

Jiaqi's Thesis Progress Report (Updated Dec. 18)

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1. To Do List during the Christmas

1. Correlated frailty - NR-algorithm
2. Using importance weights to implement MCEM
3. Multiple imputation - similar imputation step as MCEM

2. Weibull Parametric Approach and MCEM Method

From the beginning of the discussion, I have obtained the model, i.e., the hazard function is

$$h_{ij}(t_{ij}|z_j) = h_0(t_{ij}) \exp(\beta_1 g_{ij} + \beta_2 x_{ij}) z_j \quad (1)$$

where g_{ij} is the genotype, or say mutation gene status for individual i in family j , and x_{ij} is the PRS for individual i in family j . The frailty term z_j , has a pdf of $f(z)$, which can be Gamma, or log-normal, to ensure the support is always non-negative. The Weibull baseline hazard function is defined as

$$h_0(t_{ij}) = \alpha \lambda t_{ij}^{\lambda-1} \quad (2)$$

where λ is the shape parameter and α is the scale parameter. Let $\xi_{ij} = \exp(\beta_1 g_{ij} + \beta_2 x_{ij})$, the hazard function is

$$h_{ij}(t_{ij}|x_{ij}, g_{ij}, z_j) = \alpha \lambda t_{ij}^{\lambda-1} \xi_{ij} z_j \quad (3)$$

The survival function $S(t)$ can be obtained through cumulative hazard function $H(t)$

$$H(t_{ij}|x_{ij}, g_{ij}, z_j) = \int_0^t h_{ij}(u|\cdot) du \quad (4)$$

$$= \alpha \xi_{ij} z_j \lambda \int_0^t u^{\lambda-1} du \quad (5)$$

$$= \alpha \xi_{ij} z_j \lambda \cdot \frac{1}{\lambda} t_{ij}^\lambda = \alpha \xi_{ij} z_j t_{ij}^\lambda \quad (6)$$

and the survival function

$$S(t_{ij}|x_{ij}, g_{ij}, z_j) = \exp(-H(t_{ij}|\cdot)) = \exp(-\alpha \xi_{ij} z_j t_{ij}^\lambda) \quad (7)$$

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Therefore, the likelihood can be written as

$$L(\beta_1, \beta_2, \lambda, \alpha; x_{ij}, g_{ij}, t_{ij}, \delta_{ij}, z_j) = \prod_{j=1}^k \int_0^\infty \prod_{i=1}^n (\alpha \lambda t_{ij}^{\lambda-1} \xi_{ij} z_j)^{\delta_{ij}} \exp(-\alpha \xi_{ij} z_j t_{ij}^\lambda) f(z) dz \quad (8)$$

15 So the log-likelihood is

$$\ell(\beta_1, \beta_2, \lambda, \alpha; x_{ij}, g_{ij}, t_{ij}, \delta_{ij}, z_j) = \sum_{j=1}^k \log \left[\int_0^\infty \prod_{i=1}^{n_j} (h(t_{ij} | \mathbf{x}_{ij}, z_j))^{\delta_{ij}} \exp(-H(t_{ij} | \mathbf{x}_{ij}, z_j)) f(z_j) dz_j \right] \quad (9)$$

16 3. Gamma Frailty

The Laplace transform of the frailty $f(z_j) = \text{Gamma}(v_j, v_j)$, for the simplicity of the mathematical expression, the following Laplace transform will ignore the subscript, denote $\mathcal{L}(f(z)) = \phi(\cdot)$:

$$\mathcal{L}(f(z)) = \phi(s) = \int_0^\infty e^{-sz} f(z) dz \quad (10)$$

$$= \int_0^\infty e^{-sz} \frac{v^v}{\Gamma(v)} z^{v-1} e^{-vz} dz \quad (11)$$

17 Using the Gamma property: $\int_0^\infty z^{n-1} e^{-az} dz = \frac{\Gamma(n)}{a^n}$, $\phi(s)$ can be further written as

$$\phi(s) = \frac{v^v}{\Gamma(v)} \int_0^\infty e^{-(s+v)z} z^{v-1} dz = \frac{v^v}{\Gamma(v)} \cdot \frac{\Gamma(v)}{(s+v)^v} = \left(1 + \frac{s}{v}\right)^{-v} \quad (12)$$

18 The second derivative is $\frac{d^2 \phi(s)}{ds^2} = \int_0^\infty (-z)^2 e^{-sz} f(z) dz$.

The third derivative is $\frac{d^3 \phi(s)}{ds^3} = \int_0^\infty (-z)^3 e^{-sz} f(z) dz$, ... Therefore, its d -th derivative, denote $\phi(s)^{(d)}$:

$$\phi(s)^{(d)} = (-1)^d \int_0^\infty z^d e^{-sz} f(z) dz \quad (13)$$

$$= (-1)^d \frac{(v+d-1)!}{(v-1)!(s+v)^d} \left(1 + \frac{s}{v}\right)^{-v} \quad (14)$$

for some function s that does not involve with z . Let $\boldsymbol{\theta} = (\beta_1, \beta_2, \alpha, \lambda)$, the log-likelihood is

then written as

$$\ell(\boldsymbol{\theta}) = \sum_{j=1}^k \log \left[\int_0^\infty \prod_{i=1}^{n_j} (h(t_{ij}|\mathbf{x}_{ij}, z_j))^{\delta_{ij}} \exp(-H(t_{ij}|\mathbf{x}_{ij}, z_j)) f(z_j) dz_j \right] \quad (15)$$

$$= \sum_{j=1}^k \log \left[\int_0^\infty \prod_{i=1}^{n_j} (z_j h(t_{ij}|\mathbf{x}_{ij}))^{\delta_{ij}} \exp(-z_j H(t_{ij}|\mathbf{x}_{ij})) f(z_j) dz_j \right] \quad (16)$$

$$= \sum_{j=1}^k \log \left[\prod_{i=1}^{n_j} (h(t_{ij}|\mathbf{x}_{ij}))^{\delta_{ij}} \int_0^\infty z_j^{d_j} \exp(-z_j \sum_{i=1}^{n_j} H(t_{ij}|\mathbf{x}_{ij})) f(z_j) dz_j \right] \quad (17)$$

$$= \sum_{j=1}^k \log \left[\prod_{i=1}^{n_j} (h(t_{ij}|\mathbf{x}_{ij}))^{\delta_{ij}} \frac{(v + d_j - 1)!}{(v - 1)! (\sum_{i=1}^{n_j} H(t_{ij}|\mathbf{x}_{ij}) + v)^{d_j}} \left(1 + \frac{\sum_{i=1}^{n_j} H(t_{ij}|\mathbf{x}_{ij})}{v} \right)^{-v} \right] \quad (18)$$

$$= \sum_{j=1}^k \log \left[\prod_{i=1}^{n_j} ((h(t_{ij}|\mathbf{x}_{ij}))^{\delta_{ij}}) \frac{(v + d_j - 1)!}{v! v^{d_j - 1}} \left(1 + \frac{\sum_{i=1}^{n_j} H(t_{ij}|\mathbf{x}_{ij})}{v} \right)^{-v - d_j} \right] \quad (19)$$

$$= \sum_{j=1}^k \log \left[(h(\cdot))^{\delta_{ij}} \frac{(v + d_j - 1)!}{v! v^{d_j - 1}} \left(1 + \frac{\sum_{i=1}^{n_j} H(t_{ij}|\mathbf{x}_{ij})}{v} \right)^{-v - d_j} \right] \quad (20)$$

$$= \sum_{j=1}^k \left[\sum_i (\delta_{ij} \log h(\cdot)) + \log \left(\frac{(v + d_j - 1)!}{v! v^{d_j - 1}} \left(1 + \frac{\sum_{i=1}^{n_j} H(t_{ij}|\mathbf{x}_{ij})}{v} \right)^{-v - d_j} \right) \right] \quad (21)$$

19 For each family j , the ascertainment is defined to be the probability of the proband p
 20 being ascertained by the age a_{j_p} at examination, denoting A_j . Applying the ascertainment
 21 correction for the log-likelihood in family j :

$$\ell(\cdot) = \ell_j(\cdot) - \log A_j(\cdot) \quad (22)$$

note we can still apply Laplace transform here, such that

$$A_j(\cdot) = 1 - S_{j_p}(a_{j_p}|X_{j_p}) \quad (23)$$

$$= 1 - \int_Z S_{j_p}(a_{j_p}|X_{j_p}, z_j) f(z_j) dz_j \quad (24)$$

$$= 1 - \int_Z \exp(-z_j \cdot H_{j_p}(a_{j_p}|X_{j_p})) f(z_j) dz_j \quad (25)$$

$$= 1 - \left(1 + \frac{H_{j_p}(a_{j_p}|X_{j_p})}{k} \right)^{-k} \quad (26)$$

22 4. Log-Normal Frailty

The log-normal frailty is not the power-variance-function (PVF) family, so there is no closed form for Laplace transform or expressions for survivors. But we are able to estimate the Laplace transform using Gauss Hermite Quadrature. We typically standardize the log-

normal frailty Z as

$$E(\log Z) = 0 \quad (27)$$

$$\text{Var}(\log Z) = \sigma^2 \quad (28)$$

23 That is, $Z_j \sim \log\text{-Normal}(0, \sigma^2)$. The probability density function $f(z_j)$ is then

$$f(z_j) = \frac{1}{\sqrt{2\pi}\sigma} z_j^{-1} \exp\left(-\frac{\log(z_j)^2}{2\sigma^2}\right) \quad (29)$$

24 The Laplace transform is then

$$\phi(s) = \mathcal{L}(f_Z)(s) = \int_0^\infty \exp(-sz) \cdot f(z) dz \quad (30)$$

Using variable transformation, let $y = \frac{\log(z)}{\sqrt{2}\sigma}$, then $z = \exp(\sqrt{2}\sigma y)$, and $dz = \sqrt{2}\sigma \exp(\sqrt{2}\sigma y) dy$. Therefore, for d -th derivative:

$$\phi(s)^d = \int_{-\infty}^{\infty} z^d \exp(-sz) \cdot \frac{1}{\exp(\sqrt{2}\sigma y) \sigma \sqrt{2\pi}} \cdot \exp(-y^2) \cdot \sqrt{2}\sigma \exp(\sqrt{2}\sigma y) dy \quad (31)$$

$$= \int_{-\infty}^{\infty} \exp(\sqrt{2}\sigma y)^d \exp(-s \exp(\sqrt{2}\sigma y)) \cdot \frac{1}{\sqrt{\pi}} \exp(-y^2) dy \quad (32)$$

25 **Definition 1** (Gauss-Hermite Quadrature). *The integrand part can be solved using Gauss-*
 26 *Hermite Quadrature. In numerical analysis, the method can be applied in the following form:*

$$\int_{-\infty}^{\infty} \exp(-x^2) f(x) dx \approx \sum_{i=1}^n \omega_i f(x_i) \quad (33)$$

27 where n is number of sample points used, and x_i is the roots of Hermite polynomial $H_n(x)$
 28 such that $i = 1, \dots, n$, and the weights ω_i is

$$\omega_i = \frac{2^{n-1} n! \sqrt{\pi}}{n^2 [H_{n-1}(x_i)]^2} \quad (34)$$

29 Applying Definition 1, the integral of the Laplace transform is then

$$\phi(s)^d = \frac{1}{\sqrt{\pi}} \sum_{p=1}^{N_p} \omega_p \exp(-s \exp(\sqrt{2}\sigma y_p)) \exp(\sqrt{2}\sigma y_p)^d \quad (35)$$

30 Thus, substituting into the log-likelihood:

$$\ell_j(\cdot) = \sum_{i=1}^{n_j} \delta_{ij} \log(h(t_{ij} | \mathbf{x}_{ij})) + \log \left(\frac{1}{\sqrt{\pi}} \sum_{p=1}^{N_p} \left[\omega_p \exp(\sqrt{2}\sigma y_p)^{d_{ij}} \exp \left(- \sum_{i=1}^{n_j} H(t_{ij} | \mathbf{x}_{ij}) \exp(\sqrt{2}\sigma y_p) \right) \right] \right) \quad (36)$$

Similarly, the ascertainment correction in the log-normal frailty can be written as

$$A_j(\cdot) = 1 - \int_Z \exp(-z_j H_{j,p}(a_{j,p}|\mathbf{x}_{j,p})) f(z_j) dz_j \quad (37)$$

$$= 1 - \sum_{p=1}^{N_p} \omega_p \exp \left(- \left(\sum_{i=1}^{n_j} H(a_{j,p}|\mathbf{x}_{ij}) \right) \exp(\sqrt{2}\sigma y_p) \right) \quad (38)$$

5. Correlated Frailty using Kinship Matrix

Family members are correlated within one family, that we denote K as the kinship correlation matrix among all observations. This matrix ensures those individuals not from the same family automatically have a correlation of 0. The likelihood construction needs multivariate form. For $\mathbf{Z} \sim \text{MVN}(0, \sigma^2 K)$, that K has the diagonal of 1. The likelihood is

$$L(\cdot) = \int_{\mathbb{R}^n} \prod_{i=1}^n (h(t|\mathbf{x}_i, \mathbf{z}_i))^{\delta_i} \exp(-H(t|\mathbf{x}_i, \mathbf{z}_i)) f(\mathbf{z}) d\mathbf{z} \quad (39)$$

$$= \int_{\mathbb{R}^n} \prod_{i=1}^n (h(t|\mathbf{x}_i))^{\delta_i} \exp(\mathbf{z}_i)^{\delta_i} \exp(-H(t|\mathbf{x}_i) \exp(\mathbf{z}_i)) f(\mathbf{z}) d\mathbf{z} \quad (40)$$

$$= \prod_{i=1}^n (h(t|\mathbf{x}_i))^{\delta_i} \int_{\mathbb{R}^n} \exp(\delta_i \mathbf{z}_i - H(t|\mathbf{x}_i) \exp(\mathbf{z}_i)) f(\mathbf{z}) d\mathbf{z} \quad (41)$$

Applying the Laplace approximation, and taking the log for the likelihood, we obtain

$$\ell(\cdot) = \sum_{i=1}^n \left[\delta_i \log h(t|\mathbf{x}_i) \right] + \sum_{i=1}^n \left[\delta_i \hat{\mathbf{z}} - H(t_i|\mathbf{x}_i) \exp(\hat{\mathbf{z}}) \right] - \frac{1}{2} \hat{\mathbf{z}}^\top \Sigma^{-1} \hat{\mathbf{z}} \quad (42)$$

such that $\Sigma = \sigma^2 K$. Also, we treat the random effect \mathbf{z} as a vector of parameters, and use outer-loop to search for the σ , and use inner-loop to search for other parameters (baseline parameters, and β) including \mathbf{z} . The process can be achieved via Newton-Raphson algorithm. For computational efficiency, we can set $\Sigma^{-1} = L^\top L$ through Cholesky Decomposition. In this way, $\mathbf{z}L \sim \text{MVN}(0, \sigma^2 I)$. In order to apply NR-algorithm, the gradient and the hessian are required. The gradient for parameters is:

$$\frac{\partial \ell}{\partial \beta} = \sum_{i=1}^n \delta_i \mathbf{x}_i + \sum_{i=1}^n -H(t_i|\mathbf{x}_i) \mathbf{x}_i \exp(\mathbf{z}) \quad (43)$$

$$\frac{\partial \ell}{\partial \mathbf{z}} = \sum_{i=1}^n \delta_i - (t_i|\mathbf{x}_i) \exp(\hat{\mathbf{z}}) - \Sigma^{-1} \hat{\mathbf{z}} \quad (44)$$

$$\frac{\partial \ell}{\partial \alpha} = \sum_{i=1}^n \frac{\delta_i}{\alpha} + \sum_{i=1}^n -\frac{H(t_i|\mathbf{x}_i) \exp(\hat{\mathbf{z}})}{\alpha} \quad (45)$$

$$\frac{\partial \ell}{\partial \lambda} = \sum_{i=1}^n \delta_i \left(\frac{1}{\lambda} + \log(t_i) \right) + \sum_{i=1}^n -H(t_i | \mathbf{x}_i) \exp(\hat{\mathbf{z}}) \log(t_i) \quad (46)$$

43 The hessian matrix element, i.e., second partial derivative is

$$\frac{\partial^2 \ell}{\partial \boldsymbol{\beta}^\top \partial \boldsymbol{\beta}} = \sum_{i=1}^n -H(t_i | \mathbf{x}_i) \exp(\hat{\mathbf{z}}) x_{ij} x_{ik} \quad (47)$$

$$\frac{\partial^2 \ell}{\partial \mathbf{z}^\top \partial \mathbf{z}} = \sum_{i=1}^n -H(t_i | \mathbf{x}_i) \exp(\hat{\mathbf{z}}) - \Sigma^{-1} \quad (48)$$

$$\frac{\partial^2 \ell}{\partial \alpha^2} = \sum_{i=1}^n -\frac{\delta_i}{\alpha^2} \quad (49)$$

$$\frac{\partial^2 \ell}{\partial \lambda^2} = \sum_{i=1}^n -\frac{\delta_i}{\lambda^2} - H(t_i | \mathbf{x}_i) \exp(\hat{\mathbf{z}}) \log(t_i)^2 \quad (50)$$

44 5.1. Proof of $\Sigma = LL^\top$

45 Every symmetric positive definite matrix Σ can be decomposed into $\Sigma = LL^\top$, where L
46 is a lower triangular matrix with real and positive diagonal entries.

47 *Proof.* Set-ups:

48 1. Covariance matrix Σ is by definition symmetric and positive definite, e.g.

$$\Sigma = \begin{pmatrix} \sigma_{X_1}^2 & Cov(X_1, X_2) \\ Cov(X_1, X_2) & \sigma_{X_2}^2 \end{pmatrix} \quad (51)$$

49 such that $\mathbf{X}\Sigma\mathbf{X}^\top > 0$ always, and this matrix is symmetric.

50 2. Suppose \mathbf{X} has n observations, then Σ is $n \times n$, the first element is $\sigma_{11} > 0$ by definition
51 (For simplicity, we use σ_{11} rather than it's square to denote the variance). Define
52 $l_{11} = \sqrt{\sigma_{11}}$, to be the first element of L . For the first column of L , let $l_{j1} = \frac{\sigma_{j1}}{l_{11}}$ for
53 $j = 2, \dots$

54 Induction step: Assume we have first $k-1$ columns of L , consider k -th column

55 • For the diagonal element $l_{kk} = \sqrt{\sigma_{kk} - \sum_{j=1}^{k-1} l_{kj}^2}$

56 • For off-diagonals,

$$l_{ik} = \frac{\sigma_{ik} - \sum_{j=1}^{k-1} l_{ij} l_{kj}}{l_{kk}} \quad (52)$$

57 for $i = k+1, \dots, n$.

with the repetition for each column $k = 2, \dots, n$, the top-left $k \times k$ submatrix of LL^\top matches that of Σ . For example, when $k = 3$,

$$\Sigma = \begin{pmatrix} \sigma_{11} & & \\ & \sigma_{22} & \\ & & \sigma_{33} \end{pmatrix} \quad (53)$$

and

$$L = \begin{pmatrix} l_{11} & 0 & 0 \\ l_{21} & l_{22} & 0 \\ l_{31} & l_{32} & l_{33} \end{pmatrix} \quad (54)$$

then

$$LL^\top = \begin{pmatrix} l_{11} & 0 & 0 \\ l_{21} & l_{22} & 0 \\ l_{31} & l_{32} & l_{33} \end{pmatrix} \begin{pmatrix} l_{11} & l_{21} & l_{31} \\ 0 & l_{22} & l_{32} \\ 0 & 0 & l_{33} \end{pmatrix} = \begin{pmatrix} l_{11}^2 & l_{11}l_{21} & l_{11}l_{31} \\ l_{21}l_{11} & l_{21}^2 + l_{22}^2 & l_{21}l_{31} + l_{22}l_{32} \\ l_{31}l_{11} & l_{31}l_{21} + l_{32}l_{22} & l_{31}^2 + l_{32}^2 + l_{33}^2 \end{pmatrix} \quad (55)$$

Take

$$\Sigma = \begin{pmatrix} 4 & 2 & 2 \\ 2 & 3 & 1 \\ 2 & 1 & 3 \end{pmatrix} \quad (56)$$

Then by definition of Cholesky Decomposition, we can calculate $l_{11}^2 = \sigma_{11} \implies l_{11} = \sqrt{4} = 2$, and $l_{21} = \frac{\sigma_{21}}{l_{11}} = 2/2 = 1$, and $l_{31} = 1$. Similarly for l_{22}, l_{32}, l_{33} . Therefore,

$$L = \begin{pmatrix} 2 & 0 & 0 \\ 1 & \sqrt{2} & 0 \\ 1 & 0 & \sqrt{2} \end{pmatrix} \quad (57)$$

which implies

$$LL^\top = \begin{pmatrix} 2 & 0 & 0 \\ 1 & \sqrt{2} & 0 \\ 1 & 0 & \sqrt{2} \end{pmatrix} \begin{pmatrix} 2 & 1 & 1 \\ 0 & \sqrt{2} & 0 \\ 0 & 0 & \sqrt{2} \end{pmatrix} = \begin{pmatrix} 4 & 2 & 2 \\ 2 & 3 & 1 \\ 2 & 1 & 3 \end{pmatrix} = \Sigma \quad (58)$$

□

Essentially, the Cholesky Decomposition transforms the multivariate normal to a standard multivariate normal. When $\mathbf{Z} \sim \mathcal{N}(0, \Sigma)$, let $\Sigma = \mathbf{L}\mathbf{L}^\top$, then $\mathbf{Y} = \mathbf{L}^{-1}\mathbf{Z} \sim \mathcal{N}(0, \mathbf{I})$ that \mathbf{I} is the identity matrix, since $\mathbf{L}^{-1}\Sigma(\mathbf{L}^{-1})^\top = \mathbf{L}^{-1}\mathbf{L}\mathbf{L}^\top(\mathbf{L}^{-1})^\top = \mathbf{I}$. This will simplify the computational process.

71 6. Monte Carlo EM

The complete data log-likelihood for family j is $\ell_j(\boldsymbol{\theta}; h_{ij})$ where $\boldsymbol{\theta}$ consists all baseline parameters, and model coefficients say β . For each cluster j , the E-step is:

$$Q_i(\boldsymbol{\theta}|\boldsymbol{\theta}^{(r)}) = \int \ell(\boldsymbol{\theta}; h_{ij}) \cdot f(x_{mis,i}|x_{obs,i}, z_j, \boldsymbol{\theta}^{(r)}) dx_{mis,ij} \quad (59)$$

where $(X, G) \sim f(x, g|\cdot)$, and can be obtained through Gibbs Sampling, sample the size m_i for each i -th observation, $x_{i1}^*, \dots, x_{im_i}^*$ from the distribution $f(x_{mis,ij}|\cdot)$, and take $M = 1, \dots, m_i$, such that each X_{iM}^* depends on the iteration number for $r + 1$ iterations. In general:

$$\hat{Q}_i(\boldsymbol{\theta}; \boldsymbol{\theta}^{(r)}) = \frac{1}{m_i} \sum_{M=1}^{m_i} \ell(x_{iM}^*, x_{obs,ij}, t_{ij}, \boldsymbol{\theta}, z_j) \quad (60)$$

72 7. Stochastic EM?

73 8. Multiple Imputation Method

74 This method is easier to implement, because MICE package already incorporates fully
 75 conditional specification where each missing variable is imputed one at a time, conditional
 76 on others in the dataset. However, I only need to write a self-defined function to include
 77 the random effect in the imputation-step. All methods provided by MICE fail to include the
 78 frailty scenario in survival analysis. There are many sources that they considered random
 79 effects in the linear mixed effect model. I believe survival analysis with frailty should be
 80 similar.

```
## MICE for coxph with frailty
library(mice)
brca1_prs_mice$na <- nelsonaalen(data = brca1_prs_mice, timevar = "timeBC",
                                statusvar = "BC")
micesurv0 <- mice(brca1_prs_mice, maxit = 0, method = "rf")
micesurvmethod <- micesurv0$method
micesurvpred <- micesurv0$predictorMatrix
micesurvmethod[c("PRS")] <- "rf"
micesurvmethod[c("mgene")] <- "rf"
micesurvpred[, "indID"] <- 0

micesurv <- mice(brca1_prs_mice, method = micesurvmethod, predictorMatrix = micesurvpred,
                 m = 5, seed = 123)
results_mice <- with(micesurv, coxph(Surv(timeBC, BC) ~ mgene + PRS + frailty(famID, distrib
summary(pool(results_mice), exponentiate = TRUE) # Here the MI does not incorporate random s
```

Figure 1: MICE Code

81 Here I was trying to use random forest methods to impute both PRS and genotype, the
 82 performance of PRS seems good because the coefficient is close to the complete case analysis,
 83 but there is an inflation on the coefficient on genotype.