P values of GWAS studies in different populations

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1 Wald test for Generalized Linear Models:

Assume the generalized linear models (glm) has the following form:

$$\mathbb{E}(Y|X) = \mu = g^{-1}(\beta_0 + \beta_1 X_1 + \beta_2 X_2) = g^{-1}(\eta),$$

where $g(.)$ is a specific link function connecting the linear predictor η with the mean function of Y. In this case, the fisher information matrix at β can be written as

$$I_n(\beta) = XW(\beta)X^T,$$

where X denotes the design matrix and $W(\beta)$ is a diagonal matrix with each diagonal term depending on the value of β unless g is identity function. Specifically, the i^{th} diagonal term of W can be computed as

$$w_i = (\frac{\partial u_i}{\partial \eta_i})^2/\text{Var}(Y_i|X).$$

If the question of interest is to test the hypothesis $H_0 : \beta_2 = 0$ using Wald test, the test statistic can be written as

$$T = I_n^{-1}(\hat{\beta})_{[3,3]}(\hat{\beta}_2)^2,$$

where $I_n^{-1}(\hat{\beta})_{[3,3]}$ denotes the third diagonal term of the matrix $I_n^{-1}(\hat{\beta})$ and $\hat{\beta}$ is the MLE estimator. Under the null hypothesis, T asymptotically follows a Chi-Square distribution with 1 degree of freedom.

Under the alternative hypothesis that $\beta_3 = \tilde{\beta}_3 \neq 0$, the non-centrality parameter of Wald test above can be computed as

$$I_n^{-1}(\tilde{\beta})_{[3,3]}\tilde{\beta}_3^2,$$

where $\tilde{\beta}$ is the vector of true values for the regression parameters β. Since $I_n^{-1}(\tilde{\beta})_{[3,3]}$ will not be solely a function of $\tilde{\beta}_3$ unless g is identity, the power function of this Wald test will not only depend on $\tilde{\beta}_3$, but the whole vector $\tilde{\beta}$.

Define $d = -\sqrt{I_n^{-1}(\tilde{\beta})_{[3,3]}}\tilde{\beta}_3$, the theoretical power of this Wald test at $\tilde{\beta}$ can be computed as

$$1 - \Phi(d + z_{a/2}) + \Phi(d - z_{a/2}),$$

where Φ is the CDF of standard normal and $z_{a/2}$ is the $a/2$ quantile of standard normal.

2 Simulation with random samples:

Consider that two samples of size $n = 1000$ have been collected independently on two populations (European, Asian), and question of interest is to study the association between the status of a particular disease ($Y : 0/1$) and a particular SNP G with minor allele frequency (MAF) 0.3 under Hardy Weinberg Equilibrium (HWE), after controlling the effect of Z ($Z \sim N(0, \sigma = 3)$).

Assume that GWAS study has been carried out for each population to test if the SNP G is causal for Y, and the p-values are 5×10^{-4} for European population and 5×10^{-8} for Asian population, can we interpret the result as there is likely a stronger association in Asian population than European population? To answer this question, we will conduct the following simulation study.

We assume that the models that generate the observations for European population and for Asian population are the followings:

$$\textbf{Euro} : \text{logit}(\text{P}(Y = 1|G, Z)) = -0.5 + 0.8Z + 0.3G,$$

$$\textbf{Asian} : \text{logit}(\text{P}(Y = 1|G, Z)) = -0.5 + 0.1Z + 0.3G.$$

In other words, the effect of Z will be different across the two populations, but the effect of the SNP will be the same. We generated $\{G_i\}_n$ and $\{Z_i\}_n$ independently, and used the same set of covariates to generate the response variables in each population.

2.1 Summary of simulated data and P values:

In our simulation, the same sets of G and Z will be used to simulate traits in both populations. We simulated $\{G_i\}$ independently from $\{Z_i\}$, and then simulated the disease status Y using G and Z. Recall that $Z \sim N(0, 3)$ and MAF of G is 0.3. The summary of our generated data is present at below:

```
### Simulated the common Z and G
set.seed(100,sample.kind = "Rounding")
N <- 1000
G <- sample(c(0,1,2),size = N, replace = T, prob = c(0.49,0.42,0.09))
Z <- rnorm(N,sd = 3)


### Simulate each population's disease status based on Z and G
## Eur:
beta0 <- -0.5
betaZ <- 0.8
betaG <- 0.3
ylat_Eur <- beta0 + betaG*G + betaZ*Z + rlogis(N)
y_Eur <- ifelse(ylat_Eur >=0, 1, 0)

## Asia:
beta0 <- -0.5
betaZ <- 0.1
betaG <- 0.3
ylat_As <- beta0 + betaG*G + betaZ*Z + rlogis(N)
y_As <- ifelse(ylat_As >=0, 1, 0)



### Case control counts across populations:
t <- rbind(table(y_Eur),table(y_As)) %>% as_tibble()
```

```r
rownames(t) <- c("Euro","Asia")
kableExtra::kable(t, caption = "Case Control Counts across populations") %>%
  kable_styling(latex_options = "HOLD_position", font_size = 10)
```

Table 1: Case Control Counts across populations

	0	1
Euro	522	478
Asia	573	427

```r
### Case control ratio across genotypes:
t <- cbind(c(y_Eur,y_As),c(G,G)) %>% as_tibble()
colnames(t) <- c("Y","G")
t <- t %>% group_by(G) %>% summarise(ratio = sum(Y)/n())
kableExtra::kable(t, caption = "Case Control Ratio across genotypes") %>%
  kable_styling(latex_options = "HOLD_position", font_size = 10)
```

Table 2: Case Control Ratio across genotypes

G	ratio
0	0.4238901
1	0.4683841
2	0.5200000

Based on the two tables above, we can notice that the case to control ratios are similar across the two populations. Furthermore, as we can expect, the genotype group with more copies of the minor allele has higher case to control ratio. In our simulation, the samples are randomly collected from the two populations. This strategy may not be appropriate if the disease prevalence is very low, in which samples collected in a case-control design will be more appropriate. We will consider the same problem for case-control study later, and for now just focus on the case when the sample is random.

We can use Wald test to test the hypothesis $\beta_G = 0$ (i.e. G is a casual SNP) in each population:

```r
## EU:
mod_Eur <- glm(y_Eur~Z + G, family = binomial(link = "logit"))
summary(mod_Eur)$coefficients[3,4]
```

```
## [1] 0.01510122
```

```r
## Asian:
mod_As <- glm(y_As~ Z + G, family = binomial(link = "logit"))
summary(mod_As)$coefficients[3,4]
```

```
## [1] 0.008987236
```

Note that the p-values are 0.015 for European population, and 0.009 for Asian population. It is typically expected that for the population with smaller p-value, the magnitude of the association (i.e. $\tilde{\beta}_G$) should be larger. However, in this simulation example the true value of β_G is $\tilde{\beta}_G$ for both populations, and even the covariates are exactly the same.

2.2 Theoretical Power and Empirical Power:

For now, assume that the hypothesis $\beta_G = 0$ will be tested using Wald test with $\alpha = 0.05$, then we can compute the theoretical powers of the two Wald test using the simulated data $\{G_i, Z_i\}_n$ and the true parameters vectors $\tilde{\beta}_{Euro}, \tilde{\beta}_{Asia}$:

```
## Euro:
beta0 <- -0.5
betaZ <- 0.8
betaG <- 0.3
### Theoretical Power
mod_Eur <- glm(y_Eur~Z + G, family = binomial(link = "logit"))
#### Get the design matrix:
X <- cbind(rep(1,N),mod_Eur$model[,-1])
### Compute the weight matrix W:
beta <- c(beta0,betaZ,betaG)
#beta <- as.numeric(mod_Eur$coefficients)
w <- c()
for (i in 1:N) {
  si <- as.numeric(as.numeric(X[i,]) %*% beta)
  w[i] <- (dlogis(si)^2)/(plogis(si)*(1-plogis(si)))
}
I <- as.matrix(t(X)) %*% diag(w,nrow = N,ncol = N) %*% as.matrix(X)
#### Invert to get the true covariance matrix
V <- solve(I)
### Compute the power function:
delta <- sqrt(1/V[3,3])*(0-beta[3])
alpha <- 0.05
Power_EU <- 1- pnorm(delta - qnorm(alpha/2)) + pnorm(delta + qnorm(alpha/2))
Power_EU
```

```
## [1] 0.6193771
```

```
## Asia:
beta0 <- -0.5
betaZ <- 0.1
betaG <- 0.3
### Theoretical Power
mod_As <- glm(y_As~ Z + G, family = binomial(link = "logit"))
#### Get the design matrix:
X <- cbind(rep(1,N),mod_As$model[,-1])
### Compute the weight matrix W:
beta <- c(beta0,betaZ,betaG)
#beta <- as.numeric(mod_As$coefficients)
w <- c()
for (i in 1:N) {
  si <- as.numeric(as.numeric(X[i,]) %*% beta)
  w[i] <- (dlogis(si)^2)/(plogis(si)*(1-plogis(si)))
}
I <- as.matrix(t(X)) %*% diag(w,nrow = N,ncol = N) %*% as.matrix(X)
#### Invert to get the true covariance matrix
V <- solve(I)
### Compute the power function:
```

```r
delta <- sqrt(1/V[3,3])*(0-beta[3])
alpha <- 0.05
Power_AS <- 1- pnorm(delta - qnorm(alpha/2)) + pnorm(delta + qnorm(alpha/2))
Power_AS
```

```
## [1] 0.8618099
```

Based on the results above, we know in this simulation study, the power of Wald test will be 0.619 for the European population, and 0.861 for the Asian population. Note that Wald test on Asian population has quite larger power compared to on European population, despite the fact that the two samples are generated with same $\beta_G = 0.3$ and generated by the same set of $\{G_i, Z_i\}_n$. This suggests the p-values of Wald test may have very different distributions on the two populations. We can double check that our theoretical powers for both tests are correct using empirical powers:

To compute the empirical powers, we re-simulated the disease status in each population for $K = 800$ times, and compute the 800 p-values in each population:

```r
set.seed(100,sample.kind = "Rounding")
## Euro:
beta0 <- -0.5
betaZ <- 0.8
betaG <- 0.3
p1 <- c()
for (i in 1:800) {
  ylat_Eur_rep <- beta0 + betaG*G + betaZ*Z + rlogis(N)
  y_Eur_rep <- ifelse(ylat_Eur_rep >=0, 1, 0)
  mod <- glm(y_Eur_rep~Z+G, family = binomial(link = "logit"))
  p1[i] <- summary(mod)$coefficient[3,4]
}
emp_power <- mean(p1 <= alpha)
emp_power
```

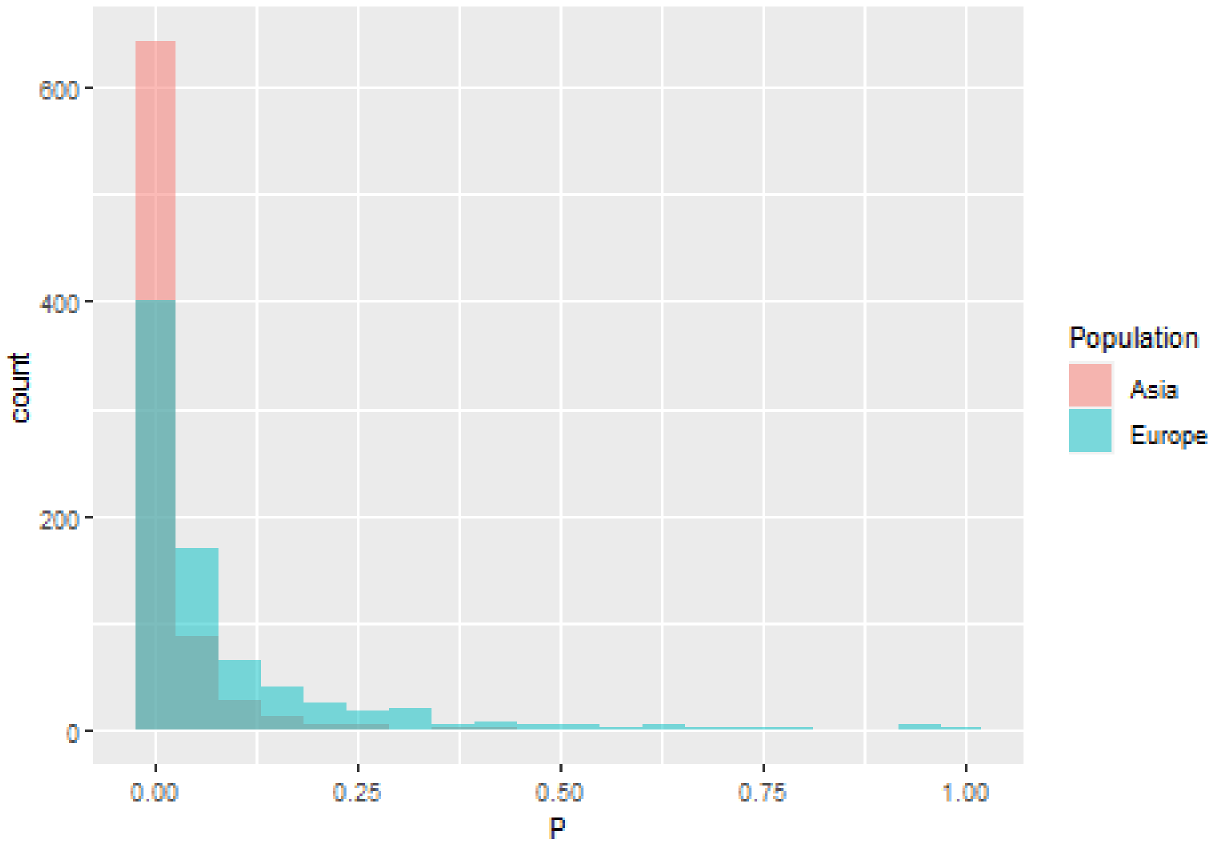
```
## [1] 0.61625
```

```r
set.seed(100,sample.kind = "Rounding")
## Asia:
beta0 <- -0.5
betaZ <- 0.1
betaG <- 0.3
p2 <- c()
for (i in 1:800) {
  ylat_As_rep <- beta0 + betaG*G + betaZ*Z + rlogis(N)
  y_As_rep <- ifelse(ylat_As_rep >=0, 1, 0)
  mod <- glm(y_As_rep~Z+G, family = binomial(link = "logit"))
  p2[i] <- summary(mod)$coefficient[3,4]
}
emp_power <- mean(p2 <= alpha)
emp_power
```

```
## [1] 0.8725
```

Based on the 800 resampling results, the empirical powers are respectively 0.616 for European population and 0.873 for Asian population. These values are quite close to the theoretical values 0.619 and 0.861 we computed above. The distributions of p-values in each population can be visualized as well:

```
### Comparison:
pcomp <- tibble(P = c(p1,p2), Population = c(rep("Europe",800),rep("Asia",800)))
pcomp %>% ggplot(aes(x = P, fill = Population)) + geom_histogram(bins = 20, alpha=0.5, position="identi
```



Based on the figure above, we can conclude that the distribution of p values in Asian population is stochastically smaller than the distribution in European population, even if their underlying β_G are both 0.3. Therefore, it shows that the magnitudes of p-values of different studies are not directly comparable, unless the generalized linear regression model being used is the ordinary linear regression model with g being identity function.

3 Simulation with Case-Control design:

In this section, we will demonstrate the same problem will also occur for studies with Case-Control design, using a new simulation example.

For the new simulation, we will continue to use the two data-generating models as in section 2. However, instead of using samples randomly simulated from the population, we are now randomly samples that are randomly sampled from case and control in the following way:

- First, use the two true models to generate two **populations** of size 3000 in the same way as in section 2.
- Secondly, among all the cases and controls in each population, randomly sample 400 observations from cases and 600 observations from controls.
- Finally, for each population, combine all the sampled cases and controls to have a sample with size 1000.

```r
### Simulated the common Z and G
set.seed(100,sample.kind = "Rounding")
N <- 5000
G <- sample(c(0,1,2),size = N, replace = T, prob = c(0.49,0.42,0.09))
Z <- rnorm(N,sd = 3)
## Eur:
beta0 <- -0.5
betaZ <- 0.8
betaG <- 0.3
ylat_Eur <- beta0 + betaG*G + betaZ*Z + rlogis(N)
y_Eur <- ifelse(ylat_Eur >= 0, 1, 0)
Eur_controls <- tibble(Y = y_Eur, G = G, Z = Z) %>% filter(Y == 0) %>% sample_n(600)
Eur_cases <- tibble(Y = y_Eur, G = G, Z = Z) %>% filter(Y == 1) %>% sample_n(400)
EU_sample <- rbind(Eur_cases,Eur_controls)
mod_Eur <- glm(Y ~ Z + G,data = EU_sample, family = binomial(link = "logit"))
summary(mod_Eur)$coefficients[3,4]
```

```
## [1] 0.007485476
```

```r
## Asia:
set.seed(100,sample.kind = "Rounding")
beta0 <- -0.5
betaZ <- 0.1
betaG <- 0.3
ylat_As <- beta0 + betaG*G + betaZ*Z + rlogis(N)
y_As <- ifelse(ylat_As >= 0, 1, 0)
As_controls <- tibble(Y = y_As, G = G, Z = Z) %>% filter(Y == 0) %>% sample_n(600)
As_cases <- tibble(Y = y_As, G = G, Z = Z) %>% filter(Y == 1) %>% sample_n(400)
As_sample <- rbind(As_cases,As_controls)
mod_As <- glm(Y ~ Z + G,data = As_sample, family = binomial(link = "logit"))
summary(mod_As)$coefficients[3,4]
```

```
## [1] 5.679744e-26
```

Using Wald test as before, we have p-value (5.679×10^{-26}) in Asian population being much less than the p-value in European population (7.489×10^{-3}). Note that we are still assuming the same $\tilde{\beta}_G$ for each population in this example.

For case-control data, we cannot directly compute the theoretical power using the formula from section 1. When a logistic regression model is fitted for case-control data, the estimated intercept parameter $\hat{\beta}_0$ will no longer have the same interpretation as the β_0 we used in the generating model. This implies that we cannot plug in $\tilde{\beta}_0 = -0.5$ as the true value for the intercept when we compute theoretical powers. However, we can still obtain the empirical powers and distribution of p-values using the same approach as before:

```
### Simulate each population's disease status based on Z and G
## Eur:
set.seed(100,sample.kind = "Rounding")
beta0 <- -0.5
betaZ <- 0.8
betaG <- 0.3
p1 <- c()
for (i in 1:800) {
  ylat_Eur <- beta0 + betaG*G + betaZ*Z + rlogis(N)
  y_Eur <- ifelse(ylat_Eur >=0, 1, 0)
  Eur_controls <- tibble(Y = y_Eur, G = G, Z = Z) %>% filter(Y == 0) %>% sample_n(600)
  Eur_cases <- tibble(Y = y_Eur, G = G, Z = Z) %>% filter(Y == 1) %>% sample_n(400)
  EU_sample <- rbind(Eur_cases,Eur_controls)
  mod_Eur <- glm(Y~Z + G,data = EU_sample, family = binomial(link = "logit"))
  p1[i] <- summary(mod_Eur)$coefficients[3,4]
}
emp_power <- mean(p1 <= alpha)
emp_power
```

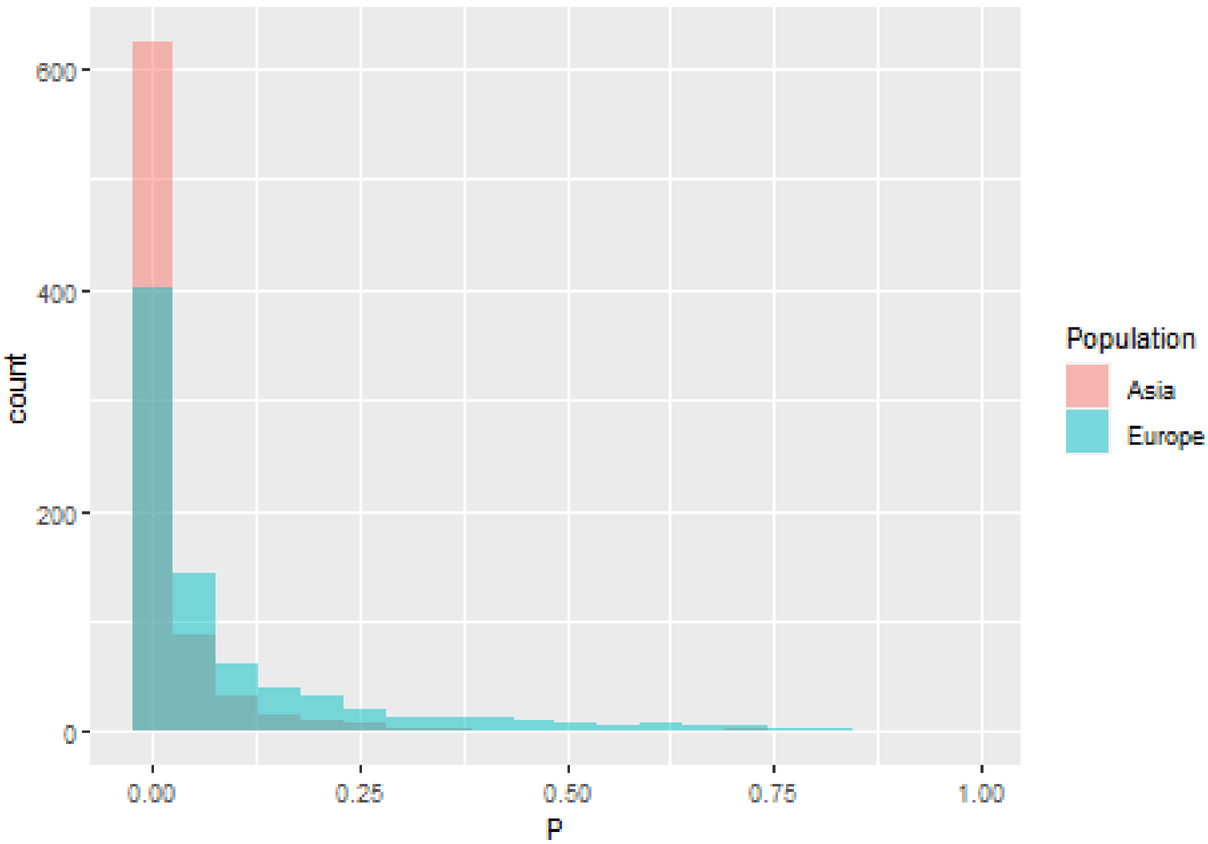
```
## [1] 0.61
```

```
## Asia:
set.seed(100,sample.kind = "Rounding")
beta0 <- -0.5
betaZ <- 0.1
betaG <- 0.3
p2 <- c()
for (i in 1:800) {
  ylat_As <- beta0 + betaG*G + betaZ*Z + rlogis(N)
  y_As <- ifelse(ylat_As >=0, 1, 0)
  As_controls <- tibble(Y = y_As, G = G, Z = Z) %>% filter(Y == 0) %>% sample_n(600)
  As_cases <- tibble(Y = y_As, G = G, Z = Z) %>% filter(Y == 1) %>% sample_n(400)
  As_sample <- rbind(As_cases,As_controls)
  mod_As <- glm(Y~Z + G,data = As_sample, family = binomial(link = "logit"))
  p2[i] <- summary(mod_As)$coefficients[3,4]
}
emp_power <- mean(p2 <= alpha)
emp_power
```

```
## [1] 0.8625
```

Again, as we have observed in section 2, the empirical powers of Wald test still differ a lot when we use case-control design (0.61 in Europe and 0.863 in Asia). We can also see the distribution of p-values for each population:

```
pcomp <- tibble(P = c(p1,p2), Population = c(rep("Europe",800),rep("Asia",800)))
pcomp %>% ggplot(aes(x = P, fill = Population)) + geom_histogram(bins = 20, alpha=0.5, position="identi
```



As we can see, the conclusion from section 2 still applies to this scenario.