Supplemental materials for: **Leveraging summary statistics to make inferences about complex phenotypes in large biobanks**

Supplement 1:

Slope proof:

Background/notation:

$$\boldsymbol{y_1} = \hat{\beta}_1 \boldsymbol{x} + \hat{\alpha}_1$$

$$\vdots$$

$$\boldsymbol{y_n} = \hat{\beta}_n \boldsymbol{x} + \hat{\alpha}_n$$

$$\boldsymbol{y_c} = c_1 \boldsymbol{y}_1 + c_2 \boldsymbol{y}_2 + \cdots + c_n \boldsymbol{y}_n$$

$$\boldsymbol{\hat{y}_c} = \hat{\beta}_c \boldsymbol{x} + \hat{\alpha}$$

Proof by mathematical induction for $\hat{\beta}$

Formula:

$For\ any\ n \in \mathbb{N},$

$$\hat{\beta}_c = c_1\hat{\beta}_1 + c_2\hat{\beta}_2 + \cdots + c_n\hat{\beta}_n$$

Base case $n = 2$, if $n = 2$:

Prove $\hat{\beta} = c_1\hat{\beta}_1 + c_2\hat{\beta}_2$

$$\hat{\beta} = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(y_i - \bar{y})}{\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

$$\hat{\beta}_1 = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(c_1 y_{1i} - c_1\overline{\boldsymbol{y_1}})}{\sum_{i=1}^{n}(x_i - \bar{x})^2} \quad \hat{\beta}_2 = \frac{\sum_{i=1}^{n}(x_i - \bar{x})(c_2 y_{2i} - c_2\overline{\boldsymbol{y_2}})}{\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

$$\boldsymbol{y_c} = \boldsymbol{y_1} + \boldsymbol{y_2}$$

$$\hat{\beta}_c\,(c_1\boldsymbol{y_1} + c_2\boldsymbol{y_2}) = \frac{\sum_{i=1}^{n}(x_i - \bar{x})((c_1 y_{1i} + c_2 y_{2i}) - (c_1\,\overline{\boldsymbol{y_1}} + c_2\overline{\boldsymbol{y_2}}))}{\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

$$= \frac{\sum_{i=1}^{n} c_1(x_i - \bar{x})(y_{1i} - \overline{\boldsymbol{y_1}}) + c_2(x_i - \bar{x})(y_{2i} - \overline{\boldsymbol{y_2}}))}{\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

By rearranging the y terms and constants, which is equivalent to $c_1\hat{\beta}_1 + c_2\hat{\beta}_2$

Inductive hypothesis:

Assume that $\hat{\beta}_c(c_1 y_1 + c_2 y_2 + \cdots + \ c_k y_k) = c_1\hat{\beta}_1 + c_2\hat{\beta}_2 + \cdots + c_k\hat{\beta}_k$for each k < n

We wish to show that $\hat{\beta}_c(T + c_{k+1}\boldsymbol{y}_{k+1})$ = $\hat{\beta}_c(c_1\boldsymbol{y}_1 + c_2\boldsymbol{y}_2 + \cdots + \ c_k\boldsymbol{y}_k + c_{k+1}\boldsymbol{y}_{k+1})$ where $T = c_1\boldsymbol{y}_1 + c_2\boldsymbol{y}_2 + \cdots + \ c_k\boldsymbol{y}_k$

By base case:

$$\hat{\beta}_c(T + c_{k+1}\boldsymbol{y}_{k+1})\ ) = \hat{\beta}_T + \ c_{k+1}\hat{\beta}_{k+1}$$

By induction hypothesis:

$$\hat{\beta}(T + y_{k+1}) = \ c_1\hat{\beta}_1 + c_2\hat{\beta}_2 + \cdots + c_k\hat{\beta}_k + c_{k+1}\hat{\beta}_{k+1} \ ▪$$

Supplement 2:

Intercept proof:

Proof by Mathematical induction for $\hat{\alpha}$

Formula:

$For\ any\ n \in \mathbb{N},$

$$\hat{\alpha}_c = c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2 + \cdots + c_n\hat{\alpha}_n$$

Base case $n = 2$, if $n = 2$:

Want to show: $\hat{\alpha}_c = c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2$

$$\hat{\alpha} = \bar{\boldsymbol{y}} - \hat{\beta}\bar{x}$$

$$\boldsymbol{y_c} = c_1\boldsymbol{y_1} + c_2\boldsymbol{y_2}$$

$$\hat{\alpha}_1 = \bar{y}_1 - \hat{\beta}_1\bar{x} \qquad \hat{\alpha}_2 = \bar{y}_2 - \hat{\beta}_2\bar{x}$$

Already shown above that $\hat{\beta}_c = c_1\hat{\beta}_1 + c_2\hat{\beta}_2$ so:

$$\hat{\alpha}_c = (c_1\bar{y}_1 + c_2\bar{y}_2) - (c_1\hat{\beta}_1 + c_2\hat{\beta}_2)\bar{x}$$

$$= c_1\bar{y}_1 - c_1\hat{\beta}_1\bar{x} + c_2\bar{y}_2 - c_2\hat{\beta}_2\bar{x}$$

By rearranging the terms, this is equivalent to $c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2$

Induction hypothesis: Assume $\hat{\alpha}_c(c_1\boldsymbol{y}_1 + c_2\boldsymbol{y}_2 + \cdots + c_k\boldsymbol{y}_k) = c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2 + \cdots + c_k\hat{\alpha}_k$ where $T = c_1\boldsymbol{y}_1 + c_2\boldsymbol{y}_2 + \cdots + c_k\boldsymbol{y}_k$

Induction step:

Want to show $\hat{\alpha}_c\ (T + c_{k+1}\boldsymbol{y}_{k+1}) = \hat{\alpha}_c(c_1\boldsymbol{y}_1 + c_2\boldsymbol{y}_2 + \cdots + c_k\boldsymbol{y}_k + c_{k+1}\boldsymbol{y}_{k+1})\ where\ T = c_1\boldsymbol{y}_1 + c_2\boldsymbol{y}_2 + \cdots + c_k\boldsymbol{y}_k$

By base case:

$$\hat{\alpha}_c(T + c_{k+1}\boldsymbol{y}_{k+1}) = \hat{\alpha}_T + \widehat{\alpha_{k+1}}$$

By assumption:

$$\hat{\alpha}_c(T + c_{k+1}\boldsymbol{y}_{k+1}) = c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2 + \cdots + c_k\hat{\alpha}_k + c_{k+1}\hat{\alpha}_{k+1} \ \blacksquare$$

Supplement 3:

Standard Error proof for the linear combination of two phenotypes:

We wish to show that

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2}{n-2}\left(\frac{c_1 c_2 \mathrm{cov}(y_1, y_2)}{\mathrm{var}(x)} - c_1 c_2 \hat{\beta}_1 \hat{\beta}_2\right)}$$

Where $\boldsymbol{y_c} = c_1\boldsymbol{y_1} + c_2\boldsymbol{y_2}$ and $\boldsymbol{\hat{y}_c} = \hat{\beta}_c\boldsymbol{x_j} + \hat{\alpha}_c$.

We begin with the formula for standard error.

$$\mathrm{SE}(\hat{\beta}_c) = \frac{\sqrt{\frac{\sum_{j=1}^{n}(y_{cj} - \hat{y}_{cj})^2}{n-2}}}{\sqrt{\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

We can substitute $c_1 y_{1j} + c_2 y_{2j}$ for y_{cj} and $(c_1\hat{\beta}_1 + c_2\hat{\beta}_2)x_j + (c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2)$ for $\hat{y}_c$.

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{\frac{\sum_{j=1}^{n}((c_1 y_{1j} + c_2 y_{2j}) - ((c_1\hat{\beta}_1 + c_2\hat{\beta}_2)x_j + (c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2)))^2}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

We now substitute $\hat{y}_{ij}$ for $\hat{\beta}_i x_j + \hat{\alpha}_i$.

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{\frac{\sum_{j=1}^{n}((c_1 y_{1j} - c_1\hat{y}_{1j}) + (c_2 y_{2j} - c_2\hat{y}_{2j}))^2}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{\frac{{c_1}^2\sum_{j=1}^{n}(y_{1j} - \hat{y}_{1j})^2 + 2c_1c_2\sum_{j=1}^{n}(y_{1j} - \hat{y}_{1j})(y_{2j} - \hat{y}_{2j}) + {c_2}^2\sum_{j=1}^{n}(y_{2j} - \hat{y}_{2j})^2}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

We can substitute $\mathrm{SE}(\hat{\beta}_i)^2$ for $\frac{\sum_{j=1}^{n}(y_{ij} - \hat{y}_{ij})^2}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}$.

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2c_1c_2\sum_{j=1}^{n}(y_{1j} - \hat{y}_{1j})(y_{2j} - \hat{y}_{2j})}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2c_1c_2\sum_{j=1}^{n}(y_{1j}y_{2j} - y_{1j}\hat{y}_{2j} - y_{2j}\hat{y}_{1j} + \hat{y}_{1j}\hat{y}_{2j})}{(n-2)\sum_{i=1}^{n}(x_i - \bar{x})^2}}$$

Next, $\hat{y}_{ij}$ is replaced by $\hat{\beta}_i x_j + \hat{\alpha}_i$.

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2c_1c_2\sum_{j=1}^{n}(y_{1j}y_{2j} - y_{1j}(\hat{\beta}_2 x_j + \hat{\alpha}_2) - y_{2j}(\hat{\beta}_1 x_j + \hat{\alpha}_1) + (\hat{\beta}_1 x_j + \hat{\alpha}_1)(\hat{\beta}_2 x_j + \hat{\alpha}_2))}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2c_1c_2\sum_{j=1}^{n}(y_{1j}y_{2j} - \hat{\beta}_2 x_j y_{1j} - \hat{\alpha}_2 y_{1j} - \hat{\beta}_1 x_j y_{2j} - \hat{\alpha}_1 y_{2j} + \hat{\beta}_1\hat{\beta}_2 {x_j}^2 + \hat{\alpha}_2\hat{\beta}_1 x_j + \hat{\alpha}_1\hat{\beta}_2 x_j + \hat{\alpha}_1\hat{\alpha}_2)}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

We now substitute $\bar{y}_i - \hat{\beta}_i\bar{x}$ for $\hat{\alpha}_i$ and rearrange the terms.

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2c_1c_2\sum_{j=1}^{n}(y_{1j}y_{2j} - \hat{\beta}_2 x_j y_{1j} - (\bar{y}_2 - \hat{\beta}_2\bar{x})y_{1j} - \hat{\beta}_1 x_j y_{2j} - (\bar{y}_1 - \hat{\beta}_1\bar{x})y_{2j} + \hat{\beta}_1\hat{\beta}_2 {x_j}^2 + (\bar{y}_2 - \hat{\beta}_2\bar{x})\hat{\beta}_1 x_j + (\bar{y}_1 - \hat{\beta}_1\bar{x})\hat{\beta}_2 x_j + (\bar{y}_1 - \hat{\beta}_1\bar{x})(\bar{y}_2 - \hat{\beta}_2\bar{x}))}{(n-2)\sum_{j=1}^{n}(x_j - \bar{x})^2}}$$

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2c_1c_2}{n-2}\left(\frac{\sum_{j=1}^{n}(y_{1j} - \bar{y}_1)(y_{2j} - \bar{y}_2)}{\sum_{j=1}^{n}(x_j - \bar{x})^2} - \hat{\beta}_1\frac{\sum_{i=1}^{n}(x_j - \bar{x})(y_{2j} - \bar{y}_2)}{\sum_{j=1}^{n}(x_j - \bar{x})^2} - \hat{\beta}_2\frac{\sum_{j=1}^{n}(x_j - \bar{x})(y_{1j} - \bar{y}_1)}{\sum_{j=1}^{n}(x_j - \bar{x})^2} + \hat{\beta}_1\hat{\beta}_2\frac{\sum_{j=1}^{n}(x_j - \bar{x})^2}{\sum_{j=1}^{n}(x_j - \bar{x})^2}\right)}$$

This simplifies to

$$\mathrm{SE}(\hat{\beta}_c) = \sqrt{{c_1}^2\mathrm{SE}(\hat{\beta}_1)^2 + {c_2}^2\mathrm{SE}(\hat{\beta}_2)^2 + \frac{2c_1c_2}{n-2}\left(\frac{\mathrm{cov}(y_1, y_2)}{\mathrm{var}(x)} - \hat{\beta}_1\hat{\beta}_2\right)} \quad \blacksquare$$

Supplement 4:

Standard Error proof for the linear combination of m phenotypes:

We want to show that

$$\mathrm{SE}(c_1\hat{\beta}_1 + c_2\hat{\beta}_2 + \ldots + c_w\hat{\beta}_w) = \sqrt{\left(\sum_{i=1}^{m} c_i{}^2\mathrm{SE}(\hat{\beta}_i)^2\right) + \frac{2}{n-2}\left(\frac{\sum_{q=1}^{m-1}\sum_{r=q+1}^{m} c_q * c_r * \mathrm{cov}(\boldsymbol{y}_q, \boldsymbol{y}_r)}{\mathrm{var}(x)} - \left(\sum_{q=1}^{m-1}\sum_{r=q+1}^{m} c_q\hat{\beta}_q c_r\hat{\beta}_r\right)\right)}$$

We have already shown that this formula holds for $w = 2$, and we wish to show that it holds for all values of w. We will prove this using mathematical induction.

First we assume that our formula is true. We want to show that the following is true:

$$\mathrm{SE}(c_1\hat{\beta}_1 + c_2\hat{\beta}_2 + \ldots + c_w\hat{\beta}_w + c_{w+1}\hat{\beta}_{w+1}) = \sqrt{\left(\sum_{i=1}^{w+1} c_i{}^2\mathrm{SE}(\hat{\beta}_i)^2\right) + \frac{2}{n-2}\left(\frac{\sum_{q=1}^{w}\sum_{r=q+1}^{w+1} c_q * c_r * \mathrm{cov}(\boldsymbol{y}_q, \boldsymbol{y}_r)}{\mathrm{var}(x)} - \left(\sum_{q=1}^{w}\sum_{r=q+1}^{w+1} c_q\hat{\beta}_q c_r\hat{\beta}_r\right)\right)}$$

We will let $y_T = c_1y_1 + c_2y_2 + \ldots + c_wy_w$ and $y_T = \hat{\beta}_T x + \hat{\alpha}_T$. By what we have already shown, we know that $\hat{\beta}_T = c_1\hat{\beta}_1 + c_2\hat{\beta}_2 + \ldots + c_w\hat{\beta}_w$ and $\hat{\alpha}_T = c_1\hat{\alpha}_1 + c_2\hat{\alpha}_2 + \ldots + c_w\hat{\alpha}_w$. Thus, by using what we have already shown to be true for $w = 2$, we know that

$$\mathrm{SE}(c_T\hat{\beta}_T + c_{w+1}\hat{\beta}_{w+1}) = \sqrt{c_T\mathrm{SE}(\hat{\beta}_T)^2 + c_{w+1}{}^2\mathrm{SE}(\hat{\beta}_{w+1})^2 + \frac{2}{n-2}\left(\frac{c_T * c_{w+1} * \mathrm{cov}(\boldsymbol{y}_T, \boldsymbol{y}_{w+1})}{\mathrm{var}(x)} - c_T\hat{\beta}_T c_{w+1}\hat{\beta}_{w+1}\right)}$$

We can now substitute for $\hat{\beta}_T$ and y_T.

$$\mathrm{SE}(c_T\hat{\beta}_T + c_{w+1}\hat{\beta}_{w+1})$$
$$= \sqrt{\sqrt{\left(\sum_{i=1}^{w} c_i{}^2\mathrm{SE}(\hat{\beta}_i)^2\right) + \frac{2}{n-2}\left(\frac{\sum_{q=1}^{w-1}\sum_{r=q+1}^{w} c_q * c_r * \mathrm{cov}(\boldsymbol{y}_q, \boldsymbol{y}_r)}{\mathrm{var}(x)} - \left(\sum_{q=1}^{w-1}\sum_{r=q+1}^{w} c_q\hat{\beta}_q c_r\hat{\beta}_r\right)\right)}^{\,2} + c_{w+1}{}^2\mathrm{SE}(\hat{\beta}_{w+1})^2 + \frac{2}{n-2}\left(\frac{c_T * c_{w+1} * \mathrm{cov}(\boldsymbol{y}_T, \boldsymbol{y}_{w+1})}{\mathrm{var}(x)} - c_T\hat{\beta}_T c_{w+1}\hat{\beta}_{w+1}\right)}$$

$$\mathrm{SE}(c_T\hat{\beta}_T + c_{w+1}\hat{\beta}_{w+1})$$
$$= \sqrt{\left(\sum_{i=1}^{w} c_i{}^2\mathrm{SE}(\hat{\beta}_i)^2\right) + c_{w+1}{}^2\mathrm{SE}(\hat{\beta}_{w+1})^2 + \frac{2}{n-2}\left(\frac{\left(\sum_{q=1}^{w-1}\sum_{r=q+1}^{w} c_q * c_r * \mathrm{cov}(\boldsymbol{y}_q, \boldsymbol{y}_r)\right) + \mathrm{cov}(c_1\boldsymbol{y}_1 + \ldots + c_w\boldsymbol{y}_w, c_{w+1}\boldsymbol{y}_{w+1})}{\mathrm{var}(x)} - \left(\sum_{q=1}^{w-1}\sum_{r=q+1}^{w} c_q\hat{\beta}_q c_r\hat{\beta}_r\right) - \left(c_1\hat{\beta}_1 + \ldots + c_w\hat{\beta}_w\right)c_{w+1}\hat{\beta}_{w+1}\right)}$$

We invoke the rule that states that $\text{cov}(\boldsymbol{a}+\boldsymbol{b},\boldsymbol{c}) = \text{cov}(\boldsymbol{a},\boldsymbol{c}) + \text{cov}(\boldsymbol{b},\boldsymbol{c})$ to proceed to the next step.

$$\text{SE}(c_T\hat{\beta}_T + c_{w+1}\hat{\beta}_{w+1})$$
$$= \sqrt{\left(\sum_{i=1}^{w+1} c_i{}^2\text{SE}(\hat{\beta}_i)^2\right) + \frac{2}{n-2}\left(\frac{\left(\sum_{q=1}^{w-1}\sum_{r=q+1}^{w} c_q * c_r * \text{cov}(\boldsymbol{y}_q,\boldsymbol{y}_r)\right) + c_1 * c_{w+1} * \text{cov}(\boldsymbol{y}_1,\boldsymbol{y}_{w+1}) + \ldots + c_w * c_{w+!} * cov(\boldsymbol{y}_w,\boldsymbol{y}_{w+1})}{\text{var}(x)} - \left(\sum_{q=1}^{w-1}\sum_{r=q+1}^{w} c_q\hat{\beta}_q c_r\hat{\beta}_r\right) - \left(c_1\hat{\beta}_1 c_{w+1}\hat{\beta}_{w+1} + \ldots + c_w\hat{\beta}_w c_{w+1}\hat{\beta}_{w+1}\right)\right)}$$

$$\text{SE}(c_T\hat{\beta}_T + c_{w+1}\hat{\beta}_{w+1}) = \sqrt{\sum_{i=1}^{w+1} c_i{}^2\text{SE}(\hat{\beta}_i)^2 + \frac{2}{n-2}\left(\frac{\sum_{q=1}^{w}\sum_{r=q+1}^{w+1} c_q * c_r * \text{cov}(\boldsymbol{y}_q,\boldsymbol{y}_r)}{\text{var}(x)} - \sum_{q=1}^{w}\sum_{r=q+1}^{w+1} c_q\hat{\beta}_q c_r\hat{\beta}_r\right)}$$

Therefore, we have shown that

$$\text{SE}(c_1\hat{\beta}_1 + c_2\hat{\beta}_2 + \ldots + c_w\hat{\beta}_w + c_{w+1}\hat{\beta}_{w+1}) = \sqrt{\left(\sum_{i=1}^{w+1} c_i{}^2\text{SE}(\hat{\beta}_i)^2\right) + \frac{2}{n-2}\left(\frac{\sum_{q=1}^{w}\sum_{r=q+1}^{w+1} c_q * c_r * \text{cov}(\boldsymbol{y}_q,\boldsymbol{y}_r)}{\text{var}(x)} - \left(\sum_{q=1}^{w}\sum_{r=q+1}^{w+1} c_q\hat{\beta}_q c_r\hat{\beta}_r\right)\right)} \quad \blacksquare$$

Supplement 5:

This table shows the results from selected SNP's of the slope from the omega index model, the slope from the omega index residual model, and the slope using our slope formula

SNP	Omega Index slope	Omega index residual model slope	Our slope estimate
rs2341541	0.128	0.129	0.129
rs33916140	0.130	0.131	0.131
rs10202153	0.146	0.149	0.149
rs7301020	0.206	0.208	0.208
rs7304591	0.202	0.204	0.204
rs10497426	0.177	0.181	0.181
rs1319458	0.129	0.131	0.131
rs651134	0.324	0.332	0.332
rs988550	0.126	0.127	0.127
rs8099359	0.146	0.149	0.149

Supplement 6:

This table shows the results from selected SNP's for the omega index model standard error, the omega index residual model standard error, the standard error calculated using the formula presented in this paper, the standard error using the formula and estimating the covariance of the phenotypes, the standard error using the formula and estimating the covariance of the phenotypes and the variance of the genotype, and the Hardy-Weinberg Equilibrium of the given SNP.

SNP	Omega3 Index standard error	Omega3 Index Residual model Standard error	Standard error using formula	Standard error estimating covariance of **y's**	Standard error estimating covariance of **y's** and variance of genotype	Hardy-Weinberg Equilibrium P-value
rs2341541	0.0291	0.0295	0.0295	0.0297	0.0297	0.806354
rs33916140	0.0292	0.0296	0.0296	0.0297	0.0297	0.762948
rs10202153	0.0347	0.0352	0.0352	0.0354	0.0356	0.059301
rs7301020	0.0484	0.0490	0.0490	0.0493	0.0489	0.029949

rs7304591	0.0485	0.0492	0.0493	0.0496	0.0493	0.092214
rs10497426	0.0359	0.0363	0.0364	0.0366	0.0370	0.00237
rs1319458	0.0287	0.0291	0.0291	0.0292	0.0293	0.225632
rs651134	0.0729	0.0739	0.0739	0.0743	0.0746	0.190229
rs988550	0.0286	0.0290	0.0290	0.0292	0.0293	0.185446
rs8099359	0.0340	0.0344	0.0344	0.0346	0.0347	0.277974

Supplement 7:

This shows the results from selected SNP's of the omega index model p-value, the omega index residual model p-value, the p-value estimate using the standard error formula and the estimated covariance of the phenotypes, and the p-value estimate with the estimated covariance of phenotypes and estimated variance of genotype.

SNP	Omega3 index p-value	Omega3 index residual model p-value	P-value estimate for estimated covariance of y's	P-value estimate for estimated covariance of y's and variance of genotype
rs2341541	1.17E-05	1.29E-05	1.44E-05	1.42E-05
rs33916140	8.55E-06	9.32E-06	1.04E-05	1.02E-05
rs10202153	2.76E-05	2.27E-05	2.52E-05	2.82E-05
rs7301020	2.08E-05	2.32E-05	2.57E-05	2.26E-05
rs7304591	3.22E-05	3.67E-05	4.05E-05	3.68E-05
rs10497426	8.34E-07	7.37E-07	8.46E-07	1.08E-06
rs1319458	6.80E-06	7.10E-06	7.96E-06	8.63E-06
rs651134	9.49E-06	7.60E-06	8.52E-06	9.29E-06
rs988550	1.13E-05	1.30E-05	1.45E-05	1.58E-05
rs8099359	1.89E-05	1.54E-05	1.71E-05	1.83E-05