ABSTRACT

Genome-wide association studies have helped identify common genetic variants that play a role in phenotypic expression. When the sample size is insufficient, genome-wide association studies are susceptible to a lack of power to detect genetic effects. Meta-analysis improves the power to detect genetic effects by combining the summary results of multiple studies. However, when genome-wide association studies have overlapping subjects, investigators must adequately address the correlation in their meta-analysis to improve power and control for type I error. We conducted simulation studies to evaluate the performance of the fixed-effect model with robust variance estimation and the Cauchy combination test to control type I error and improve power of meta-analyses of studies with overlapping subjects. The standard fixed-effect model without robust variance estimation is implemented as a naive approach to compare with methods that account for overlapping subjects. Using meta-analyses that adequately account for correlation among studies controls type I error and improves power.

KEYWORDS: Meta-analysis, Fixed Effect Model, Robust Variance Estimation, Cauchy combination test, Correlation, GWAS

INTRODUCTION

Genome-wide association studies (GWASs) have helped identify many common genetic variants that play a role in phenotypic expression.[1] However, when the sample size is insufficient, GWASs lack the power to detect genetic effects.[2,3] Hence, meta-analysis is desirable for combining study results to improve the power to detect genetic effects.[4,5] In the past few years, conducting large-scale meta-analyses has become crucial to expanding the list of known associated loci in various human conditions.[6,7] Commonly used meta-analysis methods include the fixed effects (FE) model and random effects (RE) model.[8,9]

In the wake of many large-scale meta-analyses and GWASs that share controls, it has become imperative to account for possible dependency structures resulting from overlapping subjects. Examples of projects that have genomic control data that give rise to studies with overlapping subjects include the Wellcome Trust Case Control Consortium (WTCCC)[10] and the National Institute of Mental Health (NIMH) Gejman controls[11]. The need to account for dependency structures in meta-analyses has given rise to multiple methodologies.[12,13,14,15,16] Here, in the context of overlapping subjects, we will reinforce the shortcomings of using the FE model and compare it to the FE model using robust variance estimation and the Cauchy combination test via simulation studies.[12,16]

METHODOLOGY

Fixed-Effects Model with Naïve Variance Estimation

The fixed-effects model is a standard methodology for meta-analysis and assumes that size of the effects is fixed among studies.[8,9] The two typical weighting methods use the inverse variance or sample size. Both weighting methods perform similarly but we will describe both for thoroughness. Suppose N is the number of independent studies considered for a meta-analysis. Let $\hat{\gamma}_1, \ldots, \hat{\gamma}_N$ be the N estimated genetic effect sizes. Let $\mathrm{SE}(\hat{\gamma}_\mathrm{k})$ be the standard error of $\hat{\gamma}_\mathrm{k}$ and $\mathrm{V_k} = \left(\mathrm{SE}(\hat{\gamma}_\mathrm{k})\right)^2$ be the variance for the kth study. Let $\mathrm{n_k}$ be the sample size for the kth study and $\mathrm{n_{total}}$ be the total number of participants across all N studies. Let $\mathrm{W_{se,k}} = \mathrm{V_k^{-1}}$ be the weights using the inverse variance and $\mathrm{W_{ss,k}} = \frac{\mathrm{n_k}}{\mathrm{n_{total}}}$ be the weights using the sample size. The summary effect size for the fixed effect model is

$$\gamma_{\mathrm{Naïve}} = \frac{\sum \mathrm{W_k}\hat{\gamma}_\mathrm{k}}{\sum \mathrm{W_k}},$$

where $\mathrm{W_k}$ can be either $\mathrm{W_{se,k}}$ or $\mathrm{W_{ss,k}}$. With weight either being normalized $\sum_{\mathrm{k}=1}^{\mathrm{N}} \mathrm{W_{norm,k}} = 1$ or not. To calculate the z test statistic, you divide $\gamma_{\mathrm{Naïve}}$ by $\mathrm{SE}(\hat{\gamma}_{\mathrm{Naïve}})$, which is used to obtain the corresponding p-value.

Fixed-Effects Model with Robust Variance Estimation

Lin and Sullivan[12] developed methodology to account for the possibility of overlapping subjects among studies when conducting meta-analyses. The methodology is only applicable to the fixed effect model but provided a foundation for later extensions for addressing dependencies in meta-analyses.[13,14]

Suppose N is the number of studies considered for a meta-analysis. To implement the methodology the correlation matrix for the estimated genetic effect sizes $\hat{\gamma}_1, \ldots, \hat{\gamma}_N$ conferred by overlapping subjects must be calculated. Let $\hat{\boldsymbol{\gamma}}$ be the vector of estimated genetic effect size estimates, $\hat{\boldsymbol{\gamma}} = (\hat{\gamma}_1, \ldots, \hat{\gamma}_N)$, and let

$$\mathrm{Corr}(\hat{\boldsymbol{\gamma}}) = [\mathrm{r_{kl}}]_{N \times N}$$

be the correlation matrix of $\boldsymbol{\gamma}$ where $\mathrm{r_{kl}}$ represents the correlation for $\hat{\gamma}_\mathrm{k}$ and $\hat{\gamma}_\mathrm{l}$. Each $\mathrm{r_{kl}}$ are approximated using the formula

$$\mathrm{r_{kl}} \approx \frac{\left(\mathrm{n_{kl0}}\sqrt{\frac{\mathrm{n_{k1}n_{l1}}}{\mathrm{n_{k0}n_{l0}}}} + \mathrm{n_{kl1}}\sqrt{\frac{\mathrm{n_{k0}}n_{l0}}{n_{k1}n_{l1}}}\right)}{\sqrt{\mathrm{n_k n_l}}},$$

where $\mathrm{n_{k1}}$, $\mathrm{n_{k0}}$, and $\mathrm{n_k}$ (or $\mathrm{n_{l1}}$, $\mathrm{n_{l0}}$, and $\mathrm{n_l}$) are, respectively, the number of cases, the number of controls, and the total number of subjects in the kth (or lth) study. $\mathrm{n_{kl1}}$ and $\mathrm{n_{kl0}}$ is the overlap of cases and the overlap of controls for the kth and lth study respectively. Given $\mathrm{Corr}(\hat{\boldsymbol{\gamma}})$ you can calculate the covariance matrix $\boldsymbol{\Omega} = \mathrm{Cov}(\hat{\boldsymbol{\gamma}})$.

Once $\boldsymbol{\Omega}$ has been calculated, Once $\boldsymbol{\Omega}$ has been calculated, the methodology optimally takes into account $\boldsymbol{\Omega}$ in the weights by calculating

$$\mathbf{W}_{\mathrm{robust}} = \left[\mathrm{W_{robust,1}}, \ldots, \mathrm{W_{robust,K}}\right] = \frac{\mathbf{e}^T\boldsymbol{\Omega}^{-1}}{\mathbf{e}^T\boldsymbol{\Omega}^{-1}\mathbf{e}},$$

where $\mathbf{e}$ is a $N \times 1$ vector of ones ($\mathbf{e}^\mathrm{T} = (1, \ldots, 1)$). The optimal summary effect size calculated as

$$\gamma_{\mathrm{robust}} = \mathbf{W}_{\mathrm{robust}}\hat{\boldsymbol{\gamma}},$$

The optimality γ_{robust} is formally proven in Wei and Johnson[17] and Wei, Lin, and Weissfeld[18]. To calculate the z test statistic, you divide γ_{robust} by the square root of

$$\mathrm{Var}(\gamma_{\mathrm{robust}}) = \frac{1}{\mathbf{e}^T\boldsymbol{\Omega}^{-1}\mathbf{e}},$$

which is used to obtain a corresponding p-value.

However, to enable the comparison to the naïve estimator and the Cauchy Combination Test, the summary effect size for the fixed effect model can be also calculated as

$$\gamma_{\mathrm{Robust}} = \frac{\sum \mathrm{W_j}\hat{\gamma}_\mathrm{j}}{\sqrt{\mathrm{Var}(\sum \mathrm{W_j}\hat{\gamma}_\mathrm{j})}} = \frac{\sum \mathrm{W_j}\hat{\gamma}_\mathrm{j}}{\sqrt{\sum \mathrm{W_j^2}\,\mathrm{Var}(\hat{\gamma}_\mathrm{j}) + 2\sum\sum \mathrm{W_k W_l Cov}(\hat{\gamma}_\mathrm{k}, \hat{\gamma}_\mathrm{l})}}$$

where $\mathrm{W_k}$ can be either $\mathrm{W_{se,k}}$ or $\mathrm{W_{ss,k}}$. With weight either being normalized $\sum_{\mathrm{k}=1}^{\mathrm{N}} \mathrm{W_{norm,k}} = 1$ or not. Similarly, to calculate the z test statistic, you divide γ_{Robust} by $\mathrm{SE}(\hat{\gamma}_{\mathrm{Robust}})$, which is used to obtain the corresponding p-value.

Cauchy Combination Test

Liu and Xie[16] developed methodology that allows combining individual p-values that is makes use of the Cauchy distribution to build insensitivity to arbitrary dependency structures. Suppose N is the number of independent studies considered for a meta-analysis. Let $\mathrm{p}_1, \ldots, \mathrm{p}_\mathrm{N}$ be the N independent or perfectly dependent p-values obtained and let $\mathrm{W}_{\mathrm{norm,k}}$ be the normalized weights of either $\mathrm{W}_{\mathrm{se,k}}$ or $\mathrm{W}_{\mathrm{ss,k}}$, so $\sum_{\mathrm{k}=1}^{\mathrm{N}} \mathrm{W}_{\mathrm{norm,k}} = 1$. The Cauchy combination test statistic is calculated as

$$\mathrm{T} = \sum_{\mathrm{k}=1}^{\mathrm{N}} \mathrm{W}_{\mathrm{norm,k}} \tan\{(0.5 - p_k)\pi\},$$

which is used to obtain a corresponding p-value.

SIMULATIONS

We conducted simulation studies to evaluate the performance of the fixed-effect model with robust variance estimation and the Cauchy combination test to control type I error and improve power of meta-analyses of studies with overlapping subjects. The standard fixed-effect model with naïve variance estimation is implemented as a point of reference for approaches that account for overlapping subjects.

Pairwise studies were created either with both Study 1 and Study 2 having 1,000 cases (SETUP I) or with Study 1 having 1500 cases while Study 2 having 500 cases (SETUP II). For SETUP I and SETUP II we set the number of cases to be 1,000, 2,000, 3,000, or 4,000 and varied the proportion of overlap at from 0.25 to 1.00 in increments of 0.25. In total there are 32 configurations and we generated 1 million datasets for each.

Data are created by sampling cases and controls from a population of 250,000 individuals for which generated genotype G_i at a particular SNP and outcome Y_i ($1 =$ disease, $0 =$ no disease) under the null and alternative hypothesis. The data generating mechanisms are $\mathrm{G}_\mathrm{i} \sim \mathrm{Binomial}(2, \mathrm{MAF} = 0.3)$, $\mathrm{Y}_{0,\mathrm{i}} \sim \mathrm{Bernoulli}\left(\mathrm{expit}\left(\alpha + \beta_0^{\mathrm{T}} \mathrm{X}_\mathrm{i}\right)\right)$ under the null hypothesis ($\beta_0 = 0$), and $Y_{1,i} \sim \mathrm{Bernoulli}\left(\mathrm{expit}\left(\alpha + \beta_1^{\mathrm{T}} X_i\right)\right)$ under the alternative hypothesis ($\beta_1 = 0.3$) where $\alpha = -3$ and $\mathrm{X}_\mathrm{i} = \mathrm{G}_\mathrm{i}$ for the ith subject.

Assume the following logistic regression model,

$$\mathrm{logit}(\Pr(\mathbf{Y} = 1|\mathbf{X})) = \boldsymbol{\alpha} + \boldsymbol{\beta}^{\mathrm{T}}\mathbf{X},$$

where $\mathbf{Y}$ is a vector of values denoting disease status, $\mathbf{X}$ is a matrix of a set of covariates, $\boldsymbol{\alpha}$ is the intercept and $\boldsymbol{\beta}$ is a set of regression parameters. The p-values for the genetic effect are obtained using standard generalized linear model Wald test statistics.

RESULTS

We conducted simulation studies for the meta-analysis of pairwise studies that share controls among several data configurations. The data configurations varied the number of controls (1,000, 2,000, 3,000, and 4,000) and the proportion of controls shared (1.00, 0.75, 0.50, and 0.25). The methodology implemented to assess performance of accounting for dependency structures are the FE model with naïve variance estimation, the FE model with robust variance estimation, and the Cauchy combination test for the mentioned data configurations.

Type I error rates of the implemented meta-analysis methodology for the different data configurations are shown in **Table 1** and **Table 2**. **Table 1** presents the type I error rates when using normalized $\mathrm{W}_{\mathrm{se,k}}$ weights and **Table 2** presents the same information using normalized $\mathrm{W}_{\mathrm{ss,k}}$ weights. Both **Table 1** and **Table 2** show similar results as expected. Hence, we focus on **Table 1** to describe our findings regarding type I error rates. The FE model with robust variance estimation and Cauchy combination test control for type I error well for the different dependency structures imposed. However, the FE model with robust variance estimation accounts for the dependency structure by incorporating information about the

dependencies. By contrast, the Cauchy combination test is innately built to be resistant to different dependency structures inflating its type I error. Because the FE model with naïve variance estimation did not account for the dependency structure with available information or was resistant to dependency structures inflating its type I error, its own type I error rates were flagrantly inflated. Nonetheless, it was observed that type I error decreases as the number of controls increases. The relation is revisited in the discussion section. Further investigation should be made to ensure no mistakes were made regarding the type I errors of the Cauchy combination test as there are fluctuations.

Power of the FE model with robust variance estimation and Cauchy combination test implemented for the different data configurations are shown in **Table 3** and **Table 4**, respectively. **Table 3** and **Table 4** both present the powers using normalized $W_{se,k}$ weights and normalized $W_{ss,k}$. Again, the weighting methods performed similarly for the Cauchy combination test. However, when using the normalized $W_{ss,k}$ for the FE model with robust variance estimation, some power was lost when compared to using the normalized $W_{se,k}$. For both methodologies, the power increases as the sample increases. However, the FE model with robust variance estimation achieves greater power when compared to the Cauchy combination test using the same configurations. Notably, the Cauchy combination test could not achieve desirable power for configurations where study 1 and study 2 have 2,000 cases. Further investigation is needed to assess the cause of lack of power for these configurations.

Spearman correlation values of the -$\log_{10}$(p-values) of study 1 and study 2 under the null hypothesis ($\beta = 0$) and alternative hypothesis ($\beta = 0.3$) are shown in **Table 5**. Corresponding correlation plots of the -$\log_{10}$(p-values) of study 1 and study 2 for each of the eight configurations are presented in **Figure 1** and **Figure 2**, under the null hypothesis ($\beta = 0$) and alternative hypothesis ($\beta = 0.3$), respectively. **Figure 1** and **Figure 2** are based 2000 randomly sampled paired p-values for study 1 and study 2 that are transformed using -$\log_{10}(\cdot)$. **Figure 1** shows that under the null hypothesis ($\beta = 0$) we do not see a clear linear trend for any of the configurations. **Figure 2** shows that under the alternative hypothesis ($\beta = 0.3$) there are observable linear trends for each of the configurations. However, the linear trends are obscured as the sample size increases. These observations coincide with the Spearman correlation values obtained and shown in **Table 5**.

DISCUSSION

Large-scale GWAS studies and consortiums in recent years have shared controls to alleviate genomic sequencing costs.[10,11] However, when meta-analyses are implemented to improve the power to detect genetics by combining summary results of multiple studies, there is the possibility of overlapping subjects. To address the dependency structures being introduced into meta-analyses methodologies have been developed. [12,13,14,15,16]

Here we reinforce that ignoring the dependency structure of the data when conducting meta-analyses results in inflated type I errors via the FE model with naïve variance estimation. Regarding the FE model with naïve variance estimation, we observed that type I error decreased as the number of controls increased. Lin and Sullivan[12] explain it to be the result of variance-covariance matrix and "the extra variance due to overlap is inversely proportional to"[12] the number of controls. We also reinforce that implementing methodology that use available information to account for the dependency structure (FE model with robust variance estimation) or are resilient against dependency structures (Cauchy combination test) are a path forward.[12,16] Further research can be done lessening simulation computational time by implementing "data-based resampling methods"[19] and assessing how power behaves when varying the size of the genetic effect.

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Table 1. Type I error rates ($\times 10^3$) of logistic regression association tests at the nominal significance level of 10^{-3} for different proportions of shared control samples in the combined analysis of two case-control studies (based on one million simulations) using weights $W_{se,k}$

			Proportion of Controls Shared											
No. of Cases		**No. of**	**1.00**			**0.75**			**0.50**			**0.25**		
Study 1	**Study 2**	**Controls**	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]
1000	1000	1000	0.993	0.945	5.427	1.037	0.975	3.970	1.001	0.891	2.723	0.961	0.936	1.723
1000	1000	2000	1.012	1.112*	3.549	1.035	1.119*	2.804	1.020	1.141*	2.112	0.965	1.188*	1.461
1000	1000	3000	1.028	0.975	2.772	1.059	0.953	2.266	1.048	0.958	1.823	0.954	0.942	1.294
1000	1000	4000	1.093	0.954	2.418	1.073	0.935	1.987	1.055	0.927	1.707	0.995	0.891*	1.262
1500	500	1000	0.994	0.901	5.011	1.042	0.913	3.696	1.014	0.874*	2.534	0.943	0.843*	1.635
1500	500	2000	1.004	0.946	3.240	1.046	0.932	2.645	1.018	0.965	1.971	1.011	0.929	1.474
1500	500	3000	1.019	0.954	2.592	1.068	0.969	2.152	1.060	1.039	1.737	0.978	0.951	1.307
1500	500	4000	1.073	1.100	2.259	1.050	0.994	1.943	1.035	1.039	1.624	0.996	0.977	1.238

[a]Robust variance estimator used with normalized weights $W_{norm,k} = W_{se,k} / \sum_{k=1}^{N} W_{se,k}$.

[b]Cauchy combination test used with normalized weights $W_{norm,k} = W_{se,k} / \sum_{k=1}^{N} W_{se,k}$.

[c]Naive variance estimator used with normalized weights $W_{norm,k} = W_{se,k} / \sum_{k=1}^{N} W_{se,k}$.

*Need further investigation to make sure mistakes were not made when computing values.

Table 2. Type I error rates ($\times 10^3$) of logistic regression association tests at the nominal significance level of 10^{-3} for different proportions of shared control samples in the combined analysis of two case-control studies (based on 1,000,000 simulations) using weights $W_{ss,k}$

			Proportion of Controls Shared											
No. of Cases		**No. of**	**1.00**			**0.75**			**0.50**			**0.25**		
Study 1	**Study 2**	**Controls**	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]	**Robust**[a]	**Cauchy**[b]	**Naïve**[c]
1000	1000	1000	1.002	0.942	5.401	1.007	0.983	3.944	1.014	0.897	2.714	1.008	0.093	1.723
1000	1000	2000	0.998	1.134*	3.533	0.983	1.093*	2.794	1.031	1.145*	2.100	1.012	1.184*	1.461
1000	1000	3000	1.000	0.943	2.757	1.041	0.940	2.259	1.054	0.962	1.815	0.941	0.958	1.294
1000	1000	4000	1.028	0.952	2.401	1.032	0.958	1.979	1.052	0.944	1.699	0.980	0.894*	1.262
1500	500	1000	1.000	0.815*	4.982	1.060	0.846*	3.682	1.018	0.723	2.542	1.021	0.779*	1.635
1500	500	2000	0.991	0.864*	3.180	1.027	0.861*	2.612	1.010	0.929	1.955	1.058	0.878*	1.474
1500	500	3000	1.060	0.973	2.547	1.083	0.988	2.140	1.101	0.995	1.716	1.035	0.983	1.307
1500	500	4000	1.032	1.044	2.212	1.047	0.979	1.902	1.100	1.101	1.618	1.010	0.996	1.238

[a]Robust variance estimator used with normalized weights $W_{norm,k} = W_{ss,k} / \sum_{k=1}^{N} W_{ss,k}$.

[b] Cauchy combination test used with normalized weights $W_{norm,k} = W_{ss,k} / \sum_{k=1}^{N} W_{ss,k}$

[c]Naive variance estimator used used with normalized weights $W_{norm,k} = W_{ss,k} / \sum_{k=1}^{N} W_{ss,k}$.

*Need further investigation to make sure mistakes were not made when computing values.

Table 3. Robust variance estimation power of association tests at the nominal significance level of 10^{-7} when all controls are shared in the combined analysis of two case-control studies (based on 1,000,000 simulations).

No. of Cases		No. of Controls	Normalized Weights $W_{se,k}$	Normalized Weights $W_{ss,k}$
Study 1	Study 2			
1000	1000	1000	0.449	0.423
1000	1000	2000	0.947	0.824
1000	1000	3000	0.983	0.932
1000	1000	4000	0.992	0.967
1500	500	1000	0.690	0.395
1500	500	2000	0.935	0.567
1500	500	3000	0.979	0.692
1500	500	4000	0.991	0.753

Table 4. Cauchy combination test power of association tests at the nominal significance level of 10^{-7} when all controls are shared in the combined analysis of two case-control studies (based on 1,000,000 simulations).

No. of Cases		No. of Controls	Normalized Weights $W_{se,k}$	Normalized Weights $W_{ss,k}$
Study 1	Study 2			
1000	1000	1000	0.145	0.147
1000	1000	2000	0.390	0.380
1000	1000	3000	0.514	0.516
1000	1000	4000	0.591	0.601
1500	500	1000	0.271	0.240
1500	500	2000	0.660	0.628
1500	500	3000	0.820	0.798
1500	500	4000	0.889	0.871

Table 5. $-\log_{10}$(p-value) Spearman correlations for study 1 and study 2 for under the null and alternative hypothesis (based on 1,000,000 simulations).

No. of Cases		No. of Controls	H_0: $\beta = 0$	H_1: $\beta = 0.3$
Study 1	Study 2			
1000	1000	1000	0.165	0.483
1000	1000	2000	0.069	0.322
1000	1000	3000	0.038	0.241
1000	1000	4000	0.024	0.194
1500	500	1000	0.131	0.432
1500	500	2000	0.054	0.284
1500	500	3000	0.029	0.213
1500	500	4000	0.014	0.171

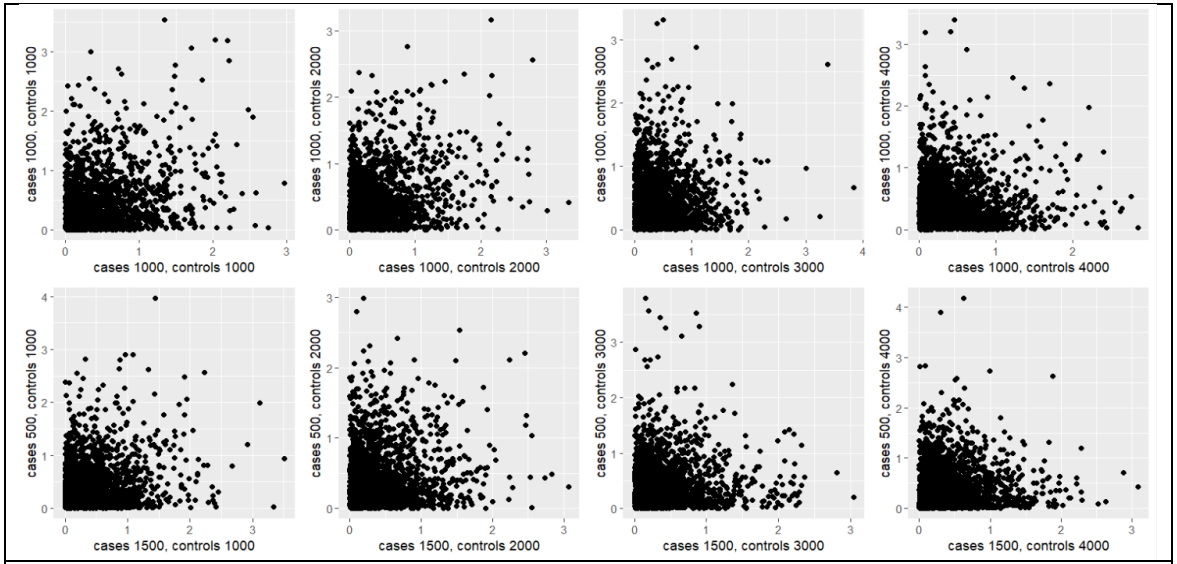

Figure 1. -$\log_{10}$(p-value) correlation plots for two case-control studies with control samples all shared under the null hypothesis (β=0) (2,000 p-values sampled from 1,000,000 p-values)

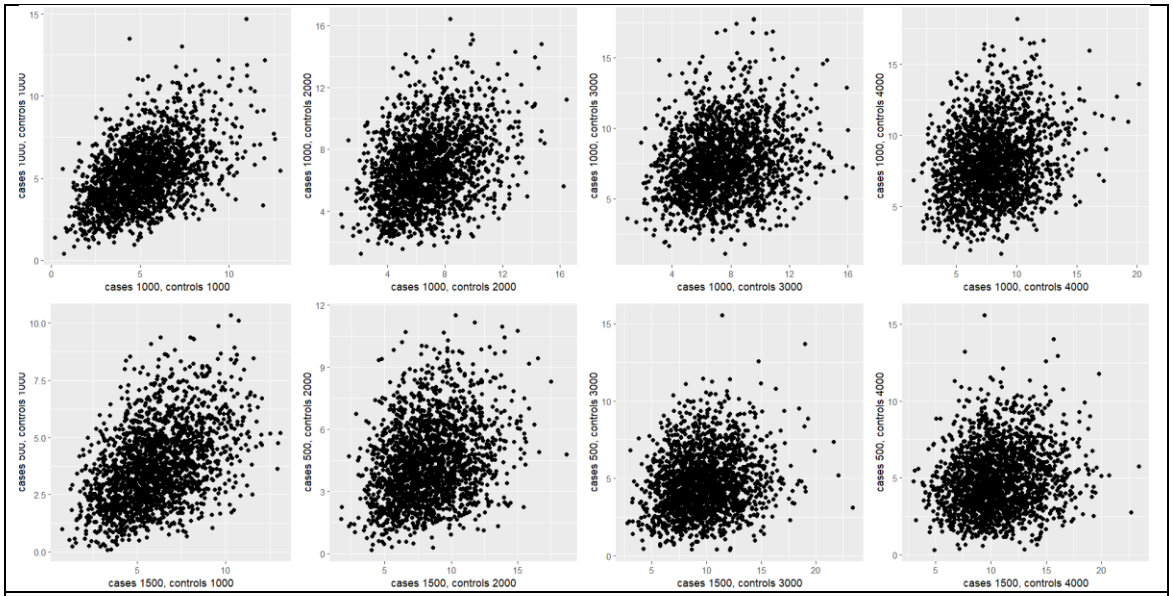

Figure 2. -$\log_{10}$(p-value) correlation plots for two case-control studies with control samples all shared under the alternative hypothesis (β=0.3) (2,000 p-values sampled from 1,000,000 p-values)