.0647	−0.0222	0.0311	−0.0266	0.0018
	θ_3	−0.0270	0.0618	−0.0416	0.0379	0.0078	0.0024
	θ_4	−0.0482	0.0529	−0.0198	0.0365	0.0383	0.0026
	θ_5	−0.0399	0.0616	−0.0284	0.0351	−0.0297	0.0031
	θ_6	−0.0694	0.0693	−0.0207	0.0399	0.0073	0.0017
2000	θ_1	−0.0168	0.0147	0.0034	0.0085	−0.0006	0.0010
	θ_2	−0.0086	0.0129	−0.0057	0.0076	−0.0361	0.0005
	θ_3	−0.0105	0.0134	−0.0028	0.0104	0.0005	0.0007
	θ_4	−0.0099	0.0100	−0.0025	0.0061	0.0291	0.0005
	θ_5	−0.0077	0.0138	−0.0056	0.0084	−0.0287	0.0005
	θ_6	−0.0098	0.0135	−0.0067	0.0093	0.0003	0.0008
4000	θ_1	−0.0143	0.0032	0.0117	0.0020	−0.0043	0.0003
	θ_2	−0.0055	0.0035	0.0013	0.0021	−0.0349	0.0002
	θ_3	−0.0121	0.0032	0.0102	0.0019	−0.0037	0.0002
	θ_4	−0.0085	0.0024	0.0043	0.0015	0.0265	0.0002
	θ_5	0.0058	0.0036	−0.0042	0.0021	−0.0309	0.0002
	θ_6	−0.0103	0.0036	0.0036	0.0020	0.0006	0.0002

Supplementary Table 21: Phenotypes are simulated from model 3, and the parameters are estimated from model 4.

		$\hat{a}$		$\hat{e}$	
N	θ	bias	var	bias	var
500	θ_1	-0.0863	0.1319	-0.0793	0.1118
	θ_2	-0.1301	0.1507	-0.0798	0.1136
	θ_3	-0.1009	0.1335	-0.0766	0.1060
	θ_4	-0.0887	0.1333	-0.0870	0.1078
	θ_5	-0.0864	0.1449	-0.1044	0.1181
	θ_6	-0.1008	0.1381	-0.0816	0.1061
1000	θ_1	-0.0325	0.0545	-0.0246	0.0351
	θ_2	-0.0425	0.0673	-0.0283	0.0346
	θ_3	-0.0211	0.0614	-0.0416	0.0390
	θ_4	-0.0413	0.0526	-0.0215	0.0387
	θ_5	-0.0390	0.0610	-0.0224	0.0297
	θ_6	-0.0692	0.0736	-0.0252	0.0451
2000	θ_1	-0.0065	0.0135	0.0034	0.0066
	θ_2	-0.0009	0.0131	-0.0098	0.0082
	θ_3	-0.0052	0.0133	-0.0032	0.0095
	θ_4	-0.0037	0.0096	-0.0044	0.0060
	θ_5	-0.0061	0.0135	-0.0057	0.0083
	θ_6	-0.0077	0.0131	-0.0061	0.0080
4000	θ_1	0.0019	0.0033	0.0047	0.0021
	θ_2	0.0018	0.0035	-0.0020	0.0021
	θ_3	-0.0045	0.0033	0.0067	0.0019
	θ_4	-0.0024	0.0024	0.0020	0.0015
	θ_5	0.0075	0.0036	-0.0047	0.0021
	θ_6	-0.0083	0.0037	0.0029	0.0020

Supplementary Table 22: Phenotypes are simulated from model 4, and the parameters are estimated from model 1.

		$\hat{a}$		$\hat{a}'$		$\hat{e}$		$\hat{e'}$	
N	θ	bias	var	bias	var	bias	var	bias	var
500	θ_1	−0.0962	0.1415	−0.0744	0.0111	−0.0984	0.0958	−0.1098	0.0078
	θ_2	−0.0620	0.0897	−0.0829	0.0108	−0.0757	0.0763	−0.0914	0.0085
	θ_3	−0.0610	0.1141	−0.0594	0.0121	−0.1081	0.1023	−0.0809	0.0092
	θ_4	−0.0680	0.1498	−0.0383	0.0118	−0.1550	0.1285	−0.0657	0.0111
	θ_5	−0.0839	0.1168	−0.0295	0.0143	−0.0994	0.1089	−0.0630	0.0111
	θ_6	−0.0760	0.1089	−0.0276	0.0107	−0.1040	0.1075	−0.0363	0.0076
1000	θ_1	−0.0318	0.0610	−0.0953	0.0076	−0.0463	0.0385	−0.1097	0.0072
	θ_2	−0.0353	0.0426	−0.0799	0.0091	−0.0262	0.0260	−0.0980	0.0066
	θ_3	−0.0314	0.0474	−0.0614	0.0087	−0.0312	0.0277	−0.0763	0.0060
	θ_4	−0.0234	0.0507	−0.0621	0.0094	−0.0491	0.0359	−0.0441	0.0064
	θ_5	−0.0300	0.0533	−0.0359	0.0100	−0.0484	0.0372	−0.0694	0.0086
	θ_6	−0.0356	0.0423	−0.0347	0.0085	−0.0294	0.0264	−0.0350	0.0060
2000	θ_1	−0.0149	0.0112	−0.0995	0.0060	−0.0035	0.0069	−0.1065	0.0041
	θ_2	0.0010	0.0112	−0.0775	0.0065	−0.0192	0.0071	−0.0944	0.0043
	θ_3	−0.0116	0.0147	−0.0642	0.0063	−0.0117	0.0080	−0.0756	0.0040
	θ_4	0.0001	0.0121	−0.0649	0.0061	−0.0195	0.0077	−0.0444	0.0042
	θ_5	−0.0187	0.0114	−0.0413	0.0063	0.0004	0.0062	−0.0591	0.0043
	θ_6	−0.0277	0.0172	−0.0411	0.0061	−0.0040	0.0093	−0.0305	0.0050
4000	θ_1	0.0016	0.0036	−0.1173	0.0034	−0.0071	0.0024	−0.0921	0.0023
	θ_2	−0.0009	0.0036	−0.0778	0.0035	−0.0065	0.0019	−0.0954	0.0023
	θ_3	−0.0001	0.0031	−0.0804	0.0039	−0.0055	0.0018	−0.0615	0.0025
	θ_4	0.0067	0.0035	−0.0775	0.0040	−0.0118	0.0023	−0.0331	0.0028
	θ_5	0.0020	0.0039	−0.0309	0.0043	−0.0069	0.0023	−0.0667	0.0029
	θ_6	−0.0044	0.0036	−0.0368	0.0032	−0.0052	0.0020	−0.0316	0.0021

Supplementary Table 23: Phenotypes are simulated from model 4, and the parameters are estimated from model 2.

		$\hat{a}$		$\hat{e}$		$\hat{e'}$	
N	θ	bias	var	bias	var	bias	var
500	θ_1	-0.0905	0.1219	-0.0693	0.0845	-0.0904	0.0050
	θ_2	-0.0927	0.1119	-0.0608	0.0804	-0.0948	0.0060
	θ_3	-0.0836	0.1286	-0.0750	0.0840	-0.0601	0.0057
	θ_4	-0.0628	0.1353	-0.1139	0.1007	-0.0322	0.0085
	θ_5	-0.1113	0.1324	-0.0694	0.0991	-0.0563	0.0072
	θ_6	-0.1145	0.1300	-0.0659	0.0879	-0.0296	0.0057
1000	θ_1	-0.0262	0.0528	-0.0366	0.0390	-0.0932	0.0021
	θ_2	-0.0447	0.0502	-0.0154	0.0275	-0.0960	0.0013
	θ_3	-0.0398	0.0515	-0.0189	0.0291	-0.0676	0.0013
	θ_4	-0.0269	0.0484	-0.0301	0.0290	-0.0348	0.0013
	θ_5	-0.0370	0.0617	-0.0409	0.0422	-0.0676	0.0028
	θ_6	-0.0488	0.0520	-0.0173	0.0275	-0.0315	0.0013
2000	θ_1	-0.0160	0.0116	0.0036	0.0069	-0.0930	0.0003
	θ_2	0.0002	0.0114	-0.0119	0.0073	-0.0947	0.0004
	θ_3	-0.0123	0.0149	-0.0046	0.0079	-0.0646	0.0004
	θ_4	-0.0006	0.0123	-0.0126	0.0078	-0.0341	0.0004
	θ_5	-0.0203	0.0126	0.0076	0.0062	-0.0611	0.0004
	θ_6	-0.0287	0.0181	0.0035	0.0087	-0.0303	0.0004
4000	θ_1	0.0015	0.0036	-0.0034	0.0024	-0.0938	0.0002
	θ_2	-0.0008	0.0036	-0.0030	0.0019	-0.0958	0.0002
	θ_3	-0.0003	0.0031	-0.0014	0.0018	-0.0636	0.0002
	θ_4	0.0066	0.0035	-0.0075	0.0022	-0.0326	0.0002
	θ_5	0.0019	0.0039	-0.0022	0.0022	-0.0607	0.0002
	θ_6	-0.0045	0.0036	-0.0018	0.0020	-0.0309	0.0002

Supplementary Table 24: Phenotypes are simulated from model 4, and the parameters are estimated from model 3.

		$\hat{a}$		$\hat{a}'$		$\hat{e}$	
N	θ	bias	var	bias	var	bias	var
500	θ_1	−0.0745	0.1137	−0.1102	0.0118	−0.0925	0.1008
	θ_2	−0.0599	0.0903	−0.0814	0.0097	−0.0825	0.0923
	θ_3	−0.0445	0.0999	−0.0915	0.0105	−0.0994	0.0969
	θ_4	−0.0284	0.1080	−0.0770	0.0118	−0.1396	0.1180
	θ_5	−0.0641	0.1087	−0.0285	0.0117	−0.0977	0.1063
	θ_6	−0.0773	0.1128	−0.0348	0.0106	−0.1065	0.1163
1000	θ_1	−0.0226	0.0498	−0.1175	0.0025	−0.0381	0.0395
	θ_2	−0.0358	0.0426	−0.0792	0.0029	−0.0182	0.0273
	θ_3	−0.0403	0.0510	−0.0775	0.0040	−0.0184	0.0268
	θ_4	−0.0285	0.0487	−0.0750	0.0038	−0.0323	0.0315
	θ_5	−0.0307	0.0574	−0.0375	0.0036	−0.0448	0.0439
	θ_6	−0.0499	0.0507	−0.0414	0.0040	−0.0175	0.0275
2000	θ_1	−0.0156	0.0114	−0.1126	0.0006	0.0033	0.0068
	θ_2	0.0002	0.0114	−0.0765	0.0006	−0.0120	0.0073
	θ_3	−0.0140	0.0161	−0.0802	0.0012	−0.0046	0.0079
	θ_4	−0.0011	0.0131	−0.0809	0.0007	−0.0129	0.0079
	θ_5	−0.0206	0.0129	−0.0349	0.0008	0.0074	0.0061
	θ_6	−0.0291	0.0180	−0.0362	0.0007	0.0036	0.0086
4000	θ_1	0.0015	0.0036	−0.1143	0.0004	−0.0035	0.0024
	θ_2	−0.0008	0.0036	−0.0785	0.0003	−0.0031	0.0019
	θ_3	−0.0002	0.0031	−0.0773	0.0003	−0.0015	0.0018
	θ_4	0.0067	0.0035	−0.0782	0.0004	−0.0077	0.0022
	θ_5	0.0019	0.0039	−0.0350	0.0004	−0.0023	0.0022
	θ_6	−0.0044	0.0036	−0.0371	0.0003	−0.0019	0.0020

Supplementary Table 25: Estimated coefficients for covariates.

	Estimate	Std. Error	t value	$Pr(>\|t\|)$	
(Intercept)	7.40E-01	5.59E-02	13.24	<2.00E-16	***
sex	-1.01E-01	9.90E-03	-10.155	<2.00E-16	***
age.reg.intelligence	-1.11E-02	6.23E-04	-17.789	<2.00E-16	***
Townsend.deprivation.index.z	-1.10E-01	4.97E-03	-22.061	<2.00E-16	***
pc1	-5.70E-03	3.15E-03	-1.807	0.07081	.
pc2	4.22E-03	3.19E-03	1.321	0.18653	
pc3	4.20E-03	3.08E-03	1.362	0.17326	
pc4	-3.72E-03	2.44E-03	-1.529	0.12626	
pc5	9.51E-04	1.29E-03	0.736	0.46184	
pc6	-1.21E-03	2.54E-03	-0.477	0.63317	
pc7	5.37E-03	2.63E-03	2.046	0.04078	*
pc8	-1.30E-03	1.41E-03	-0.924	0.35559	
pc9	-5.13E-03	2.68E-03	-1.911	0.05598	.
pc10	-5.67E-03	1.86E-03	-3.044	0.00233	**
pc11	7.60E-05	2.19E-03	0.035	0.97237	
pc12	1.20E-02	1.88E-03	6.35	2.18E-10	***
pc13	5.90E-03	2.15E-03	2.744	0.00607	**
pc14	-6.46E-03	1.57E-03	-4.12	3.80E-05	***
pc15	1.90E-03	2.04E-03	0.934	0.35017	
birth.north	-2.63E-07	4.06E-08	-6.492	8.56E-11	***
birth.east	2.72E-07	6.04E-08	4.507	6.59E-06	***
batch	1.23E-03	5.05E-04	2.442	0.01463	*

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
Residual standard error: 0.9881 on 40150 degrees of freedom
Multiple R-squared: 0.02419, Adjusted R-squared: 0.02368
F-statistic: 47.39 on 21 and 40150 DF, p-value: < 2.2e-16