

## File S2. DCCT-based simulation study

### Characterization of direct and/or indirect genetic associations for multiple traits in longitudinal studies of disease progression

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The DCCT-based simulation algorithm we developed is designed to mimic the structure of the DCCT data. As described in the main paper and presented in **Fig. 3**, we simulate  $M=5$  causal SNPs and  $K=2$  non-independent and non-competing time-to-event traits based on  $L=3$  longitudinal traits: two QTs as measured in DCCT (HbA1c and SBP) to preserve *realistic* dependencies between/within longitudinal QTs, and one QT simulated ( $U$ ) to induce *unexplained* dependency between the two simulated time-to-T1DC traits. We also assume effects of sex on SBP, and effects of T1D duration (at baseline) on both T1DC traits, as observed in the original DCCT data and specify contemporaneous association structures for the association of HbA1c and SBP on T1DC traits. We describe in detail the procedure followed to generate such DCCT-based simulated dataset. Example R script is available on GitHub (<https://github.com/brossardMyriam/Joint-model-for-multiple-trait-genetics>).

## **1. DCCT dataset used for the simulation study**

We use  $N=667$  individuals from the DCCT Conventional treatment group with longitudinal HbA1c ( $\mathbf{y}_{i,1}$ ) and SBP ( $\mathbf{y}_{i,2}$ ) measures as well as baseline covariates (sex and T1D duration) measured for each individual  $i$ . We exclude all longitudinal measures prior to the 6 month-visit due to a mild non-linear time trend observed for HbA1c (screening effect) at the beginning of the DCCT study. For a few individuals, we replace missing measures for either HbA1c or SBP by their predicted values from the linear mixed model ignoring the SNP variable. We use mean centered HbA1c and SBP measures. Throughout this section, for each individual  $i$  ( $1 \leq i \leq N = 667$ ), we denote  $\mathbf{y}_{i,1} = (y_{i,1,1}, \dots, y_{i,1,j}, \dots, y_{i,1,n_i})^T$  and  $\mathbf{y}_{i,2} = (y_{i,2,1}, \dots, y_{i,2,j}, \dots, y_{i,2,n_i})^T$  the vectors of longitudinal QT measures collected in DCCT for HbA1c ( $\mathbf{y}_{i,1}$ ) and SBP ( $\mathbf{y}_{i,2}$ ) at quarterly visit times  $\mathbf{t}_i = (t_{i,1}, \dots, t_{i,j}, \dots, t_{i,n_i})^T$  with  $t_{i,1} \leq \dots \leq t_{i,j} \leq \dots \leq t_{i,n_i}$ , where  $n_i$  corresponds to the last visit number recorded for patient  $i$ , and  $Sex_i$  and  $T1D\_duration_i$  are the baseline covariate values measured in DCCT.

## **2. Assumed underlying system model**

### **(i) Linear mixed models**

**Generating linear mixed models linking each SNP to each  $l^{\text{th}}$  QT trait ( $l \in \{1, 2, u\}$ )**

$$y_{i,l}^*(t) = \beta_{0,l} + b_{i,0,l} + (\beta_{1,l} + b_{i,1,l})t + \beta_{g,l}g_i \quad (\text{Equation 1, smooth linear QT trajectory})$$

$$y_{i,l} = y_{i,l}^*(t_i) + \varepsilon_{i,l} \quad (\text{Equation 2, QT measures at visits times } t_i)$$

$$\text{with } \varepsilon_{i,l} = (\varepsilon_{i,1,l}, \dots, \varepsilon_{i,j,l}, \dots, \varepsilon_{i,n_i,l})^T \sim N_{n_i}(\mathbf{0}, \sigma_l^2 \mathbf{I}_{n_i})$$

$$\text{Equation 2 implies that } y_{i,l} \sim N(\mathbf{X}_{i,l}\boldsymbol{\beta}_l, \mathbf{Z}_{i,l}\mathbf{D}_l\mathbf{Z}_{i,l}^T + \sigma^2\mathbf{I}_{n_i})$$

- **Observed HbA1c ( $y_{i,1}$ ):** We specify  $\mathbf{X}_{i,1} = (\mathbf{1}_{n_i}, t_i, \text{SNP1} = g_i\mathbf{1}_{n_i})$  as the design matrix for the fixed intercept, time slope and SNP1 effects on HbA1c denoted as  $\boldsymbol{\beta}_1 = (\beta_{0,1}, \beta_{1,1}, \beta_{g,1})^T$ , and  $\mathbf{Z}_{i,1} = (\mathbf{1}_{n_i}, t_i)$  as the design matrix for the random intercept and effect of time on HbA1c, with random effects  $\mathbf{b}_{i,1} = (b_{i,0,1}, b_{i,1,1})^T \sim N_2(0, \mathbf{D}_1)$  where  $\mathbf{D}_1$  is a  $2 \times 2$  positive definite covariance matrix. We denote  $\mathbf{1}_{n_i} = (1, \dots, 1, \dots, 1)^T$  as the  $n_i$ -length unit vector.
- **Observed SBP ( $y_{i,2}$ ):** We specify  $\mathbf{X}_{i,2} = (\mathbf{1}_{n_i}, t_i, \text{SNP5} = g_i\mathbf{1}_{n_i}, \text{Sex}_i\mathbf{1}_{n_i})$  as the design matrix for the fixed intercept, fixed time slope, and fixed SNP5 and sex effects on SBP denoted as  $\boldsymbol{\beta}_2 = (\beta_{0,2}, \beta_{1,2}, \beta_{g,2}, \beta_{\text{Sex},2})^T$ , and  $\mathbf{Z}_{i,2} = (\mathbf{1}_{n_i}, t_i)$  as the design matrix for the random intercept and effect of time on SBP, with random effects  $\mathbf{b}_{i,2} = (b_{i,0,2}, b_{i,1,2})^T \sim N_2(0, \mathbf{D}_2)$  where  $\mathbf{D}_2$  is a  $2 \times 2$  positive definite covariance matrix
- **Simulated latent QT risk factor  $U$  ( $y_{i,u}$ ):** We specify  $\mathbf{X}_{i,u} = (\mathbf{1}_{n_i}, t_i, \text{SNP3} = g_i\mathbf{1}_{n_i})$  as the design matrix of the fixed intercept, fixed time slope, and SNP3 effects on latent longitudinal QT  $U$  denoted as  $\boldsymbol{\beta}_u = (\beta_{0,u}, \beta_{1,u}, \beta_{g,u})^T$ , and  $\mathbf{Z}_{i,u} = (\mathbf{1}_{n_i}, t_i)$  as the design matrix for the random intercept and effect of time on  $U$ , with random effects  $\mathbf{b}_{i,u} = (b_{i,0,u}, b_{i,1,u})^T \sim N_2(0, \mathbf{D}_u)$  where  $\mathbf{D}_u$  is a  $2 \times 2$  positive definite covariance matrix.

(ii) *PH time-to-event models*

**Generating time-to-event sub-models linking SNP with direct effects and longitudinal QT trajectory effects to each  $k^{th}$  simulated time-to-T1DC trait ( $k \in \{1, 2\}$ )**

$$\lambda_{i,k}(t) = \lambda_{0,k}(t) \times \exp\{\eta_{i,k}(t) + \alpha_{u,k}y_{i,u}^*(t)\}$$

With:

- $\lambda_{0,k}(t) = \varphi_k \xi_k t^{\varphi_k - 1}$ , where  $\varphi_k$  and  $\xi_k$  are the shape and scale parameters of the Weibull model.
- $\alpha_{u,k}$  is the effect of the shared longitudinal risk factor underlying trajectory  $y_{i,u}^*(t)$  used to induce unexplained dependency between the simulated time-to-T1DC traits.

**Simulated time-to-DR ( $T_{i,1}, \delta_{i,1}$ ):**  $\eta_{i,1}(t) = \gamma_{g,1} SNP2_i + \alpha_{1,1}y_{i,1}^*(t) + \gamma_{Duration,1} T1D\_duration_i$ , where  $\gamma_{g,1}$ ,  $\alpha_{1,1}$  and  $\gamma_{Duration,1}$  are the effects of  $SNP2$ ,  $y_{i,1}^*(t)$  and  $T1D\_duration$  on DR.

**Simulated time-to-DN ( $T_{i,2}, \delta_{i,2}$ ):**  $\eta_{i,2}(t) = \gamma_{g,2} SNP4_i + \gamma'_{g,2} SNP5_i + \sum_{l=1}^2 \alpha_{l,2} y_{i,l}^*(t) + \gamma_{Duration,2} T1D\_duration_i$ , where  $\gamma_{g,2}$ ,  $\gamma'_{g,2}$ ,  $\alpha_{1,2}$ ,  $\alpha_{2,2}$  and  $\gamma_{Duration,2}$  are the effects of  $SNP4$ ,  $SNP5$ , HbA1c, SBP and  $T1D\_duration$  on DN.

### **3. Procedure for data generation under the causal genetic scenario**

Given the specified parameter values for each longitudinal sub-model,  $\boldsymbol{\Omega}_l = (\boldsymbol{\beta}_l, \boldsymbol{D}_l, \sigma_l^2)$  with  $l \in \{1, 2, u\}$  and each time-to-event sub-model,  $\boldsymbol{\Gamma}_k = (\varphi_k, \xi_k, \gamma_{g,k}, \alpha_k, \gamma_{Covs,k})$  with  $k \in \{1, 2\}$ , as well as specified minor allele frequencies vector  $\boldsymbol{p} = (p_1, \dots, p_m, \dots, p_M)$  for the  $M=5$  causal SNPs, the proposed simulation procedure proceeds in three steps. In **Step 1**, we first simulate the longitudinal vector for  $\boldsymbol{y}_{i,u}$  for the  $N$  DCCT individuals. In **Step 2**, we simulate the  $R = 1000$  replicates of  $M$  genotype data based on observed/simulated longitudinal QTs for DCCT individuals. In **Step 3**, we simulate  $R = 1000$  replicates of non-independent time-to-event traits for the  $N$  DCCT individuals using SNPs and the trajectories for *observed* (HbA1c, SBP) and *simulated* longitudinal QTs fitted on the data from **Steps 1 & 2**.

➤ **Step 1: Simulation of  $\mathbf{y}_{i,u}$**

For each DCCT individual  $i$ , we generate  $\mathbf{y}_{i,u} \sim N(\mathbf{X}_{i,u}\boldsymbol{\beta}_u, \mathbf{Z}_{i,u}\mathbf{D}_u\mathbf{Z}_{i,u}^T + \sigma_u^2\mathbf{I}_{n_i})$  where  $\mathbf{X}_{i,u}$  and  $\mathbf{Z}_{i,u}$  are the design matrices for the fixed and random effects (as defined above in Section 2) and  $\boldsymbol{\Omega}_u = (\boldsymbol{\beta}_u, \mathbf{D}_u, \sigma_u^2)$  are the specified parameter values.

➤ **Step 2: Simulation of the genetic data**

*Causal SNPs with indirect effects*

We simulate genotypes for each causal  $SNP_m$  ( $m \in \{1, 3, 5\}$ ) with MAF  $p_m$  with indirect effects on  $k^{th}$  T1DC traits via the  $l^{th}$  intermediate QT risk factor ( $l \in \{1, 2, u\}$ ) under Hardy-Weinberg and linkage equilibrium assumptions. Particularly, we draw for each SNP and each DCCT individual  $i$  ( $1 \leq i \leq N$ ),  $R$  genotypes  $g_i$  from the multinomial distribution with conditional genotype probabilities  $(\pi_{g_i=0}, \pi_{g_i=1}, \pi_{g_i=2})$  calculated for individual  $i$  at each possible genotype  $g_i \in \{0, 1, 2\}$  given longitudinal values  $(\mathbf{y}_{i,l})$  as follows:

$$\begin{aligned} \pi_{g_i} &= P(SNP_m = g_i | \mathbf{y}_{i,l}) = \frac{P(\mathbf{y}_{i,l}, SNP_m = g_i)}{P(\mathbf{y}_{i,l})} \\ &= \frac{P(\mathbf{y}_{i,l} | SNP_m = g_i) P(SNP_m = g_i)}{P(\mathbf{y}_{i,l})} \\ &= \frac{P(\mathbf{y}_{i,l} | SNP_m = g_i) P(SNP_m = g_i)}{\sum_{g_i=0}^2 P(\mathbf{y}_{i,l} | SNP_m = g_i) P(SNP_m = g_i)} \end{aligned}$$

Where:

- $P(SNP_m = g_i | \mathbf{y}_{i,l})$  denotes the conditional genotype probability for  $SNP_m$  with indirect effect induced via the  $l^{th}$  longitudinal QT risk factor.
- $P(\mathbf{y}_{i,l} | SNP_m = g_i)$  denotes the probability density function of multivariate normal distribution  $\mathbf{y}_{i,l} \sim N(\mathbf{X}_{i,l}\boldsymbol{\beta}_l, \mathbf{Z}_{i,l}\mathbf{D}_l\mathbf{Z}_{i,l}^T + \sigma^2\mathbf{I}_{n_i})$ .
- Unconditional genotype probability  $P(SNP_m = g_i)$  is specified by minor allele frequency of  $SNP_m$  ( $p_m$ ) under Hardy-Weinberg equilibrium, with  $P(SNP_m = 0) = (1 - p_m)^2$ ,  $P(SNP_m = 1) = 2p_m(1 - p_m)$  and  $P(SNP_m = 2) = p_m^2$ .

Specifically, for each individual  $i$ , we calculate conditional genotype probabilities for:

- *SNP1* ( $p_1$ ) with indirect effects on both T1DC traits via intermediate HbA1c risk factor, given observed longitudinal HbA1c measures in DCCT ( $\mathbf{y}_{i,1}$ ) as:  $\pi_{g_i} = P(SNP1 = g_i | \mathbf{y}_{i,1})$ .
- *SNP3* ( $p_3$ ) with indirect effects on both T1DC traits via the shared latent longitudinal QT risk factor  $U$ , given simulated longitudinal values for  $U$  ( $\mathbf{y}_{i,u}$ ) as:  $\pi_{g_i} = P(SNP3 = g_i | \mathbf{y}_{i,u})$ .
- *SNP5* ( $p_5$ ) with an indirect effect on DN via intermediate risk SBP factor, given observed longitudinal SBP measures in DCCT ( $\mathbf{y}_{i,2}$ ):  $\pi_{g_i} = P(SNP5 = g_i | \mathbf{y}_{i,2})$ .

#### *Causal SNPs with direct effects*

For *SNP2* ( $p_2$ ) and *SNP4* ( $p_4$ ) which have only direct effects on each  $k^{th}$  time-to-event trait, we simulate genotypes for each individual  $i$  by drawing  $R$  genotypes from the multinomial distribution with genotype probabilities ( $\pi_{g_i=0}, \pi_{g_i=1}, \pi_{g_i=2}$ ), where under the Hardy-Weinberg Equilibrium assumption  $\pi_{g_i=0} = (1 - p_m)^2$ ,  $\pi_{g_i=1} = 2p_m(1 - p_m)$  and  $\pi_{g_i=2} = p_m^2$ . As opposed to the simulation of the SNPs with indirect effects, the simulation of SNPs with direct effects depends on population probabilities that do not vary among individuals. Those SNPs are introduced in the time-to-event sub-models used to generate the time-to-event traits as described below.

#### ➤ *Step 3: Simulation of the non-independent time-to-event traits*

To generate the  $K=2$  ***non-independent*** time-to-T1DC traits ( $T_{i,k}, \delta_{i,k}$ , with  $k=1, 2$ ), we proceed as follows for each individual  $i$  ( $1 \leq i \leq N$ ) and each data replicate  $r$  ( $1 \leq r \leq R$ ):

1. We sample a censoring time  $C_i$  from a Uniform distribution on  $[0, t_{n_i}]$ , where  $t_{n_i}$  denotes the time where the last measurement is collected for individual  $i$ .
2. For each type of event  $k$  with specified parameters  $\mathbf{F}_k$ :
  - a. We compute the ***uncensored*** event times  $T_{i,k}^*$  by calculating the inverse of the cumulative of the hazard function for  $\lambda_{i,k}(t)$  using the Brent univariate root-finding method (Brent 1973; Crowther and Lambert 2013). Note that each  $\lambda_{i,k}(t)$  depends on the SNPs with direct effects simulated at **Step2** and the specified longitudinal QT trajectories for ***observed*** and ***unobserved***

longitudinal QT; the latter is used to induce the unexplained dependency between the two simulated time-to-event traits. Those longitudinal QT trajectories depend on SNPs with indirect effects and baseline covariates (for details, see assumed underlying system model in Section 2).

- b. We generate the **right-censored** event time  $T_{i,k}$  and event indicator  $\delta_{i,k}$ , as  $T_{i,k} = \min(T_{i,k}^*, C_i)$  and set  $\delta_{i,k}$  to 1 if  $T_{i,k}$  occurs before or at  $C_i$  or 0 otherwise ( $\delta_{i,k} = I(T_{i,k}^* \leq C_i)$ ).

#### 4. Specified parameter values

The specified parameter values for the longitudinal models ( $\Omega_l$  with  $l \in \{1, 2, u\}$ ), and for the time-to-event models ( $\Gamma_k$  with  $k \in \{1, 2\}$ ), as well as for the MAFs of the  $M=5$  causal SNPs ( $\mathbf{p}$ ) are shown in **Fig. 3**, and **Table S4-1**. Particularly, we specify SNP effects and MAFs of genetic associations, as well as the other parameter values in  $\Omega_l, \Gamma_k$  according to the DCCT Genetics Study and the T1DC literature, except for SBP and DN, we inflate the typical SNP effect sizes observed in the literature in  $\Omega_2, \Gamma_2$  to achieve power sufficient to detect SNP associations given the available DCCT sample size. We specify the shape and scale parameters in each  $\Gamma_k$  to generate ~54% DR and ~25% DN events, on average.

**Table S4-1. Other specified parameters in the simulation study**

| Parameters for the longitudinal QT risk factors |   |   |  |
|---|---|---|--|
|   | Observed HbA1c <sup>1</sup> (l=1)                             | Observed sBP <sup>1</sup> (l=2)                             | Simulated U (l=u)  |
| $\beta_0$ (intercept)                           | -0.07   | -4.51   | -0.31  |
| $\beta_{1,l}$ (time)                            | 0.025   | 0.32  | 0.10   |
| $\beta_{sex,l}$ (sex)                           | .   | 6.3   | .  |
| Covariance matrix of random effects             | $\begin{pmatrix} 1.30 & -0.16 \\ -0.16 & 0.073 \end{pmatrix}$ | $\begin{pmatrix} 512 & -3.19 \\ -3.19 & 1.30 \end{pmatrix}$ | $\begin{pmatrix} 2.22 & -0.21 \\ -0.21 & 2.22 \end{pmatrix}$ |
| Residual variance                               | 0.79  | 8.49  | 0.50   |
| Parameters for time-to-event traits             |   |   |  |
|   | Simulated Time-to-DR (k=1)                                    | Simulated Time-to-DN (k=2)                                  |  |
| Baseline hazard function (Weibull)              | Shape=1.01<br>Scale=0.001                                     | Shape=1.01<br>Scale=10 <sup>-12</sup>                       |  |
| $\gamma_{Duration,k}$ (T1D_duration)            | 0.20  |   |  |

<sup>1</sup>Observed HbA1c and SBP values from DCCT have been centered at the mean for the simulation study.



## **5. Procedure to simulate the SNPs under the global null genetic scenario**

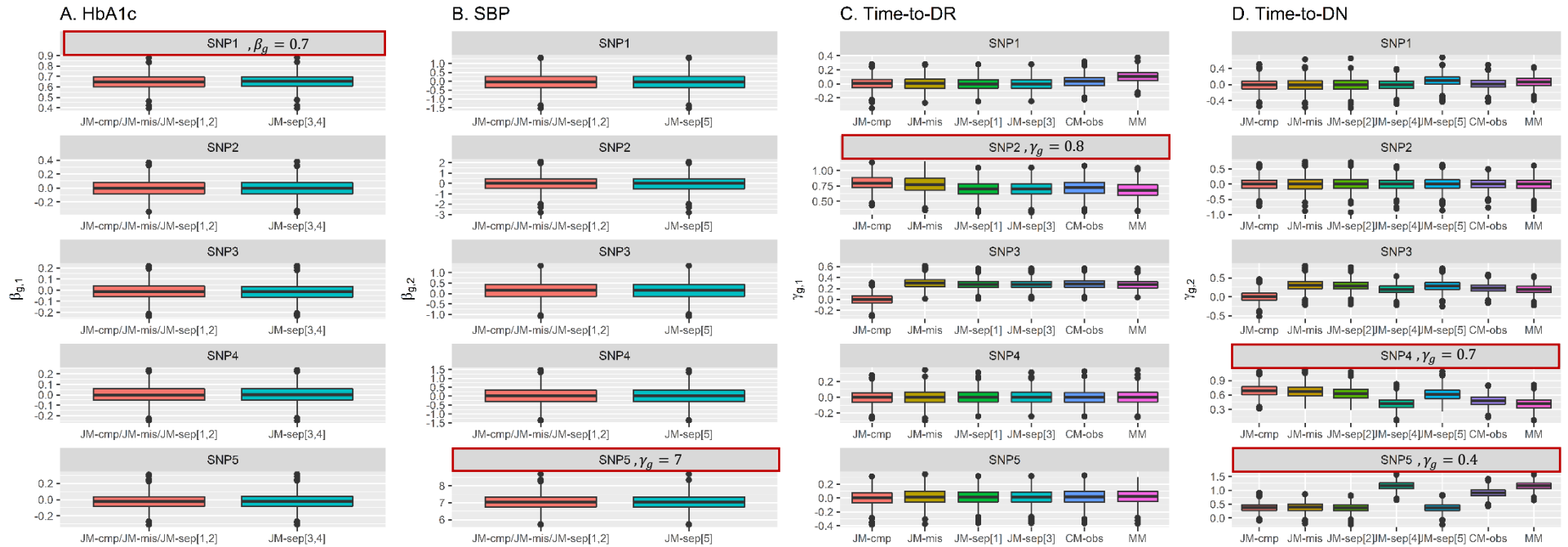
For the genetic scenario under the global null hypothesis, where none of the SNPs is associated with any traits, we simulate  $M=5$  SNPs with the exact same MAF vector  $\mathbf{p}$  as for the causal SNPs. These SNPs are simulated independently of the longitudinal and time-to-event traits with the same procedure as previously described to generate the SNPs with direct effects in **Step2** (see section 3).

## **6. Evaluation of estimation accuracy**

When the underlying genetic model entails direct and indirect association with complex traits and longitudinal QT(s) values exhibit within-subject variability, the simulation results confirm that the proposed extended joint model for multiple longitudinal and multiple time-to-event traits that incorporates trajectories of the QTs performs well: it reduces bias of the parameter estimates; provides coverage probabilities close to the nominal level (95%), and gives empirical 95% confidence intervals of the parameter estimates that are narrower around the true parameter value for all types of SNP association, even when the analysis model is not fully specified (JM-cmp and JM-mis versus all JM-sep and CM-obs models, see **Fig S6-1, Tables S6-1 to S6-5**). In particular, the largest reduction in bias for SNP effects occurs in  $\gamma_{g,k}$  parameters in JM-cmp/JM-mis analyses compared to JM-sep( $l=1; k=2$ ) and JM-sep( $l=2; k=2$ ) that respectively ignore SBP and HbA1c, and in CM-obs that ignores random variation in both QTs. Altogether, these results suggest high confidence in the estimation accuracy of the proposed multi-trait joint model, and apply when:

- (i) two correlated time-to-event traits are analyzed jointly rather than separately in the joint model (e.g. JM-cmp/JM-mis compared to JM-sep models for SNP2, SNP4 & SNP5);
- (ii) a time-to-event trait is associated with multiple intermediate longitudinal QT risk factors that are accounted in the joint model (eg. JM-cmp/JM-mis: *vs* JM-sep( $l=2; k=2$ ) for direct effect of SNP1 on time-to-DN, *vs* JM-sep( $l=1; k=2$ ) for direct effect of SNP4 on time-to-DN, and *vs* JM-sep( $l=1; k=2$ ) for direct effect of SNP5 on time-to-DN);
- (ii) a SNP has a direct effect on a time-to-event trait with a low event rate (e.g. JM-cmp/JM-mis compared to CM-obs for time-to-DN for SNP4 & SNP5);
- (iii) a SNP has an indirect effect via a longitudinal QT risk factor measured with errors (e.g. JM-cmp/JM-mis compared to CM-obs for SNP5).

Particularly, SNP1 and SNP5 which have indirect effects on both time-to-T1DC traits (DR, DN) via HbA1c (SNP1), and on DN only via SBP (SNP5), where JM-sep( $l=2; k=2$ ), JM-sep( $l=1; k=2$ ) and CM-obs exhibit large biases in  $\gamma_{g,2}$ ; these biases tend to be away from the null (towards the overall SNP effects); as for example for  $\gamma_{g,2}$  estimate for SNP5 which combines direct and indirect effects on DN via SBP, when SBP is not accounted in the analysis model (JM-sep( $l=1; k=2$ )), or when random measurement errors are ignored (CM-obs). SNP4 which has a direct effect on DN, exhibit biases in  $\gamma_{g,2}$  in JM-sep( $l=1; k=2$ ) and CM-obs towards the null. On the other hand, when a SNP (such as SNP3) has an indirect effect on both T1DC traits fully explained via the unmeasured longitudinal QT, all analyses without that QT (JM-mis, all JM-sep models or CM-obs compared to JM-cmp) produce direct SNP3 estimates biased towards the underlying overall SNP3 effect ( $\theta_{k,u} = \alpha_{u,k}\beta_{g,u} = 0.36$ , **Fig S6-1: Panels C and D**). In this scenario, use of the frailty term in JM-mis does not reduce this bias (JM-mis compared to JM-sep( $l=1,2; k=1$ ) and JM-sep( $l=1,2; k=2$ )).



**Fig. S6-1.** SNP effects estimated by the joint models of two longitudinal and two time-to-event traits (JM-cmp and JM-mis), the two separate joint models for each time-to-event trait (JM-sep( $l=1,2$ ;  $k=1$ ), JM-sep( $l=1,2$ ;  $k=2$ ), noted as JM-sep[1] and JM-sep[2]), and the three separate joint models for each longitudinal and each time-to-event trait (JM-sep( $l=1$ ;  $k=1$ ), JM-sep( $l=1$ ;  $k=2$ ), JM-sep( $l=2$ ;  $k=2$ ) noted as JM-sep[3], JM-sep[4], JM-sep[5], respectively) for each SNP on (A) HbA1c ( $\beta_{g,1}$ ), (B) SBP ( $\beta_{g,2}$ ), (C) Time-to-DR ( $\gamma_{g,1}$ ) and (D) Time-to-DN ( $\gamma_{g,2}$ ), assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the *alternative* genetic scenario from Fig. 3.

For (A) and (B), estimates from JM-cmp, JM-mis, JM-sep( $l=1,2$ ;  $k=1$ ) and JM-sep( $l=1,2$ ;  $k=2$ ), are based on the same longitudinal sub-model fitted jointly for HbA1c and SBP at Stage1; while for JM-sep[3,4] estimates are based on the same longitudinal model for HbA1c. For (C) and (D), we also compare the estimates from the joint models with the estimates from: CM-obs which corresponds to the Cox PH frailty model for both time-to-T1DC traits adjusted for observed longitudinal HbA1c and SBP measures; and from MM which corresponds to the marginal time-to-event models fitted separately for each time-to-event trait and ignoring the longitudinal traits. For each longitudinal (A, B) or time-to-T1DC trait (C, D), causal SNP associations are indicated by red boxes. For SNP3 which has indirect effects on both time-to-T1DC traits via the unmeasured longitudinal risk factor  $U$ , all models ignoring  $U$  (JM-mis, all JM-sep models, CM-obs and MM), exhibit a biased estimate for the direct SNP3 effect on T1DC traits. For SNP5 with direct and indirect effects on time-to-DN induced via SBP, JM-sep( $l=1$ ;  $k=2$ ), CM-obs, and MM overestimate the direct SNP5 effect on DN ( $\gamma_{g,2}$ ) due to ignoring within-subject random variability in SBP (CM-obs) or omitting SBP from the time-to-event models (JM-sep( $l=1$ ;  $k=2$ ), MM).

**Table S6-1. Estimation accuracy of the parameters of interest for causal SNP1 (MAF=30%) with indirect effects on both T1DC traits induced via HbA1c longitudinal risk factor, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the alternative genetic model from Fig. 3.** As noted above, JM-cmp, JM-mis, JM-sep( $l=1,2; k=1$ ) share the same estimates at Stage1, and JM-sep( $l=1; k=1$ ) and JM-sep( $l=1; k=2$ ) also share the same estimates for HbA1c longitudinal trait.

| Trait                | Parameter   | Estimation criteria   | JM-cmp      | JM-mis      | JM-sep( $l=1,2; k=1$ ) | JM-sep( $l=1; k=1$ ) | CM-obs <sup>3</sup> |
|----------------------|---|-----------------------|-------------|-------------|------------------------|----------------------|---------------------|
| HbA1c ( $l=1$ )      | $\beta_{g,l} = 0.7$   | Mean Bias             | -0.051      |             |                        | -0.047               | .                   |
|                      |   | Empirical Variance    | 0.005       |             |                        | 0.005                | .                   |
|                      |   | MSE                   | 0.007       |             |                        | 0.007                | .                   |
|                      |   | Coverage <sup>1</sup> | 0.933       |             |                        | 0.941                | .                   |
|                      |   | 95% CI <sup>2</sup>   | [0.52;0.78] |             |                        | [0.52;0.79]          | .                   |
| Time-to-DR ( $k=1$ ) | $\alpha_{1,1} = 0.2$<br>(HbA1c, $l=1$ )                             | Mean Bias             | -0.006      | -0.016      | -0.032                 | -0.033               | -0.079              |
|                      |   | Empirical Variance    | 0.002       | 0.002       | 0.002                  | 0.002                | 0.001               |
|                      |   | MSE                   | 0.002       | 0.002       | 0.003                  | 0.003                | 0.008               |
|                      |   | Coverage <sup>1</sup> | 0.955       | 0.944       | 0.901                  | 0.902                | 0.414               |
|                      |   | 95% CI <sup>2</sup>   | [0.11;0.28] | [0.10;0.27] | [0.09;0.25]            | [0.09;0.25]          | [0.05;0.19]         |
|                      | $\mu_{g,1,1} = 0.14$<br>( $\mu_{g,1,1} = \alpha_{1,1}\beta_{g,l}$ ) | Mean Bias             | -0.014      | -0.021      | -0.031                 | -0.031               | -0.062              |
|                      |   | Empirical Variance    | 0.001       | 0.001       | 0.001                  | 0.001                | 0.001               |
|                      |   | MSE                   | 0.001       | 0.001       | 0.002                  | 0.002                | 0.004               |
|                      |   | Coverage <sup>1</sup> | 0.929       | 0.908       | 0.814                  | 0.824                | 0.331               |
|                      |   | 95% CI <sup>2</sup>   | [0.07;0.19] | [0.06;0.18] | [0.05;0.16]            | [0.05;0.16]          | [0.03;0.13]         |
| Time-to-DN ( $k=2$ ) | Parameter   | Estimation criteria   | JM-cmp      | JM-mis      | JM-sep( $l=1,2; k=2$ ) | JM-sep( $l=1; k=2$ ) | CM-obs <sup>3</sup> |
|                      | $\alpha_{1,2} = 0.2$<br>(HbA1c, $l=1$ )                             | Mean Bias             | 0.002       | 0.001       | -0.018                 | <b>-0.097</b>        | <b>-0.109</b>       |
|                      |   | Empirical Variance    | 0           | 0           | 0.004                  | 0.002                | 0.002               |
|                      |   | MSE                   | 0           | 0           | 0.005                  | 0.012                | 0.014               |
|                      |   | Coverage <sup>1</sup> | 0.945       | 0.951       | 0.951                  | <b>0.695</b>         | <b>0.331</b>        |
|                      |   | 95% CI <sup>2</sup>   | [0.07;0.35] | [0.06;0.34] | [0.05;0.31]            | [0.01;0.20]          | [0.03;0.13]         |
|                      | $\mu_{g,1,2} = 0.14$<br>( $\mu_{g,1,2} = \alpha_{1,2}\beta_{g,2}$ ) | Mean Bias             | -0.003      | -0.011      | -0.022                 | -0.073               | -0.081              |
|                      |   | Empirical Variance    | 0.002       | 0.002       | 0.002                  | 0.001                | 0.001               |
|                      |   | MSE                   | 0.002       | 0.002       | 0.003                  | 0.006                | 0.008               |
|                      |   | Coverage <sup>1</sup> | 0.955       | 0.945       | 0.926                  | 0.563                | 0.438               |
|                      |   | 95% CI <sup>2</sup>   | [0.04;0.23] | [0.03;0.22] | [0.03;0.21]            | [0.003;0.13]         | [-0.003;0.19]       |

<sup>1</sup>Coverage probability, calculated as the proportion of replicates with 95% Confidence Intervals covering the specified parameter value.

<sup>2</sup>95% Confidence Interval of the effect calculated using the mean and sd from the empirical distribution of the estimates over the  $R=1000$  replicates.

<sup>3</sup>Assessment of estimation accuracy for  $\widehat{\mu}_{g,1,k}$  in CM-obs is based on  $\widehat{\alpha}_{l,k}$  from CM-obs and  $\widehat{\beta}_{g,l}$  from the bivariate linear mixed fitted for HbA1c and SBP independently of CM-obs.

**Table S6-2.** Estimation accuracy of the parameters of interest for SNP2 (MAF=10%) having a direct association on DR, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the alternative genetic model from [Fig. 3](#)

| Trait                   | Parameter          | Estimation criteria   | JM-cmp      | JM-mis      | JM-sep( $l=1,2; k=1$ ) | JM-sep( $l=1; k=1$ ) | CM-obs      | MM          |
|-------------------------|--------------------|-----------------------|-------------|-------------|------------------------|----------------------|-------------|-------------|
| Time-to-DR<br>( $k=1$ ) | $\gamma_{g,1}=0.8$ | Mean Bias             | 0.003       | -0.023      | -0.099                 | -0.099               | -0.077      | -0.115      |
|                         |                    | Variance              | 0.014       | 0.018       | 0.015                  | 0.015                | 0.016       | 0.014       |
|                         |                    | MSE                   | 0.014       | 0.019       | 0.024                  | 0.024                | 0.022       | 0.027       |
|                         |                    | Coverage <sup>1</sup> | 0.952       | 0.951       | 0.873                  | 0.871                | 0.908       | 0.841       |
|                         |                    | 95% CI <sup>2</sup>   | [0.57;1.04] | [0.51;1.04] | [0.46;0.94]            | [0.46;0.94]          | [0.48;0.97] | [0.45;0.92] |
|                         | $\alpha_{1,1}=0.2$ | Mean Bias             | 0.003       | -0.009      | -0.026                 | -0.026               | -0.071      | .           |
|                         |                    | Variance              | 0.002       | 0.002       | 0.001                  | 0.001                | 0.001       | .           |
|                         |                    | MSE                   | 0.002       | 0.002       | 0.002                  | 0.002                | 0.006       | .           |
|                         |                    | Coverage <sup>1</sup> | 0.953       | 0.959       | 0.927                  | 0.924                | 0.484       | .           |
|                         |                    | 95% CI <sup>2</sup>   | [0.12;0.28] | [0.11;0.27] | [0.10;0.25]            | [0.10;0.25]          | [0.06;0.19] | .           |

<sup>1</sup>Coverage probability, calculated as the proportion of replicates with 95% Confidence Intervals covering the specified parameter value.

<sup>2</sup>95% Confidence Interval of the effect calculated using the mean and sd from the empirical distribution of the estimates over the  $R=1000$  replicates.

**Table S6-3. Estimation accuracy of the overall effects of SNP3 (MAF=40%) with indirect effects on T1DC traits induced via U, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the alternative genetic model from Fig. 3**

| Traits                  | Parameters           | Evaluation criteria   | JM-cmp       | JM-mis       | JM-sep( $l=1,2; k=1$ ) | JM-sep( $l=1; k=1$ ) | CM-obs               | MM           |              |
|-------------------------|----------------------|-----------------------|--------------|--------------|------------------------|----------------------|----------------------|--------------|--------------|
| Time-to-DR<br>( $k=1$ ) | $\gamma_{g,1} = 0$   | Mean Bias             | 0.001        | 0.299        | 0.274                  | 0.274                | 0.28                 | 0.267        |              |
|                         |                      | Variance              | 0.008        | 0.008        | 0.007                  | 0.007                | 0.007                | 0.007        |              |
|                         |                      | MSE                   | 0.008        | 0.097        | 0.082                  | 0.082                | 0.086                | 0.078        |              |
|                         |                      | Coverage <sup>1</sup> | 0.953        | 0.101        | 0.103                  | 0.343                | 0.107                | 0.125        |              |
|                         |                      | 95% CI <sup>2</sup>   | [-0.17;0.17] | [0.12;0.48]  | [0.11;0.44]            | [0.11;0.44]          | [0.11;0.44]          | [0.10;0.43]  |              |
|                         | $\alpha_{1,1} = 0.2$ | Mean Bias             | -0.006       | -0.016       | -0.03                  | -0.03                | -0.074               | .            |              |
|                         |                      | Variance              | 0.002        | 0.002        | 0.002                  | 0.002                | 0.001                | .            |              |
|                         |                      | MSE                   | 0.002        | 0.002        | 0.002                  | 0.002                | 0.007                | .            |              |
|                         |                      | Coverage <sup>1</sup> | 0.95         | 0.944        | 0.899                  | 0.897                | <b>0.107</b>         | .            |              |
|                         |                      | 95% CI <sup>2</sup>   | [0.11;0.28]  | [0.10;0.27]  | [0.09;0.25]            | [0.11;0.44]          | [0.06;0.19]          | .            |              |
| Time-to-DN<br>( $k=2$ ) | Parameters           | Estimation criteria   | JM-cmp       | JM-mis       | JM-sep( $l=1,2; k=2$ ) | JM-sep( $l=1; k=2$ ) | JM-sep( $l=2; k=2$ ) | CM-obs       | MM           |
|                         | $\gamma_{g,2} = 0$   | Mean Bias             | 0.004        | <b>0.305</b> | <b>0.291</b>           | <b>0.197</b>         | <b>0.282</b>         | <b>0.228</b> | <b>0.195</b> |
|                         |                      | Variance              | 0.02         | 0.021        | 0.019                  | 0.015                | 0.019                | 0.014        | 0.015        |
|                         |                      | MSE                   | 0.02         | 0.114        | 0.104                  | 0.054                | 0.099                | 0.066        | 0.054        |
|                         |                      | Coverage <sup>1</sup> | 0.962        | 0.416        | 0.423                  | 0.622                | 0.785                | 0.518        | 0.674        |
|                         |                      | 95% CI <sup>2</sup>   | [-0.27;0.28] | [0.02;0.59]  | [0.02;0.56]            | [-0.05;0.44]         | [0.01;0.55]          | [-0.01;0.46] | [-0.05;0.44] |
|                         | $\alpha_{1,2} = 0.2$ | Mean Bias             | 0.01         | -0.002       | -0.015                 | -0.098               | .                    | -0.104       | .            |
|                         |                      | Variance              | 0.005        | 0.005        | 0.004                  | 0.002                | .                    | 0.002        | .            |
|                         |                      | MSE                   | 0.005        | 0.005        | 0.004                  | 0.012                | .                    | 0.013        | .            |
|                         |                      | Coverage <sup>1</sup> | 0.955        | 0.954        | 0.955                  | 0.351                | .                    | 0            | .            |
|                         |                      | 95% CI <sup>2</sup>   | [0.08;0.34]  | [0.06;0.33]  | [0.06;0.31]            | [-0.05;0.44]         | .                    | [0.06;0.09]  | .            |
|                         | $\alpha_{2,2} = 0.2$ | Mean Bias             | 0.002        | 0.001        | -0.011                 | .                    | -0.014               | -0.128       | .            |
|                         |                      | Variance              | 0            | 0            | 0                      | .                    | 0                    | 0            | .            |
|                         |                      | MSE                   | 0            | 0            | 0                      | .                    | 0                    | 0.016        | .            |
|                         |                      | Coverage <sup>1</sup> | 0.965        | 0.963        | 0.871                  | .                    | 0.806                | 0.46         | .            |
|                         |                      | 95% CI <sup>2</sup>   | [0.17;0.23]  | [0.17;0.23]  | [0.16;0.21]            | .                    | [0.16;0.21]          | [0.01;0.18]  | .            |

<sup>1</sup>Coverage probability, calculated as the proportion of replicates with 95% Confidence Intervals covering the specified parameter value.

<sup>2</sup>95% Confidence Interval of the effect calculated using the mean and sd from the empirical distribution of the estimates over the  $R=1000$  replicates.

**Table S6-4. Estimation accuracy of the parameters of interest in the time-to-event sub-model for SNP4 (MAF=30%) having a direct association on DN, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the alternative genetic model from Fig. 3**

| Trait                | Parameters           | Evaluation criteria   | JM-cmp      | JM-mis      | JM-sep( $l=1,2; k=2$ ) | JM-sep( $l=1; k=2$ ) | JM-sep( $l=2; k=2$ ) | CM-obs      | MM          |
|----------------------|----------------------|-----------------------|-------------|-------------|------------------------|----------------------|----------------------|-------------|-------------|
| Time-to-DN ( $k=2$ ) | $\gamma_{g,2} = 0.7$ | Mean Bias             | -0.014      | -0.028      | -0.076                 | -0.281               | -0.088               | -0.216      | -0.283      |
|                      |                      | Variance              | 0.016       | 0.019       | 0.017                  | 0.014                | 0.017                | 0.012       | 0.014       |
|                      |                      | MSE                   | 0.016       | 0.02        | 0.023                  | 0.093                | 0.025                | 0.059       | 0.094       |
|                      |                      | Coverage <sup>1</sup> | 0.944       | 0.943       | 0.892                  | 0.344                | 0.88                 | 0.501       | 0.337       |
|                      |                      | 95% CI <sup>2</sup>   | [0.44;0.93] | [0.40;0.94] | [0.37;0.88]            | [0.19;0.65]          | [0.36;0.87]          | [0.27;0.70] | [0.18;0.65] |
|                      | $\alpha_{1,2} = 0.2$ | Mean Bias             | 0.022       | 0.007       | -0.008                 | -0.096               | .                    | -0.102      | .           |
|                      |                      | Variance              | 0.005       | 0.005       | 0.004                  | 0.002                | .                    | 0.002       | .           |
|                      |                      | MSE                   | 0.005       | 0.005       | 0.004                  | 0.011                | .                    | 0.012       | .           |
|                      |                      | Coverage <sup>1</sup> | 0.937       | 0.954       | 0.959                  | 0.684                | .                    | 0.464       | .           |
|                      |                      | 95% CI <sup>2</sup>   | [0.09;0.36] | [0.07;0.34] | [0.07;0.32]            | [0.02;0.19]          | .                    | [0.01;0.19] | .           |
|                      | $\alpha_{2,2} = 0.2$ | Mean Bias             | 0.013       | 0.01        | -0.005                 | .                    | -0.008               | -0.126      | .           |
|                      |                      | Variance              | 0           | 0           | 0                      | .                    | 0                    | 0           | .           |
|                      |                      | MSE                   | 0           | 0           | 0                      | .                    | 0                    | 0.016       | .           |
|                      |                      | Coverage <sup>1</sup> | 0.903       | 0.939       | 0.943                  | .                    | 0.919                | 0           | .           |
|                      |                      | 95% CI <sup>2</sup>   | [0.19;0.24] | [0.18;0.24] | [0.17;0.22]            | .                    | [0.17;0.22]          | [0.06;0.09] | .           |

<sup>1</sup>Coverage probability, calculated as the proportion of replicates with 95% Confidence Intervals covering the specified parameter value.

<sup>2</sup>95% Confidence Interval of the effect, calculated using the mean and sd from the empirical distribution of the estimates over the  $R=1000$  replicates.

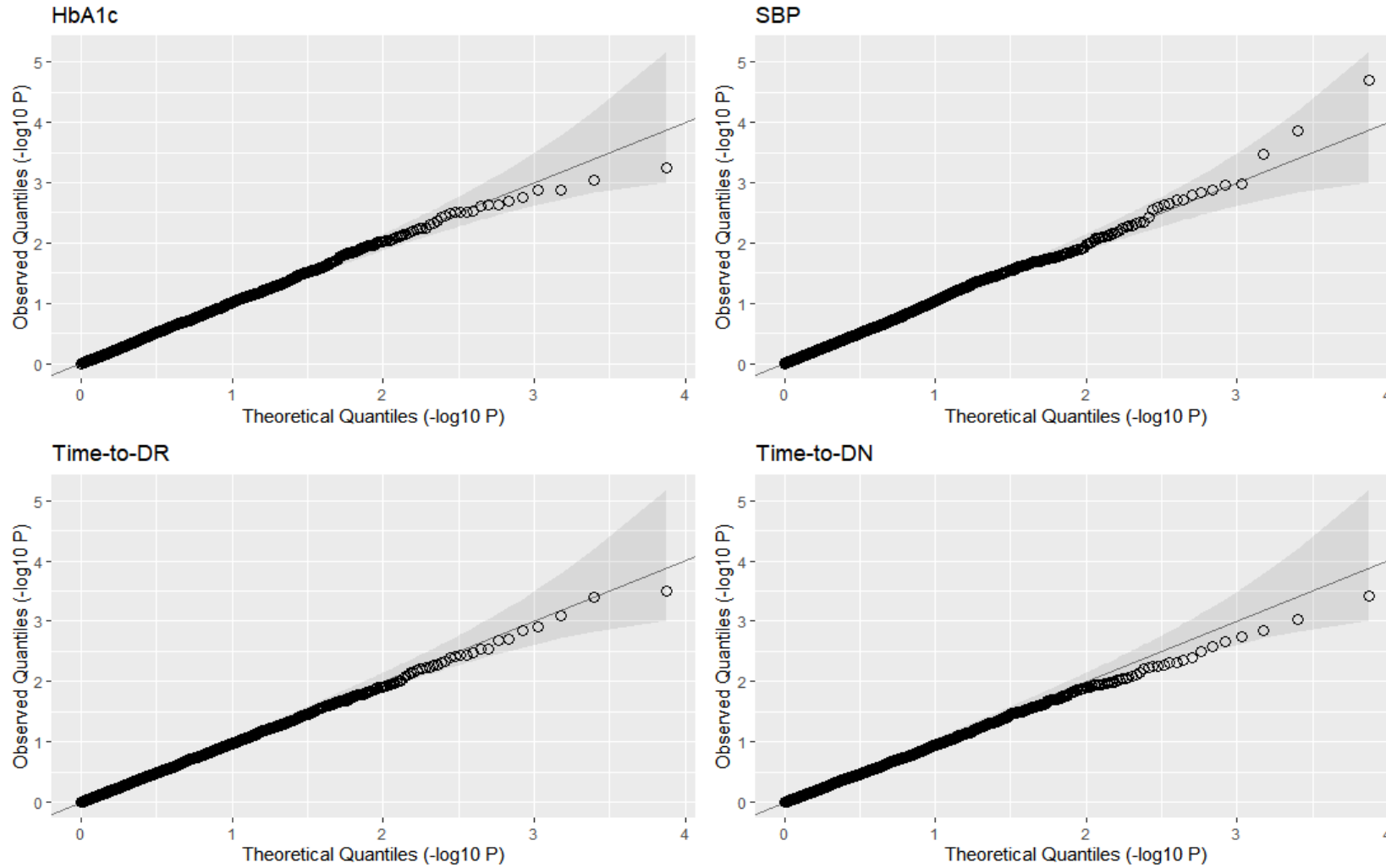
**Table S6-5.** Estimation accuracy of parameters of interest for SNP5 (MAF=20%) with a direct effect and an indirect effect on Time-to-DN induced via SBP, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the alternative genetic model from **Fig. 3**

| Trait                | Parameter   | Evaluation criteria   | JM-cmp      | JM-mis      | JM-sep( $l=1,2; k=2$ ) | JM-sep( $l=2; k=2$ ) | CM-obs <sup>3</sup> | MM          |
|----------------------|---|-----------------------|-------------|-------------|------------------------|----------------------|---------------------|-------------|
| SBP ( $l=2$ )        | $\beta_{g,2} = 7$   | Mean Bias             | 0.046       |             |                        | 0.039                | .                   | .           |
|                      |   | Variance              | 0.208       |             |                        | 0.208                | .                   | .           |
|                      |   | MSE                   | 0.210       |             |                        | 0.209                | .                   | .           |
|                      |   | Coverage <sup>1</sup> | 0.99        |             |                        | 0.999                | .                   | .           |
|                      |   | 95% CI <sup>2</sup>   | [6.15;7.94] |             |                        | [6.15;7.95]          | .                   | .           |
| Time-to-DN ( $k=2$ ) | $\gamma_{g,2} = 0.4$  | Mean Bias             | -0.020      | -0.009      | -0.036                 | -0.029               | 0.505               | 0.762       |
|                      |   | Variance              | 0.024       | 0.028       | 0.026                  | 0.026                | 0.023               | 0.022       |
|                      |   | MSE                   | 0.025       | 0.029       | 0.027                  | 0.027                | 0.278               | 0.602       |
|                      |   | Coverage <sup>1</sup> | 0.941       | 0.948       | 0.894                  | 0.980                | 0.04                | 0.01        |
|                      |   | 95% CI <sup>2</sup>   | [0.07;0.69] | [0.06;0.72] | [0.05;0.68]            | [0.05;0.69]          | [0.61;1.20]         | [0.88;1.45] |
|                      | $\alpha_{2,2} = 0.2$  | Mean Bias             | -0.008      | -0.010      | -0.023                 | -0.026               | -0.138              | .           |
|                      |   | Variance              | <0.001      | <0.001      | <0.001                 | <0.001               | <0.001              | .           |
|                      |   | MSE                   | <0.001      | <0.001      | 0.001                  | 0.001                | 0.019               | .           |
|                      |   | Coverage <sup>1</sup> | 0.912       | 0.911       | 0.570                  | 0.482                | 0                   | .           |
|                      |   | 95% CI <sup>2</sup>   | [0.16;0.22] | [0.16;0.22] | [0.15;0.23]            | [0.15;0.2]           | [0.05;0.08]         | .           |
|                      | $\mu_{g,2,2} = 1.4$<br>( $\mu_{g,2,2} = \alpha_{2,2}\beta_{g,2}$ )      | Mean Bias             | -0.051      | -0.059      | -0.155                 | -0.176               | -0.965              | .           |
|                      |   | Variance              | 0.018       | 0.019       | 1.542                  | 0.015                | 0.003               | .           |
|                      |   | MSE                   | 0.02        | 0.022       | 1.566                  | 0.046                | 0.933               | .           |
|                      |   | Coverage <sup>1</sup> | 0.971       | 0.963       | 0.54                   | 0.719                | <0.001              | .           |
|                      |   | 95% CI <sup>2</sup>   | [1.09;1.61] | [1.07;1.61] | [1.00;1.49]            | [-0.07;0.42]         | [0.33;0.54]         | .           |
|                      | $\theta_{2,2} = 1.8$<br>( $\theta_{2,2} = \mu_{g,2,2} + \gamma_{g,2}$ ) | Mean Bias             | -0.074      | -0.071      | -0.194                 | -0.205               | -0.462              | .           |
|                      |   | Variance              | 0.031       | 0.035       | 0.029                  | -0.556               | 0.023               | .           |
|                      |   | MSE                   | 0.037       | 0.04        | 0.067                  | 0.071                | 0.236               | .           |
|                      |   | 95% CI <sup>2</sup>   | [1.38;2.08] | [1.36;2.10] | [1.27;1.95]            | [1.26;1.93]          | [1.04;1.64]         | .           |

<sup>1</sup>Coverage probability, calculated as the proportion of replicates with 95% Confidence Intervals covering the specified parameter value.<sup>2</sup>95% Confidence Interval of the effect calculated using the mean and sd from the empirical distribution of the estimates over the  $R=1000$  replicates.<sup>3</sup>For CM-obs, estimation accuracy for  $\mu_{g,2,2}$  and  $\theta_{2,2}$ , are based on  $\widehat{\beta}_{g,2}$  from the bivariate longitudinal sub-model for HbA1c and SBP fitted independently of CM-obs.



## 7. Single parameter test validity for each of $\beta_{g,l}$ and $\gamma_{g,k}$ assessed under the global null genetic scenario



**Fig. S7-1** Quantile-quantile plots of the  $P$ -values from the Wald tests for each SNP effect in longitudinal ( $\beta_{g,l}$ , upper) and time-to-event sub-models ( $\gamma_{g,k}$ , bottom) of the complete joint model (JM-cmp), assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the *global null* genetic scenario. For each trait, SNP association  $P$ -values obtained for all  $M=5$  SNPs and all replicates are pooled, yielding  $R=5000$  replicates per plot.

**Table S7-2. Empirical type-1 errors for hypothesis tests of each of  $\beta_{g,l}$  and  $\gamma_{g,k}$  based on the complete joint model (JM-cmp) and the other compared models, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects, with SNPs simulated under the global null genetic simulation scenario.**

| Null SNPs         | Models                 | $P^*=0.05$ threshold (5%)  |                          |                          |                          | $P^*=0.01$ threshold (1%)  |                          |                          |                          |
|-------------------|------------------------|----------------------------|--------------------------|--------------------------|--------------------------|----------------------------|--------------------------|--------------------------|--------------------------|
|                   |                        | $\beta_{g,1}=0$<br>(HbA1c) | $\beta_{g,2}=0$<br>(SBP) | $\gamma_{g,1}=0$<br>(DR) | $\gamma_{g,2}=0$<br>(DN) | $\beta_{g,1}=0$<br>(HbA1c) | $\beta_{g,2}=0$<br>(SBP) | $\gamma_{g,1}=0$<br>(DR) | $\gamma_{g,2}=0$<br>(DN) |
| SNP1<br>(MAF=30%) | JM-cmp                 | 5.2                        | 5.8                      | 4.4                      | 4.8                      | 1.5                        | 1.1                      | 0.9                      | 0.8                      |
|                   | JM-mis                 | 5.2                        | 5.8                      | 3.6                      | 4.9                      | 1.5                        | 1.1                      | 1.1                      | 0.8                      |
|                   | JM-sep( $l=1,2; k=1$ ) | 5.2                        | 5.8                      | 3.8                      | .                        | 1.5                        | 1.1                      | 1.1                      | .                        |
|                   | JM-sep( $l=1,2; k=2$ ) | 5.2                        | 5.8                      | .                        | 5.2                      | 1.5                        | 1.1                      | .                        | 1.1                      |
|                   | JM-sep( $l=1; k=1$ )   | 5.6                        | .                        | 4.0                      | .                        | 1.3                        | .                        | 0.9                      | .                        |
|                   | JM-sep( $l=1; k=2$ )   | 5.6                        | .                        | .                        | 4.6                      | 1.3                        | .                        | .                        | 0.5                      |
|                   | JM-sep( $l=2; k=2$ )   | .                          | 5.9                      | .                        | 4.6                      | .                          | 1.2                      | .                        | 1.1                      |
|                   | CM-obs                 | .                          | .                        | 2.9                      | 4.8                      | .                          | .                        | 1.0                      | 0.8                      |
|                   | MM                     | .                          | .                        | 4.3                      | 4.8                      | .                          | .                        | 1.3                      | 0.7                      |
| SNP2<br>(MAF=10%) | JM-cmp                 | 5.5                        | 6.0                      | 5.8                      | 3.9                      | 1.0                        | 1.2                      | 0.9                      | 0.8                      |
|                   | JM-mis                 | 5.5                        | 6.0                      | 4.5                      | 3.8                      | 1.0                        | 1.2                      | 0.9                      | .                        |
|                   | JM-sep( $l=1,2; k=1$ ) | 5.5                        | 6.0                      | 5.0                      | .                        | 1.0                        | 1.2                      | 1.0                      | .                        |
|                   | JM-sep( $l=1,2; k=2$ ) | 5.5                        | 6.0                      | .                        | 4.4                      | 1.0                        | 1.2                      | .                        | 0.9                      |
|                   | JM-sep( $l=1; k=1$ )   | 5.0                        | .                        | 5.0                      | .                        | 1.4                        | .                        | 1.0                      | .                        |
|                   | JM-sep( $l=1; k=2$ )   | 5.0                        | .                        | .                        | 5.1                      | 1.4                        | .                        | .                        | 1.1                      |
|                   | JM-sep( $l=2; k=2$ )   | .                          | 6.7                      | .                        | 4.9                      | .                          | 1.1                      | .                        | 1.0                      |
|                   | CM-obs                 | .                          | .                        | 4.5                      | 4.1                      | .                          | .                        | 0.7                      | 0.8                      |
|                   | MM                     | .                          | .                        | 4.8                      | 4.9                      | .                          | .                        | 0.7                      | 1.3                      |
| SNP3<br>(MAF=40%) | JM-cmp                 | 4.0                        | 6.7                      | 4.3                      | 4.5                      | 0.9                        | 1.1                      | 0.8                      | 1.3                      |
|                   | JM-mis                 | 4.0                        | 6.7                      | 4.6                      | 3.9                      | 0.9                        | 1.1                      | 0.6                      | 0.9                      |
|                   | JM-sep( $l=1,2; k=1$ ) | 4.0                        | 6.7                      | 4.7                      | .                        | 0.9                        | 1.1                      | 0.8                      | .                        |
|                   | JM-sep( $l=1,2; k=2$ ) | 4.0                        | 6.7                      | .                        | 4.4                      | 0.9                        | 1.1                      | .                        | 1.0                      |
|                   | JM-sep( $l=1; k=1$ )   | 4.1                        | .                        | 4.6                      | .                        | 1.2                        | .                        | 0.9                      | .                        |
|                   | JM-sep( $l=1; k=2$ )   | 4.1                        | .                        | .                        | 4.6                      | 1.2                        | .                        | .                        | 0.7                      |
|                   | JM-sep( $l=2; k=2$ )   | .                          | 6.5                      | .                        | 4.8                      | .                          | 0.9                      | .                        | 1.3                      |
|                   | CM-obs                 | .                          | .                        | 4.2                      | 4.3                      | .                          | .                        | 0.8                      | 0.9                      |
|                   | MM                     | .                          | .                        | 4.7                      | 4.8                      | .                          | .                        | 0.9                      | 0.8                      |
| SNP4<br>(MAF=30%) | JM-cmp                 | 4.8                        | 6.3                      | 3.9                      | 4.9                      | 1.1                        | 1.2                      | 0.6                      | 0.8                      |
|                   | JM-mis                 | 4.8                        | 6.3                      | 4.9                      | 4.7                      | 1.1                        | 1.2                      | 0.3                      | 0.9                      |
|                   | JM-sep( $l=1,2; k=1$ ) | 4.8                        | 6.3                      | 4.9                      | .                        | 1.1                        | 1.2                      | 0.7                      | .                        |
|                   | JM-sep( $l=1,2; k=2$ ) | 4.8                        | 6.3                      | .                        | 5.1                      | 1.1                        | 1.2                      | .                        | 1.0                      |
|                   | JM-sep( $l=1; k=1$ )   | 5.0                        | .                        | 4.6                      | .                        | 1.0                        | .                        | 0.4                      | .                        |
|                   | JM-sep( $l=1; k=2$ )   | 5.0                        | .                        | .                        | 5.0                      | 1.0                        | .                        | .                        | 1.0                      |
|                   | JM-sep( $l=2; k=2$ )   | .                          | 5.6                      | .                        | 4.8                      | .                          | 1.1                      | .                        | 0.9                      |
|                   | CM-obs                 | .                          | .                        | 4.8                      | 4.8                      | .                          | .                        | 0.2                      | 0.5                      |
|                   | MM                     | .                          | .                        | 5.1                      | 5.1                      | .                          | .                        | 0.2                      | 1.0                      |
| SNP5<br>(MAF=20%) | JM-cmp                 | 5.0                        | 5.5                      | 4.7                      | 5.6                      | 1.1                        | 1.4                      | 1.0                      | 0.8                      |
|                   | JM-mis                 | 5.0                        | 5.5                      | 4.6                      | 4.5                      | 1.1                        | 1.4                      | 0.8                      | 0.9                      |
|                   | JM-sep( $l=1,2; k=1$ ) | 5.0                        | 5.5                      | 5.2                      | .                        | 1.1                        | 1.4                      | 1.1                      | .                        |
|                   | JM-sep( $l=1,2; k=2$ ) | 5.0                        | 5.5                      | .                        | 5.0                      | 1.1                        | 1.4                      | .                        | 1.2                      |
|                   | JM-sep( $l=1; k=1$ )   | 5.1                        | .                        | 5.3                      | .                        | 1.0                        | .                        | 1.2                      | .                        |
|                   | JM-sep( $l=1; k=2$ )   | 5.1                        | .                        | .                        | 4.9                      | 1.0                        | .                        | .                        | 0.9                      |
|                   | JM-sep( $l=2; k=2$ )   | .                          | 5.6                      | .                        | 5.4                      | .                          | 1.3                      | .                        | 1.6                      |
|                   | CM-obs                 | .                          | .                        | 4.6                      | 4.1                      | .                          | .                        | 0.8                      | 0.7                      |
|                   | MM                     | .                          | .                        | 4.7                      | 4.1                      | .                          | .                        | 1.3                      | 0.8                      |

Type-1 errors are shown in percentage (%) and are computed for each SNP and each genetic association parameter as the proportion of replicates that reject the null hypothesis at significance threshold  $P^*$ . Departure from nominal Type-1 error for null parameters is shown in red. Asymptotic 95% confidence intervals at  $P^*=5\%$ : [3.649;6.351],  $P^*=1\%$ : [0.383;1.617]. This table is an extended version of Table 2 to include type-1 errors for CM-obs and MM.

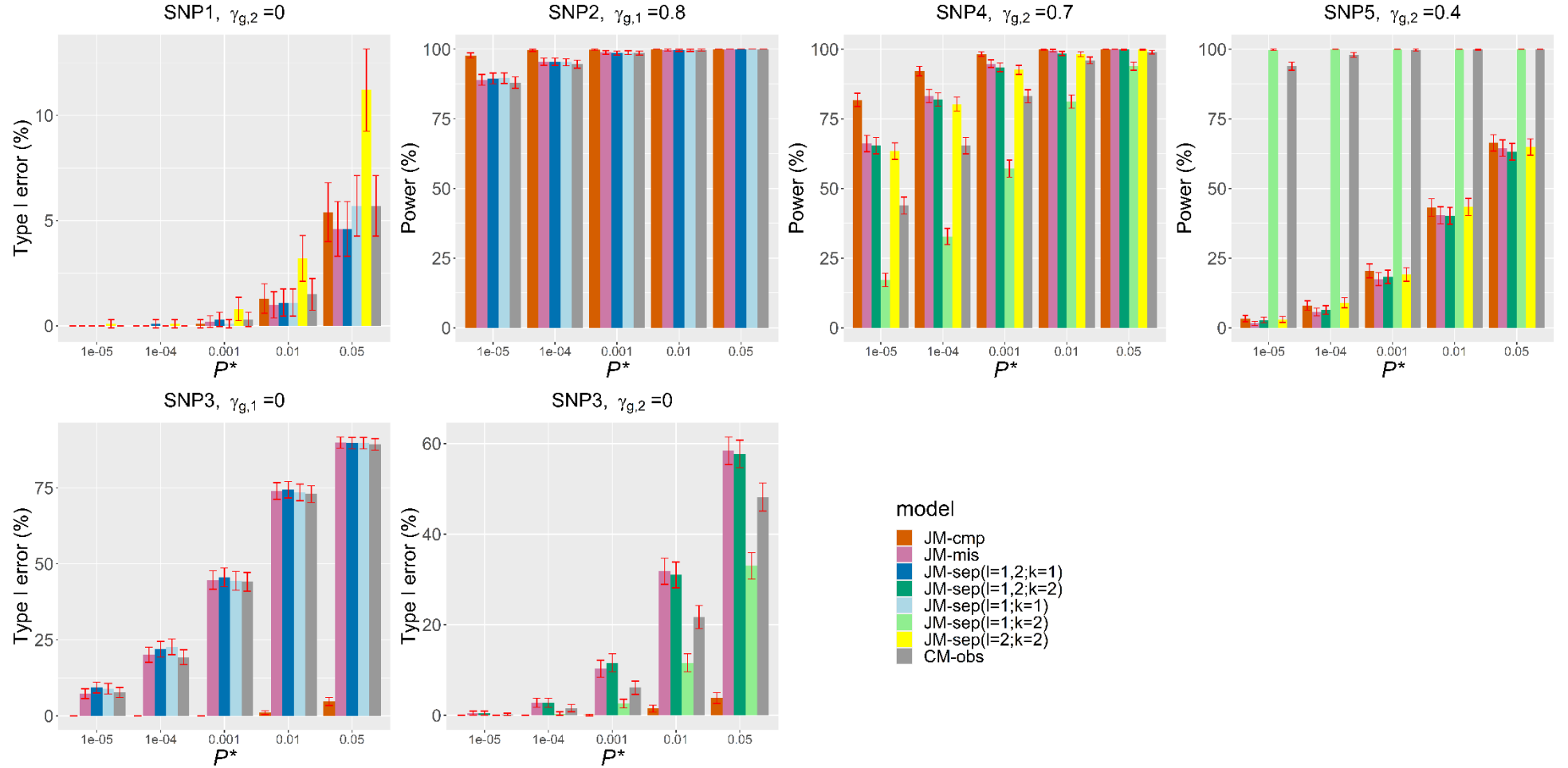
## 8. Empirical type-1 errors & powers of single parameter tests for each of $\beta_{g,l}$ and $\gamma_{g,k}$ assessed under the alternative genetic scenario

**Table S8-1.** Empirical type-1 errors & powers for hypothesis tests of each of  $\beta_{g,l}$  and  $\gamma_{g,k}$  based on the complete joint model (JM-cmp) and all the other compared models, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects, with SNPs simulated under the alternative genetic scenario from Fig. 3.

| Causal SNPs  | Models                 | $P^*=0.05$ threshold (5%) |                      |                      |                      | $P^*=0.01$ threshold (1%) |                      |                      |                      | $P^*=0.001$ threshold (0.1%) |                      |                      |                      |
|--|------------------------|---------------------------|----------------------|----------------------|----------------------|---------------------------|----------------------|----------------------|----------------------|------------------------------|----------------------|----------------------|----------------------|
|  |                        | $\beta_{g,1}$<br>HbA1c    | $\beta_{g,2}$<br>SBP | $\gamma_{g,1}$<br>DR | $\gamma_{g,2}$<br>DN | $\beta_{g,1}$<br>HbA1c    | $\beta_{g,2}$<br>SBP | $\gamma_{g,1}$<br>DR | $\gamma_{g,2}$<br>DN | $\beta_{g,1}$<br>HbA1c       | $\beta_{g,2}$<br>SBP | $\gamma_{g,1}$<br>DR | $\gamma_{g,2}$<br>DN |
| SNP1<br>(MAF<br>=30%)<br><br>$\beta_{g,1} = 0.7$<br>$\beta_{g,2} = 0$<br>$\gamma_{g,1} = 0$<br>$\gamma_{g,2} = 0$                      | JM-cmp                 | <b>100</b>                | 5.1                  | 4.1                  | 5.4                  | <b>100</b>                | 0.7                  | 0.7                  | 1.3                  | <b>100</b>                   | 0                    | 0                    | 0.1                  |
|  | JM-mis                 | <b>100</b>                | 5.1                  | 4.2                  | 4.6                  | <b>100</b>                | 0.7                  | 0.5                  | 1                    | <b>100</b>                   | 0                    | 0                    | 0.2                  |
|  | JM-sep( $l=1,2; k=1$ ) | <b>100</b>                | 5.1                  | 4.7                  | .                    | <b>100</b>                | 0.7                  | 0.3                  | .                    | <b>100</b>                   | 0                    | 0                    | .                    |
|  | JM-sep( $l=1,2; k=2$ ) | <b>100</b>                | 5.1                  | .                    | 4.6                  | <b>100</b>                | 0.7                  | .                    | 1.1                  | <b>100</b>                   | 0                    | .                    | 0.3                  |
|  | JM-sep( $l=1; k=1$ )   | <b>100</b>                | .                    | 4.6                  | .                    | <b>100</b>                | .                    | 0.6                  | .                    | <b>100</b>                   | .                    | 0                    | .                    |
|  | JM-sep( $l=1; k=2$ )   | <b>100</b>                | .                    | .                    | 5.7                  | <b>100</b>                | .                    | .                    | 1.1                  | <b>100</b>                   | .                    | .                    | 0.1                  |
|  | JM-sep( $l=2; k=2$ )   | .                         | 5.2                  | .                    | 11.2                 | .                         | 0.9                  | .                    | 3.2                  | .                            | 0                    | .                    | 0.8                  |
|  | CM-obs                 | .                         | .                    | 6.4                  | 5.7                  | .                         | .                    | 0.7                  | 1.5                  | .                            | .                    | 0.1                  | 0.3                  |
|  | MM                     | .                         | .                    | 20.4                 | 8.7                  | .                         | .                    | 8                    | 3.1                  | .                            | .                    | 1.2                  | 0.3                  |
| SNP2<br>(MAF<br>=10%)<br><br>$\beta_{g,1} = 0$<br>$\beta_{g,2} = 0$<br>$\gamma_{g,1} = 0.8$<br>$\gamma_{g,2} = 0$                      | JM-cmp                 | 6.6                       | 5.4                  | <b>100</b>           | 3.9                  | 1.3                       | 1.2                  | <b>100</b>           | 1.4                  | 0                            | 0.2                  | <b>99.8</b>          | 0.5                  |
|  | JM-mis                 | 6.6                       | 5.4                  | <b>100</b>           | 4.6                  | 1.3                       | 1.2                  | <b>99.7</b>          | 1.0                  | 0                            | 0.2                  | <b>98.8</b>          | 0.3                  |
|  | JM-sep( $l=1,2; k=1$ ) | 6.6                       | 5.4                  | <b>100</b>           | .                    | 1.3                       | 1.2                  | <b>99.6</b>          | .                    | 0                            | 0.2                  | <b>98.6</b>          | .                    |
|  | JM-sep( $l=1,2; k=2$ ) | 6.6                       | 5.4                  | .                    | 5.2                  | 1.3                       | 1.2                  | .                    | 1.4                  | 0                            | 0.2                  | .                    | 0.4                  |
|  | JM-sep( $l=1; k=1$ )   | 6.1                       | .                    | <b>100</b>           | .                    | 1.6                       | .                    | <b>99.6</b>          | .                    | 0                            | .                    | <b>98.7</b>          | .                    |
|  | JM-sep( $l=1; k=2$ )   | 6.1                       | .                    | .                    | 4.6                  | 1.6                       | .                    | .                    | 1.0                  | 0                            | .                    | .                    | 0.2                  |
|  | JM-sep( $l=2; k=2$ )   | .                         | 5.2                  | .                    | 4.7                  | .                         | 1.4                  | .                    | 1.3                  | .                            | 0.3                  | .                    | 0.4                  |
|  | CM-obs                 | .                         | .                    | <b>100</b>           | 4.5                  | .                         | .                    | <b>99.7</b>          | 1.4                  | .                            | .                    | <b>98.6</b>          | 0                    |
|  | MM                     | .                         | .                    | <b>100</b>           | 4.4                  | .                         | .                    | <b>99.7</b>          | 0.8                  | .                            | .                    | <b>98.3</b>          | 0.3                  |
| SNP3<br>(MAF<br>=40%)<br><br>$\beta_{g,1} = 0$<br>$\beta_{g,2} = 0$<br>$\beta_{g,u} = 0.8$<br>$\gamma_{g,1} = 0$<br>$\gamma_{g,2} = 0$ | JM-cmp                 | 4.5                       | 4.6                  | 4.7                  | 3.8                  | 1                         | 0.7                  | 1.0                  | 1.5                  | 0                            | 0                    | 0                    | 0.1                  |
|  | JM-mis                 | 4.5                       | 4.6                  | 89.9                 | 58.4                 | 1                         | 0.7                  | 74.0                 | 31.8                 | 0                            | 0                    | 44.7                 | 10.3                 |
|  | JM-sep( $l=1,2; k=1$ ) | 4.5                       | 4.6                  | 89.7                 | .                    | 1                         | 0.7                  | 74.4                 | .                    | 0                            | .                    | 45.6                 | .                    |
|  | JM-sep( $l=1,2; k=2$ ) | 4.5                       | 4.6                  | .                    | 57.7                 | 1                         | 0.7                  | .                    | 31.0                 | 0                            | 0                    | .                    | 11.6                 |
|  | JM-sep( $l=1; k=1$ )   | 4.8                       | .                    | 89.7                 | .                    | 1.2                       | .                    | 73.5                 | .                    | 0                            | .                    | 44.4                 | .                    |
|  | JM-sep( $l=1; k=2$ )   | 4.8                       | .                    | .                    | 33.0                 | 1.2                       | .                    | .                    | 11.6                 | 0                            | .                    | .                    | 2.6                  |
|  | JM-sep( $l=2; k=2$ )   | .                         | 4.4                  | .                    | 56.4                 | .                         | 0.8                  | .                    | 30.6                 | .                            | 0                    | .                    | 10.4                 |
|  | CM-obs                 | .                         | .                    | 89.3                 | 48.2                 | .                         | .                    | 73.0                 | 21.7                 | .                            | .                    | 44.1                 | 6.1                  |
|  | MM                     | .                         | .                    | 87.5                 | 32.6                 | .                         | .                    | 71.9                 | 12.3                 | .                            | .                    | 42.8                 | 2.6                  |
| SNP4<br>(MAF<br>=30%)<br><br>$\beta_{g,1} = 0$<br>$\beta_{g,2} = 0$<br>$\gamma_{g,1} = 0$<br>$\gamma_{g,2} = 0.7$                      | JM-cmp                 | 5.4                       | 4.8                  | 6.0                  | <b>100</b>           | 1.4                       | 1                    | 1.5                  | <b>99.9</b>          | 0.3                          | 0                    | 0                    | <b>98.3</b>          |
|  | JM-mis                 | 5.4                       | 4.8                  | 5.4                  | <b>100</b>           | 1.4                       | 1                    | 1                    | <b>99.5</b>          | 0.3                          | 0                    | 0.1                  | <b>94.8</b>          |
|  | JM-sep( $l=1,2; k=1$ ) | 5.4                       | 4.8                  | 5.1                  | .                    | 1.4                       | 1                    | 0.9                  | .                    | 0.3                          | 0                    | 0.2                  | .                    |
|  | JM-sep( $l=1,2; k=2$ ) | 5.4                       | 4.8                  | .                    | <b>99.9</b>          | 1.4                       | 1                    | .                    | <b>98.5</b>          | 0.3                          | 0                    | .                    | <b>93.5</b>          |
|  | JM-sep( $l=1; k=1$ )   | 6.1                       | .                    | 5.1                  | .                    | 0.9                       | .                    | 1                    | .                    | 0.2                          | .                    | 0.2                  | .                    |
|  | JM-sep( $l=1; k=2$ )   | 6.1                       | .                    | .                    | <b>93.9</b>          | 0.9                       | .                    | .                    | <b>81.2</b>          | 0.2                          | .                    | .                    | 57.1                 |
|  | JM-sep( $l=2; k=2$ )   | .                         | 4.8                  | .                    | <b>99.9</b>          | .                         | 1                    | .                    | <b>98.2</b>          | .                            | 0                    | .                    | <b>92.6</b>          |
|  | CM-obs                 | .                         | .                    | 4.6                  | <b>98.9</b>          | .                         | .                    | 1.0                  | <b>96.0</b>          | .                            | .                    | 0.1                  | <b>83.1</b>          |
|  | MM                     | .                         | .                    | 5.0                  | <b>94.1</b>          | .                         | .                    | 1.1                  | <b>80.6</b>          | .                            | .                    | 0.2                  | <b>56.5</b>          |
| SNP5<br>(MAF<br>=20%)<br><br>$\beta_{g,1} = 0$<br>$\beta_{g,2} = 7$<br>$\gamma_{g,1} = 0$<br>$\gamma_{g,2} = 0.4$                      | JM-cmp                 | 2.8                       | <b>100</b>           | 5.5                  | <b>66.4</b>          | 1.1                       | <b>100</b>           | 1.1                  | <b>43.2</b>          | 0                            | <b>100</b>           | 0.1                  | <b>20.5</b>          |
|  | JM-mis                 | 2.8                       | <b>100</b>           | 4.6                  | <b>64.5</b>          | 1.1                       | <b>100</b>           | 0.6                  | <b>40.4</b>          | 0                            | <b>100</b>           | 0                    | <b>17.5</b>          |
|  | JM-sep( $l=1,2; k=1$ ) | 2.8                       | <b>100</b>           | 4.8                  | .                    | 1.1                       | <b>100</b>           | 0.8                  | .                    | 0                            | <b>100</b>           | 0                    | .                    |
|  | JM-sep( $l=1,2; k=2$ ) | 2.8                       | <b>100</b>           | .                    | <b>63.2</b>          | 1.1                       | <b>100</b>           | .                    | <b>40.2</b>          | 0                            | <b>100</b>           | .                    | <b>18.3</b>          |
|  | JM-sep( $l=1; k=1$ )   | 2.8                       | .                    | 4.6                  | .                    | 0.8                       | .                    | 0.8                  | .                    | 0                            | .                    | 0                    | .                    |
|  | JM-sep( $l=1; k=2$ )   | 2.8                       | .                    | .                    | <b>100</b>           | 0.8                       | .                    | .                    | <b>100</b>           | 0                            | .                    | .                    | <b>100</b>           |
|  | JM-sep( $l=2; k=2$ )   | .                         | <b>100</b>           | .                    | <b>64.9</b>          | .                         | <b>100</b>           | .                    | <b>43.4</b>          | .                            | <b>100</b>           | .                    | <b>19.1</b>          |
|  | CM-obs                 | .                         | .                    | 4.8                  | <b>100</b>           | .                         | .                    | 0.6                  | <b>99.9</b>          | .                            | .                    | 0                    | <b>99.7</b>          |
|  | MM                     | .                         | .                    | 5.2                  | <b>100</b>           | .                         | .                    | 0.8                  | <b>100.0</b>         | .                            | .                    | 0.1                  | <b>100</b>           |

Type-1 errors & powers are shown in percentage (%) and are computed for each SNP and each genetic association parameter as the proportion of replicates that reject the null hypothesis at significance threshold  $P^*$ . Power for parameters under the generating model scenarios of SNP association, as simulated in Fig 3, are shown in bold. Departure from nominal Type-1 errors for null parameters is shown in red. Asymptotic 95% confidence intervals at  $P^*=5\%$ : [3.649;6.351],  $P^*=1\%$ : [0.383;1.617],  $P^*=0.1\%$ : [0;0.295]. SNP1, SNP3 and SNP5 have indirect effects on T1DC traits, such that their associations with the T1DC traits are detectable with the marginal Cox PH time-to-event trait model (MM).

**Fig S8-1.** Empirical type-1 errors (SNP1, SNP3) and powers (SNP2, SNP4, SNP5) for hypothesis tests of each of  $\gamma_{g,k}$  based on the complete joint model (JM-cmp) and the other compared models, assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects, with SNPs simulated under the alternative scenario from [Fig. 3](#).



Vertical red lines correspond to the 95% binomial proportion confidence interval calculated using the following formula:  $q \pm 1.96 \times \sqrt{\frac{q(1-q)}{R}}$ , where  $q$  corresponds to the empirical type -1 error (SNP1, SNP3) or power (SNP2, SNP4, SNP5).

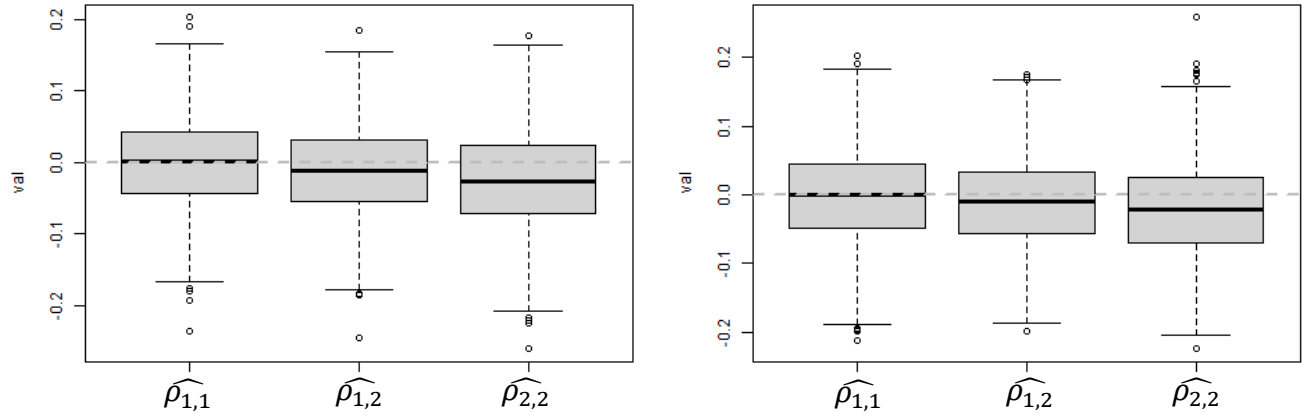
## **9. Evaluation of the accuracy of the procedure for classification of SNP association**

In **sections 9.1 and 9.2**, we find that the bootstrap correlation values  $\widehat{\rho}_{l,k}$  between  $\widehat{\beta}_{g,l}$  and  $\widehat{\gamma}_{g,k}$  are low for each QT/TTE trait pair ( $l; k$ ) under the *global null* genetic scenario for all joint model analyses (means across replicates  $|\widehat{\rho}_{l,k}| < 0.05$ ) which is in agreement with the expected null correlation under the global null genetic scenario (as discussed in the Manuscript). Those  $\widehat{\rho}_{l,k}$  also tend to be low under the alternative genetic scenario, particularly for the joint models (**section 9.2 and Tables 3-7**). In **section 9.2**, we also describe the calculation of the expected classification frequencies (considering  $\rho_{l,k}$ ) for each category of association, and we confirm the accuracy of the classification procedure under the global null genetic scenario (as judged by empirical classification frequencies being close to the expected frequencies). Finally, in **section 9.3**, we show that increasing  $\rho_{l,k}$  has only little effect on the expected classification frequencies under both (null and alternative) genetic simulation scenarios.

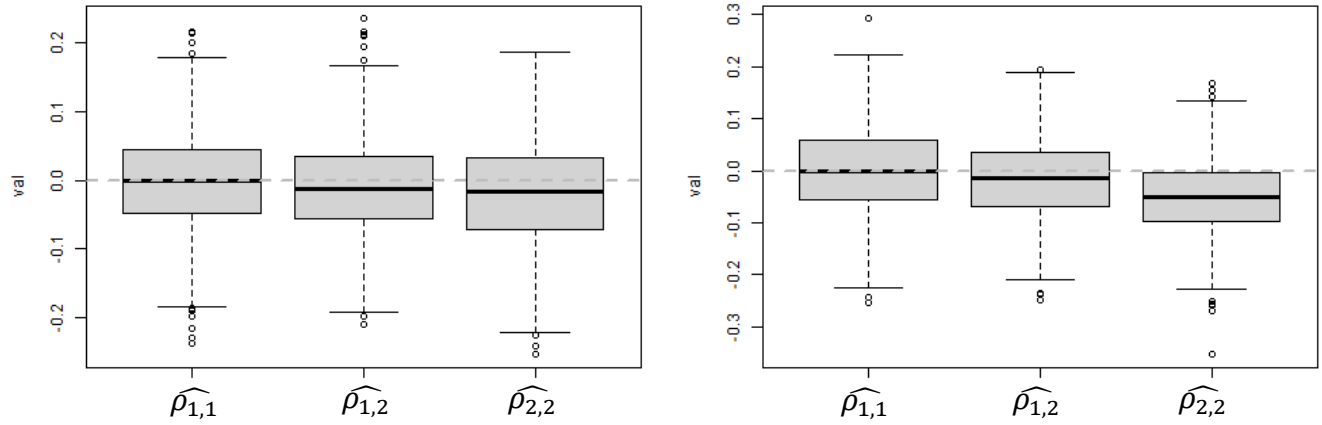
### **9.1 Distribution of $\rho_{l,k}$ under the global null and genetic alternative simulation scenarios**

The bootstrap correlation values  $\widehat{\rho}_{l,k}$  between  $\widehat{\beta}_{g,l}$  and  $\widehat{\gamma}_{g,k}$  obtained in JM-cmp under the global null and alternative genetic scenarios tend to be distributed around 0, as illustrated for the examples of SNP1 (**Fig S9.1-1**) and SNP5 (**Fig S9.1-2**). The means of  $\widehat{\rho}_{l,k}$  across replicates tend to be low for all the joint models fitted under the global null genetic scenario (**Table S9.2-2**) and under the alternative scenarios (**Tables 3-8**) which agree with the theoretical expectation.

**Fig S9.1-1.** Illustration of the bootstrap correlation values  $\widehat{\rho}_{l,k}$  obtained in JM-cmp for SNP1 across replicates simulated under the *global null* (left panel) and *alternative* (right panel) genetic simulation scenarios.



**Fig S9.1-2.** Illustration of the bootstrap correlation values  $\widehat{\rho}_{l,k}$  obtained in JM-cmp for SNP5 across replicates simulated under the *global null* (left panel) and *alternative* (right panel) genetic simulation scenarios.



## **9.2 Approach to assess accuracy of the procedure for classification of direct and/or indirect SNP association**

To assess the accuracy of the procedure from **Table 1** for classification of SNP association, we compare the *empirical* classification frequencies (from simulation studies) to the *expected* classification frequencies; the later are calculated under the assumption that  $\widehat{\mathbf{Z}}_g = \left( \widehat{Z}_{\beta_{g,l}} = \widehat{\beta}_{g,l} / \widehat{\sigma}_{\beta_{g,l}}, \widehat{Z}_{\gamma_{g,k}} = \widehat{\gamma}_{g,k} / \widehat{\sigma}_{\gamma_{g,k}} \right)^T$  constructed from  $\widehat{\beta}_{g,l}$  and  $\widehat{\gamma}_{g,k}$ , estimated from the joint model (or

other compared models) and their bootstrap standard errors ( $\widehat{\sigma_{\beta_{g,l}}}$  and  $\widehat{\sigma_{\gamma_{g,k}}}$ ), asymptotically follows a bivariate normal distribution under the large sample theory, ie:

$$\widehat{\mathbf{Z}}_g \sim N_2(E[\mathbf{Z}_g], \mathbf{H})$$

Where:

- $E[\mathbf{Z}_g] = \left( E[Z_{\beta_{g,l}}], E[Z_{\gamma_{g,k}}] \right)^T$ , and
- $\mathbf{H} = \begin{pmatrix} 1 & \rho_{l,k} \\ \rho_{l,k} & 1 \end{pmatrix}$  with  $\rho_{l,k} = Cor(Z_{\beta_{g,l}}, Z_{\gamma_{g,k}}) = \sigma_{\beta_{g,l}\gamma_{g,k}} / (\sigma_{\beta_{g,l}} \times \sigma_{\gamma_{g,k}})$ ,

where  $\sigma_{\beta_{g,l}\gamma_{g,k}}$  correspond to the covariance between  $\beta_{g,l}$  and  $\gamma_{g,k}$ .

Particularly, we calculate the bivariate normal probability ( $p_f$ ) that  $\widehat{\mathbf{Z}}_g$  belongs to the region(s) of integration defined in **Table S9.2-1** for each category of association, where each  $p_f$  is defined as:

$$p_f = \int_{a_1}^{a_2} \int_{b_1}^{b_2} f(\mathbf{Z}_g, \rho_{l,k}) dz$$

with:

- $f(\mathbf{Z}_g, \rho_{l,k}) = \frac{1}{2\pi\sqrt{(1-\rho_{l,k}^2)}} \exp \left[ -\frac{\frac{1}{2}((Z_{\beta_{g,l}})^2 + (Z_{\gamma_{g,k}})^2 - 2\rho_{l,k}Z_{\beta_{g,l}}Z_{\gamma_{g,k}})}{1-\rho_{l,k}^2} \right]$   
and  $-\infty \leq Z_{\beta_{g,l}} \leq +\infty, -\infty \leq Z_{\gamma_{g,k}} \leq +\infty$
- $a_1, a_2 \in \mathbb{R} (a_1 < a_2)$  and  $b_1, b_2 \in \mathbb{R} (b_1 < b_2)$  correspond to the integrand limits for, respectively,  $Z_{\beta_{g,l}}$  and  $Z_{\gamma_{g,k}}$  as defined in **Table S9.2-1**.

**Table S9.2-1. Calculation of the *expected* classification frequencies for each category of SNP association at significance level  $P^*=0.05$  (corresponding to a critical value  $|Z_\alpha| = 1.96$ ), and assuming  $\widehat{Z}_g \sim N_2(E[Z_g], H)$**

| Category of SNP association | Hypothesis tested                              | Regions of integration  | Calculated bivariate normal integral for the probability that $\widehat{Z}_g$ belongs to each region of integration using the R package <i>mvtnorm</i> (Genz et al. 2021):<br>pmvnorm(mean= $E[Z_g]$ , corr= $H$ , lower=( $a_1, b_1$ ), upper=( $a_2, b_2$ )) | Expected classification frequency <sup>1</sup> at desired level |
|-----------------------------|--|---|--|---|
| Indirect                    | $\beta_{g,l} \neq 0$ AND $\gamma_{g,k} = 0$    | $Z_{\beta_{g,l}} < -Z_\alpha$<br>& $-Z_\alpha \leq Z_{\gamma_{g,k}} \leq Z_\alpha$                            | $p_{I1} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (-\text{Inf}, -Z_\alpha), \text{upper} = (-Z_\alpha, Z_\alpha))$  | $p_I = p_{I1} + p_{I2}$   |
|                             |  | $Z_{\beta_{g,l}} > Z_\alpha$<br>& $-Z_\alpha \leq Z_{\gamma_{g,k}} \leq Z_\alpha$                             | $p_{I2} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (Z_\alpha, -Z_\alpha), \text{upper} = (+\text{Inf}, Z_\alpha))$   |   |
| Direct                      | $\beta_{g,l} = 0$ AND $\gamma_{g,k} \neq 0$    | $-Z_\alpha \leq Z_{\beta_{g,l}} \leq Z_\alpha$<br>& $Z_{\gamma_{g,k}} < -Z_\alpha$                            | $p_{D1} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (-Z_\alpha, -\text{Inf}), \text{upper} = (Z_\alpha, -Z_\alpha))$  | $p_D = \alpha p_{D1} + p_{D2}$                                  |
|                             |  | $-Z_\alpha \leq Z_{\beta_{g,l}} \leq Z_\alpha$<br>& $Z_{\gamma_{g,k}} > Z_\alpha$                             | $p_{D2} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (-Z_\alpha, Z_\alpha), \text{upper} = (Z_\alpha, +\text{Inf}))$   |   |
| Direct & Indirect           | $\beta_{g,l} \neq 0$ AND $\gamma_{g,k} \neq 0$ | $Z_{\beta_{g,l}} < -Z_\alpha$<br>& $Z_{\gamma_{g,k}} < -Z_\alpha$   | $p_{DI1} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (-\text{Inf}, -\text{Inf}), \text{upper} = (-Z_\alpha, -Z_\alpha))$  | $p_{D\&I} = p_{DI1} + p_{DI2} + p_{DI3} + p_{DI4}$              |
|                             |  | $Z_{\beta_{g,l}} > Z_\alpha$<br>& $Z_{\gamma_{g,k}} > Z_\alpha$   | $p_{DI2} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (Z_\alpha, Z_\alpha), \text{upper} = (+\text{Inf}, +\text{Inf}))$  |   |
|                             |  | $Z_{\beta_{g,l}} < -Z_\alpha$<br>& $Z_{\gamma_{g,k}} > Z_\alpha$  | $p_{DI3} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (-\text{Inf}, Z_\alpha), \text{upper} = (-Z_\alpha, +\text{Inf}))$   |   |
|                             |  | $Z_{\beta_{g,l}} > Z_\alpha$<br>& $Z_{\gamma_{g,k}} < -Z_\alpha$  | $p_{DI4} = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (Z_\alpha, -\text{Inf}), \text{upper} = (+\text{Inf}, -Z_\alpha))$   |   |
| Not Direct & Not Indirect   | $\beta_{g,l} = 0$ AND $\gamma_{g,k} = 0$       | $-Z_\alpha \leq \widehat{Z}_{\beta_{g,l}} \leq Z_\alpha$<br>& $-Z_\alpha \leq Z_{\gamma_{g,k}} \leq Z_\alpha$ | $p_N = \text{pmvnorm}(\text{mean} = E[Z_g], \text{corr} = H, \text{lower} = (-Z_\alpha, -Z_\alpha), \text{upper} = (Z_\alpha, Z_\alpha))$  | $p_N$   |

<sup>1</sup>We calculated the *expected* classification frequencies under the assumption that  $p_I + p_D + p_{D\&I} + p_N = 1$ .



**Table S9.2-2.** Means of bootstrap standard errors for  $\beta_{g,l}$  and  $\gamma_{g,k}$  and their correlation, and SNP association classification frequencies based on the complete joint model and the other compared models at significance threshold  $P^*=0.05$ , assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects, with SNPs simulated under the *global null* genetic scenario

| SNPs                  | Trait pairs                              | Compared Models                     | Mean Bootstrap SE's and Correlation <sup>1</sup> |                                   |                        | Expected <sup>2</sup> and Empirical <sup>3</sup> classification frequencies (%) |        |                   |                           |
|-----------------------|--|-------------------------------------|--|-----------------------------------|------------------------|---|--------|-------------------|---------------------------|
|                       |  |                                     | $\widehat{\sigma}_{\beta_{g,l}}$                 | $\widehat{\sigma}_{\gamma_{g,k}}$ | $\widehat{\rho}_{l,k}$ | Indirect  | Direct | Direct & Indirect | Not Direct & Not Indirect |
| Expected <sup>2</sup> |  |                                     |  |                                   |                        | 4.75  | 4.75   | 0.25              | 90.25                     |
| SNP1<br>(MAF=30%)     | HbA1c( <i>l</i> =1)/<br>DR( <i>k</i> =1) | JM-cmp                              | 0.006  | 0.007                             | -0.001                 | 4.9   | 4.1    | 0.3               | 90.7                      |
|                       |  | JM-mis                              | 0.006  | 0.009                             | -0.002                 | 4.9   | 3.3    | 0.3               | 91.5                      |
|                       |  | JM-sep( <i>l</i> =1,2; <i>k</i> =1) | 0.006  | 0.007                             | -0.002                 | 4.9   | 3.5    | 0.3               | 91.3                      |
|                       |  | JM-sep( <i>l</i> =1; <i>k</i> =1)   | 0.006  | 0.007                             | -0.004                 | 5.4   | 3.8    | 0.2               | 90.6                      |
|                       |  | CM-obs                              | 0.006  | 0.008                             | 0.039                  | 5   | 2.7    | 0.2               | 92.1                      |
|                       | HbA1c( <i>l</i> =1)/<br>DN( <i>k</i> =2) | JM-cmp                              | 0.006  | 0.018                             | -0.013                 | 4.9   | 4.5    | 0.3               | 90.3                      |
|                       |  | JM-mis                              | 0.006  | 0.020                             | -0.012                 | 4.8   | 4.5    | 0.4               | 90.3                      |
|                       |  | JM-sep( <i>l</i> =1,2; <i>k</i> =2) | 0.006  | 0.018                             | -0.010                 | 4.8   | 4.8    | 0.4               | 90                        |
|                       |  | JM-sep( <i>l</i> =1; <i>k</i> =2)   | 0.006  | 0.016                             | 0.008                  | 5.2   | 4.2    | 0.4               | 90.2                      |
|                       |  | CM-obs                              | 0.006  | 0.014                             | 0.022                  | 4.8   | 4.4    | 0.4               | 90.4                      |
|                       | SBP( <i>l</i> =2)/<br>DN( <i>k</i> =2)   | JM-cmp                              | 0.217  | 0.018                             | -0.026                 | 5.4   | 4.4    | 0.4               | 89.8                      |
|                       |  | JM-mis                              | 0.217  | 0.020                             | -0.021                 | 5.2   | 4.3    | 0.6               | 89.9                      |
|                       |  | JM-sep( <i>l</i> =1,2; <i>k</i> =2) | 0.217  | 0.018                             | -0.018                 | 5.3   | 4.7    | 0.5               | 89.5                      |
|                       |  | JM-sep( <i>l</i> =2; <i>k</i> =2)   | 0.216  | 0.017                             | -0.016                 | 5.5   | 4.2    | 0.4               | 89.9                      |
|                       |  | CM-obs                              | 0.217  | 0.014                             | 0.320                  | 5   | 4      | 0.8               | 90.2                      |
| SNP2<br>(MAF=10%)     | HbA1c( <i>l</i> =1)/<br>DR( <i>k</i> =1) | JM-cmp                              | 0.014  | 0.018                             | -0.005                 | 5.5   | 5.8    | 0                 | 88.7                      |
|                       |  | JM-mis                              | 0.014  | 0.021                             | -0.007                 | 5.5   | 4.5    | 0                 | 90                        |
|                       |  | JM-sep( <i>l</i> =1,2; <i>k</i> =1) | 0.014  | 0.017                             | -0.007                 | 5.4   | 4.9    | 0                 | 89.6                      |
|                       |  | JM-sep( <i>l</i> =1; <i>k</i> =1)   | 0.014  | 0.017                             | -0.004                 | 4.9   | 4.9    | 0                 | 90.1                      |
|                       |  | CM-obs                              | 0.014  | 0.019                             | 0.033                  | 5.5   | 4.5    | 0                 | 90                        |
|                       | HbA1c( <i>l</i> =1)/<br>DN( <i>k</i> =2) | JM-cmp                              | 0.014  | 0.043                             | -0.017                 | 5.5   | 3.9    | 0                 | 90.6                      |
|                       |  | JM-mis                              | 0.014  | 0.048                             | -0.017                 | 5.5   | 3.8    | 0                 | 90.7                      |
|                       |  | JM-sep( <i>l</i> =1,2; <i>k</i> =2) | 0.014  | 0.042                             | -0.016                 | 5.4   | 4.3    | 0                 | 90.3                      |
|                       |  | JM-sep( <i>l</i> =1; <i>k</i> =2)   | 0.014  | 0.039                             | 0.004                  | 4.9   | 5      | 0.1               | 90                        |
|                       |  | CM-obs                              | 0.014  | 0.035                             | 0.017                  | 5.5   | 4.1    | 0                 | 90.4                      |
|                       | SBP( <i>l</i> =2)/                       | JM-cmp                              | 0.508  | 0.043                             | -0.019                 | 6   | 3.9    | 0                 | 90.1                      |

|                          |                                |                        |       |       |        |     |     |     |             |
|--------------------------|--------------------------------|------------------------|-------|-------|--------|-----|-----|-----|-------------|
|                          | DN( $k=2$ )                    | JM-mis                 | 0.508 | 0.048 | -0.013 | 5.9 | 3.6 | 0.2 | <b>90.3</b> |
|                          |                                | JM-sep( $l=1,2; k=2$ ) | 0.508 | 0.042 | -0.009 | 5.8 | 4.2 | 0.2 | <b>89.8</b> |
|                          |                                | JM-sep( $l=2; k=2$ )   | 0.508 | 0.042 | -0.004 | 6.3 | 4.5 | 0.4 | <b>88.8</b> |
|                          |                                | CM-obs                 | 0.508 | 0.035 | 0.324  | 5.8 | 3.9 | 0.2 | <b>90.1</b> |
| <b>SNP3</b><br>(MAF=40%) | HbA1c( $l=1$ )/<br>DR( $k=1$ ) | JM-cmp                 | 0.005 | 0.006 | -0.005 | 3.8 | 4.1 | 0.2 | <b>91.9</b> |
|                          |                                | JM-mis                 | 0.005 | 0.008 | -0.006 | 3.8 | 4.4 | 0.2 | <b>91.6</b> |
|                          |                                | JM-sep( $l=1,2; k=1$ ) | 0.005 | 0.006 | -0.006 | 3.9 | 4.6 | 0.1 | <b>91.4</b> |
|                          |                                | JM-sep( $l=1; k=1$ )   | 0.005 | 0.006 | -0.004 | 4.0 | 4.5 | 0.1 | <b>91.4</b> |
|                          |                                | CM-obs                 | 0.005 | 0.007 | 0.035  | 3.9 | 4.1 | 0.1 | <b>91.9</b> |
|                          | HbA1c( $l=1$ )/<br>DN( $k=2$ ) | JM-cmp                 | 0.005 | 0.015 | -0.009 | 3.6 | 4.1 | 0.2 | <b>92.1</b> |
|                          |                                | JM-mis                 | 0.005 | 0.017 | -0.009 | 3.8 | 4.2 | 0.1 | <b>91.9</b> |
|                          |                                | JM-sep( $l=1,2; k=2$ ) | 0.005 | 0.015 | -0.008 | 3.8 | 4.2 | 0.2 | <b>91.8</b> |
|                          |                                | JM-sep( $l=1; k=2$ )   | 0.005 | 0.014 | 0.008  | 3.9 | 4.4 | 0.2 | <b>91.5</b> |
|                          |                                | CM-obs                 | 0.005 | 0.007 | 0.024  | 3.9 | 4.2 | 0.2 | <b>91.7</b> |
|                          | SBP( $l=2$ )/<br>DN( $k=2$ )   | JM-cmp                 | 0.188 | 0.015 | -0.028 | 6.4 | 4.2 | 0.3 | <b>89.1</b> |
|                          |                                | JM-mis                 | 0.188 | 0.017 | -0.022 | 6.2 | 4.1 | 0.3 | <b>89.4</b> |
|                          |                                | JM-sep( $l=1,2; k=2$ ) | 0.188 | 0.015 | -0.017 | 6.4 | 4.1 | 0.3 | <b>89.2</b> |
|                          |                                | JM-sep( $l=2; k=2$ )   | 0.188 | 0.015 | -0.016 | 6.1 | 4.4 | 0.4 | <b>89.1</b> |
|                          |                                | CM-obs                 | 0.188 | 0.012 | 0.320  | 6   | 3.6 | 0.3 | <b>90.1</b> |
| <b>SNP4</b><br>(MAF=30%) | HbA1c( $l=1$ )/<br>DR( $k=1$ ) | JM-cmp                 | 0.006 | 0.007 | -0.002 | 4.7 | 3.8 | 0.1 | <b>91.4</b> |
|                          |                                | JM-mis                 | 0.006 | 0.009 | -0.004 | 4.7 | 4.8 | 0.1 | <b>90.4</b> |
|                          |                                | JM-sep( $l=1,2; k=1$ ) | 0.006 | 0.007 | -0.005 | 4.5 | 4.6 | 0.3 | <b>90.6</b> |
|                          |                                | JM-sep( $l=1; k=1$ )   | 0.006 | 0.007 | -0.007 | 4.7 | 4.3 | 0.3 | <b>90.7</b> |
|                          |                                | CM-obs                 | 0.006 | 0.008 | 0.036  | 4.7 | 4.7 | 0.1 | <b>90.5</b> |
|                          | HbA1c( $l=1$ )/<br>DN( $k=2$ ) | JM-cmp                 | 0.006 | 0.018 | -0.012 | 4.5 | 4.6 | 0.3 | <b>90.6</b> |
|                          |                                | JM-mis                 | 0.006 | 0.020 | -0.012 | 4.5 | 4.4 | 0.3 | <b>90.8</b> |
|                          |                                | JM-sep( $l=1,2; k=2$ ) | 0.006 | 0.018 | -0.012 | 4.5 | 4.8 | 0.3 | <b>90.4</b> |
|                          |                                | JM-sep( $l=1; k=2$ )   | 0.006 | 0.016 | 0.007  | 5   | 5   | 0   | <b>90</b>   |
|                          |                                | CM-obs                 | 0.006 | 0.014 | 0.020  | 4.8 | 4.8 | 0   | <b>90.4</b> |
|                          | SBP( $l=2$ )/<br>DN( $k=2$ )   | JM-cmp                 | 0.216 | 0.018 | -0.027 | 6.1 | 4.7 | 0.2 | <b>89</b>   |
|                          |                                | JM-mis                 | 0.216 | 0.020 | -0.022 | 6   | 4.4 | 0.3 | <b>89.3</b> |
|                          |                                | JM-sep( $l=1,2; k=2$ ) | 0.216 | 0.018 | -0.018 | 5.8 | 4.6 | 0.3 | <b>89.3</b> |
|                          |                                | JM-sep( $l=2; k=2$ )   | 0.215 | 0.017 | -0.009 | 5.3 | 4.5 | 0.3 | <b>89.9</b> |
|                          |                                | CM-obs                 | 0.216 | 0.014 | 0.323  | 5.7 | 4.2 | 0.6 | <b>89.5</b> |
|                          | HbA1c( $l=1$ )/                | JM-cmp                 | 0.008 | 0.010 | -0.004 | 4.9 | 4.6 | 0.1 | <b>90.4</b> |

|                          |                        |                    |       |       |        |     |     |     |             |
|--------------------------|------------------------|--------------------|-------|-------|--------|-----|-----|-----|-------------|
| <b>SNP5</b><br>(MAF=20%) | DR(k=1)                | JM-mis             | 0.008 | 0.012 | -0.004 | 4.6 | 4.2 | 0.4 | <b>90.8</b> |
|                          |                        | JM-sep(l=1,2; k=1) | 0.008 | 0.009 | -0.005 | 4.7 | 4.9 | 0.3 | <b>90.1</b> |
|                          |                        | JM-sep(l=1; k=1)   | 0.008 | 0.009 | -0.003 | 4.7 | 4.9 | 0.4 | <b>90</b>   |
|                          |                        | CM-obs             | 0.008 | 0.010 | 0.036  | 4.7 | 4.3 | 0.3 | <b>90.7</b> |
|                          | HbA1c(l=1)/<br>DN(k=2) | JM-cmp             | 0.008 | 0.023 | -0.011 | 4.9 | 5.5 | 0.1 | <b>89.5</b> |
|                          |                        | JM-mis             | 0.008 | 0.026 | -0.010 | 4.9 | 4.4 | 0.1 | <b>90.6</b> |
|                          |                        | JM-sep(l=1,2; k=2) | 0.008 | 0.023 | -0.010 | 4.9 | 4.9 | 0.1 | <b>90.1</b> |
|                          |                        | JM-sep(l=1; k=2)   | 0.008 | 0.021 | 0.007  | 4.8 | 4.6 | 0.3 | <b>90.3</b> |
|                          |                        | CM-obs             | 0.008 | 0.019 | 0.022  | 4.9 | 4   | 0.1 | <b>91</b>   |
|                          | SBP(l=2)/<br>DN(k=2)   | JM-cmp             | 0.285 | 0.023 | -0.020 | 5.5 | 5.6 | 0   | <b>88.9</b> |
|                          |                        | JM-mis             | 0.285 | 0.026 | -0.014 | 5.3 | 4.3 | 0.2 | <b>90.2</b> |
|                          |                        | JM-sep(l=1,2; k=2) | 0.285 | 0.023 | -0.011 | 5.2 | 4.7 | 0.3 | <b>89.8</b> |
|                          |                        | JM-sep(l=2; k=2)   | 0.283 | 0.023 | -0.007 | 5.4 | 5.2 | 0.2 | <b>89.2</b> |
|                          |                        | CM-obs             | 0.285 | 0.019 | 0.326  | 5.2 | 3.8 | 0.3 | <b>90.7</b> |

<sup>1</sup>Mean Bootstrap SE's  $\sigma_{\beta_{g,l}}$  and  $\sigma_{\gamma_{g,k}}$  for respectively  $\beta_{g,l}$  and  $\gamma_{g,k}$ , and their correlation  $\rho_{l,k}$  over the  $R=1000$  replicates generated under the global null genetic scenario.

<sup>2</sup>We calculated the *expected* classification frequencies for each category of association as the probability to classify a SNP association as direct, indirect, direct and indirect, or not direct and not indirect under the assumption that  $\widehat{\mathbf{Z}}_g = (\widehat{Z}_{\beta_{g,l}}, \widehat{Z}_{\gamma_{g,k}})^T$ , constructed from the SNP effect estimates ( $\widehat{\beta}_{g,l}$  and  $\widehat{\gamma}_{g,k}$ ) and their bootstrap standard errors ( $\widehat{\sigma}_{\beta_{g,l}}$  and  $\widehat{\sigma}_{\gamma_{g,k}}$ ) as  $\widehat{Z}_{\beta_{g,l}} = \widehat{\beta}_{g,l} / \widehat{\sigma}_{\beta_{g,l}}$  and  $\widehat{Z}_{\gamma_{g,k}} = \widehat{\gamma}_{g,k} / \widehat{\sigma}_{\gamma_{g,k}}$  from JM-cmp, asymptotically follows a bivariate normal distribution, that is  $\widehat{\mathbf{Z}}_g \sim N_2(E[\mathbf{Z}_g], \mathbf{H})$ ; where  $E[\mathbf{Z}_g]$  is the vector of expectations, and  $\mathbf{H} = \begin{pmatrix} 1 & \rho_{l,k} \\ \rho_{l,k} & 1 \end{pmatrix}$  with  $\rho_{l,k} = \text{Cor}(Z_{\beta_{g,l}}, Z_{\gamma_{g,k}}) = \sigma_{\beta_{g,l}\gamma_{g,k}} / (\sigma_{\beta_{g,l}} \times \sigma_{\gamma_{g,k}})$  and  $\sigma_{\beta_{g,l}\gamma_{g,k}}$ , the bootstrap covariance between  $\beta_{g,l}$  and  $\gamma_{g,k}$ . Under the global null hypothesis, we assumed  $E[\mathbf{Z}_g] = (0,0)^T$  and  $\widehat{\rho}_{l,k} = \widehat{\sigma}_{\beta_{g,l}\gamma_{g,k}} / (\widehat{\sigma}_{\beta_{g,l}} \times \widehat{\sigma}_{\gamma_{g,k}})$ , where *True*  $\beta_{g,l}$  and *True*  $\gamma_{g,k}$  are the SNP effect parameter values specified to simulate the SNP association being tested, and  $\widehat{\sigma}_{\beta_{g,l}}$ ,  $\widehat{\sigma}_{\gamma_{g,k}}$ , and  $\widehat{\sigma}_{\beta_{g,l}\gamma_{g,k}}$ , correspond to the average of the bootstrap variances and covariances from JM-cmp over the  $R=1000$  replicates generated under the global null genetic scenario. When  $\rho_{l,k} < 0.4$ , we found negligible effect of  $\rho_{l,k}$  on the classification frequencies under the null genetic scenario (see **Table S9.3-1**).

<sup>3</sup>Empirical classification frequencies (shown as a percentage, %) for each SNP association under the *global null* genetic simulation scenario at significance  $P^*$  for  $\beta_{g,l}$  and  $\gamma_{g,k}$  hypothesis tests. We calculated the *empirical* classification frequencies for each category of association, as the proportion of replicates using the procedure described in **Table 1** at  $P^* = P_{\beta}^* = P_{\gamma}^* = 0.05$ . The results for the correct classification category under the *global null genetic* simulation scenario are shown in bold.

### **9.3 Assessment of sensitivity of the expected classification frequencies to increasing $\rho_{l,k}$**

We investigate the effect of increasing  $\rho_{l,k}$  on the expected classification frequencies. We recalculate the expected classification frequencies as described in 9.2, but with  $\rho_{l,k}$  varying from 0 (no dependence) to 1 (complete dependence). Under the *global null* genetic hypothesis, when  $\rho_{l,k} < 0.4$  the expected classification frequencies show minor changes (**Table S9.3-1**), and no change for any  $\rho_{l,k}$  values under the alternate genetic simulation scenario (as illustrated for the examples of SNP1 and SNP5 in **Tables S9.3-2 and S9.3-3**).

**Table S9.3-1. Effect of increasing correlation  $\rho_{l,k}$  between genetic  $\beta_{g,l}$  and  $\gamma_{g,k}$  on the expected classification frequencies at  $P^*=0.05$  under the *global null* genetic scenario**

| $\rho_{l,k}$              | Expected <sup>1</sup> classification frequencies (%) under the <i>global null</i> genetic scenario at significance threshold $P^*=0.05$ |        |                   |                         |
|---------------------------|---|--------|-------------------|-------------------------|
|                           | Indirect  | Direct | Indirect & Direct | Not Direct & Not Direct |
| 0 (Complete independence) | 4.75  | 4.75   | 0.25              | <b>90.25</b>            |
| 0.05                      | 4.74  | 4.74   | 0.26              | <b>90.26</b>            |
| 0.1                       | 4.72  | 4.72   | 0.28              | <b>90.28</b>            |
| 0.15                      | 4.69  | 4.69   | 0.31              | <b>90.31</b>            |
| 0.2                       | 4.64  | 4.64   | 0.36              | <b>90.36</b>            |
| 0.25                      | 4.59  | 4.59   | 0.41              | <b>90.41</b>            |
| 0.3                       | 4.51  | 4.51   | 0.49              | <b>90.49</b>            |
| 0.35                      | 4.43  | 4.43   | 0.57              | <b>90.57</b>            |
| 0.4                       | 4.32  | 4.32   | 0.68              | <b>90.68</b>            |
| 0.45                      | 4.21  | 4.21   | 0.79              | <b>90.79</b>            |
| 0.5                       | 4.07  | 4.07   | 0.93              | <b>90.93</b>            |
| 0.55                      | 3.92  | 3.92   | 1.08              | <b>91.08</b>            |
| 0.6                       | 3.75  | 3.75   | 1.25              | <b>91.25</b>            |
| 0.65                      | 3.56  | 3.56   | 1.44              | <b>91.44</b>            |
| 0.7                       | 3.35  | 3.35   | 1.65              | <b>91.65</b>            |
| 0.75                      | 3.1   | 3.1    | 1.9               | <b>91.9</b>             |
| 0.8                       | 2.81  | 2.81   | 2.19              | <b>92.19</b>            |
| 0.85                      | 2.46  | 2.46   | 2.54              | <b>92.54</b>            |
| 0.9                       | 2.04  | 2.04   | 2.96              | <b>92.96</b>            |
| 0.95                      | 1.46  | 1.46   | 3.54              | <b>93.54</b>            |
| 1 (Complete dependence)   | 0   | 0      | 5                 | <b>95</b>               |

<sup>1</sup>Assuming  $\widehat{\mathbf{Z}}_g \sim N_2(E[\mathbf{Z}_g], \mathbf{H})$ , and under the global null genetic hypothesis  $E[\mathbf{Z}_g] = (0,0)^T$ , and  $\rho_{l,k}$  varying from 0 (complete independence) to 1 (complete dependence).

**Table S9.3-2.** Effect of increasing correlation  $\rho_{1,1}$  between genetic effects  $\beta_{g,1}$  and  $\gamma_{g,1}$  on the expected classification frequencies at  $P^*=0.05$  under the *alternative* genetic scenario, for the example of SNP1 association with HbA1c/DR

| Correlation<br>$\rho_{1,1}$ | Expected classification frequencies (%) for SNP1 association with HbA1c/DR <sup>1</sup> |          |                   |                         |
|-----------------------------|---|----------|-------------------|-------------------------|
|                             | Indirect  | Direct   | Indirect & Direct | Not Direct & Not Direct |
| 0 (Complete independence)   | <b>95</b>   | 3.32E-12 | 5                 | 6.31E-11                |
| 0.05                        | <b>95</b>   | 4.30E-12 | 5                 | 6.21E-11                |
| 0.1                         | <b>95</b>   | 7.33E-12 | 5                 | 5.91E-11                |
| 0.15                        | <b>95</b>   | 1.25E-11 | 5                 | 5.39E-11                |
| 0.2                         | <b>95</b>   | 1.99E-11 | 5                 | 4.65E-11                |
| 0.25                        | <b>95</b>   | 2.90E-11 | 5                 | 3.74E-11                |
| 0.3                         | <b>95</b>   | 3.89E-11 | 5                 | 2.75E-11                |
| 0.35                        | <b>95</b>   | 4.84E-11 | 5                 | 1.80E-11                |
| 0.4                         | <b>95</b>   | 5.61E-11 | 5                 | 1.03E-11                |
| 0.45                        | <b>95</b>   | 6.15E-11 | 5                 | 4.93E-12                |
| 0.5                         | <b>95</b>   | 6.45E-11 | 5                 | 1.88E-12                |
| 0.55                        | <b>95</b>   | 6.59E-11 | 5                 | 5.33E-13                |
| 0.6                         | <b>95</b>   | 6.63E-11 | 5                 | 8.88E-14                |
| 0.65                        | <b>95</b>   | 6.64E-11 | 5                 | 0                       |
| 0.7                         | <b>95</b>   | 6.64E-11 | 5                 | -1.11E-14               |
| 0.75                        | <b>95</b>   | 6.64E-11 | 5                 | -1.11E-14               |
| 0.8                         | <b>95</b>   | 6.64E-11 | 5                 | -1.11E-14               |
| 0.85                        | <b>95</b>   | 6.64E-11 | 5                 | -1.11E-14               |
| 0.9                         | <b>95</b>   | 6.64E-11 | 5                 | -1.11E-14               |
| 0.95                        | <b>95</b>   | 6.64E-11 | 5                 | 0                       |
| 1 (Complete dependence)     | <b>95</b>   | 6.64E-11 | 5                 | 0                       |

<sup>1</sup>Assuming  $\widehat{\mathbf{Z}}_g \sim N_2(E[\mathbf{Z}_g], \mathbf{H})$ , with under the *alternative* genetic hypothesis  $E[\mathbf{Z}_g] = (0.7/\widehat{\sigma}_{\beta_{g,1}}, 0)^T$ , where  $\widehat{\sigma}_{\beta_{g,1}}$  correspond to the bootstrap standard error for  $\beta_{g,1}$  in JM-cmp, and  $\rho_{1,1}$  varies from 0 (complete independence) to 1 (complete dependence). The correct SNP association category as simulated in **Fig 3** is shown in bold.

**Table S9.3-3.** Effect of increasing correlation  $\rho_{2,2}$  between genetic effects  $\beta_{g,2}$  and  $\gamma_{g,2}$  on the expected classification frequencies at  $P^*=0.05$  under the *alternative* genetic scenario, for the example of SNP5 direct & indirect association with SBP/DN

| Correlation<br>$\rho_{2,2}$ | Expected classification frequencies <sup>1</sup> (%) for SNP5 association with SBP/DN |          |                   |                         |
|-----------------------------|---|----------|-------------------|-------------------------|
|                             | Indirect  | Direct   | Direct & Indirect | Not Direct & Not Direct |
| 0 (Complete independence)   | 28.77   | 1.79E-24 | <b>71.23</b>      | 0                       |
| 0.05                        | 28.77   | 1.44E-23 | <b>71.23</b>      | 0                       |
| 0.1                         | 28.77   | 9.15E-23 | <b>71.23</b>      | 0                       |
| 0.15                        | 28.77   | 4.68E-22 | <b>71.23</b>      | 0                       |
| 0.2                         | 28.77   | 1.97E-21 | <b>71.23</b>      | 0                       |
| 0.25                        | 28.77   | 6.90E-21 | <b>71.23</b>      | 0                       |
| 0.3                         | 28.77   | 2.03E-20 | <b>71.23</b>      | 0                       |
| 0.35                        | 28.77   | 5.06E-20 | <b>71.23</b>      | 0                       |
| 0.4                         | 28.77   | 1.07E-19 | <b>71.23</b>      | 0                       |
| 0.45                        | 28.77   | 1.92E-19 | <b>71.23</b>      | 0                       |
| 0.5                         | 28.77   | 2.93E-19 | <b>71.23</b>      | 0                       |
| 0.55                        | 28.77   | 3.86E-19 | <b>71.23</b>      | 0                       |
| 0.6                         | 28.77   | 4.47E-19 | <b>71.23</b>      | 0                       |
| 0.65                        | 28.77   | 4.74E-19 | <b>71.23</b>      | 0                       |
| 0.7                         | 28.77   | 4.80E-19 | <b>71.23</b>      | 0                       |
| 0.75                        | 28.77   | 4.81E-19 | <b>71.23</b>      | 0                       |
| 0.8                         | 28.77   | 4.81E-19 | <b>71.23</b>      | 0                       |
| 0.85                        | 28.77   | 4.81E-19 | <b>71.23</b>      | 0                       |
| 0.9                         | 28.77   | 4.81E-19 | <b>71.23</b>      | 0                       |
| 0.95                        | 28.77   | 4.81E-19 | <b>71.23</b>      | 0                       |
| 1 (Complete dependence)     | 28.77   | 4.81E-19 | <b>71.23</b>      | 0                       |

<sup>1</sup>Assuming  $\widehat{\mathbf{Z}}_g \sim N_2(E[\mathbf{Z}_g], \mathbf{H})$ , with under the *alternative* genetic hypothesis  $E[\mathbf{Z}_g] = \left(7/\widehat{\sigma}_{\beta_{g,2}}, 0.4/\widehat{\sigma}_{\gamma_{g,2}}\right)^T$ , where  $\widehat{\sigma}_{\beta_{g,2}}$  corresponds to the bootstrap standard error for  $\widehat{\beta}_{g,2}$  in JM-cmp, and  $\rho_{2,2}$  varies from 0 (complete independence) to 1 (complete dependence). The correct SNP association category as simulated in **Fig. 3** is shown in bold.

## **10. Empirical classification frequencies for each SNP association under the *global null* genetic scenario**

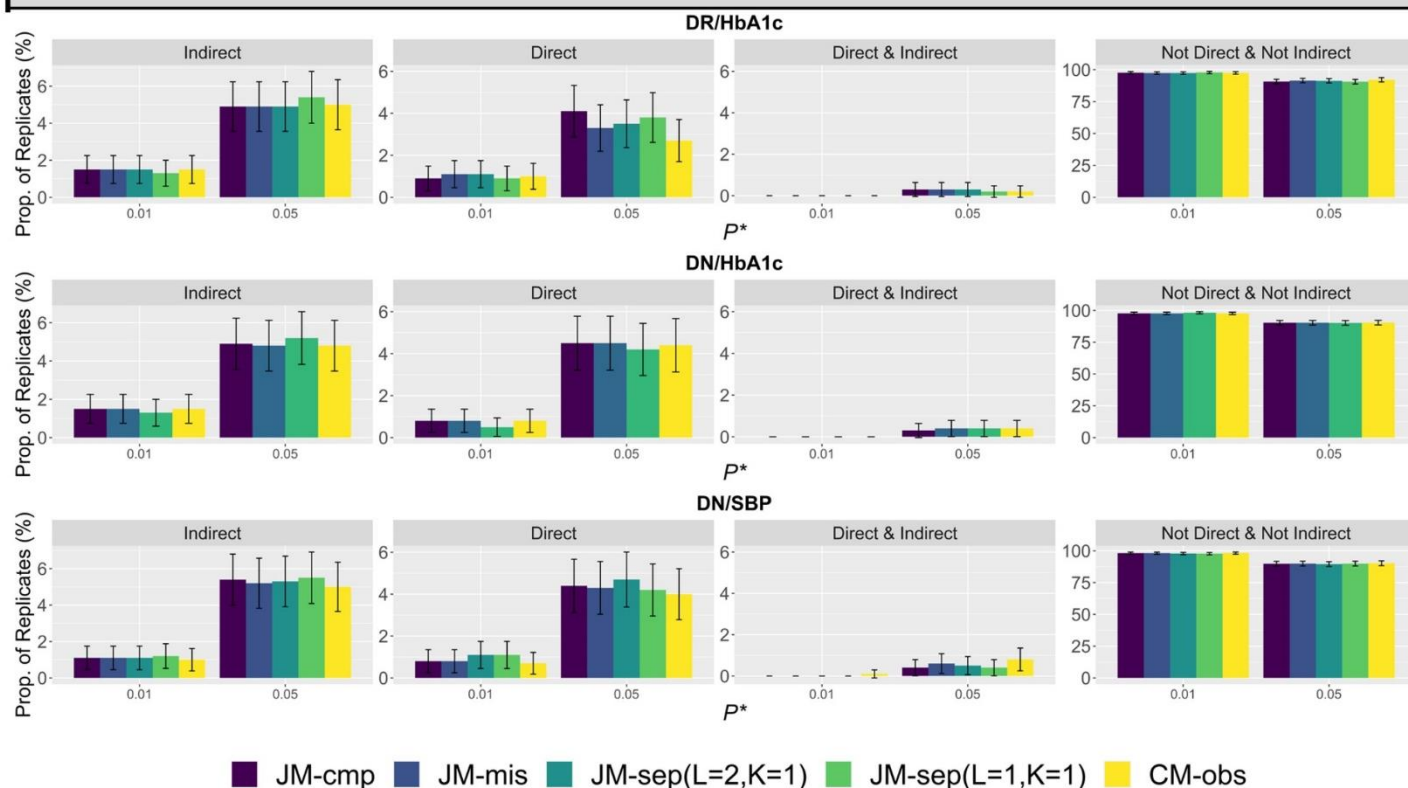
**Fig. S10-1.** Empirical classification frequencies of each SNP as direct and/or indirect association with each time-to-T1DC trait (DR, DN) through each observed longitudinal QT (HbA1c, SBP), assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the *global null* genetic scenario.

As explained in Materials and Methods, joint models are fitted separately for each SNP, and the SNP association is tested with each of the longitudinal traits (HbA1c, SBP) and each of the time-to-T1DC traits (time-to-DR, time-to-DN). JM-sep( $L=2, K=1$ ) refers to the two separate joint models of two longitudinal with one time-to-event trait (*ie* JM-sep( $l=1,2; k=1$ ) and JM-sep( $l=1,2; k=2$ )); while JM-sep( $L=1, K=1$ ) refers to the three separate joint models of one longitudinal with one time-to-event traits (*ie* JM-sep( $l=1; k=1$ ), JM-sep( $l=1; k=2$ ), JM-sep( $l=2; k=2$ )). For each classification frequency (noted as  $\widehat{CF}$ ), we calculate the 95% binomial proportion confidence interval as  $\widehat{CF} \pm 1.96 \times \sqrt{\frac{\widehat{CF}(1-\widehat{CF})}{R}}$ , where  $R = 1000$  replicates). Classification frequencies for the category of direct and indirect SNP association appears conservative because the hypothesis testing procedure requires the joint significance of the two SNP effects,  $\beta_{g,l}$  and  $\gamma_{g,k}$ .

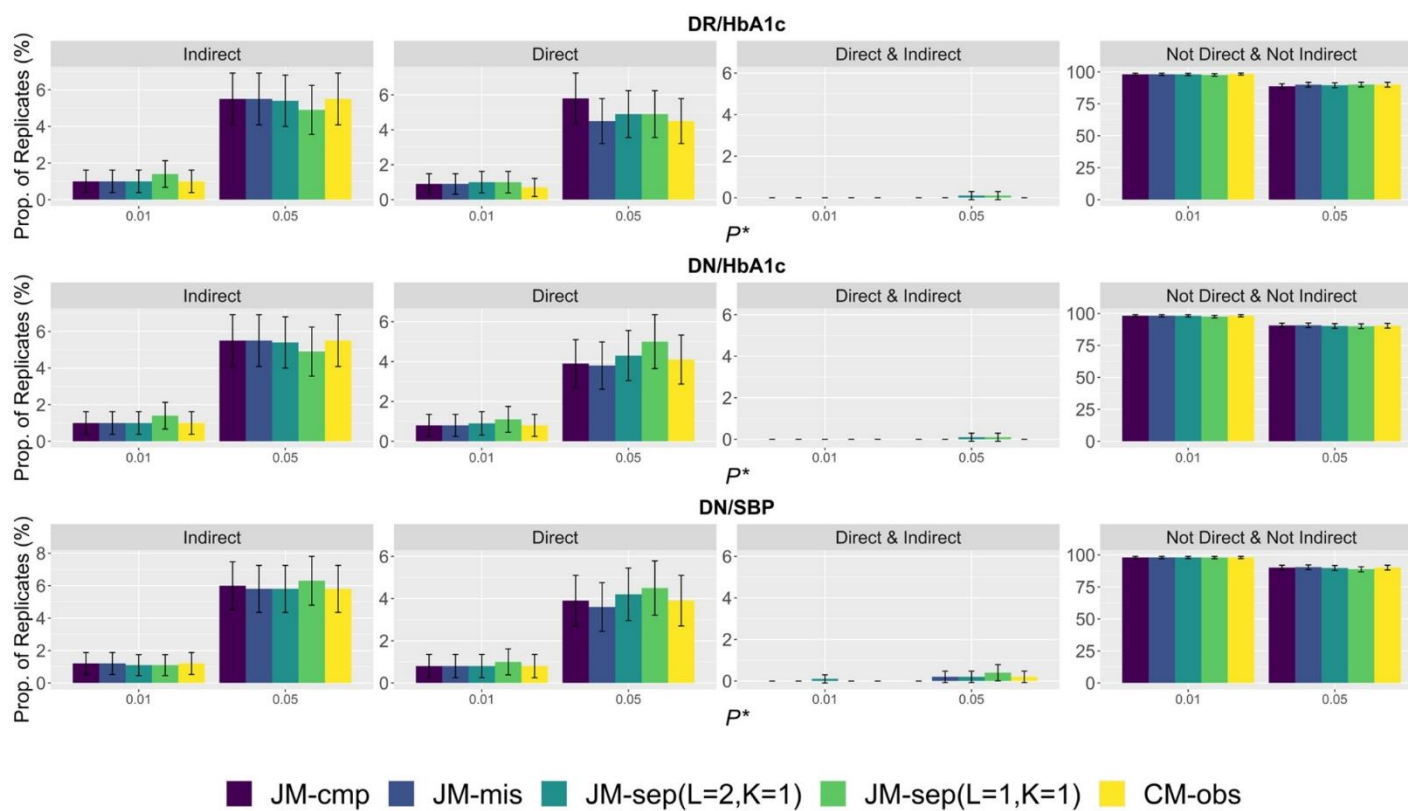
(See plots on pages 33-35)



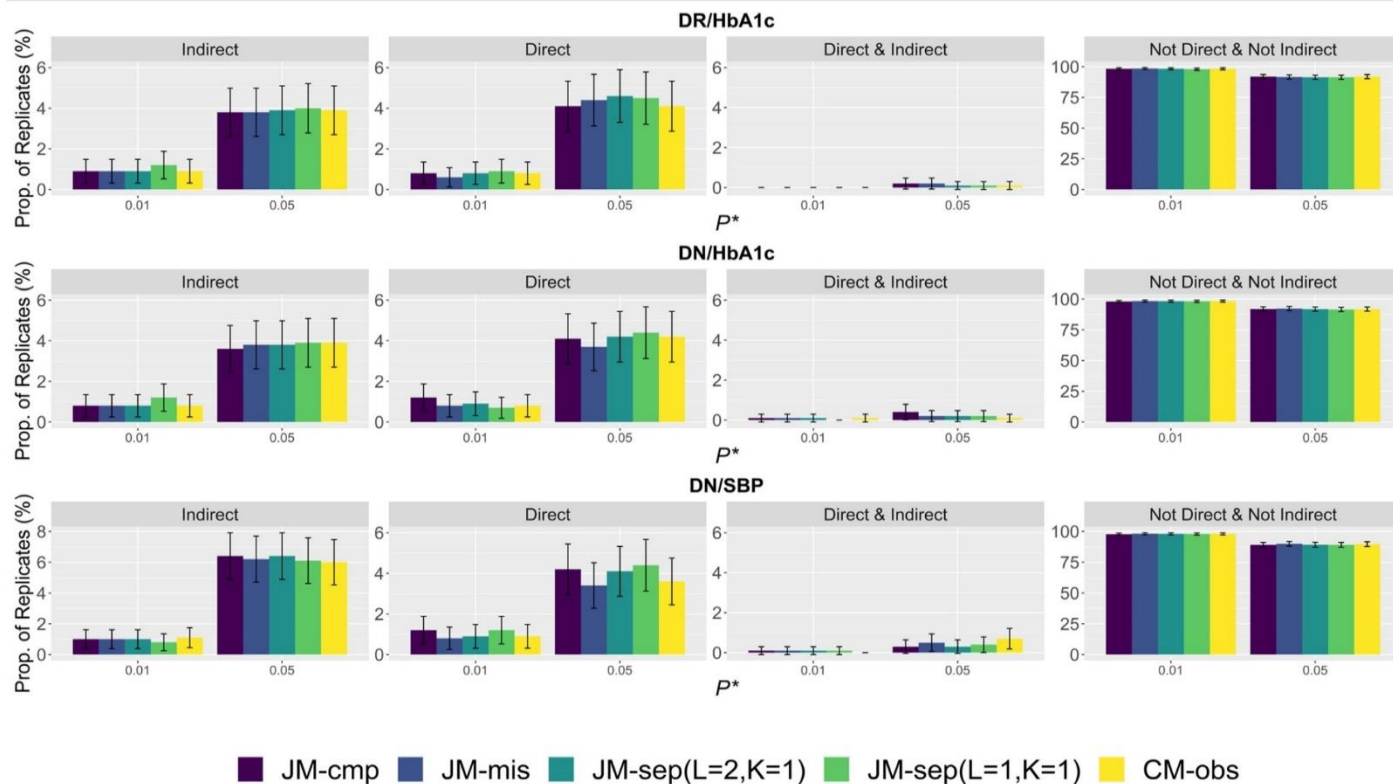
## SNP1



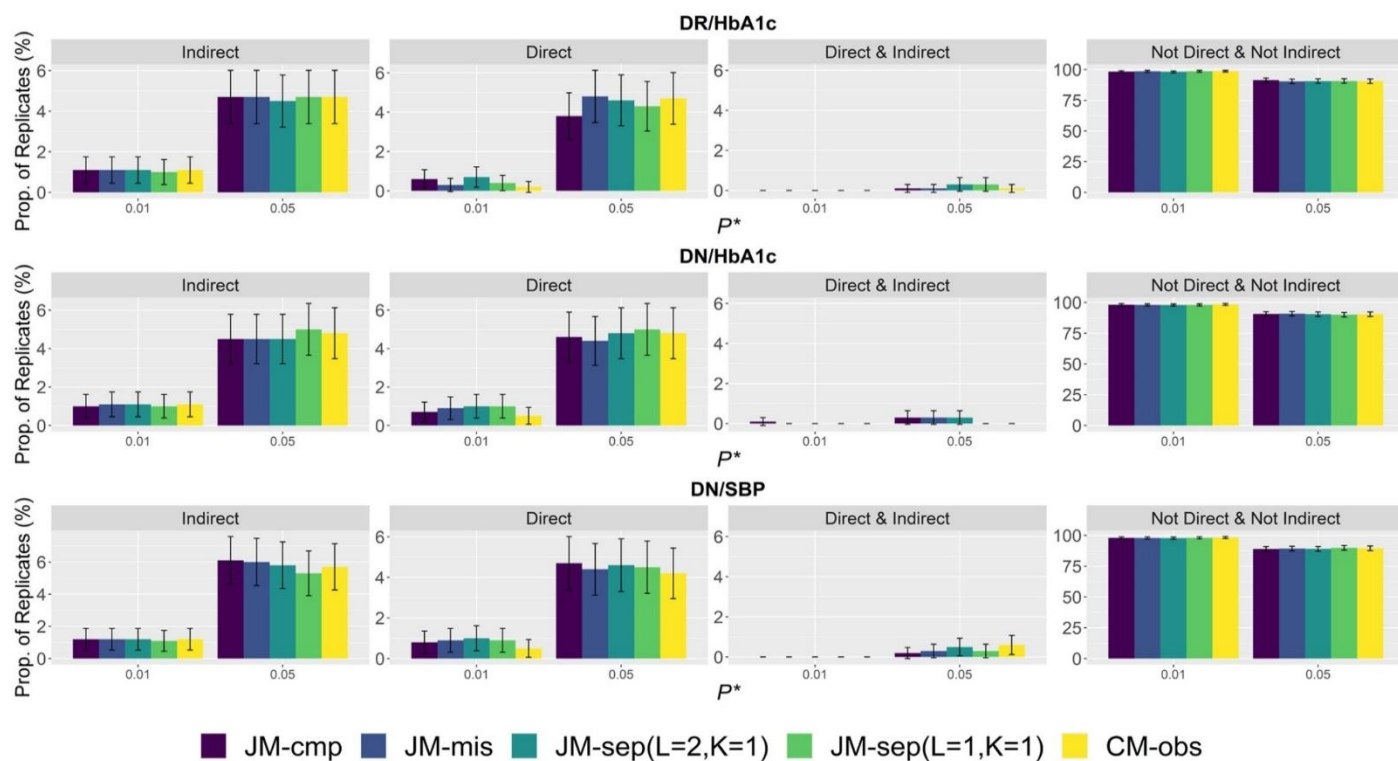
## SNP2



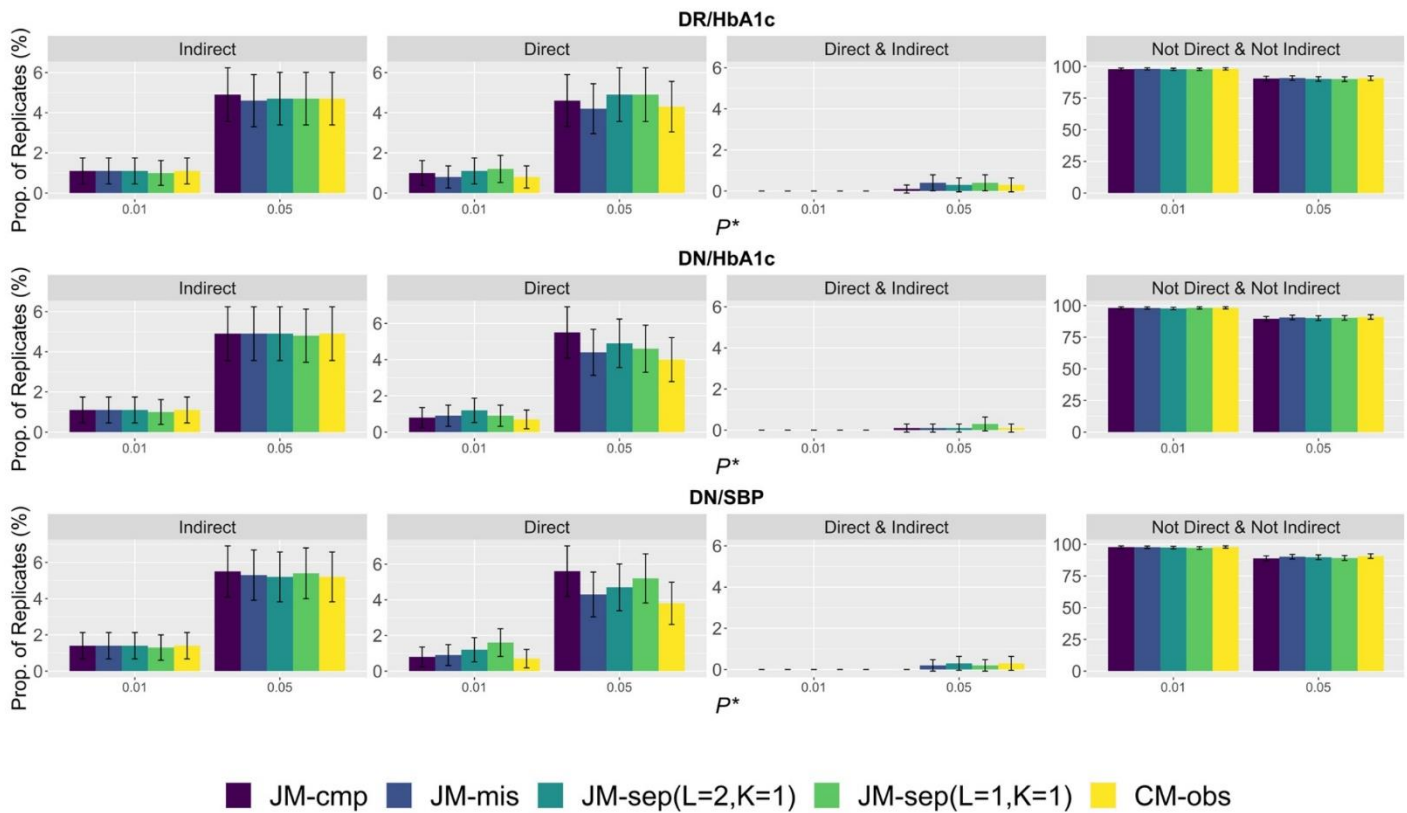
## SNP3



## SNP4



SNP5



# 11. Empirical classification frequencies for each SNP association under the *alternative* simulation scenario

**Table S11-1.** Empirical classification frequencies (shown as a percentage, %) for each SNP association assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects, with SNPs simulated under the *alternative* simulation scenario from **Fig. 3**. Classification rates under the correct scenarios of SNP association, as simulated in **Fig. 3** are shown in bold.

| Causal SNPs from Fig. 3 | Genetic Parameter Values                  | Trait pairs                            | Models                 | $P^*=0.05$ threshold |             |                   |                           | $P^*=0.01$ threshold |             |                   |                           | $P^*=0.001$ threshold |             |                   |                           |
|-------------------------|---|--|------------------------|----------------------|-------------|-------------------|---------------------------|----------------------|-------------|-------------------|---------------------------|-----------------------|-------------|-------------------|---------------------------|
|                         |   |  |                        | Indirect             | Direct      | Direct & Indirect | Not Direct & Not Indirect | Indirect             | Direct      | Direct & Indirect | Not Direct & Not Indirect | Indirect              | Direct      | Direct & Indirect | Not Direct & Not Indirect |
| SNP1<br>(MAF=30%)       | $\beta_{g,1} = 0.7$<br>$\gamma_{g,1} = 0$ | DR<br>( $k=1$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | <b>95.9</b>          | 0           | 4.1               | 0                         | <b>99.3</b>          | 0           | 0.7               | 0                         | <b>99.9</b>           | 0           | 0.1               | 0                         |
|                         |   |  | JM-mis                 | <b>95.8</b>          | 0           | 4.2               | 0                         | <b>99.5</b>          | 0           | 0.5               | 0                         | <b>100</b>            | 0           | 0                 | 0                         |
|                         |   |  | JM-sep( $l=1,2; k=1$ ) | <b>95.3</b>          | 0           | 4.7               | 0                         | <b>99.7</b>          | 0           | 0.3               | 0                         | <b>100</b>            | 0           | 0                 | 0                         |
|                         |   |  | JM-sep( $l=1; k=1$ )   | <b>95.4</b>          | 0           | 4.6               | 0                         | <b>99.4</b>          | 0           | 0.6               | 0                         | <b>100</b>            | 0           | 0                 | 0                         |
|                         |   |  | CM-obs                 | <b>93.6</b>          | 0           | 6.4               | 0                         | <b>99.3</b>          | 0           | 0.7               | 0                         | <b>99.9</b>           | 0           | 0.1               | 0                         |
|                         | $\beta_{g,1} = 0.7$<br>$\gamma_{g,2} = 0$ | DN<br>( $k=2$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | <b>94.6</b>          | 0           | 5.4               | 0                         | <b>98.7</b>          | 0           | 1.3               | 0                         | <b>99.9</b>           | 0           | 0.1               | 0                         |
|                         |   |  | JM-mis                 | <b>95.4</b>          | 0           | 4.6               | 0                         | <b>99.0</b>          | 0           | 1.0               | 0                         | <b>99.8</b>           | 0           | 0.2               | 0                         |
|                         |   |  | JM-sep( $l=1,2; k=2$ ) | <b>95.4</b>          | 0           | 4.6               | 0                         | <b>98.9</b>          | 0           | 1.1               | 0                         | <b>99.7</b>           | 0           | 0.3               | 0                         |
|                         |   |  | JM-sep( $l=1; k=2$ )   | <b>94.3</b>          | 0           | 5.7               | 0                         | <b>98.9</b>          | 0           | 1.1               | 0                         | <b>99.9</b>           | 0           | 0.1               | 0                         |
|                         |   |  | CM-obs                 | <b>94.3</b>          | 0           | 5.7               | 0                         | <b>98.5</b>          | 0           | 1.5               | 0                         | <b>99.7</b>           | 0           | 0.3               | 0                         |
|                         | $\beta_{g,2} = 0$<br>$\gamma_{g,2} = 0$   | DN<br>( $k=2$ )/<br>SBP<br>( $l=2$ )   | JM-cmp                 | 5                    | 5.3         | 0.1               | <b>89.6</b>               | 0.7                  | 1.3         | 0                 | <b>98.0</b>               | 0                     | 0.1         | 0                 | <b>99.9</b>               |
|                         |   |  | JM-mis                 | 5.1                  | 4.6         | 0                 | <b>90.3</b>               | 0.7                  | 1.0         | 0                 | <b>98.3</b>               | 0                     | 0.2         | 0                 | <b>99.8</b>               |
|                         |   |  | JM-sep( $l=1,2; k=2$ ) | 5.1                  | 4.6         | 0                 | <b>90.3</b>               | 0.7                  | 1.1         | 0                 | <b>98.2</b>               | 0                     | 0.3         | 0                 | <b>99.7</b>               |
|                         |   |  | JM-sep( $l=2; k=2$ )   | 4.3                  | 10.3        | 0.9               | <b>84.5</b>               | 0.9                  | 3.2         | 0                 | <b>95.9</b>               | 0.1                   | 0.8         | 0                 | <b>99.1</b>               |
|                         |   |  | CM-obs                 | 4.5                  | 5.1         | 0.6               | <b>89.8</b>               | 0.7                  | 1.5         | 0                 | <b>97.8</b>               | 0                     | 0.3         | 0                 | <b>99.7</b>               |
| SNP2<br>(MAF=10%)       | $\beta_{g,1} = 0$<br>$\gamma_{g,1} = 0.8$ | DR<br>( $k=1$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | 0                    | <b>93.4</b> | 6.6               | 0                         | 0                    | <b>98.7</b> | 1.3               | 0                         | 0                     | <b>99.8</b> | 0                 | 0.2                       |
|                         |   |  | JM-mis                 | 0                    | <b>93.4</b> | 6.6               | 0                         | 0                    | <b>98.4</b> | 1.3               | 0.3                       | 0                     | <b>98.8</b> | 0                 | 1.2                       |
|                         |   |  | JM-sep( $l=1,2; k=1$ ) | 0                    | <b>93.4</b> | 6.6               | 0                         | 0                    | <b>98.3</b> | 1.3               | 0.4                       | 0                     | <b>98.6</b> | 0                 | 1.4                       |
|                         |   |  | JM-sep( $l=1; k=1$ )   | 0                    | <b>93.9</b> | 6.1               | 0                         | 0                    | <b>98</b>   | 1.6               | 0.4                       | 0                     | <b>98.7</b> | 0                 | 1.3                       |
|                         |   |  | CM-obs                 | 0                    | <b>93.4</b> | 6.6               | 0                         | 0                    | <b>98.4</b> | 1.3               | 0.3                       | 0                     | <b>98.6</b> | 0                 | 1.4                       |
|                         | $\beta_{g,1} = 0$<br>$\gamma_{g,2} = 0$   | DN<br>( $k=2$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | 6.4                  | 3.7         | 0.2               | <b>89.7</b>               | 1.3                  | 1.4         | 0                 | <b>97.3</b>               | 0                     | 0.5         | 0                 | <b>99.5</b>               |
|                         |   |  | JM-mis                 | 6.3                  | 4.3         | 0.3               | <b>89.1</b>               | 1.3                  | 1.0         | 0                 | <b>97.7</b>               | 0                     | 0.3         | 0                 | <b>99.7</b>               |
|                         |   |  | JM-sep( $l=1,2; k=2$ ) | 6.2                  | 4.8         | 0.4               | <b>88.6</b>               | 1.3                  | 1.4         | 0                 | <b>97.3</b>               | 0                     | 0.4         | 0                 | <b>99.6</b>               |
|                         |   |  | JM-sep( $l=1; k=2$ )   | 6.1                  | 4.6         | 0                 | <b>89.3</b>               | 1.6                  | 1           | 0                 | <b>97.4</b>               | 0                     | 0.2         | 0                 | <b>99.8</b>               |
|                         |   |  | CM-obs                 | 6.6                  | 4.5         | 0                 | <b>88.9</b>               | 1.3                  | 1.4         | 0                 | <b>97.3</b>               | 0                     | 0           | 0                 | <b>100.0</b>              |
|                         | $\beta_{g,2} = 0$<br>$\gamma_{g,2} = 0$   | DN<br>( $k=2$ )/<br>SBP<br>( $l=2$ )   | JM-cmp                 | 5.4                  | 3.9         | 0                 | <b>90.7</b>               | 1.2                  | 1.4         | 0                 | <b>97.4</b>               | 0.2                   | 0.5         | 0                 | <b>99.3</b>               |
|                         |   |  | JM-mis                 | 5.4                  | 4.6         | 0                 | <b>90.0</b>               | 1.2                  | 1.0         | 0                 | <b>97.8</b>               | 0.2                   | 0.3         | 0                 | <b>99.5</b>               |
|                         |   |  | JM-sep( $l=1,2; k=2$ ) | 5.3                  | 5.1         | 0.1               | <b>89.5</b>               | 1.2                  | 1.4         | 0                 | <b>97.4</b>               | 0.2                   | 0.4         | 0                 | <b>99.4</b>               |
|                         |   |  | JM-sep( $l=2; k=2$ )   | 5.0                  | 4.5         | 0.2               | <b>90.3</b>               | 1.4                  | 1.3         | 0                 | <b>97.3</b>               | 0.3                   | 0.4         | 0                 | <b>99.3</b>               |
|                         |   |  | CM-obs                 | 5.0                  | 4.1         | 0.4               | <b>90.5</b>               | 1.2                  | 1.4         | 0                 | <b>97.4</b>               | 0.2                   | 0           | 0                 | <b>99.8</b>               |
| SNP3<br>(MAF=40%)       | $\beta_{g,1} = 0$                         | DR<br>( $k=1$ )                        | JM-cmp                 | 4.3                  | 4.5         | 0.2               | <b>91.0</b>               | 1.0                  | 1           | 0                 | <b>98.0</b>               | 0                     | 0           | 0                 | <b>100.0</b>              |
|                         |   |  | JM-mis                 | 0.7                  | 86.1        | 3.8               | <b>9.4</b>                | 0.3                  | 73.3        | 0.7               | <b>25.7</b>               | 0                     | 44.7        | 0                 | <b>55.3</b>               |

|                   |  |  |                        |      |             |             |             |      |             |             |             |      |             |             |             |
|-------------------|--|--|------------------------|------|-------------|-------------|-------------|------|-------------|-------------|-------------|------|-------------|-------------|-------------|
|                   | $\beta_{g,U} = 0.8$<br>$\gamma_{g,1} = 0$                      | /HbA1c<br>( $l=1$ )                    | JM-sep( $l=1,2; k=1$ ) | 0.6  | 85.8        | 3.9         | <b>9.7</b>  | 0.3  | 73.7        | 0.7         | <b>25.3</b> | 0    | 45.6        | 0           | <b>54.4</b> |
|                   |  |  | JM-sep( $l=1; k=1$ )   | 0.5  | 85.4        | 4.3         | <b>9.8</b>  | 0.5  | 72.8        | 0.7         | <b>26</b>   | 0    | 44.4        | 0           | <b>55.6</b> |
|                   |  |  | CM-obs                 | 0.7  | 85.5        | 3.8         | <b>10.0</b> | 0.3  | 72.3        | 0.7         | <b>26.7</b> | 0    | 44.1        | 0           | <b>55.9</b> |
|                   | $\beta_{g,1} = 0$<br>$\beta_{g,U} = 0.8$<br>$\gamma_{g,2} = 0$ | DN<br>( $k=2$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | 4.5  | 3.8         | 0           | <b>91.7</b> | 1.0  | 1.5         | 0           | <b>97.5</b> | 0    | 0.1         | 0           | <b>99.9</b> |
|                   |  |  | JM-mis                 | 1.7  | 55.6        | 2.8         | <b>39.9</b> | 0.7  | 31.5        | 0.3         | <b>67.5</b> | 0    | 10.3        | 0           | <b>89.7</b> |
|                   |  |  | JM-sep( $l=1,2; k=2$ ) | 1.6  | 54.8        | 2.9         | <b>40.7</b> | 0.8  | 30.8        | 0.2         | <b>68.2</b> | 0    | 11.6        | 0           | <b>88.4</b> |
|                   |  |  | JM-sep( $l=1; k=2$ )   | 3.2  | 31.4        | 1.6         | <b>63.8</b> | 1.1  | 11.5        | 0.1         | <b>87.3</b> | 0    | 2.6         | 0           | <b>97.4</b> |
|                   |  |  | CM-obs                 | 2.3  | 46.0        | 2.2         | <b>49.5</b> | 0.9  | 21.6        | 0.1         | <b>77.4</b> | 0    | 6.1         | 0           | <b>93.9</b> |
|                   | $\beta_{g,2} = 0$<br>$\beta_{g,U} = 0.8$<br>$\gamma_{g,2} = 0$ | DN<br>( $k=2$ )/<br>SBP<br>( $l=2$ )   | JM-cmp                 | 4.4  | 3.6         | 0.2         | <b>91.8</b> | 0.7  | 1.5         | 0           | <b>97.8</b> | 0    | 0.1         | 0           | <b>99.9</b> |
|                   |  |  | JM-mis                 | 1.8  | 55.6        | 2.8         | <b>39.8</b> | 0.6  | 31.7        | 0.1         | <b>67.6</b> | 0    | 10.3        | 0           | <b>89.7</b> |
|                   |  |  | JM-sep( $l=1,2; k=2$ ) | 1.8  | 54.9        | 2.8         | <b>40.5</b> | 0.6  | 30.9        | 0.1         | <b>68.4</b> | 0    | 11.6        | 0           | <b>88.4</b> |
|                   |  |  | JM-sep( $l=2; k=2$ )   | 1.8  | 53.8        | 2.6         | <b>41.8</b> | 0.7  | 30.5        | 0.1         | <b>68.7</b> | 0    | 10.4        | 0           | <b>89.6</b> |
|                   |  |  | CM-obs                 | 1.4  | 45.0        | 3.2         | <b>50.4</b> | 0.6  | 21.6        | 0.1         | <b>77.7</b> | 0    | 6.1         | 0           | <b>93.9</b> |
| SNP4<br>(MAF=30%) | $\beta_{g,1} = 0$<br>$\gamma_{g,1} = 0$                        | DR<br>( $k=1$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | 4.9  | 5.5         | 0.5         | <b>89.1</b> | 1.4  | 1.5         | 0           | <b>97.1</b> | 0.3  | 0           | 0           | <b>99.7</b> |
|                   |  |  | JM-mis                 | 5.0  | 5.0         | 0.4         | <b>89.6</b> | 1.4  | 1.0         | 0           | <b>97.6</b> | 0.3  | 0.1         | 0           | <b>99.6</b> |
|                   |  |  | JM-sep( $l=1,2; k=1$ ) | 5.1  | 4.8         | 0.3         | <b>89.8</b> | 1.4  | 0.9         | 0           | <b>97.7</b> | 0.3  | 0.2         | 0           | <b>99.5</b> |
|                   |  |  | JM-sep( $l=1; k=1$ )   | 5.7  | 4.7         | 0.4         | <b>89.2</b> | 0.9  | 1.0         | 0           | <b>98.1</b> | 0.2  | 0.2         | 0           | <b>99.6</b> |
|                   |  |  | CM-obs                 | 5.0  | 4.2         | 0.4         | <b>90.4</b> | 1.4  | 1.0         | 0           | <b>97.6</b> | 0.3  | 0.1         | 0           | <b>99.6</b> |
|                   | $\beta_{g,1} = 0$<br>$\gamma_{g,2} = 0.7$                      | DN<br>( $k=2$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | 0    | <b>94.6</b> | 5.4         | 0           | 0    | <b>98.5</b> | 1.4         | 0.1         | 0    | <b>98.0</b> | 0.3         | 1.7         |
|                   |  |  | JM-mis                 | 0    | <b>94.6</b> | 5.4         | 0           | 0    | <b>98.1</b> | 1.4         | 0.5         | 0    | <b>94.5</b> | 0.3         | 5.2         |
|                   |  |  | JM-sep( $l=1,2; k=2$ ) | 0    | <b>94.5</b> | 5.4         | 0.1         | 0    | <b>97.1</b> | 1.4         | 1.5         | 0    | <b>93.2</b> | 0.3         | 6.5         |
|                   |  |  | JM-sep( $l=1; k=2$ )   | 0.3  | <b>88.1</b> | 5.8         | 5.8         | 0.1  | <b>80.4</b> | 0.8         | 18.7        | 0    | <b>56.9</b> | 0.2         | 42.9        |
|                   |  |  | CM-obs                 | 0    | <b>93.5</b> | 5.4         | 1.1         | 0.1  | <b>94.7</b> | 1.3         | 3.9         | 0    | <b>82.8</b> | 0.3         | 16.9        |
|                   | $\beta_{g,2} = 0$<br>$\gamma_{g,2} = 0.7$                      | DN<br>( $k=2$ )/<br>SBP<br>( $l=2$ )   | JM-cmp                 | 0    | <b>95.2</b> | 4.8         | 0           | 0    | <b>98.9</b> | 1           | 0.1         | 0    | <b>98.3</b> | 0           | 1.7         |
|                   |  |  | JM-mis                 | 0    | <b>95.2</b> | 4.8         | 0           | 0    | <b>98.5</b> | 1           | 0.5         | 0    | <b>94.8</b> | 0           | 5.2         |
|                   |  |  | JM-sep( $l=1,2; k=2$ ) | 0    | <b>95.1</b> | 4.8         | 0.1         | 0    | <b>97.5</b> | 1           | 1.5         | 0    | <b>93.5</b> | 0           | 6.5         |
|                   |  |  | JM-sep( $l=2; k=2$ )   | 0    | <b>95.1</b> | 4.8         | 0.1         | 0    | <b>97.2</b> | 1           | 1.8         | 0    | <b>92.6</b> | 0           | 7.4         |
|                   |  |  | CM-obs                 | 0.1  | <b>94.2</b> | 4.7         | 1.0         | 0.2  | <b>95.2</b> | 0.8         | 3.8         | 0    | <b>83.1</b> | 0           | 16.9        |
| SNP5<br>(MAF=20%) | $\beta_{g,1} = 0$<br>$\gamma_{g,1} = 0$                        | DR<br>( $k=1$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | 2.4  | 5.1         | 0.4         | <b>92.1</b> | 1.1  | 1.1         | 0           | <b>97.8</b> | 0    | 0.1         | 0           | <b>99.9</b> |
|                   |  |  | JM-mis                 | 2.4  | 4.2         | 0.4         | <b>93.0</b> | 1.0  | 0.5         | 0.1         | <b>98.4</b> | 0    | 0           | 0           | <b>100</b>  |
|                   |  |  | JM-sep( $l=1,2; k=1$ ) | 2.4  | 4.4         | 0.4         | <b>92.8</b> | 1.0  | 0.7         | 0.1         | <b>98.2</b> | 0    | 0           | 0           | <b>100</b>  |
|                   |  |  | JM-sep( $l=1; k=1$ )   | 2.6  | 4.4         | 0.2         | <b>92.8</b> | 0.8  | 0.8         | 0           | <b>98.4</b> | 0    | 0           | 0           | <b>100</b>  |
|                   |  |  | CM-obs                 | 2.4  | 4.4         | 0.4         | <b>92.8</b> | 1.0  | 0.5         | 0.1         | <b>98.4</b> | 0    | 0           | 0           | <b>100</b>  |
|                   | $\beta_{g,1} = 0$<br>$\gamma_{g,2} = 0.4$                      | DN<br>( $k=2$ )/<br>HbA1c<br>( $l=1$ ) | JM-cmp                 | 1.1  | <b>64.7</b> | 1.7         | 32.5        | 0.9  | <b>43.0</b> | 0.2         | 55.9        | 0    | <b>20.5</b> | 0           | 79.5        |
|                   |  |  | JM-mis                 | 0.8  | <b>62.5</b> | 2.0         | 34.7        | 0.8  | <b>40.1</b> | 0.3         | 58.8        | 0    | <b>17.5</b> | 0           | 82.5        |
|                   |  |  | JM-sep( $l=1,2; k=2$ ) | 1.2  | <b>61.6</b> | 1.6         | 35.6        | 0.8  | <b>39.9</b> | 0.3         | 59.0        | 0    | <b>18.3</b> | 0           | 81.7        |
|                   |  |  | JM-sep( $l=1; k=2$ )   | 0    | <b>97.2</b> | 2.8         | 0           | 0    | <b>99.2</b> | 0.8         | 0           | 0    | <b>100</b>  | 0           | 0           |
|                   |  |  | CM-obs                 | 0    | <b>97.2</b> | 2.8         | 0           | 0    | <b>98.8</b> | 1.1         | 0.1         | 0    | <b>99.7</b> | 0           | 0.3         |
|                   | $\beta_{g,2} = 7$<br>$\gamma_{g,2} = 0.4$                      | DN<br>( $k=2$ )/<br>SBP<br>( $l=2$ )   | JM-cmp                 | 33.6 | 0           | <b>66.4</b> | 0           | 56.8 | 0           | <b>43.2</b> | 0           | 79.5 | 0           | <b>20.5</b> | 0           |
|                   |  |  | JM-mis                 | 35.5 | 0           | <b>64.5</b> | 0           | 59.6 | 0           | <b>40.4</b> | 0           | 82.5 | 0           | <b>17.5</b> | 0           |
|                   |  |  | JM-sep( $l=1,2; k=2$ ) | 36.8 | 0           | <b>63.2</b> | 0           | 59.8 | 0           | <b>40.2</b> | 0           | 81.7 | 0           | <b>18.3</b> | 0           |
|                   |  |  | JM-sep( $l=2; k=2$ )   | 35.1 | 0           | <b>64.9</b> | 0           | 56.6 | 0           | <b>43.4</b> | 0           | 80.9 | 0           | <b>19.1</b> | 0           |
|                   |  |  | CM-obs                 | 0    | 0           | <b>100</b>  | 0           | 0.1  | 0           | <b>99.9</b> | 0           | 0.3  | 0           | <b>99.7</b> | 0           |

**Fig. S11-1 Empirical classification frequencies of each SNP as direct and/or indirect association with each time-to-T1DC trait (DR, DN) through each observed longitudinal trait (HbA1c, SBP), assessed using  $R=1000$  replicates of  $N=667$  DCCT subjects simulated under the *alternative* genetic scenario from [Fig. 3](#).**

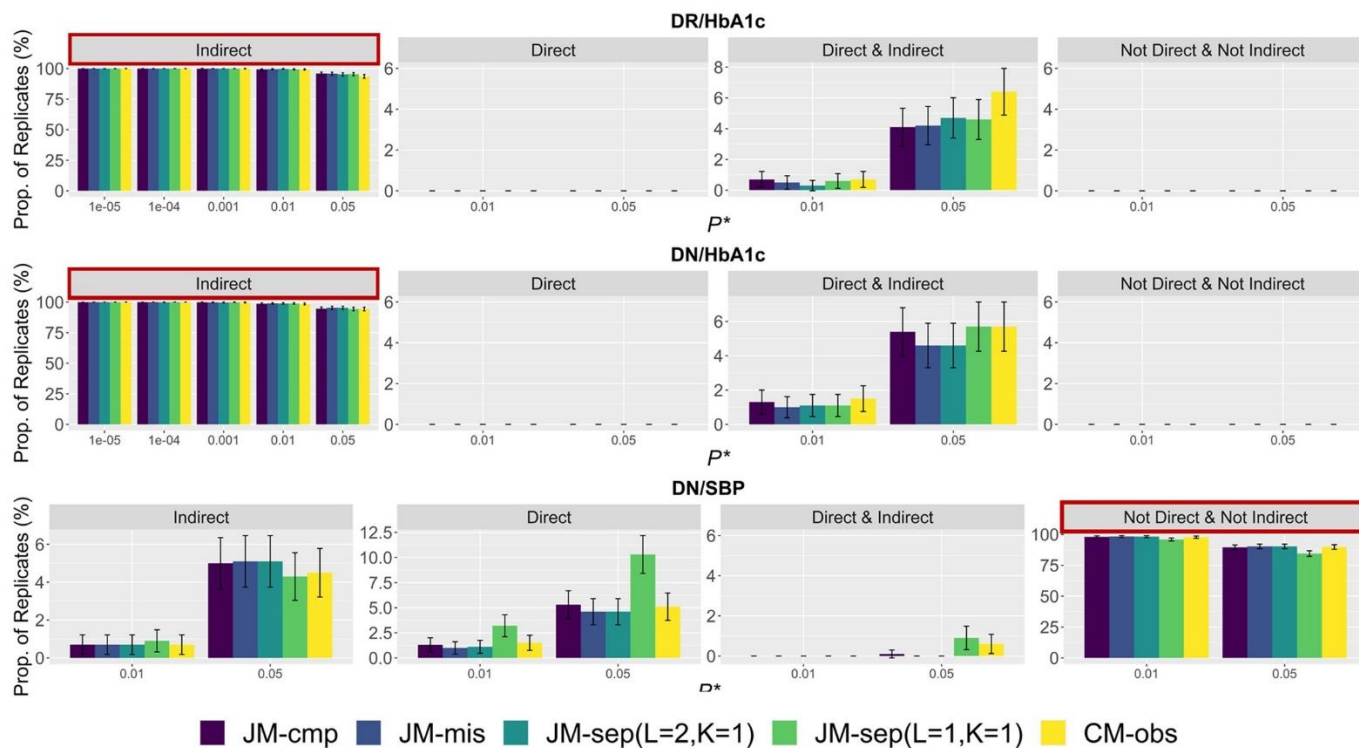
Panels with underlying causal associations are indicated by red boxes for each SNP; other associations represent misclassified associations. As explained in Materials and Methods, joint models are fitted separately for each SNP, and the SNP association is tested with each of the longitudinal traits (HbA1c, SBP) and each of the time-to-T1DC traits (time-to-DR, time-to-DN). For each classification frequency (noted as  $\widehat{CR}$ ), we calculate the 95% binomial proportion confidence interval as  $\widehat{CR} \pm 1.96 \times \sqrt{\frac{\widehat{CR}(1-\widehat{CR})}{R}}$ , where  $R = 1000$  replicates).

JM-sep( $L=2; K=1$ ) denotes the two separate joint models fitted for the two longitudinal QTs (HbA1c, SBP) with one time-to-event trait (*ie* JM-sep( $l=1,2; k=1$ ) and JM-sep( $l=1,2; k=2$ )); while JM-sep( $L=1; K=1$ ) denotes the three separate joint models fitted respectively for each trait pair HbA1c/DR (JM-sep( $l=1; k=1$ )), HbA1c/DN (JM-sep( $l=1; k=2$ )), SBP/DN (JM-sep( $l=1; k=1$ )) trait pairs.

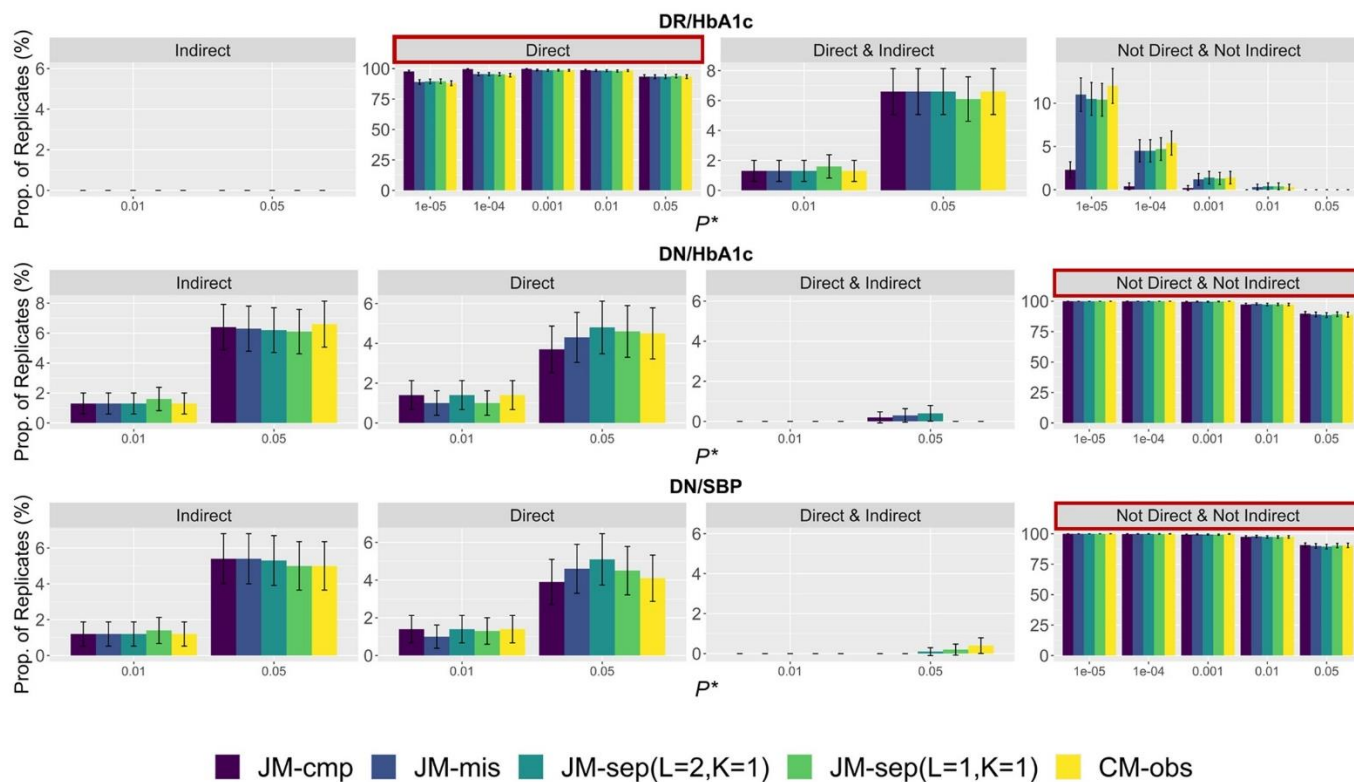
(See plots on pages 39-41)



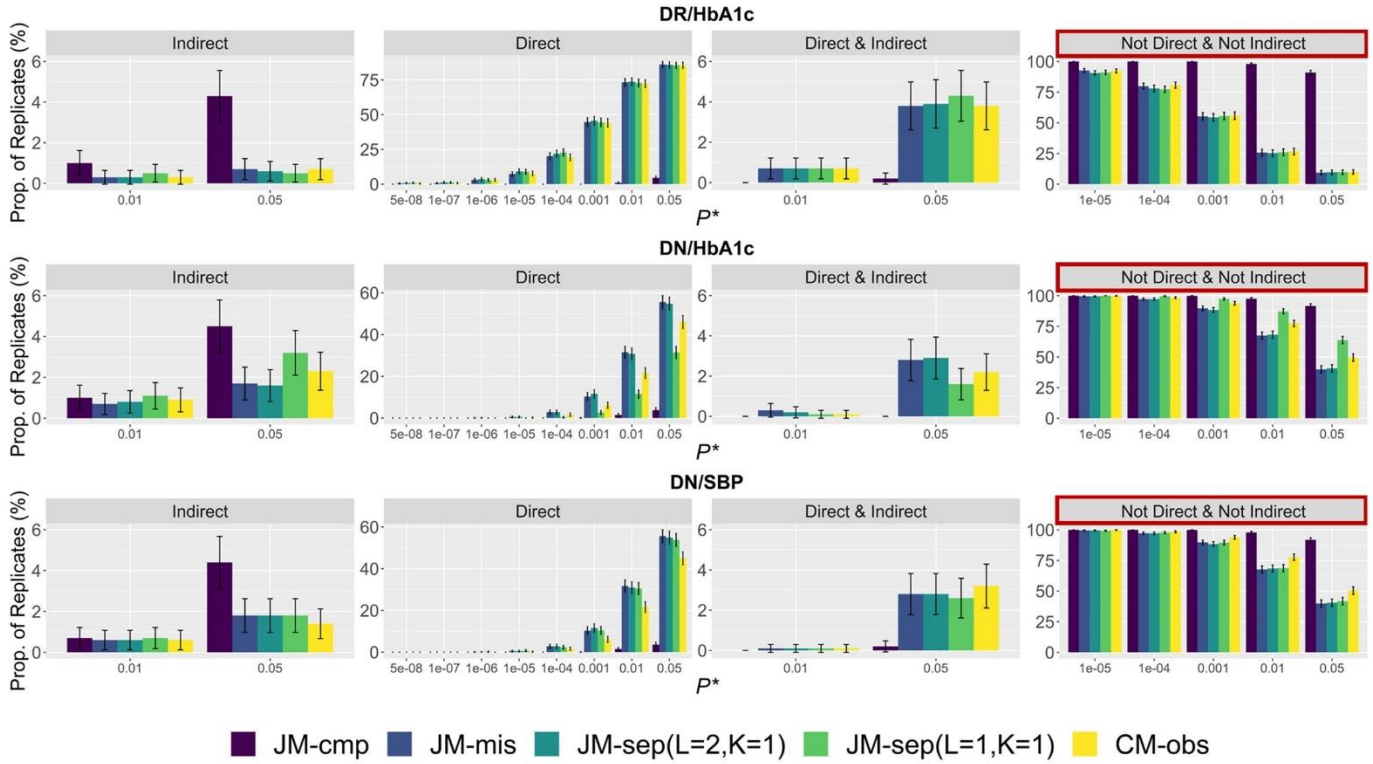
## SNP1



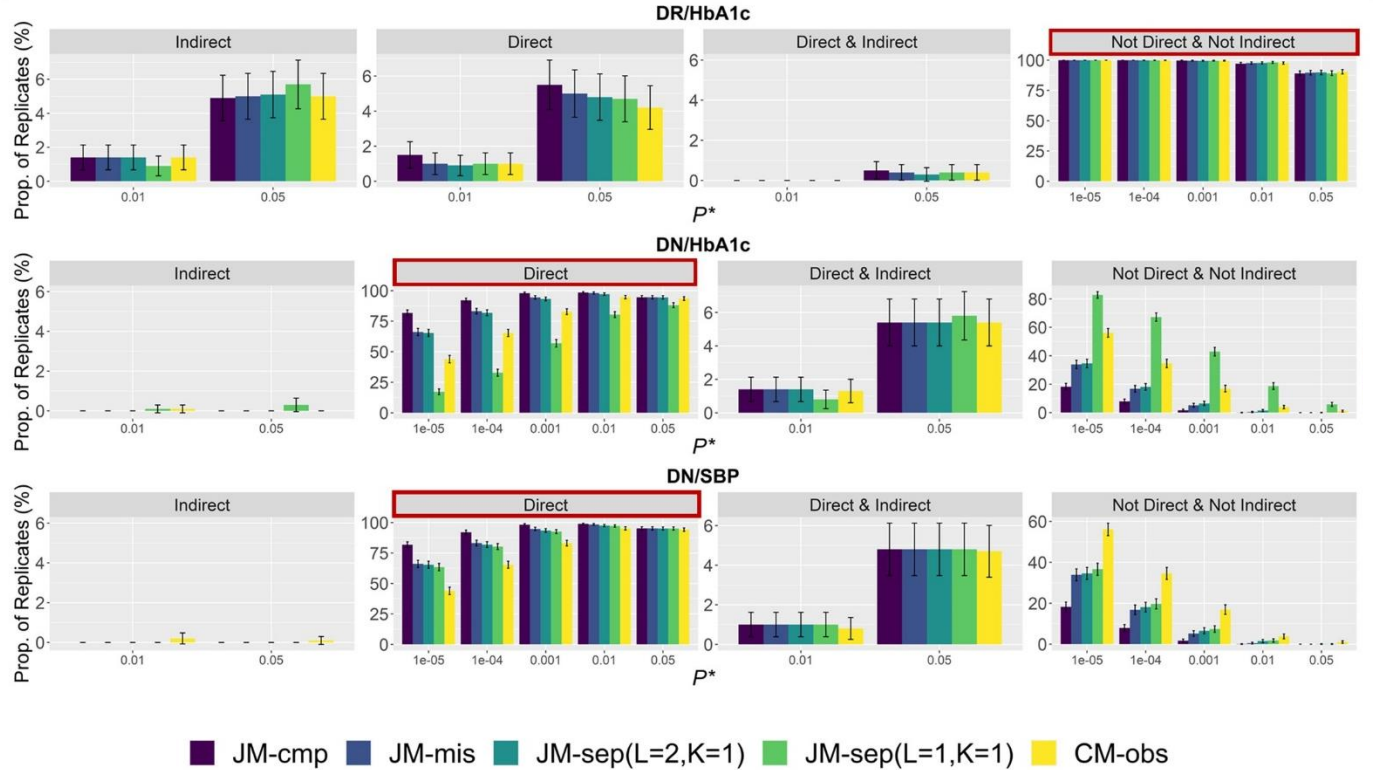
## SNP2



## SNP3

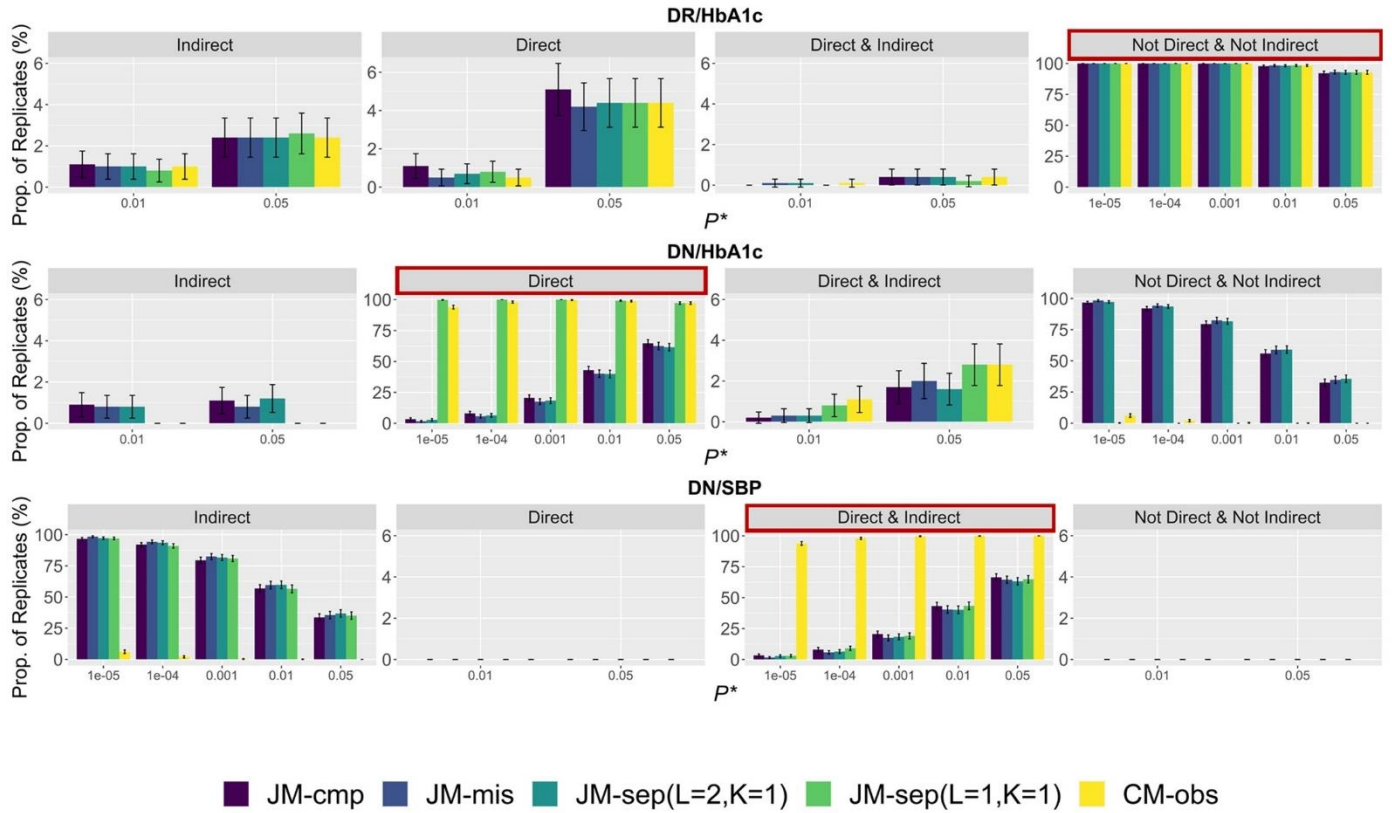


## SNP4





# SNP5



## **Cited literature**

Brent, RP. 1973. Algorithms for minimization without derivatives, Chapter 4. Prentice- Hall, Englewood Cliffs, NJ. ISBN 0-13-022335-2.

Crowther MJ, Lambert PC. 2013. Simulating biologically plausible complex survival data. Stat Med. 32(23):4118–4134. doi:10.1002/sim.5823.

Genz A, Bretz F, Miwa T, Mi X, Leisch F, Scheipl F, Hothorn T. 2021. {mvtnorm}: Multivariate Normal and t Distributions. <https://cran.r-project.org/package=mvtnorm>.