An efficient Bayesian meta-analysis approach for studying cross-phenotype genetic associations

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1 Abstract

Simultaneous analysis of genetic associations with multiple phenotypes may reveal shared genetic susceptibility across traits (pleiotropy). For a locus exhibiting overall pleiotropy, it is important to identify which specific traits underlie this association. We propose a Bayesian meta-analysis approach (termed CPBayes) that uses summary-level data across multiple phenotypes to simultaneously measure the evidence of aggregate-level pleiotropic association and estimate an optimal subset of traits associated with the risk locus. This method uses a unified Bayesian statistical framework based on a spike and slab prior. CPBayes performs a fully Bayesian analysis by employing the Markov chain Monte Carlo (MCMC) technique Gibbs sampling. It takes into account heterogeneity in the size and direction of the genetic effects across traits. It can be applied to both cohort data and separate studies of multiple traits having overlapping or non-overlapping subjects. Simulations show that CPBayes produces a substantially better accuracy in the selection of associated traits underlying a pleiotropic signal than the subset-based meta-analysis ASSET. We used CPBayes to undertake a genome-wide pleiotropic association study of 22 traits in the large Kaiser GERA cohort and detected nine independent pleiotropic loci associated with at least two phenotypes. This includes a locus at chromosomal region 1q24.2 which exhibits an association simultaneously with the risk of five different diseases: Dermatophytosis, Hemorrhoids, Iron Deficiency, Osteoporosis, and Peripheral Vascular Disease. The GERA cohort analysis suggests that CPBayes is more powerful than ASSET with respect to detecting independent pleiotropic variants. We provide an R-package 'CPBayes' implementing the proposed method.

Keywords: Pleiotropy, selection, non-null traits, summary statistics, Bayes factor, MCMC.

2 Introduction

Genome-wide association studies (GWASs) have detected loci associated with multiple different traits and diseases (i.e., pleiotropy). For example, pleiotropy has been observed for different types of cancers [Sakoda et al., 2013], immune-mediated diseases [Parkes et al., 2013], and psychiatric disorders [Parkes et al., 2013]. As a specific example, Ellinghaus et al. [2016] demonstrated shared genetic susceptibility to five chronic inflammatory diseases: ankylosing spondylitis, Crohn's disease, psoriasis, primary sclerosing cholangitis, and ulcerative colitis. Pickrell et al. [2016] systematically compared genetic architecture of 42 phenotypes and reported substantial pleiotropy. Analyzing pleiotropy provides a better understanding of shared pathways and biological mechanisms common to multiple different diseases/phenotypes. From the perspective of clinical genetics, the discovery of a locus simultaneously associated with multiple diseases can support the use of a common therapeutic intervention.

When evaluating a group of phenotypes, one may only expect a subset of them to exhibit pleiotropy. For example, the Global Lipids Genetics Consortium [2013] discovered novel pleiotropic loci associated with different subsets of blood lipid traits. In particular, variants in the genes *RSPO3*, *FTO*, *VEGFA*, *PEPD* were associated with HDL and triglycerides, but not with total cholesterol or LDL. Hence, in addition to evaluating the evidence of overall pleiotropic association, it is crucial to determine which traits are associated with the risk locus to better interpret the pleiotropic signal. Another important consideration is the availability of individual level data from multiple GWASs of different phenotypes. When accessing individual level data is difficult, one can use more readily available genome-wide summary statistics for various phenotypes.

With such data, pleiotropy can be assessed using fixed-effects meta-analysis approach which assumes that the true effects across studies are homogeneous. However, the effects of a genetic variant on various traits may be more heterogeneous than the effects of a genetic variant on a specific phenotype across different studies. The random-effects meta-analysis allows for heterogeneity but can be under-powered in association studies. Moreover, neither the fixed-effects nor the random-effects meta-analysis facilitates a simultaneous selection of associated/non-null traits. To address this, a subset-based fixed-effects meta-analysis ASSET [Bhattacharjee et al., 2012] simultaneously provides a p-value evaluating the evidence of aggregate-level pleiotropic association and an optimal subset of associated/non-null traits. It can adjust for correlation between summary statistics due to sharing of subjects across studies. Recent studies [Ellinghaus et al., 2016; Carty et al., 2014] have used ASSET as a primary tool for pleiotropy analysis.

In this article, we propose a Bayesian meta-analysis approach (termed CPBayes) that simultaneously provides a measure of the evidence of aggergate-level pleiotropic association and an optimal subset of associated traits underlying a pleiotropic signal. The evidence of aggregate-level pleiotropic association is measured by a Bayes factor (BF) and a posterior probability of null association (PPNA). CPBayes explicitly takes into account correlation between summary statistics. For multiple case-control studies of different diseases, the summary statistics across traits become correlated mainly due to sample overlap between studies (e.g., con-

trols). Similarly, for a cohort study, summary statistics across traits are correlated due to assessing multiple phenotypes for the same group of individuals. CPBayes considers heterogeneity both in the size and direction of genetic effects across phenotypes. It also estimates the posterior probability of each phenotype being associated with the risk locus that quantifies the relative contribution of the traits underlying a pleiotropic signal.

The Bayesian framework of CPBayes is based on the spike and slab prior, which is commonly used due to its appropriateness and simplicity in solving two-class classification problems. The application of the spike and slab prior in genetic association studies is gradually increasing [Zhou et al., 2013; Wen and Stephens, 2014; Vilhjálmsson et al., 2015]. With a spike and slab prior, the spike element represents a null effect, and the slab component represents a non-null effect. The spike part can either be a positive mass at zero (Dirac spike) or be a normal distribution with mean zero and a small variance (continuous spike). We design the Gibbs samplers for these two type of prior spikes for both uncorrelated and correlated summary statistics across traits.

We demonstrate by simulations that the continuous spike offers better accuracy in the selection of associated traits than the Dirac spike. The former is also computationally much faster than the latter due to simpler analytic expressions of the full conditional posterior distributions of the model parameters. Hence, we adopted the continuous spike for constructing CPBayes. We explore the performance of CPBayes in various simulation scenarios and compare its efficiency in selecting the non-null traits compared to ASSET. CPBayes resembles ASSET in that both methods simultaneously draw inference on the evidence of aggregate-level pleiotropic association and on the optimal subset of non-null traits underlying a pleiotropic signal. But, we show here that the key advantage of CPBayes is that it selects the non-null traits with substantially higher specificity (proportion of null traits discarded from the optimal subset) than ASSET while maintaining a good level of sensitivity (proportion of associated traits included in the subset). We also compare CPBayes and ASSET in the analysis of 22 phenotypes in the large Kaiser "Resource for Genetic Epidemiology Research on Adult Health and Aging" (GERA) cohort [dbGaP Study Accession: phs000674.v1.p1]. CPBayes identified nine independent pleiotropic loci associated with at least two phenotypes including a locus at chromosomal region 1q24.2 that exhibits an association with five different diseases: Dermatophytosis, Hemorrhoids, Iron Deficiency, Osteoporosis, and Peripheral Vascular Disease. ASSET identified larger number of independent pleiotropic loci associated with more than one trait, but selected many phenotypes with very weak genetic effects. We provide an R-package 'CPBayes' implementing the proposed method for a general use by other investigators.

3 Material and methods

Let $Y_1, \ldots, Y_K$ denote K phenotypes, G denote genotype at a single nucleotide polymorphism (SNP), and W denote a set of covariates. Suppose, a generalized linear model (GLM) is separately fit for each phenotype as: $g(E(Y_j)) = \alpha_j + \beta_j G + \gamma_j^{'} W$, $j = 1, \ldots, K$. Let $\hat{\beta}_1, \ldots, \hat{\beta}_K$ denote the estimates (e.g., maximum likelihood estimates) of $\beta_1, \ldots, \beta_K$ with the corresponding standard errors $s_1, \ldots, s_K$. Let $\hat{\boldsymbol{\beta}} = (\hat{\beta}_1, \ldots, \hat{\beta}_K)$, $\boldsymbol{\beta} = (\beta_1, \ldots, \beta_K)$, and $\boldsymbol{s} = (s_1, \ldots, s_K)$. Now suppose that we only have the summary statistics (e.g., $\hat{\boldsymbol{\beta}}$ and $\boldsymbol{s}$). For a large sample size, we can assume that $\hat{\beta}_j | \beta_j, \sigma_j \sim \mathrm{N}(\beta_j, \sigma_j^2)$. Since s_j is a consistent estimator of σ_j, it is commonly used in place of σ_j. Hence, we assume that $\hat{\beta}_j | \beta_j \sim \mathrm{N}(\beta_j, s_j^2)$. If $\hat{\beta}_1, \ldots, \hat{\beta}_K$ are uncorrelated, $\hat{\beta}_j | \beta_j \overset{ind}{\sim} \mathrm{N}(\beta_j, s_j^2)$; $j = 1, \ldots, K$. If $\hat{\beta}_1, \ldots, \hat{\beta}_K$ are correlated with a covariance matrix S, we assume that $\hat{\boldsymbol{\beta}} | \boldsymbol{\beta} \sim \mathrm{MVN}(\boldsymbol{\beta}, S)$.

3.1 Continuos spike

The continuous spike and slab prior in our context [George and McCulloch, 1993; Malsiner-Walli and Wagner, 2011] is described as: for $j = 1, \ldots, K$,

$$\begin{aligned} \beta_j | z_j, \tau, d &\overset{ind}{\sim} (1 - z_j) \times N(0, \tau^2) + z_j \times N(0, \left(\frac{\tau}{d}\right)^2); \ \tau > 0, \ 0 < d < 1, \ \left(\frac{\tau}{d}\right)^2 > \tau^2 \\ & P(z_j = 1 | q) = q; \ P(z_j = 0 | q) = (1 - q); \ 0 < q < 1 \\ & q | c_1, c_2 \sim \mathrm{Beta}(c_1, c_2); \ d | e_1, e_2 \sim \mathrm{Beta}(e_1, e_2) \end{aligned} \tag{1}$$

The latent variable z_j denotes the association status of Y_j. When $z_j = 0$, $\beta_j \sim N(0, \tau^2)$, and when $z_j = 1$, $\beta_j \sim N(0, (\frac{\tau}{d})^2)$, where $(\frac{\tau}{d})^2 > \tau^2$. The usefulness of such a formulation is that τ can be set small enough so that, if $z_j = 0$, $|\beta_j|$ would probably be very small to safely be considered as zero (Y_j is not associated with the SNP), and d can be chosen sufficiently small (so $\frac{1}{d} >> 1$) such that, if $z_j = 1$, β_j can be considered as non-zero (Y_j is associated with the SNP). Of note, without the latent variables $Z = (z_1, \ldots, z_K)$, it is not possible to distinguish between a null and a non-null effect, because β_j is always non-zero under both the spike and slab distributions. The proportion of traits having a non-null genetic effect is denoted by q. For simplicity and reduction in computational cost, we consider τ as fixed. We also choose $c_1 = c_2 = e_1 = e_2 = 1$ which correspond to the uniform$(0, 1)$ distribution. The parameter d is updated in a given range subject to the slab variance $(\frac{\tau}{d})^2$ varying in a pre-fixed range. We describe the continuous spike and slab prior in the context of modeling pleiotropy with an example diagram in Figure 1.

3.2 Dirac spike

The Dirac spike in the current context [Mitchell and Beauchamp, 1988; Malsiner-Walli and Wagner, 2011] is given by: for $j = 1, \ldots, K$,

$$\begin{aligned} \beta_j | q, b &\overset{i.i.d.}{\sim} (1-q) \times \delta_{\{0\}}(\beta_j) + q \times \mathrm{N}(0, b^2) \\ q | c_1, c_2 &\sim \mathrm{Beta}(c_1, c_2),\ 0 < q < 1 \end{aligned} \tag{2}$$

Here, $\delta_{\{0\}}(\beta_j) = 1$ if $\beta_j = 0$, and $\delta_{\{0\}}(\beta_j) = 0$ if $\beta_j \neq 0$. Clearly, under no association, $\beta_j = 0$. The proportion of associated traits is given by q. Note that, the Dirac spike can be obtained from the continuous spike by first setting $\tau = 0$ and $\frac{\tau}{d} = b$ in Equation 1, and then integrating out the latent variables Z from the model.

3.3 Statistical inference on pleiotropy by employing MCMC

To perform a fully Bayesian analysis, we implement MCMC by the Gibbs sampling algorithm to generate posterior samples of the model parameters based on which we draw the statistical inference for pleiotropy. We derive the Gibbs samplers for both uncorrelated and correlated summary statistics. Here we describe the inference procedure for the continuous spike. The Gibbs sampling algorithm for the continuous spike (Algorithm 1) is outlined in the Appendix, and the algorithm for the Dirac spike (Algorithm 2) is stated in the supplementary materials. The mathematical derivation of the full conditional posterior distributions underlying the Gibbs samplers are also given in the supplementary materials.

Let $\{\boldsymbol{\beta}^{(i)}, Z^{(i)}, q^{(i)}, d^{(i)};\ i = 1, \ldots, N\}$ denote N posterior samples of $(\boldsymbol{\beta}, Z, q, d)$ obtained by MCMC after a certain burn-in period. First, we want to test the global null hypothesis of no association (H_0) against the global alternative hypothesis of association with at least one trait (H_1). Since, for the continuous spike, the latent association status distinguishes between an association being null or non-null, we set $H_0 : z_1 = \ldots = z_K = 0$ ($Z = 0$) versus $H_1 :$ at least one of $z_1, \ldots, z_K = 1$ ($Z \neq 0$).

3.3.1 Bayes factor (BF)

Let D denote the summary statistic data at a SNP across traits. The Bayes Factor for testing H_1 against H_0 is given by:

$$\mathrm{BF} = \frac{P(D|H_1)}{P(D|H_0)} = \frac{P(H_1|D)}{P(H_0|D)} \frac{P(H_0)}{P(H_1)} = \frac{P(Z \neq 0|D)}{P(Z = 0|D)} \frac{P(Z = 0)}{P(Z \neq 0)} = \frac{\text{Posterior odds}}{\text{Prior odds}} \tag{3}$$

The posterior odds of H_1 vs. $H_0 = \frac{P(Z \neq 0|D)}{P(Z=0|D)} = \frac{1-P(Z=0|D)}{P(Z=0|D)}$, and the prior odds of H_1 vs. $H_0 = \frac{P(Z \neq 0)}{P(Z=0)} = \frac{1-P(Z=0)}{P(Z=0)}$. Of note, $P(z_j = 1) = E(q) = \frac{c_1}{c_1+c_2} = p_1$. Let $p_0 = 1 - p_1$. Since, z_js are independently distributed in the prior, $P(Z = 0) = p_0^K$, and $P(Z \neq 0) = 1 - p_0^K$. So the prior odds $= \frac{1-p_0^K}{p_0^K}$. The analytic calculation of $P(Z = 0|D)$ is intractable. Hence, we estimate this conditional probability based on the posterior sample of

the model parameters. Note that $P(Z=0|D) = \int\int\int P(Z=0|\boldsymbol{\beta}, q, d, D) f(\boldsymbol{\beta}, q, d|D) d(\boldsymbol{\beta}) d(q) d(d)$. Thus,

$$P(Z=0|D) = E_{\boldsymbol{\beta},q,d|D} P(Z=0|\boldsymbol{\beta}, q, d, D) \approx \frac{1}{N}\sum_{i=1}^{N} P(Z=0|\boldsymbol{\beta}^{(i)}, q^{(i)}, d^{(i)}, D), \tag{4}$$

where $(\boldsymbol{\beta}^{(i)}, q^{(i)}, d^{(i)})$ denotes the ith posterior sample of $(\boldsymbol{\beta}, q, d)$ obtained by the MCMC. We note that the full conditional posterior distributions of $z_1, \ldots, z_K$ are independent (see step 5 in Algorithm 1 and the derivation of full conditional distributions of $z_1, \ldots, z_K$ in the supplementary materials). Hence, $P(Z = 0|\boldsymbol{\beta}^{(i)}, q^{(i)}, d^{(i)}, D) = \prod_{j=1}^{K} P(z_j = 0|\boldsymbol{\beta}^{(i)}, q^{(i)}, d^{(i)}, D)$. This independence property of the full conditional posterior distributions of $z_1, \ldots, z_K$ is crucial for the explicit estimation of the Bayes factor.

3.3.2 Posterior probability of null association (PPNA)

We consider another measure for evaluating the aggregate-level pleiotropic association, termed the posterior probability of null association (PPNA). This is based on the posterior probability of association (PPA) introduced in Stephens and Balding [2009]. The posterior odds (PO) of H_1 versus H_0 is $\frac{P(H_1|D)}{P(H_0|D)}$. The PPA is given by:

$$\text{PPA} = \frac{\text{PO}}{1 + \text{PO}} \tag{5}$$

We define PPNA $= 1 -$ PPA, which can be viewed as a Bayesian analog of the p-value [Stephens and Balding, 2009]. If the data supports H_1, the PPNA should be close to zero, and if the data supports H_0, it should be close to one (similar to a p-value). The posterior odds is computed in the same way as described above for the Bayes factor.

3.3.3 Selection of optimal subset of associated traits

For $i = 1, \ldots, N$, let $S_i = \{Y_j : z_j^{(i)} = 1;\ j = 1, \ldots, K\}$ denote the subset of associated traits detected in the ith posterior sample. That subset of traits which is observed with the maximum frequency in the posterior sample is estimated as the optimal subset of associated traits. Note that it is the maximum a posteriori (MAP) estimate of the optimal subset. Let PPA_j denote the trait-specific posterior probability of association which is estimated as $\frac{1}{N}\sum_{i=1}^{N} z_j^{(i)}$ for the phenotype Y_j. PPA_j provides a better insight into a pleiotropic signal. It quantifies the relative contribution of the traits underlying a pleiotropic signal. We note that, even if a trait is not selected as non-null, the estimated PPA_j for the trait may not be negligible, e.g., 25%. An interpretation of such a phenomenon is that even though the estimated genetic effect on a phenotype was not substantial enough to make into the optimal subset, the possibility of the genetic variant having a pleiotropic effect on the trait along with those in the optimal subset seems promising.

The direction of association between each non-null trait and a genetic variant can be estimated based on the posterior sample of $\boldsymbol{\beta}$. The posterior probability that Y_j is positively associated is estimated as the

proportion of positive β_j among the posterior sample of β_j. Y_j is classified as being positively associated if this estimated proportion is greater than half.

The posterior mean, median, and the 95% credible interval (Bayesian analog of the frequentist confidence interval) of the true genetic effect on each phenotype can be computed based on the posterior sample of the association parameters.

3.4 Specifying the variance of the spike and slab distributions

We set τ^2 (the variance parameter of the spike distribution) to a fixed value 10^{-4} after extensive experimentation with simulated data. If β (log(odds ratio)) follows $N(0, 10^{-4})$, then $P(0.98 < e^{\beta} < 1.02) = 0.954$. It implies that under the spike distribution (no association), the odds ratio for association between a variant and single trait will vary between 0.98 and 1.02 with a prior probability of 95.4%. In the MCMC, we updated the slab variance $(\frac{\tau}{d})^2$ in the range $(0.8 - 1.2)$ with the median value equal to 1. If $\beta \sim N(0, 1)$, then $P(e^{\beta} < 0.95 \text{ or } e^{\beta} > 1.05) = 0.96$, which implies that under the slab distribution (association) with variance one, the odds ratio is smaller than 0.95 (a negative association) or larger than 1.05 (a positive association) with a prior probability of 96%. We also explored other choices for these parameters by simulations, such as, $\tau^2 = 10^{-3}, 10^{-2}$, and $(\frac{\tau}{d})^2$ in a range $(0.5 - 1.0)$, $(0.7 - 1.1)$, etc. The values used here ($\tau^2 = 10^{-4}$, $(\frac{\tau}{d})^2$ in the range $(0.8 - 1.2)$) gave a high level of specificity while maintaining an overall good level of sensitivity. We note that the choice of the spike variance (τ^2) and the ratio of the slab and spike variances ($\frac{1}{d^2}$) directly impact the selection accuracy [George and McCulloch, 1993].

3.5 Estimating the correlation between summary statistics

The summary statistics across traits can be correlated due to overlap or close genetic relatedness among subjects across different studies. For case-control studies, Zaykin and Kozbur [2010] and Lin and Sullivan [2009] derived a simple formula of correlation among $\hat{\beta}_1, \ldots, \hat{\beta}_K$. For $k, l \in \{1, \ldots, K\}$ and $k \neq l$,

$$corr(\hat{\beta}_k, \hat{\beta}_l) = \left(n_{kl}^{(11)} \sqrt{\frac{n_k^{(0)} n_l^{(0)}}{n_k^{(1)} n_l^{(1)}}} + n_{kl}^{(00)} \sqrt{\frac{n_k^{(1)} n_l^{(1)}}{n_k^{(0)} n_l^{(0)}}} \right) \Big/ \sqrt{n_k n_l} \tag{6}$$

Here $n_k^{(1)}$, $n_k^{(0)}$, and n_k (or $n_l^{(1)}$, $n_l^{(0)}$, and n_l) denote the number of cases, controls, and total sample size for the study of Y_k (or Y_l); $n_{kl}^{(11)}$ and $n_{kl}^{(00)}$ denote the number of cases and controls shared between the studies of Y_k and Y_l. Let $n_{kl}^{(10)}$ be the number of overlapping subjects that are cases for Y_k but controls for Y_l; similarly, let $n_{kl}^{(01)}$ be the number of shared subjects that are controls for Y_k but cases for Y_l. Here, the above formula can be generalized to:

$$corr(\hat{\beta}_k, \hat{\beta}_l) = \left(n_{kl}^{(11)} \sqrt{\frac{n_k^{(0)} n_l^{(0)}}{n_k^{(1)} n_l^{(1)}}} - n_{kl}^{(10)} \sqrt{\frac{n_k^{(0)} n_l^{(1)}}{n_k^{(1)} n_l^{(0)}}} - n_{kl}^{(01)} \sqrt{\frac{n_k^{(1)} n_l^{(0)}}{n_k^{(0)} n_l^{(1)}}} + n_{kl}^{(00)} \sqrt{\frac{n_k^{(1)} n_l^{(1)}}{n_k^{(0)} n_l^{(0)}}} \right) \Big/ \sqrt{n_k n_l} \tag{7}$$

This formula is accurate when none of the phenotypes $Y_1, \ldots, Y_K$ is associated with the SNP or environmental covariates. An alternative strategy [Zhu et al., 2015; Pickrell et al., 2016] is based on using genome-wide summary statistics data to estimate the correlation structure, which is useful when the environmental covariates are associated with the phenotypes or the number of cases or controls shared across studies are not available.

3.6 A combined strategy for correlated summary statistics

For strongly correlated summary statistics, when a majority of the traits are associated with the risk locus (non-sparse scenario), the Gibbs sampler can sometimes be trapped in a local mode rather than the global mode of the posterior distribution due to possible multi-modality of the posterior distribution of model parameters. We observed this pattern in our simulation study. It may result in an incorrect selection of associated traits, reducing the robustness of CPBayes. We noticed that, in such a scenario, if the summary statistics are assumed to be uncorrelated, the MCMC does not get trapped in a local mode and moves around the global mode. But ignoring the correlation can give a lower Bayes factor and sensitivity of the selected traits. Hence, for correlated summary statistics we combine the correlated and the uncorrelated versions of CPBayes as follows. First, we execute CPBayes considering the correlation among $\hat{\beta}_1, \ldots, \hat{\beta}_K$. Let A denote the selected subset of non-null traits that contains K_1 traits. Let B denote the subset of K_1 traits that have the smallest univariate association p-values. If A and B match, we accept the results; otherwise, we implement CPBayes assuming that $\hat{\beta}_1, \ldots, \hat{\beta}_K$ are uncorrelated and take the results obtained. Note that, if A is empty, we accept the results obtained by the correlated version of CPBayes.

4 Simulation study

We consider multiple case-control studies with or without shared controls. We also consider a cohort study where the data on multiple disease states are available for a group of individuals. First, we specify the simulation model and generate the phenotype and genotype data. After computing the summary statistics based on the simulated data, we assume that only the summary-level data are available. For case-control studies with no overlapping subjects, we implement the uncorrelated version of CPBayes and ASSET. For case-control studies with overlapping subjects or a cohort study, we estimate the correlation structure of summary statistics based on the formula given in the Equation 7, and use the combined strategy of CPBayes and the correlated version of ASSET.

Let K_1 denote the number of associated phenotypes among K phenotypes. Suppose, K_1^+ traits are positively associated and K_1^- traits are negatively associated ($K_1 = K_1^+ + K_1^-$). We consider two different choices of the minor allele frequency (MAF) at the risk SNP (denoted by m): 0.3 and 0.1.

For non-overlapping case-control studies, we consider a separate group of 7000 cases and 10000 controls

in each study. For overlapping case-control studies, we consider a distinct set of 7000 cases in each study, and a common set of 10000 controls shared across all the studies. For multiple case-control studies, we consider $K = 5$ $(K_1 = 0, 1, 2, 3, 4)$, $K = 10$ $(K_1 = 0, 2, 4, 6, 8)$, and $K = 15$ $(K_1 = 0, 3, 6, 9)$. We simulate the odds ratio for a non-null trait at random from $(1.05 - 1.25)$ in each replication under a simulation scenario. We consider the genetic effects to be all positive, and also both positive and negative. For each disease, we assume an overall disease prevalence of 10% in the whole population. We simulate the genotype data in cases and controls based on the standard logistic model of disease probability conditioning on the genotype: $\text{logit}(P(\text{case}|G)) = \alpha + \beta G$, where G is the genotype at the risk SNP coded as the minor allele count $(0, 1,$ or $2)$. In the cohort study, we consider 15000 individuals. First, we generate the continuous traits from a multivariate normal distribution based on the simulation model described in Majumdar et al. [2016]. We choose the trait-specific heritability due to the quantitative trait locus (QTL) at random from $(0.2\% - 0.5\%)$. Finally, we dichotomize each continuous phenotype into a binary trait subject to an overall disease prevalence of 10%. For the cohort studies, we considered $K = 5$ $(K_1 = 0, 1, 2, 3)$, $K = 10$ $(K_1 = 0, 2, 4, 6)$, and $K = 15$ $(K_1 = 0, 3, 6, 9)$ to save computing time and space.

Note that the Bayes factor and PPNA are not comparable to the p-value. While evaluating the aggregate-level pleiotropic association, we provide various summary measures of $\log_{10}$(Bayes factor) (abbreviated as $\log_{10}$BF), -$\log_{10}$(PPNA) (denoted as -$\log_{10}$PPNA), and -$\log_{10}$(ASSET p-value) (denoted by -$\log_{10}$ASTpv) obtained across 500 replications. Under the global null hypothesis of no association $(K_1 = 0)$, we describe the summary measures in Table 1 (for non-overlapping case-control studies), 2 (for overlapping case-control studies), and S2 (for a cohort study). The summary measures in these three tables show that $\log_{10}$BF and -$\log_{10}$PPNA are very well-controlled under the global null hypothesis. The maximum of $\log_{10}$BF in the three tables is observed to be negative (BF < 1). Hence, all the quantiles of $\log_{10}$BF also appear to be negative. For example, in Table 1, for $K = 5$ and $m = 0.3$, 75%, 95%, 99% quantiles and the maximum of $\log_{10}$BF are -2.68, -2.35, -1.94, and -1.46, respectively. We also observe that 95%, 99% quantiles and the maximum of -$\log_{10}$PPNA are smaller than those for -$\log_{10}$ASTpv in all the three tables. For example, in Table 2, for $K = 10$ and $m = 0.1$, 95% and 99% quantiles, and the maximum of -$\log_{10}$PPNA are 0.07, 0.15, and 1.01, respectively; whereas the same for -$\log_{10}$ASTpv are 0.98, 1.91, and 3.42, respectively.

When at least one of the phenotypes is associated $(K_1 \geq 1)$, we present the summary measures in Table S3, S4, S5, S6, S7 (for non-overlapping case-control studies); S8, S9, S10, S11, S12 (for overlapping case-control studies); and S13, S14, S15 (for cohort study). To save space, we provide all of these tables in the supplementary material. As expected, given a choice of K, $\log_{10}$BF and -$\log_{10}$PPNA increase as K_1 increases. For example, in Table S3 (for 5 non-overlapping case-control studies), for $K_1 = 1$ $(K_1^+ = 1, K_1^- = 0)$ and $m = 0.3$, the mean and median of $\log_{10}$BF are 11.05 and 5.12; whereas for $K_1 = 2$ $(K_1^+ = 2, K_1^- = 0)$ and $m = 0.3$, the mean and median of $\log_{10}$BF are 31.70 and 27.99. Similarly, in Table S10 (for 10 overlapping case-control studies), for $K_1 = 2$ $(K_1^+ = 2, K_1^- = 0)$ and $m = 0.1$, the mean and median of $\log_{10}$BF are 9.70 and 3.30;

whereas for $K_1 = 4$ ($K_1^+ = 4, K_1^- = 0$) and $m = 0.1$, the mean and median of $\log_{10}$BF are 25.97 and 14.82. For overlapping case-control studies and a cohort study, for the same choice of K_1, when the non-null effects are both positive and negative, $\log_{10}$BF and -$\log_{10}$PPNA tend to increase in comparison with when all the non-null effects are positive. For example, in Table S10 (for 10 overlapping case-control studies), for $K_1^+ = 4, K_1^- = 0$ ($K_1 = 4$) and $m = 0.3$, the mean and median of $\log_{10}$BF are 57.66 and 53.68; whereas for $K_1^+ = 2, K_1^- = 2$ ($K_1 = 4$) and $m = 0.3$, the mean and median of $\log_{10}$BF are 77.81 and 72.52. Similarly, in Table S14 (for binary cohort with 10 phenotypes), for $K_1^+ = 2, K_1^- = 0$ ($K_1 = 2$) and $m = 0.3$, the mean and median of $\log_{10}$BF are 15.43 and 6.94; whereas for $K_1^+ = 1, K_1^- = 1$ ($K_1 = 2$) and $m = 0.3$, the mean and median of $\log_{10}$BF are 25.82 and 19.64. However, for non-overlapping case-control studies, we do not observe such a trend with respect to the direction of the non-null effects. We also observe that -$\log_{10}$ASTpv behaves similarly to $\log_{10}$BF and -$\log_{10}$PPNA.

In Figure 2, we have plotted $\log_{10}$BF and -$\log_{10}$PPNA for 100 replications in the same set-up of five non-overlapping and overlapping case-control studies considered above. We chose MAF = 0.3. As expected, when none of the phenotypes is associated, $\log_{10}$BF cluster below zero and -$\log_{10}$PPNA cluster close to zero (Figure 2). And, the measures tend to increase as the number of associated traits increases (Figure 2).

For overlapping case-control studies and cohort study, we implemented the combined strategy of CPBayes. For each simulation scenario in Table S8, S9, S10, S11, S12 (for overlapping case-control studies), and S13, S14, S15 (for a cohort study), we provide the percentage of replications in which the combined strategy chose the uncorrelated version (denoted by uncor%). From the tables, we observe that uncor% increases as K_1 increases for a given choice of K. For example, in Table S11 (for 10 overlapping case control studies), for $m = 0.3$, uncor% increases from 3% to 6.4% as K_1 increases from 6 ($K_1^+ = 6, K_1^- = 0$) to 8 ($K_1^+ = 8, K_1^- = 0$). Similarly, in Table S15 (for a cohort study with 15 phenotypes), for $m = 0.1$, uncor% increases from 5.8% to 8.4% as K_1 increases from 6 ($K_1^+ = 6, K_1^- = 0$) to 9 ($K_1^+ = 9, K_1^- = 0$). For a sparse scenario when less than half of the traits are associated (e.g., $K_1 = 3$ and $K = 15$), uncor% is substantially smaller than that for a non-sparse scenario (e.g., $K_1 = 9$ and $K = 15$). For example, in Table S12 (for 15 overlapping case-control studies), for $m = 0.1$, uncor% is 11% when $K_1 = 3$ ($K_1^+ = 2, K_1^- = 1$), and it increases to 26.2% when $K_1 = 9$ ($K_1^+ = 5, K_1^- = 4$). Similarly, in Table S15 (for a cohort study with 15 phenotypes), for $m = 0.3$, uncor% increases from 4.8% to 7.6% when K_1 increases from 3 ($K_1^+ = 2, K_1^- = 1$) to 9 ($K_1^+ = 5, K_1^- = 4$).

To evaluate the accuracy of selection of associated traits in a simulation scenario, we computed the average specificity and sensitivity obtained across 500 replications. We present the comparison of the selection accuracy between CPBayes and ASSET in Figure 3 (for non-overlapping case-control studies), Figure 4 (for overlapping case-control studies), and Figure S2 (for cohort study). CPBayes yielded a very good level of specificity (consistently more than 95%) which is substantially higher than that of ASSET. For example, in Figure 3 (for non-overlapping case-control studies), while CPBayes' specificity is $> 97\%$, the specificity of ASSET varies in the range $46\% - 98\%$ when $K = 5$, and in a range $53\% - 99\%$ when $K = 10$. Similary, in

Figure 4 (for overlapping case-control studies), the specificity of ASSET varies in a range $49\% - 99\%$ when $K = 5$, and in $62\% - 100\%$ when $K = 10$.

CPBayes also offers an overall good level of sensitivity. For five non-overlapping case-control studies (Figure 3), CPBayes produced a sensitivity of $79\% - 89\%$ when MAF $= 0.3$ and $64\% - 76\%$ when MAF $= 0.1$; ASSET yielded slightly higher sensitivity of $86\% - 100\%$ (with $50\% - 98\%$ specificity) when MAF $= 0.3$, and a higher sensitivity of $85\% - 98\%$ (with $46\% - 90\%$ specificity) when MAF $= 0.1$. In Figure 3, we observe a similar pattern for $K = 10$ and $K = 15$. ASSET's higher sensitivity than CPBayes appears to come at the expense of a substantially lower specificity.

For overlapping case-control studies (Figure 4), CPBayes gave a substantially better sensitivity than ASSET (along with substantially better specificity) for a majority of the simulation scenarios. For example, when $K = 10$ and $m = 0.3$, the sensitivity was $82\% - 89\%$ for CPBayes, and $39\% - 73\%$ for ASSET, except for the case $K_1^+ = 1, K_1^- = 1$ when ASSET had 100% sensitivity. Similarly, for $K = 10$ and $m = 0.1$, the sensitivity was $57\% - 73\%$ for CPBayes and $39\% - 71\%$ for ASSET except for the choice $K_1^+ = 1, K_1^- = 1$ when ASSET had 96% sensitivity. For $K = 15$ and $m = 0.3$, the sensitivity was $82\% - 87\%$ for CPBayes and $38\% - 82\%$ for ASSET. For $K = 15$ and $m = 0.1$, the sensitivity was $60\% - 70\%$ for CPBayes and $35\% - 79\%$ for ASSET.

For a cohort study, CPBayes and ASSET both consistently exhibited good levels of sensitivity. For some cases, ASSET had a higher sensitivity than CPBayes, though generally with lower specificity. We also observe that when the non-null effects are all positive, the specificity of ASSET is smaller compared to when the non-null effects are both positive and negative. However, CPBayes performed more robustly with respect to the direction of non-null effects.

We also carried out a simulation study for 50 traits. We considered the same set-up of overlapping case-control studies considered above and $K_1 = 0, 5, 10$. Since ASSET is computationally very slow for 50 traits due to an extremely large number of possible subsets of traits, we only implemented CPBayes. Different summary measures of $\log_{10}$BF and -$\log_{10}$PPNA obtained across 200 replications are described in Table S16. The mean specificity and sensitivity are provided in Table S17. We observe that CPBayes performs similarly as for 5, 10, or 15 overlapping studies (discussed above).

5 GERA cohort analysis

To investigate the performance of CPBayes using real data, we analyzed the large genome-wide association study from the Kaiser "Resource for Genetic Epidemiology Research on Adult Health and Aging" (GERA) cohort data obtained from dbGaP [dbGaP Study Accession: phs000674.v1.p1]. We also analyzed the data by ASSET. For simplicity's sake, we restricted our analysis to 62,318 European-American individuals, who constitute more than 75% of the dbGaP data. We tested 657,184 SNPs genotyped across 22 autosomal

chromosomes for their potential pleiotropic effects on 22 phenotypes in the GERA cohort (Table S18). Note that in the dbGaP data, the cancers are collapsed into a single variable (any cancer). Therefore, we could only use an overall cancer categorization even though the genetic architecture is likely heterogeneous across different cancers. We provide the trait-trait correlation matrix in Table S24. The phenotypes are correlated modestly with a maximum correlation of 0.36 observed between Hypertension and Dyslipidemia.

Before our analysis, we undertook the following QC steps. First, we removed individuals with: over 3% of genotypes missing; any missing information on covariates (described below); genotype heterozygosity outside six standard deviations; first degree relatives; or discordant sex information. This left us with 53,809 individuals. Next, we removed SNPs with: MAF < 0.01; 10% or more missingness; or deviation from HWE at a level of significance 10^{-5}. This leaves 601,175 SNPs that were tested for pleiotropic association by CPBayes and ASSET. We adjusted the analysis for the following covariates: age, gender, smoking status, BMI category, and 10 principal components of ancestry (PCs). We tested the single-trait association for each of the 22 phenotypes by a logistic regression of the case-control status on the genotype incorporating the same set of adjusting covariates. We used SNP-trait effect estimates (log odds ratios) and their standard errors in CPBayes and ASSET. Since the summary statistics are correlated, we used the combined strategy of CPBayes and the correlated version of ASSET.

As we have environmental covariates in the GERA study, we estimated the correlation matrix of the effect estimates using the genome-wide summary statistics data [Zhu et al., 2015]. First, we extracted all of the SNPs for each of which the trait-specific univariate p-values are > 0.1 across 22 traits. This ensures that each SNP is either weakly or not associated with any of the 22 phenotypes. Then we selected a set of 24,510 independent SNPs from the initial set of null SNPs by using a threshold of $r^2 < 0.1$ (r: the correlation between the genotypes at a pair of SNPs). Finally, we computed the correlation matrix of the effect estimates as the sample correlation matrix of $\hat{\beta}_1, \ldots, \hat{\beta_{22}}$ across the selected 24,510 independent null SNPs.

We apply the conventional genome-wide (GW) level of statistical significance 5×10^{-8} for ASSET (equivalent to -$\log_{10}$(ASSET p-value) > 7.30). It is tough to decide on an appropriate GW cut-off for $\log_{10}$BF of CPBayes. Of note, Bhattacharjee et al. [2012] and Majumdar et al. [2016] demonstrated by simulations that ASSET appropriately controls for the false positive rate. We observed in our simulation study that, under the global null hypothesis of no association, CPBayes always produced a negative $\log_{10}$BF (Table 1, 2, S2). Hence $\log_{10}$BF was always smaller than -$\log_{10}$ASTpv under the null hypothesis. So, for contrasting the results obtained by the two methods, we set the cut-off of $\log_{10}$BF as 7.30, the same as for -$\log_{10}$ASTpv. This cut-off may be somewhat conservative for CPBayes, because in the simulation study, CPBayes produced substantially smaller $\log_{10}$BF than -$\log_{10}$ASTpv under the global null hypothesis (Table 1, 2, S2). Based on the GW cut-off, CPBayes identified 314 SNPs and ASSET detected 394 SNPs. By definition, each of these SNPs is associated with at least one of the 22 phenotypes. We note that CPBayes and ASSET identified a common set of 253 SNPs.

Many of the associated SNPs are expected to be in linkage disequilibrium (LD). On each chromosome, we identified the LD blocks by using a threshold of $r^2 = 0.25$. For CPBayes, we identified 49 associated LD blocks, and for ASSET, we detected 30 associated LD blocks. For each of the 394 SNPs detected by ASSET, the optimal subset of non-null traits always included more than one phenotype. So for ASSET, within each LD block, we chose the SNP having the minimum p-value of aggregate-level pleiotropic association. We present the results for these lead SNPs in Table S20, S21, S22, and S23. CPBayes selected more than one trait for 63 among 314 SNPs. Within each LD block identified by CPBayes, we chose the SNP associated with the maximum number of phenotypes. If multiple SNPs satisfy this criterion, we chose the one having the maximum $\log_{10}$BF. If every SNP in a block is associated with one trait, we chose the SNP with the maximum $\log_{10}$BF. In Table 3, we present the results for the independent pleiotropic SNPs at which CPBayes selected at least two phenotypes. In Table S19, we report the selected independent SNPs at which CPBayes detected one trait. In all the tables describing the results of CPBayes and ASSET, we provide the trait-specific univariate association p-values for contrast's sake. In all the tables for CPBayes, we also present the estimated trait-specific posterior probability of association (PPA_j) and the direction of association for the selected phenotypes (genotype was coded as the number of wild allele).

Even though CPBayes detected a smaller number of GW-significant SNPs (314) than ASSET (394), the former identified a substantially larger number of LD blocks than the later (49 versus 30). For example, CPBayes identified one SNP on chromosome 18 associated with Peripheral Vascular Disease, but ASSET did not detect any SNP on this chromosome. Specifically, CPBayes detected rs8092654 ($\log_{10}\text{BF} = 12.24$) at which ASSET yielded a p-value of 0.13. In the NHGRI-EBI GWAS catalog, rs8092654 is reported as an eQTL hit for the ZNF611 gene in the peripheral blood monocytes tissue. As another example, on chromosome 11, CPBayes detected three LD blocks. From Table S19 for CPBayes, we observe that the lead SNPs of the blocks are rs1799963 (11p11.2), rs964184 (11q23.3), and rs55975204 (11q13.2) which are associated with Peripheral Vascular Disease (univariate p-value: 1.19×10^{-8}), Dyslipidemia (univariate p-value: 5.49×10^{-28}), and Osteoporosis (univariate p-value: 2.0×10^{-9}), respectively. But, ASSET detected only one LD block on chromosome 11, which contains SNPs that are mainly associated with Dyslipidemia. In this block, the lead SNP for ASSET (rs964184) also turned out to be the lead SNP for CPBayes in the corresponding LD block containing the SNPs associated with Dyslipidemia. So, ASSET missed the signals for Peripheral Vascular Disease and Osteoporosis. We note that, in the NHGRI-EBI GWAS catalog, rs1799963 is reported to be associated with venous thromboembolism, and rs964184 is reported as associated with LDL cholesterol, triglycerides, and total cholesterol. And, rs55975204 is in LD ($r^2 = 0.9$) with rs12286536 which is an eQTL hit for the CPT1A and MTL5 genes in the whole blood tissue. These findings suggest that in certain situations CPBayes may detect associations not detected by ASSET.

For each SNP detected by ASSET, the selected subset of non-null traits always contained more than one phenotype (Table S20, S21, S22, S23). For a majority of the SNPs, the subset of non-null traits

included some phenotypes that have large univariate association p-values (so, weak effects). For example, rs2300430 (1q31.3) was detected by both the methods (first SNP in Table S20 and S19); ASSET selected Allergic Rhinitis, Depressive Disorder, Dermatophytosis, Hemorrhoids, Insomnia, Macular Degeneration, Osteoporosis, and Peptic Ulcer, which have trait-specific univariate p-values equal to: 0.34, 0.18, 0.09, 0.36, 0.47, 2.57×10^{-77}, 0.09, and 0.74, respectively. In contrast, CPBayes only selected Macular Degeneration (Table S20). This suggests that CPBayes selects only those phenotypes having substantially strong genetic effects, while ASSET may select many more traits with lower specificity as seen in our simulation study.

CPBayes detected nine independent GW significant pleiotropic SNPs, for which it selected at least two phenotypes as non-null (Table 3). For example, at rs6025 (1q24.2), it selected a maximum of 5 phenotypes: Dermatophytosis, Hemorrhoids, Iron Deficiency, Osteoporosis, and Peripheral Vascular Disease, which have univariate p-values equal to 0.0018, 0.0014, 0.0004, 0.0002, and 6.81×10^{-14}, respectively. We present a forest plot for this pleiotropic signal in Figure 5. ASSET also identified this SNP and selected the same five traits as CPBayes. Interestingly, the SNP was positively associated with Dermatophytosis, Hemorrhoids, and Iron Deficiency, but negatively associated with Osteoporosis and Peripheral Vascular Disease (Figure 5). At rs10455872 (6q25.3), CPBayes selected Cardiovascular Disease, Dyslipidemia, and Peripheral Vascular Disease (Figure 6). ASSET selected these three traits and five more phenotypes with large univariate p-values. At rs651007 (9q34.2), CPBayes detected pleiotropy with Dyslipidemia and Peripheral Vascular Disease, whereas ASSET detected both of these and other phenotypes with weak genetic effects (Figure 7). CPBayes detected two independent pleiotropic SNPs in the chromosomal region 6p21.32: rs3830123 and rs9275476 (Table 3). The r^2 value between rs3830123 and rs9275476 was 0.016. We also found that a disjoint set of phenotypes are associated with the two SNPs: Asthma, Type 2 Diabetes, and Macular Degeneration are associated with rs9275476; Cancers and Dyslipidemia are associated with rs3830123. CPBayes also detected four other pleiotropic loci: rs7601401 (2p16.1) (Abdominal Hernia and Osteoarthritis), rs17661572 (2p21) (Allergic Rhinitis and Insomnia), rs387608 (6p21.33) (Cancers and Macular Degeneration), and rs4506565 (10q25.2) (Type 2 Diabetes and Dyslipidemia). CPBayes detected 22 pair-wise trait-trait pleiotropic signals which we present in Table 4.

For CPBayes, the trait-specific posterior probability of association (PPA_j) provides a better insight into the relative strength of association between a pleiotropic variant and the selected non-null traits. For example, at rs6025, PPA_j for Dermatophytosis, Hemorrhoids, Iron Deficiency, Osteoporosis, and Peripheral Vascular Disease are $70\%, 73.6\%, 95.3\%, 87.8\%$, and 100%, respectively (Table 3). This implies that the association with Peripheral Vascular Disease is the strongest among the five selected phenotypes. At some of the GW significant SNPs detected by CPBayes (Table 3 and S19), a few phenotypes produced a non-negligible value of PPA_j but were left out from the optimal subset of non-null traits. In Table 5, we list these SNPs and the corresponding phenotypes having a PPA_j larger than 25%. For example, at rs849135 (7p15.1), CPBayes only selected Type 2 Diabetes (Table 3), but Asthma also produced a PPA_j of 40.2%.

Thus, even though the effect of rs849135 on Asthma was not strong enough to make into the optimal subset, a further consideration of the pleiotropic effect of rs849135 on Type 2 Diabetes and Asthma looks promising. At rs76075198 (19q13.31), CPBayes only selected Dyslipidemia (Table 3), but Peripheral Vascular Disease also produced a PPA_j of 44.9%. We observe a similar phenomenon for the other two SNPs in Table 5.

We note that a majority of the SNPs detected by the two methods (Table 3, S19, S20, and S21) are already reported in the NHGRI-EBI GWAS catalog. For example, rs6025 (1q24.2) has been associated with inflammatory bowel disease and venous thromboembolism. rs10455872 (6q25.3) has been associated with myocardial infarction, response to statins (LDL cholesterol change), coronary artery disease, and aortic valve calcification. rs651007 (9q34.2) has been associated with iron status biomarkers (ferritin levels), blood metabolite levels, serum alkaline phosphatase levels, and end-stage coagulation. We also note that the combined strategy of CPBayes used the uncorrelated version only for 19 SNPs among all the 601,175 SNPs analyzed, and for none of the 314 SNPs identified in the primary genome-wide screening.

6 Discussion

We have proposed a Bayesian meta-analysis approach for pleiotropic association analysis based on summary-level data. It simultaneously evaluates the evidence of aggregate-level pleiotropic association and estimates an optimal subset of traits associated with the risk locus under a unified Bayesian statistical framework. The method is implemented by Gibbs sampling designed for both uncorrelated and correlated summary statistics. We have conducted an extensive simulation study and analyzed the large GERA cohort for evaluating the performance of CPBayes.

An appealing feature of CPBayes is that, in addition to $\log_{10}\text{BF}$, PPNA, and an optimal subset of non-null traits, it simultaneously provides other interesting insights into an observed pleiotropic signal. For example, it estimates a trait-specific posterior probability of association (PPA_j), the direction of association, posterior mean/median, and the credible interval of the unknown true effect. As demonstrated in the real data application, even if CPBayes does not select a phenotype in the optimal subset of non-null traits which is defined as the MAP estimate (see the methods section), PPA_j for the phenotype may not be negligible. It may help an investigator to better explain a pleiotropic signal. One can also define the optimal subset of associated traits as $\{Y_j : \text{PPA}_j > p\}$, where p can be chosen as 0.5 (known as the median model), or other values. Based on our simulations, the MAP estimate and the median model lead to almost the same level of specificity and sensitivity. Such flexibility in making inference on pleiotropy are mainly due to the MCMC construction underlying CPBayes.

In contrast to ASSET, the major advantage of CPBayes is that it selects the non-null traits underlying a pleiotropic signal with a substantially higher accuracy. A possible reason behind this is that CPBayes performs the selection probabilistically through updating the latent association status by MCMC. ASSET

selects that subset of traits as non-null which maximizes the observed value of a weighted linear combination of the normalized univariate association statistics corresponding to the phenotypes belonging to a subset. So, given the summary statistics, ASSET does not select the non-null traits probabilistically based on the distribution of the summary statistics. We also note that ASSET is based on the framework of a fixed effects meta analysis and assumes that the effects in a given direction (positive/negative) are the same in size. But we observed in our real data application that, in a given direction, the effects of a variant across phenotypes may often be heterogeneous. CPBayes allows heterogeneity simultaneously in the direction and size of the effects. Table S1 summarizes key features of CPBayes and ASSET.

While assessing the selection accuracy, we have placed more emphasis on specificity than sensitivity. This was because a higher sensitivity at the expense of a lower specificity can lead to a false selection of too many traits as non-null. CPBayes consistently maintained a very good level of specificity while offering a good level of sensitivity across a wide range of simulation scenarios. While CPBayes produced a limited number of pleiotropic SNPs associated with more than one phenotype in the analysis of GERA cohort, these pleiotropic signals seem highly promising. Hence, the non-null traits for a pleiotropic variant selected by CPBayes are more reliable than those detected by ASSET.

Note that the continuous spike inherits the infinitesimal-model assumption that every SNP contributes to the variation of a trait, and the distinction is made between a negligible and a significant contribution, whereas the Dirac spike assigns the null effects explicitly to zero. From the perspective of heritability estimation, the infinitesimal-model assumption is more relevant since many SNPs with small effects underlie the variation of a phenotype. We conducted a simulation study (provided in the supplementary material) to compare the continuous spike and the Dirac spike. We found that the continuous spike offers better accuracy in the selection of non-null traits than the Dirac spike. The continuous spike is also computationally much faster (2-3 times) than the Dirac spike. Hence, we adopted the continuous spike for constructing CPBayes. We also note that, the latent association status (Z) could only be used in the model for the continuous spike. For the Dirac spike, the inclusion of Z in the model makes the corresponding MCMC reducible, and hence non-convergent to its stationary distribution (details not provided). Also, for the continuous spike, the full conditional posterior distributions of $z_1, \ldots, z_K$ are independent which leads to an explicit estimation of the Bayes factor based on the MCMC sample. But, for the Dirac spike, the explicit estimation of the Bayes factor appears to be extremely difficult in the correlated case, because the full conditional posterior distributions of $\beta_1, \ldots, \beta_K$ are not independent for correlated summary statistics.

In related work, Han and Eskin [2012] proposed a modified random effects meta analysis for combining heterogeneous studies coupled with a Bayesian approach to provide a better interpretation of an observed signal of aggregate-level association. They investigated how to combine heterogeneous genetic studies across different populations/ethnicities. However, they did not address how to account for a possible correlation between the summary statistics while selecting the most important studies underlying an observed signal of

aggregate-level association. Hence we compared CPBayes only with ASSET.

We note that we did not explicitly compare CPBayes and ASSET with respect to power, because the Bayes factor and the p-value are not directly comparable. Computing a p-value based on the Bayes factor is computationally very expensive, and moreover, the approximation may not be accurate at a genome-wide scale. On the other hand, determining the cut-off of the Bayes factor corresponding to a given choice of the false positive rate is also time consuming and may become computationally infeasible for a false positive rate at the genome-wide scale, e.g., 5×10^{-8}. Hence, we preserved the fully Bayesian essence of CPBayes. In the GERA cohort analysis, CPBayes primarily detected smaller number of SNPs than ASSET (314 versus 394) by using a seemingly conservative cut-off of $\log_{10}$BF (discussed in the real data application section). But, among the primarily identified genome-wide significant SNPs, CPBayes detected substantially larger number of associated LD blocks than ASSET (49 versus 30). ASSET completely missed some loci which were detected by CPBayes. These findings indicate that CPBayes is powerful to identify pleiotropic variants.

We have evaluated CPBayes primarily for SNP by SNP analysis. However, one possible approach to implement the method for a gene-based association analysis is as follows. First, implement PrediXcan [Gamazon et al., 2015] to impute the expression level of a gene. Next, regress each phenotype individually on the imputed gene expression level and compute the estimate of the association parameter (β) along with the corresponding standard error. Finally, we can implement CPBayes on these summary statistics to conduct a gene-level pleiotropy analysis. We note that the method can also be applied to observational studies of non-genetic exposures.

For a larger number of phenotypes, CPBayes is computationally faster than ASSET. For example, in the analysis of 22 traits in the GERA cohort, CPBayes took an average run time of 4.5 hours for 1,000 SNPs, and ASSET took an average run time of 9 hours for 1,000 SNPs. However, as the number of traits decreases, ASSET gradually becomes faster due to the reduction in the number of all possible subsets of traits. That said, CPBayes is computationally feasible and can be implemented at a genome-wide scale. As expected, the uncorrelated version of CPBayes is at least twice as fast as the correlated version of CPBayes. In future work, we aim to investigate whether the computing speed of CPBayes can be increased by using a variational Bayes approach or by using an optimization technique (e.g., EM algorithm or its variants) instead of using MCMC, while preserving the efficiency of the method. We also plan to explore whether fitting multiple (3 or 4) slab distributions instead of a single slab can better model the non-null effects in the presence of extreme effect size heterogeneity.

In summary, CPBayes is a sensitive and specific approach for detecting associated traits underlying a pleiotropic signal. CPBayes has a strong theoretical foundation and allows for heterogeneity in both the direction and size of effects. In addition to parameters of primary interest (e.g., the measures of overall pleiotropic association, the optimal subset of associated traits), it provides other interesting insights into a pleiotropic signal (e.g., the trait-specific posterior probability of association, the direction of association). It

is computationally feasible and faster than ASSET for a larger number of traits. A user-friendly R-package 'CPBayes' is provided for general use by other investigators.

Appendix A

Here we state the Gibbs sampling algorithm for the continuous spike described in Equation 1. It is a desirable practice to provide a MCMC with a good initial value of the model parameters for faster convergence to its stationary distribution. Hence we use the false discovery rate controlling procedure proposed by Benjamini and Yekutieli [2001] (BY procedure) which is robust to arbitrary correlation structure of multiple test statistics. We apply the BY procedure on the univariate association p-values of K traits at an FDR level of 0.05 and assign $z_j = 1$ if Y_j is found to be significantly associated, otherwise set $z_j = 0$; $j = 1, \ldots, K$. We also choose an initial value of q as the proportion of non-null traits detected by the BY procedure (the boundary situations of no/all non-null traits are taken care of appropriately).

Define $\Sigma_2 = diag(\tau_1^2, \ldots, \tau_K^2)$ (a diagonal matrix with diagonal elements $\tau_1^2, \ldots, \tau_K^2$), where $\tau_j = \tau$ if $z_j = 0$; and $\tau_j = \frac{\tau}{d}$ if $z_j = 1$; $j = 1, \ldots, K$. So $\boldsymbol{\beta}|Z \sim \text{MVN}(\underset{\sim}{0}, \Sigma_2)$. Let $\Sigma_1 = S$. Also, let $\boldsymbol{\beta}_{-j} = (\beta_1, \ldots, \beta_{j-1}, \beta_{j+1}, \ldots, \beta_K)$, and $Z_{-j} = (z_1, \ldots, z_{j-1}, z_{j+1}, \ldots, z_K)$.

Algorithm 1 Gibbs sampling for continuous spike in correlated case

1: *Start*:
2: Assign the initial values of Z and q as described above.
3: *loop*:
4: Simulate $\boldsymbol{\beta}$ from its full conditional posterior distribution: $\boldsymbol{\beta}|Z, q, d, \hat{\boldsymbol{\beta}} \sim \text{MVN}[(\Sigma_1^{-1} + \Sigma_2^{-1})^{-1}\Sigma_1^{-1}\hat{\boldsymbol{\beta}}, (\Sigma_1^{-1} + \Sigma_2^{-1})^{-1}]$.
5: For $j = 1, \ldots, K$, update z_j using the full conditional posterior probability: $P(z_j = 0|Z_{-j}, \boldsymbol{\beta}, q, d, \hat{\boldsymbol{\beta}}) = \frac{1}{1+\text{ratio}_j}$, where $\text{ratio}_j = \frac{q}{1-q}\, d \exp[-\frac{\beta_j^2}{2\tau^2}(d^2 - 1)]$.
6: Let $k_1 = \sum_{j=1}^{K} z_j$, $k_0 = K - k_1$. Update q using $q|\boldsymbol{\beta}, Z, d, \hat{\boldsymbol{\beta}} \sim \text{Beta}(c_1 + k_1, c_2 + k_0)$.
7: We assume that $e_1 = e_2 = 1$. Update d from its full conditional posterior distribution in a fixed range so that the slab variance $(\frac{\tau}{d})^2$ varies in a given range (v_0, v_1), and let the corresponding range of d be given by: $d_0 < d < d_1$. If $k_1 = \sum_{j=1}^{K} z_j > 0$, then $d = \sqrt{\frac{y}{2C}}$, where $C = \frac{1}{2\tau^2}\sum_{j:z_j=1}\beta_j^2$, and y follows a truncated $(2Cd_0^2 < y < 2Cd_1^2)$ central $\chi^2_{k_1+1}$ distribution. If $k_1 = 0$, d is updated from the truncated $(d_0 < d < d_1)$ Beta(1,1) distribution.
8: **goto** *loop* until all the MCMC iterations are finished.

We note that, d can be updated using the truncated central χ^2 distribution as long as the second shape parameter of its Beta prior (e_2) is 1.

If the summary statistics are uncorrelated, step 4 of Algorithm 1 is modified as: for $j = 1, \ldots, K$, update β_j by sampling from its full conditional posterior distribution: $\beta_j|\boldsymbol{\beta}_{-j}, Z, q, d, \hat{\boldsymbol{\beta}} \sim \text{N}(\frac{\sigma_j^2}{s_j^2}\hat{\beta}_j, \sigma_j^2)$, where $\frac{1}{\sigma_j^2} = \frac{1}{s_j^2} + \frac{1}{\tau_j^2}$. All the other steps remain the same as in the Algorithm 1.

Acknowledgements

This work was supported by the National Institutes of Health grants R01CA088164, U01CA127298, R25CA112355, and the UCSF Goldberg-Benioff Program in Cancer Translational Biology. We thank Thomas Hoffmann, Prasenjit Ghosh, and Moumita Das for important discussions relating to this work. The GERA cohort data came from a grant, the Resource for Genetic Epidemiology Research in Adult Health and Aging (RC2 AG033067; Schaefer and Risch, PIs) awarded to the GERA Permanente Research Program on Genes, Environment, and Health (RPGEH) and the UCSF Institute for Human Genetics. The RPGEH was supported by grants from the Robert Wood Johnson Foundation, the Wayne and Gladys Valley Foundation, the Ellison Medical Foundation, GERA Permanente Northern California, and the GERA Permanente National and Northern California Community Benefit Programs. The RPGEH and the Resource for Genetic Epidemiology Research in Adult Health and Aging are described in the following publication, Schaefer C. et al., The GERA Permanente Research Program on Genes, Environment and Health: Development of a Research Resource in a Multi-Ethnic Health Plan with Electronic Medical Records, In preparation. The authors do not have any conflict of interest.

References

Benjamini, Y. and Yekutieli, D. (2001). The control of the false discovery rate in multiple testing under dependency. *Annals of statistics*, pages 1165–1188.

Bhattacharjee, S., Rajaraman, P., Jacobs, K. B., Wheeler, W. A., Melin, B. S., Hartge, P., Yeager, M., Chung, C. C., Chanock, S. J., Chatterjee, N., et al. (2012). A subset-based approach improves power and interpretation for the combined analysis of genetic association studies of heterogeneous traits. *The American Journal of Human Genetics*, 90(5):821–835.

Carty, C. L., Bhattacharjee, S., Haessler, J., Cheng, I., Hindorff, L. A., Aroda, V., Carlson, C. S., Hsu, C.-N., Wilkens, L., Liu, S., et al. (2014). Comparative analysis of metabolic syndrome components in over 15,000 african americans identifies pleiotropic variants: Results from the page study. *Circulation: Cardiovascular Genetics*, pages 505–513.

Ellinghaus, D., Jostins, L., Spain, S. L., Cortes, A., Bethune, J., Han, B., Park, Y. R., Raychaudhuri, S., Pouget, J. G., Hübenthal, M., et al. (2016). Analysis of five chronic inflammatory diseases identifies 27 new associations and highlights disease-specific patterns at shared loci. *Nature genetics*.

Gamazon, E. R., Wheeler, H. E., Shah, K. P., Mozaffari, S. V., Aquino-Michaels, K., Carroll, R. J., Eyler, A. E., Denny, J. C., Nicolae, D. L., Cox, N. J., et al. (2015). A gene-based association method for mapping traits using reference transcriptome data. *Nature genetics*, 47(9):1091–1098.

George, E. I. and McCulloch, R. E. (1993). Variable selection via gibbs sampling. *Journal of the American Statistical Association*, 88(423):881–889.

Han, B. and Eskin, E. (2012). Interpreting meta-analyses of genome-wide association studies. *PLoS Genet*, 8(3):e1002555.

Lin, D.-Y. and Sullivan, P. F. (2009). Meta-analysis of genome-wide association studies with overlapping subjects. *The American Journal of Human Genetics*, 85(6):862–872.

Majumdar, A., Haldar, T., and Witte, J. S. (2016). Determining which phenotypes underlie a pleiotropic signal. *Genetic epidemiology*.

Malsiner-Walli, G. and Wagner, H. (2011). Comparing spike and slab priors for bayesian variable selection. *Austrian Journal of Statistics*, 40(4):241–264.

Mitchell, T. J. and Beauchamp, J. J. (1988). Bayesian variable selection in linear regression. *Journal of the American Statistical Association*, 83(404):1023–1032.

Parkes, M., Cortes, A., van Heel, D. A., and Brown, M. A. (2013). Genetic insights into common pathways and complex relationships among immune-mediated diseases. *Nature Reviews Genetics*, 14(9):661–673.

Pickrell, J. K., Berisa, T., Liu, J. Z., Ségurel, L., Tung, J. Y., and Hinds, D. A. (2016). Detection and interpretation of shared genetic influences on 42 human traits. *Nature genetics*.

Sakoda, L. C., Jorgenson, E., and Witte, J. S. (2013). Turning of cogs moves forward findings for hormonally mediated cancers. *Nat Genet*, 45(4):345–8.

Stephens, M. and Balding, D. J. (2009). Bayesian statistical methods for genetic association studies. *Nature Reviews Genetics*, 10(10):681–690.

Vilhjálmsson, B. J., Yang, J., Finucane, H. K., Gusev, A., Lindström, S., Ripke, S., Genovese, G., Loh, P.-R., Bhatia, G., Do, R., et al. (2015). Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *The American Journal of Human Genetics*, 97(4):576–592.

Wen, X. and Stephens, M. (2014). Bayesian methods for genetic association analysis with heterogeneous subgroups: from meta-analyses to gene-environment interactions. *The annals of applied statistics*, 8(1):176.

Zaykin, D. V. and Kozbur, D. O. (2010). P-value based analysis for shared controls design in genome-wide association studies. *Genetic epidemiology*, 34(7):725–738.

Zhou, X., Carbonetto, P., and Stephens, M. (2013). Polygenic modeling with bayesian sparse linear mixed models. *PLoS Genet*, 9(2):e1003264.

Zhu, X., Feng, T., Tayo, B. O., Liang, J., Young, J. H., Franceschini, N., Smith, J. A., Yanek, L. R., Sun, Y. V., Edwards, T. L., et al. (2015). Meta-analysis of correlated traits via summary statistics from gwass with an application in hypertension. *The American Journal of Human Genetics*, 96(1):21–36.

Global Lipids Genetics Consortium (2013). Discovery and refinement of loci associated with lipid levels. *Nature genetics*, 45(11):1274-1283.

Figure 1: An example diagram of the continuous spike and slab prior used by CPBayes to model pleiotropy. In this diagram, the spike variance is chosen as 0.1. However, we set this value to 10^{-4} in our simulation study and real data analysis (a diagram corresponding to this choice is presented in Figure S1 in the supplementary material.)

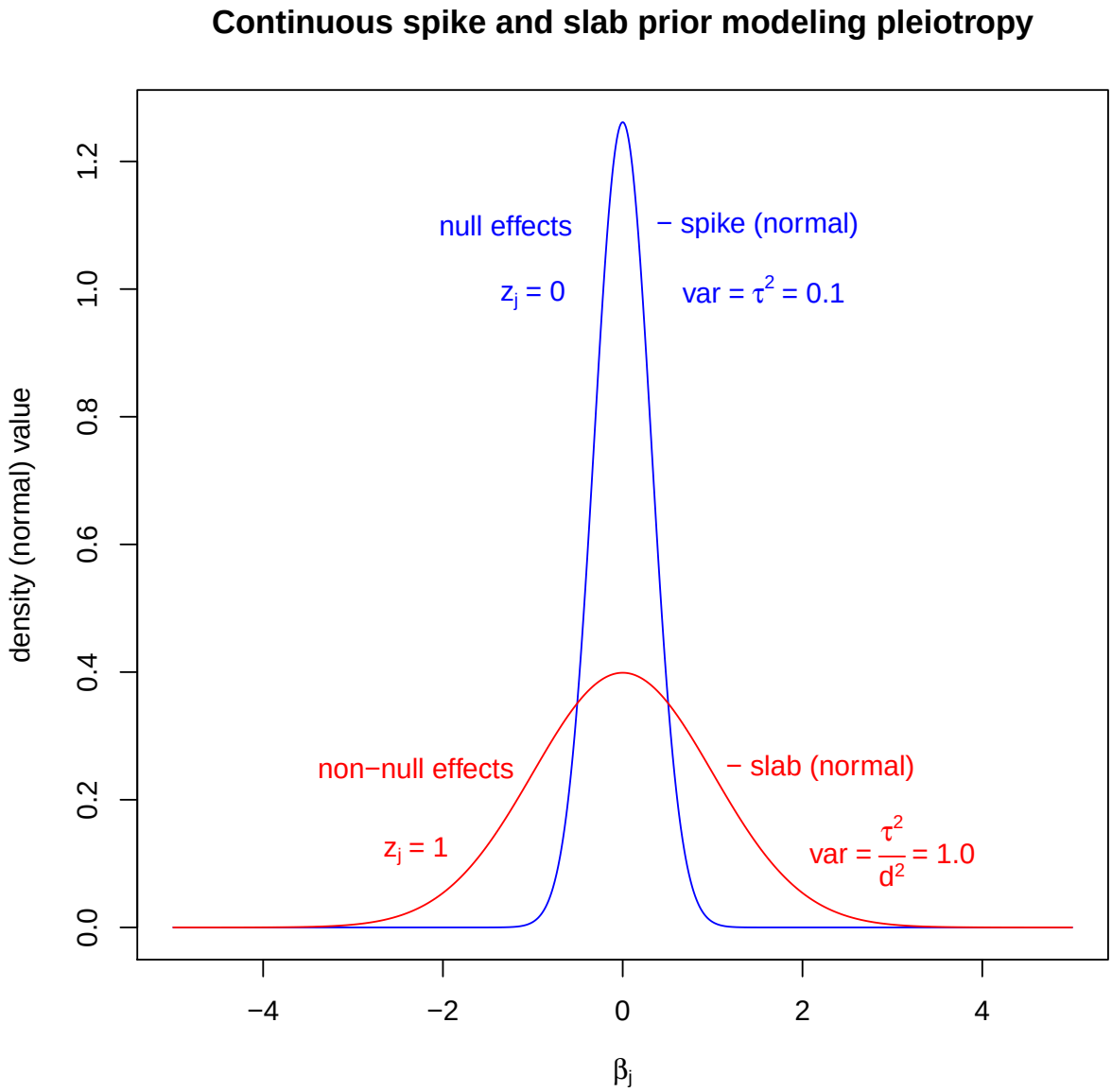


Table 1: Simulation study results. Summary of measures of the evidence of the overall pleiotropic association under the global null hypothesis of no association when multiple case-control studies are considered without any overlapping subjects. We considered a separate group of 7000 cases and 10000 controls in each study.

						quantiles						
K	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
5	0.3	$\log_{10}$BF	-2.76	0.22	-3.02	-2.99	-2.92	-2.82	-2.68	-2.35	-1.94	-1.46
		-$\log_{10}$PPNA	0.03	0.02	0.01	0.01	0.02	0.02	0.03	0.06	0.13	0.32
		-$\log_{10}$ASTpv	0.48	0.47	0.00	0.01	0.13	0.33	0.68	1.45	1.97	2.88
	0.1	$\log_{10}$BF	-2.57	0.28	-2.86	-2.81	-2.74	-2.65	-2.49	-2.12	-1.39	-0.26
		-$\log_{10}$PPNA	0.05	0.08	0.02	0.02	0.02	0.03	0.04	0.09	0.35	1.25
		-$\log_{10}$ASTpv	0.43	0.44	0.00	0.005	0.11	0.30	0.60	1.24	2.14	2.63
10	0.3	$\log_{10}$BF	-4.29	0.22	-4.59	-4.51	-4.42	-4.35	-4.22	-3.92	-3.54	-2.41
		-$\log_{10}$PPNA	0.03	0.04	0.01	0.01	0.02	0.02	0.03	0.05	0.11	0.70
		-$\log_{10}$ASTpv	0.32	0.42	0.00	0.00	0.04	0.17	0.44	1.14	1.82	2.99
	0.1	$\log_{10}$BF	-4.09	0.23	-4.42	-4.34	-4.24	-4.15	-4.01	-3.65	-3.18	-2.55
		-$\log_{10}$PPNA	0.04	0.04	0.02	0.02	0.02	0.03	0.04	0.09	0.22	0.59
		-$\log_{10}$ASTpv	0.30	0.38	0.00	0.00	0.04	0.17	0.44	1.05	1.66	2.53
15	0.3	$\log_{10}$BF	-5.76	0.20	-6.04	-5.96	-5.88	-5.81	-5.70	-5.36	-4.99	-4.20
		-$\log_{10}$PPNA	0.03	0.03	0.01	0.02	0.02	0.02	0.03	0.06	0.12	0.48
		-$\log_{10}$ASTpv	0.24	0.38	0.00	0.00	0.001	0.08	0.34	0.89	1.42	4.37
	0.1	$\log_{10}$BF	-5.55	0.23	-5.85	-5.78	-5.69	-5.61	-5.49	-5.13	-4.61	-4.16
		-$\log_{10}$PPNA	0.05	0.04	0.02	0.02	0.03	0.03	0.04	0.09	0.25	0.51
		-$\log_{10}$ASTpv	0.24	0.41	0.00	0.00	0.00	0.08	0.32	1.05	1.78	4.40

Legend: K - total number of phenotypes, m - allele frequency at the marker SNP; $K = 5$, 10, 15, and $m = 0.3$, 0.1. The following abbreviations denote – $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$ASTpv: -$\log_{10}$(ASSET p-value). For multiple studies with no overlapping subjects, the uncorrelated version of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table 2: Summary of measures for the evidence of the overall pleiotropic association under the global null hypothesis of no association when multiple case-control studies with overlapping subjects are considered. We considered a distinct set of 7000 cases in each study and a common set of 10000 controls shared across all the studies.

						quantile						
K	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
5	0.3	$\log_{10}$BF	-2.88	0.18	-3.10	-3.06	-3.00	-2.93	-2.81	-2.49	-2.12	-2.04
		-$\log_{10}$PPNA	0.02	0.01	0.01	0.01	0.01	0.02	0.02	0.04	0.09	0.11
		-$\log_{10}$ASTpv	0.26	0.38	0.00	6.18E-05	0.02	0.10	0.34	1.03	1.75	2.34
	0.1	$\log_{10}$BF	-2.67	0.24	-2.94	-2.89	-2.83	-2.75	-2.58	-2.18	-1.79	-1.22
		-$\log_{10}$PPNA	0.03	0.04	0.02	0.02	0.02	0.02	0.03	0.08	0.18	0.46
		-$\log_{10}$ASTpv	0.27	0.41	0.00	2.35E-05	0.02	0.10	0.32	1.17	1.72	3.43
10	0.3	$\log_{10}$BF	-4.40	0.18	-4.64	-4.59	-4.52	-4.45	-4.34	-4.04	-3.76	-3.41
		-$\log_{10}$PPNA	0.02	0.01	0.01	0.01	0.01	0.02	0.02	0.04	0.07	0.15
		-$\log_{10}$ASTpv	0.15	0.36	0.00	0.00	0.00	0.0003	0.04	0.98	1.62	2.19
	0.1	$\log_{10}$BF	-4.20	0.23	-4.47	-4.43	-4.35	-4.26	-4.12	-3.78	-3.39	-2.05
		-$\log_{10}$PPNA	0.03	0.05	0.01	0.02	0.02	0.02	0.03	0.07	0.15	1.01
		-$\log_{10}$ASTpv	0.15	0.39	0.00	0.00	0.00	6.71E-06	0.04	0.98	1.91	3.42
15	0.3	$\log_{10}$BF	-5.90	0.15	-6.12	-6.07	-6.01	-5.93	-5.84	-5.60	-5.38	-5.19
		-$\log_{10}$PPNA	0.02	0.01	0.01	0.01	0.01	0.02	0.02	0.03	0.06	0.08
		-$\log_{10}$ASTpv	0.10	0.33	0.00	0.00	0.00	0.00	0.002	0.81	1.62	2.27
	0.1	$\log_{10}$BF	-5.68	0.21	-5.96	-5.89	-5.81	-5.73	-5.61	-5.32	-4.82	-4.15
		-$\log_{10}$PPNA	0.03	0.03	0.02	0.02	0.02	0.03	0.03	0.06	0.17	0.52
		-$\log_{10}$ASTpv	0.13	0.42	0.00	0.00	0.00	0.00	0.003	1.03	2.22	3.37

Legend: K - total number of phenotypes, m - allele frequency at the marker SNP; K = 5, 10, 15, and m = 0.3, 0.1. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$ASTpv: -$\log_{10}$(ASSET p-value). For multiple studies with overlapping subjects, since the summary statistics are correlated, the combined strategy of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Figure 2: Simulation study results. Bayes factor and PPNA for five non-overlapping and overlapping case-control studies across 100 replications. The red colored band presents (mean − standard deviation, mean + standard deviation) of the Bayes factor or PPNA across the replications.

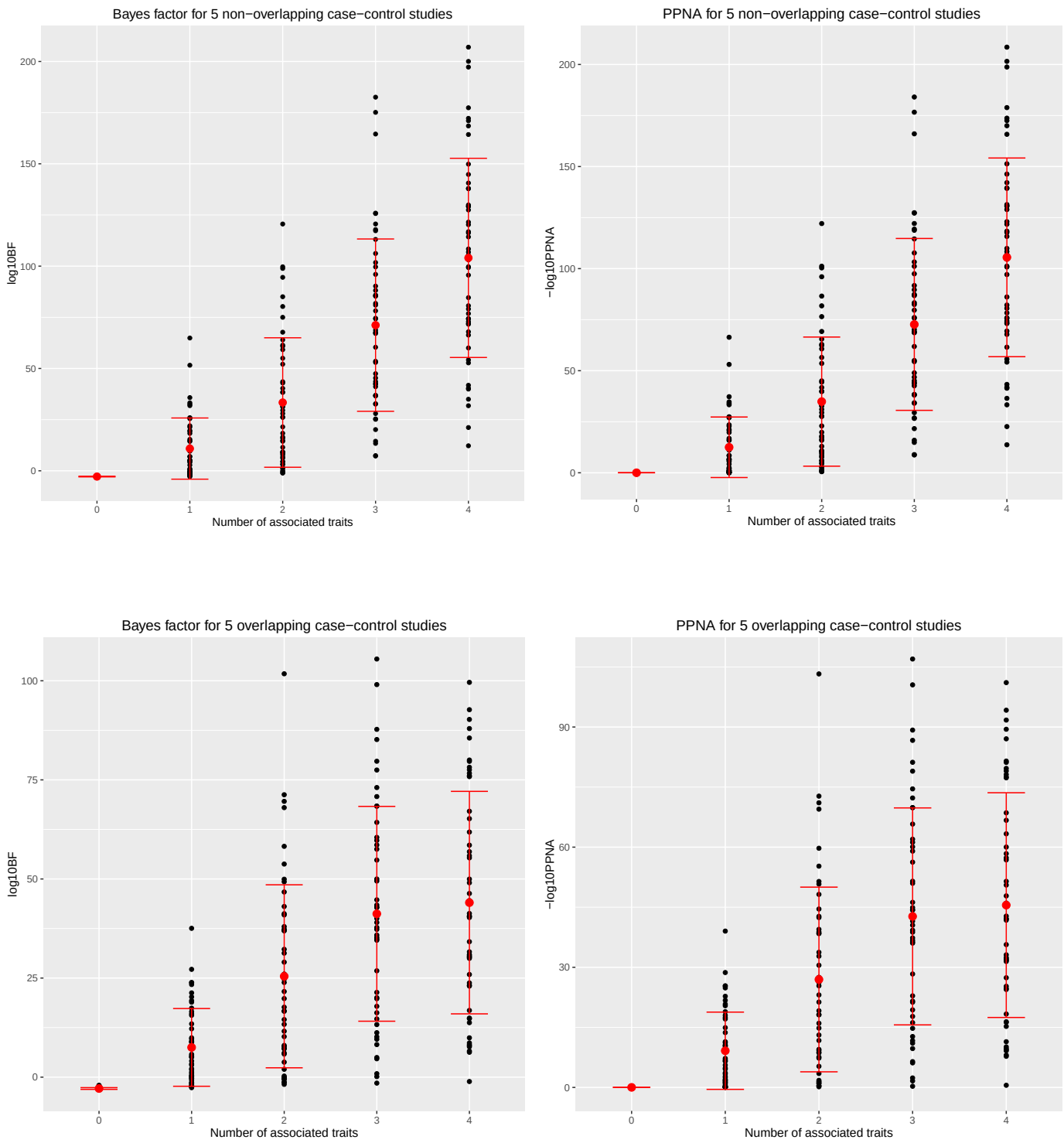


Figure 3: Simulation study results. Comparison of the accuracy of selection of associated traits by CPBayes and ASSET for multiple non-overlapping case-control studies. The total number of phenotypes/studies is denoted by K and m denotes the minor allele frequency at the risk SNP.

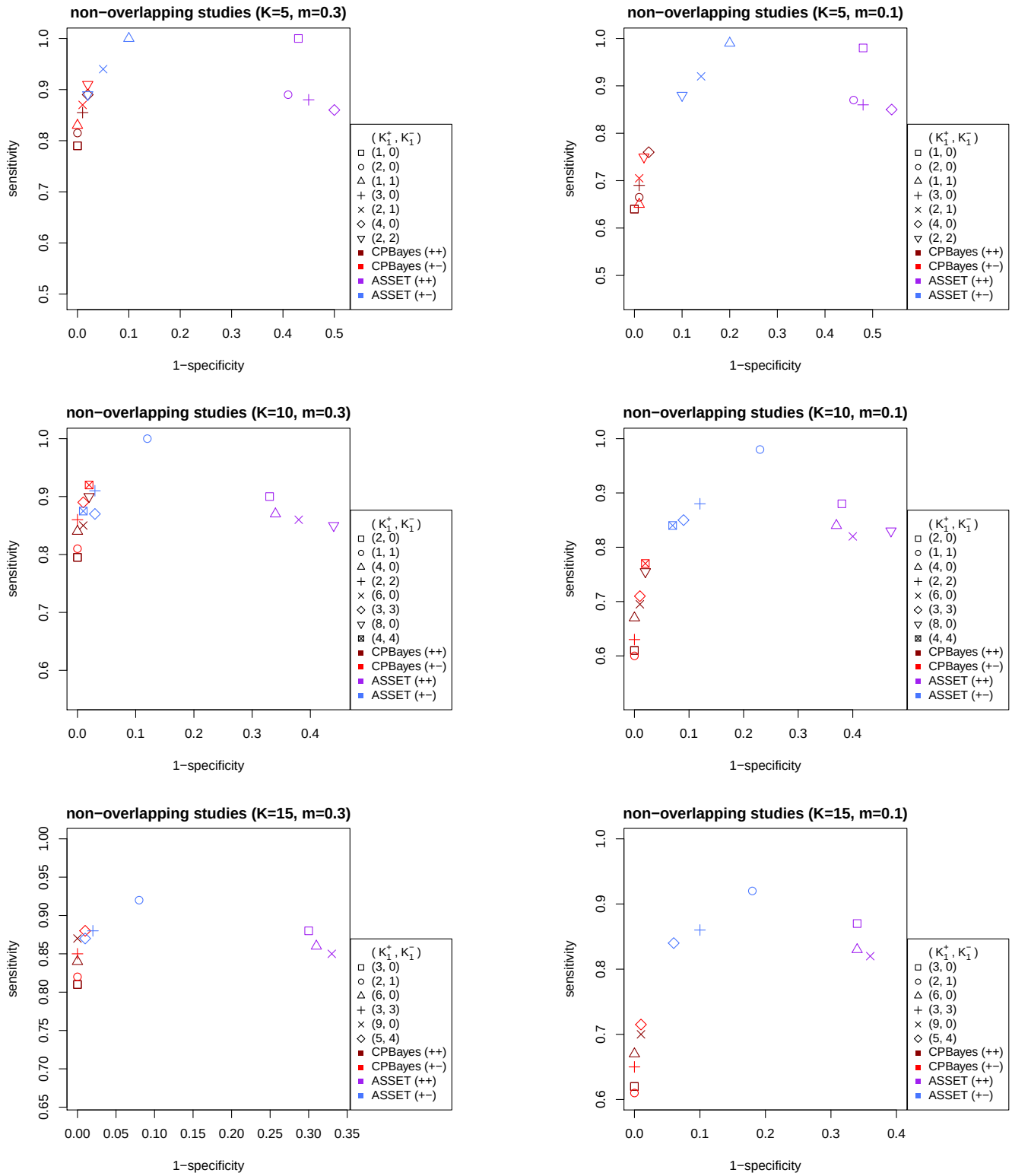


Figure 4: Comparison of the accuracy of selection of associated traits by CPBayes and ASSET for multiple overlapping case-control studies. The total number of phenotypes/studies is denoted by K and m denotes the minor allele frequency at the risk SNP.

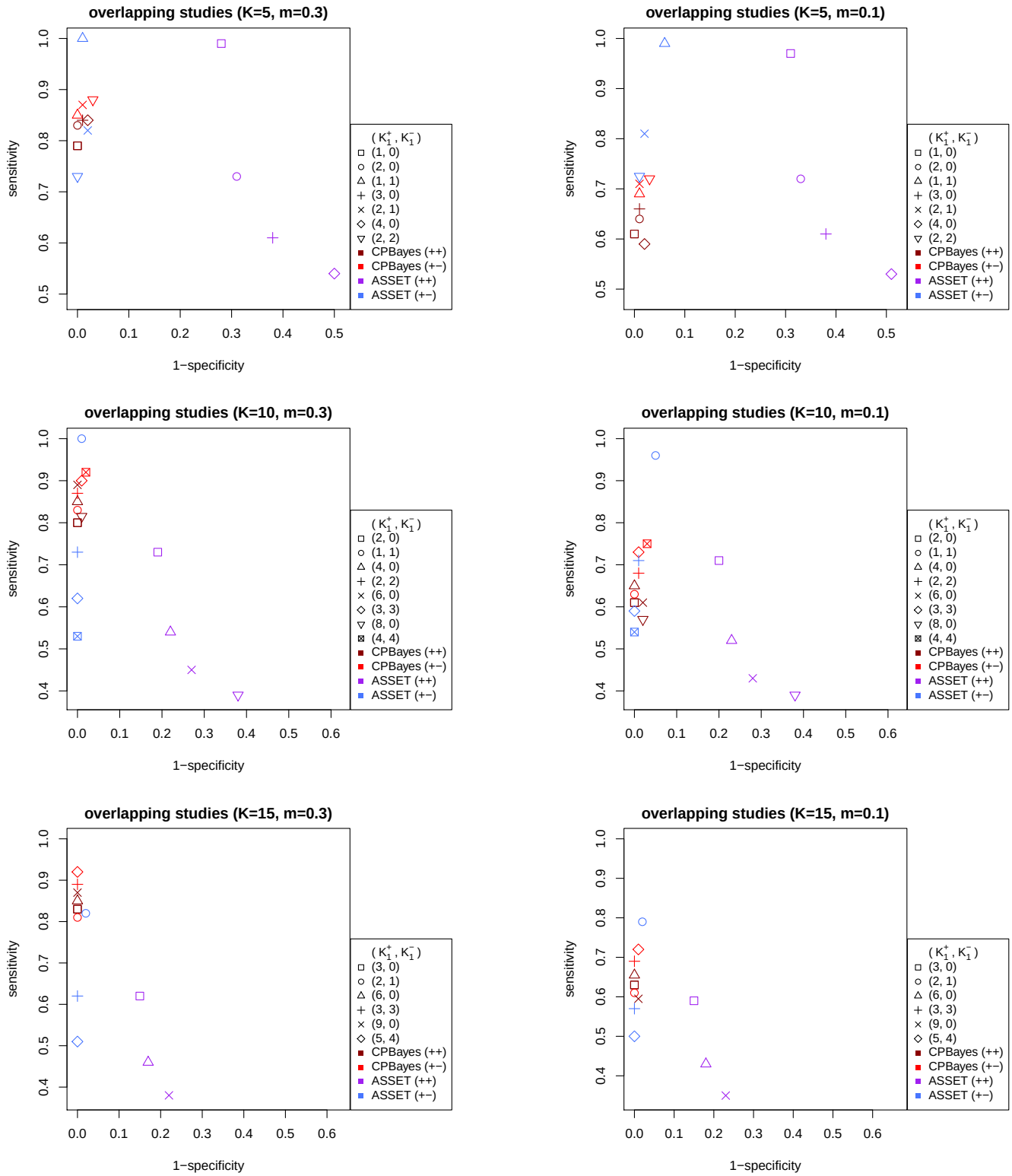


Table 3: Independent pleiotropic SNPs detected by CPBayes which are associated with at least two phenotypes.

rsID	chrom band	CPBayes $\log_{10}$BF	CPBayes PPNA	Subset of associated traits	PPA_j	Direction	Univariate p-values
rs6025	1q24.2	270.68	4.97E-278	Dermatophytosis	70%	positive	0.0018
				Hemorrhoids	73.6%	positive	0.0014
				Iron Deficiency	95.3%	positive	0.0004
				Osteoporosis	87.8%	negative	0.0002
				Peripheral Vascular Disease	100%	negative	6.81E-14
rs7601401	2p16.1	9.69	4.91E-17	Abdominal Hernia	100%	positive	3.88E-12
				Osteoarthritis	86.7%	positive	3.46E-06
rs17661572	2p21	8.47	8.10E-16	Allergic Rhinitis	94%	negative	4.32E-05
				Insomnia	98.4%	positive	0.0001
rs387608	6p21.33	29.06	2.07E-36	Cancers	54.7%	positive	0.0001
				Macular Degeneration	100%	positive	4.29E-12
rs10455872	6q25.3	26.20	1.49E-33	Cardiovascular Disease	72.9%	negative	6.14E-05
				Dyslipidemia	100%	negative	6.97E-15
				Peripheral Vascular Disease	66.8%	negative	0.0002
rs3830123	6p21.32	22.31	1.16E-29	Cancers	99.9%	negative	1.01E-07
				Dyslipidemia	100%	negative	5.55E-13
rs9275476	6p21.32	22.10	1.88E-29	Asthma	100%	negative	5.61E-08
				Type 2 Diabetes	100%	negative	4.27E-06
				Macular Degeneration	56%	positive	0.0011
rs651007	9q34.2	24.72	4.57E-32	Dyslipidemia	100%	negative	2.89E-15
				Peripheral Vascular Disease	100%	negative	9.55E-08
rs4506565	10q25.2	117.08	1.96E-124	Type 2 Diabetes	100%	negative	2.02E-55
				Dyslipidemia	60.6%	negative	1.33E-06

Legend: The chromosome band of a SNP is denoted by 'chrom band'. Direction means whether the SNP is positively or negatively associated with the phenotype.

Table 4: Pairwise trait-trait pleiotropic signals detected by CPBayes

	Dyslipidemia	Hemorrhoids	Insomnia	Iron Deficiency	Macular Degeneration	Osteoarthritis	Osteoporosis	Peripheral Vascular Disease	Type 2 Diabetes
Abdominal Hernia						rs7601401 (2p16.1)			
Allergic Rhinitis			rs17661572 (2p21)						
Asthma					rs9275476 (6p21.32)				rs9275476 (6p21.32)
Cancers	rs3830123 (6p21.32)				rs387608 (6p21.33)				
Cardiovascular Disease	rs10455872 (6q25.3)							rs10455872 (6q25.3)	
Dermatophytosis		rs6025 (1q24.2)		rs6025 (1q24.2)			rs6025 (1q24.2)	rs6025 (1q24.2)	
Dyslipidemia								rs10455872 (6q25.3) rs651007 (9q34.2)	rs4506565 (10q25.2)
Hemorrhoids				rs6025 (1q24.2)			rs6025 (1q24.2)	rs6025 (1q24.2)	
Iron Deficiency							rs6025 (1q24.2)	rs6025 (1q24.2)	
Macular Degeneration									rs9275476 (6p21.32)
Osteoporosis								rs6025 (1q24.2)	

Table 5: Pleiotropy results by CPBayes for those SNPs in Table 3 and S19, at which some phenotypes (colored blue) were not selected in the optimal subset of non-null traits but produced a non-negligible value of trait-specific posterior probability of association (PPA_j).

rsID	chrom band	CPBayes log10BF	CPBayes PPNA	Important phenotypes	PPA_j	Univariate p-values
rs115946033	3q25.32	8.59	6.07E-16	Depressive Disorder	37.2%	0.0008
				Type 2 Diabetes	100%	3.83E-07
rs849135	7p15.1	7.66	5.22E-15	Asthma	40.2%	2.19E-05
				Type 2 Diabetes	100%	1.79E-14
rs76517520	10p13	13.60	5.95E-21	Macular Degeneration	25.7%	0.02
				Peptic Ulcer	100%	1.39E-05
rs76075198	19q13.31	41.56	6.53E-49	Dyslipidemia	100%	5.29E-11
				Peripheral Vascular Disease	44.9%	0.0067

Figure 5: Forest plot for pleiotropic signal at rs6025 on chromosome 1. Phenotypes selected by either of the two methods are plotted. Blue colored bands present the primary trait-specific univariate odds ratio estimate with the corresponding 95% confidence interval. Red colored bands present the posterior mean of the trait-specific odds ratio along with the corresponding 95% credible interval obtained by CPBayes. The y-axis represents the value of odds ratio as 1 (null association). The $\log_{10}$BF obtained by CPBayes and -$\log_{10}$(ASSET p-value) (-$\log_{10}$ASTpv) are provided. Whether a phenotype was selected by a method is indicated by 'Yes' or 'No'. Trait-specific univariate association p-values are also provided.

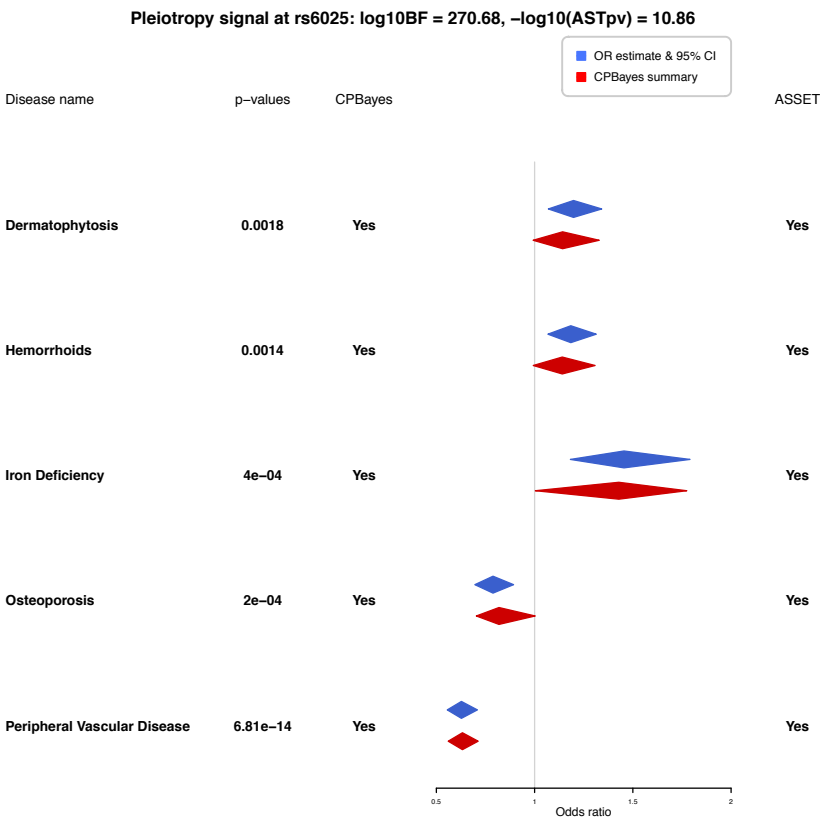


Figure 6: Forest plot for pleiotropic signal at rs10455872 on chromosome 6. Phenotypes selected by either of the two methods are plotted. Blue colored bands present the primary trait-specific univariate odds ratio estimate with the corresponding 95% confidence interval. Red colored bands present the posterior mean of the trait-specific odds ratio along with the corresponding 95% credible interval obtained by CPBayes. The y-axis represents the value of odds ratio as 1 (null association). The $\log_{10}$BF obtained by CPBayes and -$\log_{10}$(ASSET p-value) (-$\log_{10}$ASTpv) are provided. Whether a phenotype was selected by a method is indicated by 'Yes' or 'No'. Trait-specific univariate association p-values are also provided.

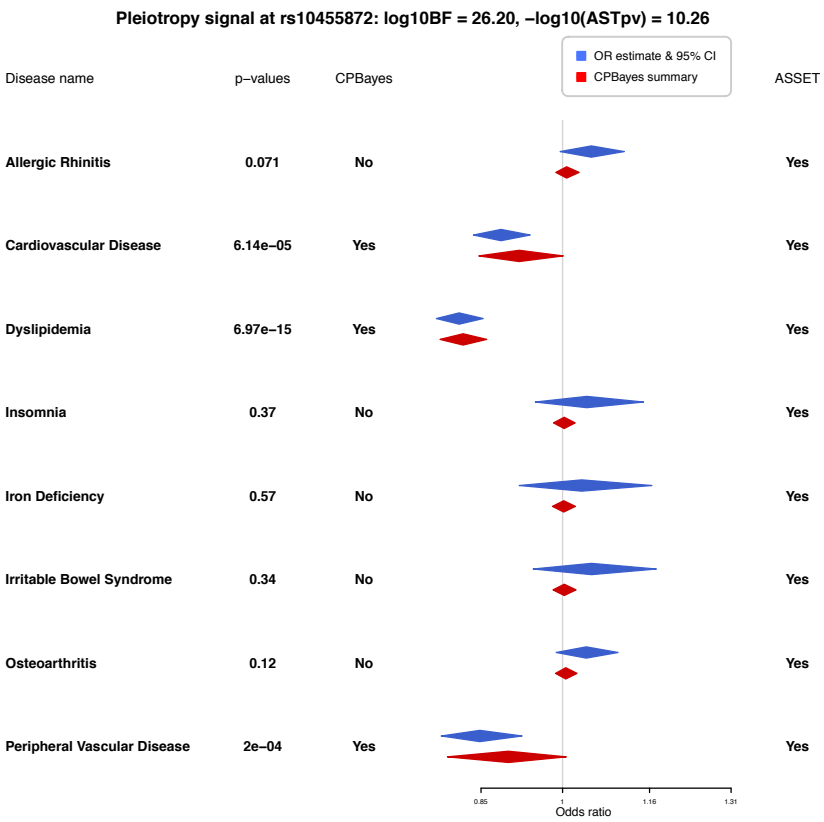
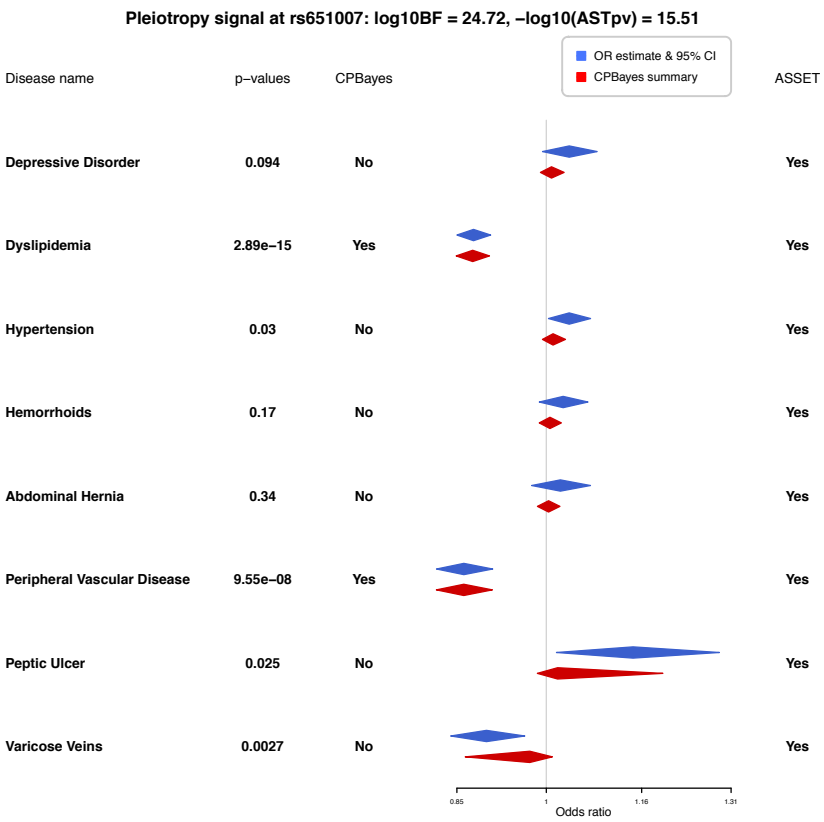


Figure 7: Forest plot for pleiotropic signal at rs651007 on chromosome 9. Phenotypes selected by either of the two methods are plotted. Blue colored bands present the primary trait-specific univariate odds ratio estimate with the corresponding 95% confidence interval. Red colored bands present the posterior mean of the trait-specific odds ratio along with the corresponding 95% credible interval obtained by CPBayes. The y-axis represents the value of odds ratio as 1 (null association). The $\log_{10}$BF obtained by CPBayes and -$\log_{10}$(ASSET p-value) (-$\log_{10}$ASTpv) are provided. Whether a phenotype was selected by a method is indicated by 'Yes' or 'No'. Trait-specific univariate association p-values are also provided.



Supplementary materials for "An efficient Bayesian meta-analysis approach for studying cross-phenotype genetic associations" by Arunabha Majumdar, Tanushree Haldar, Sourabh Bhattacharya, John S. Witte.

7 Outline of mathematical derivation of the full conditional posterior distributions for the continuous spike

7.1 Correlated case

Here we derive the full conditional posterior distributions of the model parameters to perform Gibbs sampling for correlated summary statistics. If S is the covariance matrix of $\hat{\boldsymbol{\beta}}$,

$$\hat{\boldsymbol{\beta}}|\boldsymbol{\beta}, S \sim \text{MVN}(\boldsymbol{\beta}, S).$$

For $j = 1, \ldots, K$,

$$\begin{aligned}
&\beta_j|z_j, \tau, d \overset{ind}{\sim} (1 - z_j)\ N(0, \tau^2) + z_j\ N(0, \left(\frac{\tau}{d}\right)^2);\ \ \tau > 0,\ 0 < d < 1,\ \left(\frac{\tau}{d}\right)^2 > \tau^2 \\
&P(z_j = 1|q) = q;\ \ P(z_j = 0|q) = (1 - q);\ 0 < q < 1 \\
&q|c_1, c_2 \sim \text{Beta}(c_1, c_2) \Rightarrow P(z_j = 1) = E(q) = \frac{c_1}{c_1 + c_2} \\
&d|e_1, e_2 \sim \text{Beta}(e_1, e_2)
\end{aligned} \tag{8}$$

So, $\beta_j|z_j = 0, \tau \sim \text{N}(0, \tau^2)$ and $\beta_j|z_j = 1, \tau, d \sim \text{N}(0, (\frac{\tau}{d})^2)$. Let $\Sigma_1 = S$. Define, $\Sigma_2 = diag(\tau_1^2, \ldots, \tau_K^2)$ (a diagonal matrix with the diagonal elements $\tau_1^2, \ldots, \tau_K^2$), where $\tau_j = \tau$ if $z_j = 0$, and $\tau_j = \frac{\tau}{d}$ if $z_j = 1$, $j = 1, \ldots, K$. So,

$$\boldsymbol{\beta}|Z, \tau, d \sim \text{MVN}(\underset{\sim}{0}, \Sigma_2), \tag{9}$$

7.1.1 Full conditional posterior distribution of $\boldsymbol{\beta}$

Let $[U]$ denote a generic notation of the probability distribution of a random variable U, and $[U_1|U_2]$ denote a generic notation of the conditional probability distribution of U_1 given U_2. We have considered fixed choice of τ. Hence we drop it from the set of conditional parameters while writing the expressions of the full conditional distributions. For example, we write $[\boldsymbol{\beta}|Z, q, d, \hat{\boldsymbol{\beta}}]$ instead of $[\boldsymbol{\beta}|Z, q, \tau, d, \hat{\boldsymbol{\beta}}]$. Note that,

$$[\boldsymbol{\beta}|Z, q, d, \hat{\boldsymbol{\beta}}] \propto [\hat{\boldsymbol{\beta}}, \boldsymbol{\beta}, Z, q, d] \propto [\hat{\boldsymbol{\beta}}|\boldsymbol{\beta}]\ [\boldsymbol{\beta}|Z, d] \tag{10}$$

Applying standard techniques from linear algebra and distribution theory of multivariate normal, one can obtain that:

$$\boldsymbol{\beta}|Z, q, d, \hat{\boldsymbol{\beta}} \sim \text{MVN}[(\Sigma_1^{-1} + \Sigma_2^{-1})^{-1}\Sigma_1^{-1}\hat{\boldsymbol{\beta}}, (\Sigma_1^{-1} + \Sigma_2^{-1})^{-1}] \tag{11}$$

Note that Σ_2 is dependent on Z, and Z influences the full conditional posterior distribution of $\boldsymbol{\beta}$ through the specification of Σ_2.

7.1.2 Full conditional posterior distribution of Z

Let $Z_{-j} = (z_1, \ldots, z_{j-1}, z_{j+1}, \ldots, z_K)$. Note that, $P(z_j = 0|Z_{-j}, \boldsymbol{\beta}, q, d, \hat{\boldsymbol{\beta}}) \propto [\beta_j|z_j = 0]\ [z_j = 0|q]$. Similarly, $P(z_j = 1|Z_{-j}, \boldsymbol{\beta}, q, d, \hat{\boldsymbol{\beta}}) \propto [\beta_j|z_j = 1, d]\ [z_j = 1|q]$. Combining these two equations, we obtain that:

$$P(z_j = 0|Z_{-j}, \boldsymbol{\beta}, q, d, \hat{\boldsymbol{\beta}}) = \frac{1}{1 + \text{ratio}_j}, \text{ where ratio}_j = \frac{q}{1-q}\ d\ \exp[-\frac{\beta_j^2}{2\tau^2}\ (d^2 - 1)] \tag{12}$$

We note that the full conditional posterior distribution of z_j does not depend on Z_{-j}. Hence, the full conditional distributions of $z_1, \ldots, z_K$ are independent.

7.1.3 Full conditional posterior distribution of q

Note that, $[q|\boldsymbol{\beta}, Z, d, \hat{\boldsymbol{\beta}}] \propto [Z|q]\ [q] \propto \prod_{j=1}^{K}[z_j|q]\ [q]$. Let $k_1 = \sum_{j=1}^{K} z_j$, and $k_0 = K - k_1$. Then it can easily be derived that:

$$q|\boldsymbol{\beta}, Z, d, \hat{\boldsymbol{\beta}} \sim \text{Beta}(c_1 + k_1, c_2 + k_0) \tag{13}$$

7.1.4 Full conditional posterior distribution of d

We assume that $e_2 = 1$ and derive a closed-form full conditional posterior distribution of d under this restriction. Let $\sum_{j:z_j=1} z_j = k_1$.

<u>Case 1</u>: $k_1 > 0$

Of note, $[d|\boldsymbol{\beta}, Z, q, \hat{\boldsymbol{\beta}}] \propto \prod_{j:z_j=1}[\beta_j|z_j = 1, d]\ [d] \propto \exp[-C \times d^2] \times d^{(k_1+e_1)-1}$, where $C = \frac{1}{2\tau^2}\sum_{j:z_j=1}\beta_j^2$. We consider the following transformation of variable: $y = 2Cd^2$. It can be derived that: $y\ \sim \chi^2_{k_1+e_1}$ under the assumption that $y > 0$.

Suppose that, we want to update the slab variance $(\frac{\tau}{d})^2$ in a range (say, $v_0 - v_1$) such that the corresponding range of d is given by: $d_0 < d < d_1$. Using the above transformation of variable, the corresponding range of y is given by: $2Cd_0^2 < y < 2Cd_1^2$. Hence, $y\ \sim$ truncated central $\chi^2_{k_1+e_1}$, where $2Cd_0^2 < y < 2Cd_1^2$. Finally, the updated d can be obtained by using the transformation $d = \sqrt{\frac{y}{2C}}$.

<u>Case 2</u>: $k_1 = 0$

It can easily be shown that: $d|\boldsymbol{\beta}, Z, q, \hat{\boldsymbol{\beta}} \sim$ truncated Beta$(e_1, 1)$, where $d_0 < d < d_1$.

In the Algorithm 1 in main text, we considered $e_1 = 1$, which is a natural choice under the absence of any prior information.

7.2 Uncorrelated case

When the summary statistics are uncorrelated, the full conditional posterior distributions of all the parameters except $\boldsymbol{\beta}$ remain the same as in the correlated case (described above). Now the full conditional distributions of $\beta_1, \ldots, \beta_K$ become independent. For $j = 1, \ldots, K$,

$$\hat{\beta}_j|\beta_j \overset{ind}{\sim} \mathrm{N}(\beta_j, s_j^2), \text{ and } [\beta_j|\boldsymbol{\beta}_{-j}, Z, q, d, \hat{\boldsymbol{\beta}}] \propto [\hat{\beta}_j|\beta_j] \times [\beta_j|z_j, d] \tag{14}$$

Using the above equation, it's easy to derive the full conditional distribution as: for $j = 1, \ldots, K$, $\beta_j|\boldsymbol{\beta}_{-j}, Z, q, d, \hat{\boldsymbol{\beta}} \overset{ind}{\sim} \mathrm{N}(\frac{\sigma_j^2}{s_j^2}\hat{\beta}_j, \sigma_j^2)$, where $\frac{1}{\sigma_j^2} = \frac{1}{s_j^2} + \frac{1}{\tau_j^2}$.

8 Gibbs sampling algorithm for the Dirac spike

Here we outline the Gibbs sampler for the Dirac spike. We apply the BY procedure [Benjamini and Yekutieli, 2001] on the univariate association p-values of K traits at an FDR level of 0.05 and assign $\beta_j = \hat{\beta}_j$ (since $\hat{\beta}_j$ is a consistent estimator of β_j) if Y_j is found to be associated, otherwise we set $\beta_j = 0$; $j = 1, \ldots, K$. We also choose an initial value of q as the proportion of non-null/associated traits detected by the BY procedure (the boundary situations of no/all non-null traits are taken care of appropriately).

Let $\boldsymbol{\beta}_{-j} = \{\beta_1, \ldots, \beta_{j-1}, \beta_{j+1}, \ldots, \beta_K\}$. Consider the following partition of S:

$$S = \begin{bmatrix} s_j^2 & S_{j,-j} \\ S_{-j,j} & S_{-j,-j} \end{bmatrix}$$

Let $\bar{\sigma}_j^2 = s_j^2 - (S_{j,-j} \times S_{-j,-j}^{-1} \times S_{-j,j})$, and $m_{j,-j} = \hat{\beta}_j - (S_{j,-j} \times S_{-j,-j}^{-1} \times (\hat{\boldsymbol{\beta}}_{-j} - \boldsymbol{\beta}_{-j}))$.

Algorithm 2 Gibbs sampling for the Dirac spike for correlated summary statistics

1: *Start*:
2: Assign the initial values of $\boldsymbol{\beta}$ and q as discussed above.
3: *loop*:
4: For $j = 1, \ldots, K$, update β_j as follows: set $\beta_j = 0$ with probability $P(\beta_j = 0|\boldsymbol{\beta}_{-j}, q, b, \hat{\boldsymbol{\beta}}) = \frac{1}{1+\text{ratio}_j}$, where $\text{ratio}_j = \frac{q}{(1-q)}\frac{\sigma_j}{b}e^{\frac{m^2_{j,-j}\times\sigma^2_j}{2\sigma^4_j}}$. If β_j is selected to be non-zero, simulate it from $\beta_j|\boldsymbol{\beta}_{-j}, q, b, \hat{\boldsymbol{\beta}} \sim \text{N}(\frac{\sigma^2_j m_{j,-j}}{\bar{\sigma}^2_j}, \sigma^2_j)$, where $\frac{1}{\sigma^2_j} = \frac{1}{\bar{\sigma}^2_j} + \frac{1}{b^2}$.
5: Let $k_0 = \#\{\beta_j : \beta_j = 0,\ j = 1, \ldots, K\}$. Update q using it's full conditional posterior distribution which is a mixture of (k_0+1) Beta distributions as follows: for $j = 0, 1, \ldots, k_0$, $q|\boldsymbol{\beta}, b, \hat{\boldsymbol{\beta}} \sim \text{Beta}(c_1+K-j, c_2+j)$ with probability $\propto \binom{k_0}{j}(\frac{1}{\sqrt{2\pi}\times b})^{K-j} \times Beta(c_1+K-j, c_2+j)$. Here $Beta(r_1, r_2)$ denotes the normalizing constant of a $\text{Beta}(r_1, r_2)$ distribution.
6: Let $b = \frac{1}{v}$, where $v > 0$. Suppose, we want to update b in a given range (b_0, b_1), and the corresponding range of v is given by: (v_0, v_1). We consider a uniform prior on v. Let $k_1 = K - k_0$ and $t_j = K - j + 1$.

If $k_1 > 0$, let $C = \sum_{j=1}^{K} \beta^2_j$. We update v using the transformation: $v = \frac{\sqrt{y}}{\sqrt{C}}$, where y follows a mixture of $(k_0 + 1)$ distributions – the jth distribution is a truncated (between v_0^2C – v_1^2C) central chi-square distribution with degree of freedom t_j, $j = 0, 1, \ldots, k_0$. The jth distribution is selected with probability $w_j \propto w_j^{(1)}w_j^{(2)}w_j^{(3)}w_j^{(4)}$; $w_j^{(1)} = \frac{1}{(2\pi)^{\frac{K-j}{2}}}\binom{k_0}{j}(1-q)^j q^{K-j}$, $w_j^{(2)} = \frac{1}{2(v_1-v_0)}\frac{1}{C^{\frac{t_j}{2}}}$, $w_j^{(3)} = 2^{\frac{t_j}{2}} \times \Gamma(\frac{t_j}{2})$, $w_j^{(4)} = P(v_0^2C < \chi^2_{t_j} < v_1^2C)$, where $\chi^2_{t_j}$ is a central chi-square distribution with d.f. t_j.

If $k_1 = 0$, the full conditional posterior distribution of v is a mixture of $(K + 1)$ distributions. For $j = 0, 1, \ldots, K$, the jth distribution of the mixture is given by: $t_j \times \frac{v^{K-j}}{v_1^{t_j} - v_0^{t_j}}$, $v_0 < v < v_1$; and it is selected with probability $w_j \propto w_j^{(1)} \times w_j^{(2)}$, where $w_j^{(1)} = \frac{1}{v_1-v_0}\frac{1}{(2\pi)^{\frac{K-j}{2}}}\binom{K}{j}(1-q)^j q^{K-j}$ and $w_j^{(2)} = \frac{1}{t_j}(v_1^{t_j} - v_0^{t_j})$.
7: **goto** *loop* until all MCMC iterations are finished.

If the summary statistics are uncorrelated, step 4 of Algorithm 2 is modified as: for $j = 1, \ldots, K$, set $\beta_j = 0$ with probability $P(\beta_j = 0|\boldsymbol{\beta}_{-j}, q, b, \hat{\boldsymbol{\beta}}) = \frac{1}{1+\text{ratio}_j}$, where $\text{ratio}_j = (\frac{q}{1-q}) \times \frac{\sigma_j}{b} \times \exp[\frac{\hat{\beta}^2_j\sigma^2_j}{2s^4_j}]$, and $\frac{1}{\sigma^2_j} = \frac{1}{s^2_j} + \frac{1}{b^2}$; if β_j is selected to be non-zero, simulate it from $\beta_j|\boldsymbol{\beta}_{-j}, q, b, \hat{\boldsymbol{\beta}} \sim \text{N}(\frac{\sigma^2_j}{s^2_j}\hat{\beta}_j, \sigma^2_j)$. All the other steps of the algorithm remain the same.

9 Outline of mathematical derivation of the full conditional posterior distributions for the Dirac spike

9.1 Correlated case

$$\hat{\beta}_j|\beta_j \sim \text{N}(\beta_j, s^2_j), \text{ and } \hat{\boldsymbol{\beta}}|\boldsymbol{\beta}, S \sim \text{MVN}(\boldsymbol{\beta}, S)$$

$$\beta_j|q, b \overset{i.i.d.}{\sim} (1-q) \times \delta_{\{0\}}(\beta_j) + q \times \text{N}(0, b^2);\ q|c_1, c_2 \sim \text{Beta}(c_1, c_2),\ 0 < q < 1.$$

$\delta_{\{0\}}(\beta_j)$ is defined as: $\delta_{\{0\}}(\beta_j) = 1$ when $\beta_j = 0$, and $\delta_{\{0\}}(\beta_j) = 0$ when $\beta_j \neq 0$. The full likelihood of the model is given by: $[\hat{\boldsymbol{\beta}}|\boldsymbol{\beta}] \times [\boldsymbol{\beta}|q, b] \times [q] \times [b]$, where $[\boldsymbol{\beta}|q, b] = \prod_{j=1}^{K}[\beta_j|q, b]$. Next we derive the full conditional posterior distributions of different parameters. Let $\hat{\boldsymbol{\beta}}_{-j} = \{\hat{\beta}_1, \ldots, \hat{\beta}_{j-1}, \hat{\beta}_{j+1}, \ldots, \hat{\beta}_K\}$ and $\boldsymbol{\beta}_{-j} = \{\beta_1, \ldots, \beta_{j-1}, \beta_{j+1}, \ldots, \beta_K\}$.

9.1.1 Full conditional posterior distribution of $\boldsymbol{\beta}$

For $j = 1$, it can be shown that:

$$\begin{aligned}[\beta_1|\boldsymbol{\beta}_{-1}, q, b, \hat{\boldsymbol{\beta}}] &\propto [\hat{\boldsymbol{\beta}}, \beta_1, \boldsymbol{\beta}_{-1}, q, b] \\ &\propto [\hat{\beta}_1|\hat{\boldsymbol{\beta}}_{-1}, \beta_1, \boldsymbol{\beta}_{-1}, q, b] \times [\hat{\boldsymbol{\beta}}_{-1}, \beta_1, \boldsymbol{\beta}_{-1}, q, b] \\ &\propto [\hat{\beta}_1|\hat{\boldsymbol{\beta}}_{-1}, \boldsymbol{\beta}] \times [\beta_1|q, b]\end{aligned} \tag{15}$$

A general result: Suppose, $Y \sim \text{MVN}(\mu, \Sigma)$ and (Y_1, Y_2) is a partition of Y with the corresponding partition of the mean vector and the covariance matrix as: $\mu = (\mu_1, \mu_2)$ and

$$\Sigma = \begin{bmatrix} \Sigma_{11} & \Sigma_{12} \\ \Sigma_{21} & \Sigma_{22} \end{bmatrix}$$

Then, $Y_1|Y_2 = y_2 \sim \text{MVN}(\bar{\mu}, \bar{\Sigma})$, where $\bar{\mu} = \mu_1 + \Sigma_{12}\Sigma_{22}^{-1}(y_2 - \mu_2)$ and $\bar{\Sigma} = \Sigma_{11} - \Sigma_{12}\Sigma_{22}^{-1}\Sigma_{21}$.

Using the above general result, we can obtain $[\hat{\beta}_1|\hat{\boldsymbol{\beta}}_{-1}, \boldsymbol{\beta}]$. Let the partition of S according to the partition of $\boldsymbol{\beta} = (\beta_1, \boldsymbol{\beta}_{-1})$ be given by:

$$S = \begin{bmatrix} S_{11} & S_{1,-1} \\ S_{-1,1} & S_{-1,-1} \end{bmatrix}$$

Here, $S_{11} = s_1^2$ is a scalar, $S_{1,-1}(= (s_2^2, \ldots, s_K^2))$ is a vector of length $(K-1)$, $S_{-1,-1}$ is a matrix of order $(K-1) \times (K-1)$. Thus, $\hat{\beta}_1|\hat{\boldsymbol{\beta}}_{-1}, \boldsymbol{\beta} \sim \text{MVN}(\bar{\mu}_1, \bar{\Sigma}_1)$, where $\bar{\mu}_1 = \beta_1 + S_{1,-1} \times S_{-1,-1}^{-1} \times (\hat{\boldsymbol{\beta}}_{-1} - \beta_{-1}) = \beta_1 + \Sigma_{1,-1} \times (\hat{\boldsymbol{\beta}}_{-1} - \beta_{-1})$; $\Sigma_{1,-1} = S_{1,-1} \times S_{-1,-1}^{-1}$. And, $\bar{\Sigma}_1 = S_{11} - S_{1,-1} \times S_{-1,-1}^{-1} \times S_{-1,1} = \bar{\sigma}_1^2$, say. Thus,

$$[\hat{\beta}_1|\hat{\boldsymbol{\beta}}_{-1}, \boldsymbol{\beta}] = \frac{1}{\sqrt{2\pi}\bar{\sigma}_1} e^{-\frac{1}{2\bar{\sigma}_1^2}(\beta_1 - m_{1,-1})^2}; \text{ where } m_{1,-1} = \hat{\beta}_1 - \Sigma_{1,-1}(\hat{\boldsymbol{\beta}}_{-1} - \boldsymbol{\beta}_{-1}). \tag{16}$$

Hence,

$$\begin{aligned}[\beta_1|\boldsymbol{\beta}_{-1}, q, b, \hat{\boldsymbol{\beta}}] &= [\hat{\beta}_1|\hat{\boldsymbol{\beta}}_{-1}, \boldsymbol{\beta}] \times [\beta_1|q, b] \\ &= \frac{1}{\sqrt{2\pi}\bar{\sigma}_1} e^{-\frac{1}{2\bar{\sigma}_1^2}(\beta_1 - m_{1,-1})^2} \times [(1-q) \times \delta_{\{0\}}(\beta_1) + q \times \frac{1}{\sqrt{2\pi}b} e^{-\frac{\beta_1^2}{2b^2}}]\end{aligned} \tag{17}$$

It is straightforward to derive from the above equation that:

$$\begin{aligned}[\beta_1|\boldsymbol{\beta}_{-1}, q, b, \hat{\boldsymbol{\beta}}] &= 0, \text{ with probability } \propto (1-q) \times \frac{1}{\sqrt{2\pi}\bar{\sigma}_1} e^{-\frac{m_{1,-1}^2}{2\bar{\sigma}_1^2}} \\ &= \text{N}(\frac{\sigma_1^2 m_{1,-1}}{\bar{\sigma}_1^2}, \sigma_1^2), \text{ with probability } \propto q \times \frac{\sigma_1}{\sqrt{2\pi}\bar{\sigma}_1 b} e^{-\frac{m_{1,-1}^2}{2\bar{\sigma}_1^2}(1 - \frac{\sigma_1^2}{\bar{\sigma}_1^2})},\end{aligned} \tag{18}$$

where $\frac{1}{\sigma_1^2} = \frac{1}{\bar{\sigma}_1^2} + \frac{1}{b^2}$. Hence, $\sigma_1^2 = \frac{1}{\frac{1}{\bar{\sigma}_1^2} + \frac{1}{b^2}}$.

More explicitly,

$$[\beta_1|\boldsymbol{\beta}_{-1}, q, b, \hat{\boldsymbol{\beta}}] = \mathrm{pr}_1 \times \delta_{\{0\}}(\beta_1) + (1-\mathrm{pr}_1) \times \mathrm{N}(\frac{\sigma_1^2 m_{1,-1}}{\bar{\sigma}_1^2}, \sigma_1^2), \tag{19}$$

where $\mathrm{pr}_1 = \frac{1}{1+\mathrm{ratio}_1}$, and $\mathrm{ratio}_1 = \frac{q}{(1-q)}\frac{\sigma_1}{b}e^{\frac{m_{1,-1}^2 \times \sigma_1^2}{2\bar{\sigma}_1^4}}$

9.1.2 Full conditional posterior distribution of q

Next we derive the full conditional distribution of q. Let k_0 be the number of zeros in $\boldsymbol{\beta}$, and k_1 $(= K - k_0)$ be the number of non-zero elements in $\boldsymbol{\beta}$. Let $dnorm(x, \mu, \sigma)$ denote the probability density function of a normal distribution at x with mean μ and variance σ^2. Under the Dirac spike, since β_j has a positive mass $(1-q)$ at 0, $[\beta_j = 0|q, b] = (1-q) + q \times dnorm(0, 0, b)$. Let $\boldsymbol{\beta}_{obs}$ denote an observed value of $\boldsymbol{\beta}$ in a MCMC iteration.

$$\begin{aligned}
[q|\boldsymbol{\beta} = \boldsymbol{\beta}_{obs}, b, \hat{\boldsymbol{\beta}}] &\propto [\hat{\boldsymbol{\beta}}, \boldsymbol{\beta} = \boldsymbol{\beta}_{obs}, q, b] \\
&\propto [\boldsymbol{\beta} = \boldsymbol{\beta}_{obs}|q, b] \times [q] \\
&= \prod_{j=1}^{K} [\beta_j = \beta_{j,obs}|q, b] \times [q] \\
&= \prod_{i:\beta_{i,obs}=0} [\beta_i = \beta_{i,obs}|q, b] \times \prod_{i:\beta_{i,obs}\neq 0} [\beta_i = \beta_{i,obs}|q, b] \times [q] \\
&= \{(1-q) + q \times dnorm(0,0,b)\}^{k_0} \times \prod_{i:\beta_{i,obs}\neq 0} q \times dnorm(\beta_{i,obs}, 0, b) \times [q] \\
&= \{(1-q) + q \times \frac{1}{\sqrt{2\pi}b}\}^{k_0} \times \prod_{i:\beta_{i,obs}\neq 0} q \times \frac{1}{\sqrt{2\pi}b} e^{-\frac{\beta_{i,obs}^2}{2b^2}} \times [q] \\
&= \{(1-q) + q \times \frac{1}{\sqrt{2\pi}b}\}^{k_0} \times q^{k_1} \times (\frac{1}{\sqrt{2\pi}b})^{k_1} e^{-\frac{\sum_{i:\beta_{i,obs}\neq 0}\beta_{i,obs}^2}{2b^2}} \times [q] \\
&= \sum_{j=0}^{k_0} \binom{k_0}{j} \times (1-q)^j \times q^{k_0-j} \times (\frac{1}{\sqrt{2\pi}b})^{k_0-j} \times q^{k_1} \times (\frac{1}{\sqrt{2\pi}b})^{k_1} \times e^{-\frac{const}{b^2}} \times [q];\ const = \frac{\sum_{i=1}^{K}\beta_{i,obs}^2}{2} \\
&\propto \sum_{j=0}^{k_0} \binom{k_0}{j} \times (1-q)^j \times q^{k_0-j+k_1} \times (\frac{1}{\sqrt{2\pi}b})^{k_0-j+k_1} \times \frac{1}{Beta(c_1, c_2)} q^{c_1-1}(1-q)^{c_2-1} \\
&\propto \sum_{j=0}^{k_0} \binom{k_0}{j} (\frac{1}{\sqrt{2\pi}b})^{K-j} \times Beta(c_1+K-j, c_2+j) \times [q \sim \mathrm{Beta}(c_1+K-j, c_2+j)]
\end{aligned} \tag{20}$$

Thus, the full conditional posterior distribution of q is a mixture of (k_0+1) Beta distributions as follows: for $j = 0, 1, \ldots, k_0$, $q|\boldsymbol{\beta}, b, \hat{\boldsymbol{\beta}} \sim \mathrm{Beta}(c_1+K-j, c_2+j)$ with probability $\propto \binom{k_0}{j}(\frac{1}{\sqrt{2\pi}b})^{K-j} \times Beta(c_1+K-j, c_2+j)$. Here $Beta(r_1, r_2)$ denotes the normalizing constant of the $\mathrm{Beta}(r_1, r_2)$ distribution.

9.1.3 Full conditional posterior distribution of b

Since $b > 0$, let $b = \frac{1}{v}$, where $v > 0$. Thus, for $j = 1, \ldots, K$, $\beta_j | q, v \overset{i.i.d.}{\sim} (1-q) \times \delta_{\{0\}}(\beta_j) + q \times \mathrm{N}(0, \frac{1}{v^2})$. Suppose, we want to update b in a given range (b_0, b_1). Let the corresponding range of v be given by (v_0, v_1). We assume a uniform prior on v. So, $[v] = \frac{1}{v_1 - v_0}$, where $v_0 < v < v_1$. Suppose, $(\beta_{1,obs}, \ldots, \beta_{K,obs})$ denote an observed value of $(\beta_1, \ldots, \beta_K)$ in a MCMC iteration. Let $k_1 = \#\{\beta_j \neq 0 : j = 1, \ldots, K\}$.

<u>Case 1</u>: $k_1 > 0$

$$
\begin{aligned}
[v|\boldsymbol{\beta}, q, \hat{\boldsymbol{\beta}}] &\propto [\hat{\boldsymbol{\beta}}, \boldsymbol{\beta}, q, v] \\
&\propto [\boldsymbol{\beta}|q, v] \times [v] \\
&= \prod_{j=1}^{K} [\beta_j | q, v] \times [v] \\
&= \prod_{i:\beta_{i,obs}=0} [\beta_i = \beta_{i,obs} | q, v] \prod_{i:\beta_{i,obs}\neq 0} [\beta_i = \beta_{i,obs} | q, v] \times [v] \\
&= \prod_{i:\beta_{i,obs}=0} \{(1-q) + q \times \frac{v}{\sqrt{2\pi}}\} \prod_{i:\beta_{i,obs}\neq 0} q \times \frac{v}{\sqrt{2\pi}} \, e^{-\frac{v^2 \beta_{i,obs}^2}{2}} \times [v] \\
&= \{(1-q) + q \times \frac{v}{\sqrt{2\pi}}\}^{k_0} \times q^{k_1} \times \frac{v^{k_1}}{(\sqrt{2\pi})^{k_1}} \times e^{-\frac{v^2}{2}C} \times [v], \text{ where } C = \sum_{i=1}^{K} \beta_{i,obs}^2 \\
&= \sum_{j=0}^{k_0} \binom{k_0}{j} \times (1-q)^j \times q^{K-j} \times \frac{1}{(\sqrt{2\pi})^{K-j}} \times v^{K-j} \times e^{-\frac{v^2}{2}C} \times [v] \\
&= \sum_{j=0}^{k_0} w_j^1 \times v^{K-j} \times e^{-\frac{v^2}{2}C} \times [v], \text{ where } w_j^1 = \binom{k_0}{j} \times (1-q)^j \times q^{K-j} \times \frac{1}{(\sqrt{2\pi})^{K-j}} \\
&\propto \sum_{j=0}^{k_0} w_j^1 \times \frac{1}{v_1 - v_0} v^{K-j} \times e^{-\frac{v^2}{2}C}, \; v_0 < v < v_1.
\end{aligned}
\tag{21}
$$

Now we consider the transformation: $y = v^2 C \Rightarrow v = \frac{\sqrt{y}}{\sqrt{C}}$, and $v_0^2 C < y < v_1^2 C$. Using the above equation, we obtain that y follows a mixture of $(k_0 + 1)$ truncated central chi-square distributions as follows:
for $j = 0, \ldots, k_0$, $y \sim$ truncated central $\chi^2_{t_j}$ with probability w_j, where $v_0^2 C < y < v_1^2 C$ and $t_j = K - j + 1$. The mixture weight w_j is given by: $w_j \propto w_j^{(1)} w_j^{(2)} w_j^{(3)} w_j^{(4)}$; $w_j^{(1)} = \frac{1}{(2\pi)^{\frac{K-j}{2}}} \binom{k_0}{j} (1-q)^j q^{K-j}$, $w_j^{(2)} = \frac{1}{2(v_1 - v_0)} \frac{1}{C^{\frac{t_j}{2}}}$, $w_j^{(3)} = 2^{\frac{t_j}{2}} \times \Gamma(\frac{t_j}{2})$, $w_j^{(4)} = P(v_0^2 C < \chi^2_{t_j} < v_1^2 C)$. The updated v is obtained from updated y using the transformation: $v = \frac{\sqrt{y}}{\sqrt{C}}$.

<u>Case 2</u>: $k_1 = 0$

Similarly, if $k_1 = 0$, we can derive the full conditional posterior distribution of v which appears to be a mixture of $(K + 1)$ distributions. For $j = 0, 1, \ldots, K$, the jth distribution of the mixture is given by: $t_j \times \frac{v^{K-j}}{v_1^{t_j} - v_0^{t_j}}$, $v_0 < v < v_1$. Here $t_j = K - j + 1$. The probability of the jth mixture component is given by:

$w_j \propto w_j^{(1)} \times w_j^{(2)}$; $w_j^{(1)} = \frac{1}{v_1 - v_0} \frac{1}{(2\pi)^{\frac{K-j}{2}}} \binom{K}{j} (1-q)^j q^{K-j}$ and $w_j^{(2)} = \frac{1}{t_j}(v_1^{t_j} - v_0^{t_j})$.

9.2 Uncorrelated case

For uncorrelated summary statistics, the full conditional posterior distribution of all the parameters except $\boldsymbol{\beta}$ remain the same. The derivation of full conditional posterior distribution of $\boldsymbol{\beta}$ for uncorrelated summary statistics is straightforward and will easily follow from the derivation for correlated summary statistics.

Figure S1: A diagram presenting the continuous spike and slab prior modeling pleiotropy with the spike variance $\tau^2 = 10^{-4}$.

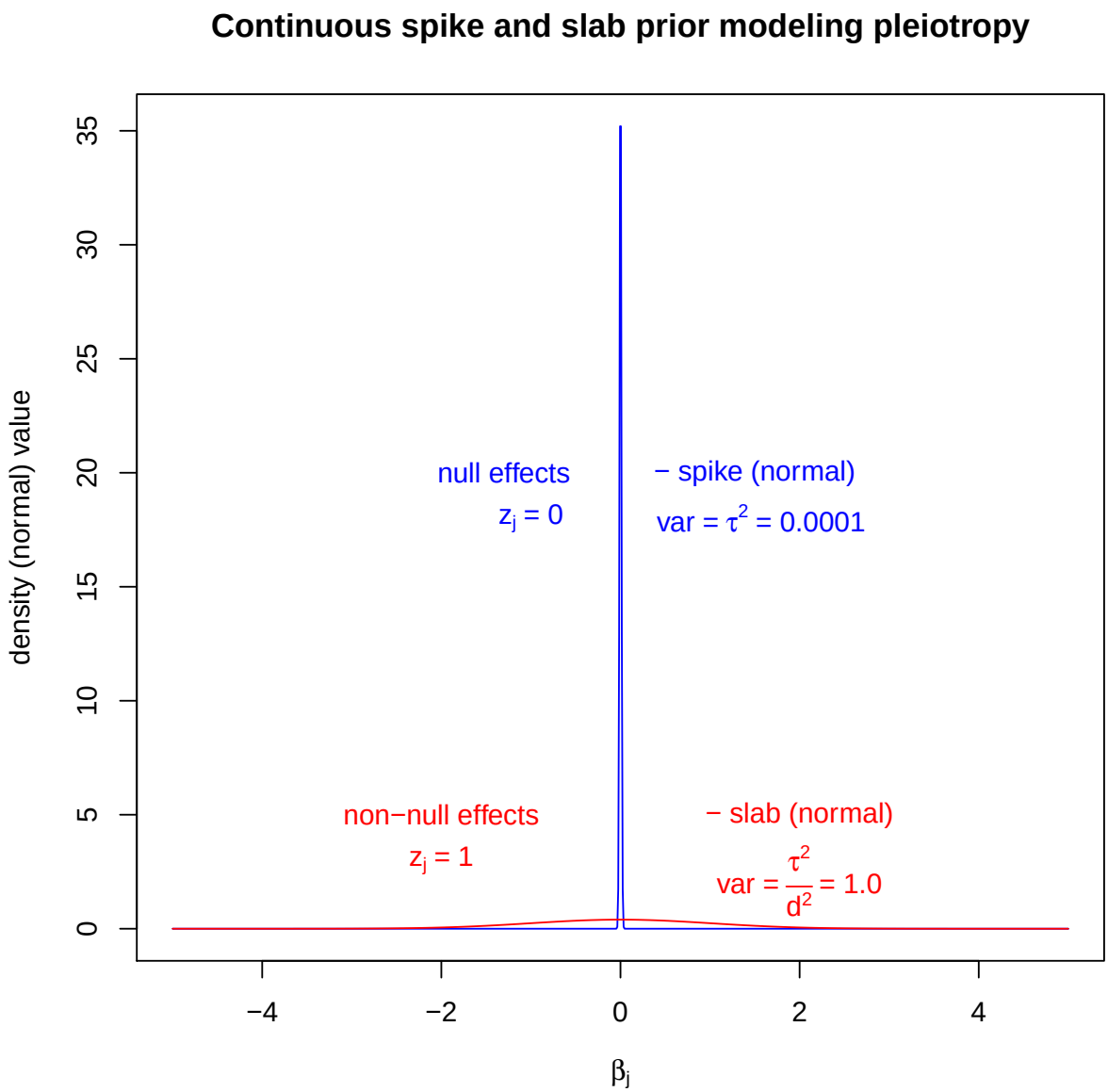


Table S1: Main features of CPBayes and ASSET

Features	CPBayes	ASSET
Paradigm	Bayesian	Frequentist
Measure of overall pleiotropic association	Bayes factor PPNA	P-value
Simultaneous selection of non-null traits	Yes	Yes
Specificity of selection	High	Low-moderate
Sensitivity of selection	Moderate-high	Low-high
Heterogeneity in direction of effects	Yes	Yes
Heterogeneity in size of effects	Yes	No

Table S2: Summary of measures for the evidence of the overall pleiotropic association under the global null hypothesis of no association when a cohort study with 15000 individuals is considered.

						quantile						
K	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
5	0.3	$\log_{10}$BF	-2.55	0.28	-2.83	-2.80	-2.72	-2.62	-2.47	-2.10	-1.55	-0.003
		-$\log_{10}$PPNA	0.05	0.09	0.02	0.02	0.02	0.03	0.04	0.09	0.27	1.50
		-$\log_{10}$ASTpv	0.36	0.53	0.00	0.004	0.06	0.20	0.45	1.21	2.32	6.20
	0.1	$\log_{10}$BF	-2.30	0.34	-2.68	-2.61	-2.52	-2.40	-2.21	-1.78	-0.66	-0.35
		-$\log_{10}$PPNA	0.08	0.13	0.03	0.03	0.04	0.05	0.08	0.18	0.89	1.17
		-$\log_{10}$ASTpv	0.36	0.45	0.00	0.002	0.06	0.20	0.50	1.28	2.13	3.48
10	0.3	$\log_{10}$BF	-4.07	0.24	-4.37	-4.31	-4.23	-4.14	-3.99	-3.67	-3.14	-2.58
		-$\log_{10}$PPNA	0.04	0.05	0.02	0.02	0.03	0.03	0.04	0.09	0.24	0.57
		-$\log_{10}$ASTpv	0.18	0.50	0.00	0.00	0.00	0.02	0.14	0.80	2.34	4.72
	0.1	$\log_{10}$BF	-3.87	0.26	-4.21	-4.13	-4.04	-3.94	-3.78	-3.32	-2.89	-2.57
		-$\log_{10}$PPNA	0.07	0.06	0.03	0.03	0.04	0.05	0.07	0.17	0.36	0.57
		-$\log_{10}$ASTpv	0.15	0.31	0.00	0.00	0.00	0.02	0.15	0.72	1.69	2.12
15	0.3	$\log_{10}$BF	-5.54	0.31	-5.82	-5.78	-5.69	-5.60	-5.48	-5.13	-4.88	-0.14
		-$\log_{10}$PPNA	0.05	0.20	0.02	0.02	0.03	0.03	0.05	0.09	0.16	4.37
		-$\log_{10}$ASTpv	0.07	0.50	0.00	0.00	0.00	0.00	0.00	0.19	1.38	8.27
	0.1	$\log_{10}$BF	-5.30	0.27	-5.66	-5.58	-5.49	-5.37	-5.19	-4.77	-4.27	-4.10
		-$\log_{10}$PPNA	0.08	0.07	0.03	0.04	0.04	0.06	0.08	0.19	0.44	0.56
		-$\log_{10}$ASTpv	0.06	0.25	0.00	0.00	0.00	0.00	0.01	0.27	1.11	3.28

Legend: K - total number of phenotypes, m - allele frequency at the marker SNP; $K = 5$, 10, 15, and $m = 0.3$, 0.1. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$ASTpv: -$\log_{10}$(ASSET p-value). For a cohort study, since the summary statistics are correlated, the combined strategy of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S3: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **5 non-overlapping** case-control studies. Here **1** and **2** among **5** traits are associated.

						quantile						
K_1^+,K_1^-	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
1,0	0.3	$\log_{10}$BF	11.05	15.21	-2.98	-2.54	-0.77	5.12	19.30	42.71	61.24	70.26
		-$\log_{10}$PPNA	12.71	15.06	0.01	0.04	0.80	6.61	20.80	44.20	62.73	71.76
		-$\log_{10}$ASTpv	7.73	5.74	0.06	0.82	2.97	6.44	11.68	18.36	23.98	26.34
	0.1	$\log_{10}$BF	4.22	10.17	-2.81	-2.65	-2.00	-0.51	6.95	24.89	45.04	56.89
		-$\log_{10}$PPNA	6.02	9.97	0.02	0.03	0.12	1.03	8.44	26.38	46.54	58.38
		-$\log_{10}$ASTpv	3.48	2.83	0.01	0.25	1.13	2.75	5.16	8.73	11.92	14.65
2,0	0.3	$\log_{10}$BF	31.70	26.39	-2.78	-1.03	9.11	27.99	48.92	80.29	102.88	126.71
		-$\log_{10}$PPNA	33.22	26.36	0.02	0.59	10.60	29.48	50.41	81.79	104.37	128.21
		-$\log_{10}$ASTpv	15.27	7.92	0.23	3.44	9.27	14.67	20.05	29.14	34.48	43.27
	0.1	$\log_{10}$BF	15.00	19.73	-2.74	-1.99	-0.03	6.88	24.90	57.87	78.48	90.53
		-$\log_{10}$PPNA	16.58	19.65	0.02	0.12	1.48	8.37	26.39	59.36	79.97	92.02
		-$\log_{10}$ASTpv	6.54	3.84	0.07	1.28	3.24	6.08	9.06	13.53	16.44	19.03
1,1	0.3	$\log_{10}$BF	28.15	23.99	-2.75	-0.70	7.78	24.71	42.89	72.80	98.50	117.92
		-$\log_{10}$PPNA	29.67	23.96	0.02	0.86	9.28	26.20	44.38	74.29	100.00	119.41
		-$\log_{10}$ASTpv	15.41	7.92	0.57	3.82	9.20	14.96	20.57	29.46	36.45	41.72
	0.1	$\log_{10}$BF	11.18	17.06	-2.61	-2.09	-0.16	3.28	17.60	44.54	70.04	141.15
		-$\log_{10}$PPNA	12.76	16.99	0.03	0.10	1.35	4.77	19.09	46.03	71.53	142.64
		-$\log_{10}$ASTpv	6.32	3.63	0.19	1.31	3.76	5.61	8.63	12.94	16.11	24.97

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with no overlapping subjects, the uncorrelated version of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S4: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **5 non-overlapping** case-control studies. Here **3** and **4** among **5** traits are associated.

						quantile						
K_1^+, K_1^-	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
3,0	0.3	$\log_{10}$BF	61.61	40.01	-2.44	4.61	30.29	58.08	85.48	134.62	175.19	197.55
		-$\log_{10}$PPNA	63.11	40.00	0.05	6.11	31.78	59.57	86.97	136.11	176.68	199.04
		-$\log_{10}$ASTpv	22.88	10.03	1.13	8.78	15.36	21.96	28.93	41.63	50.08	53.57
	0.1	$\log_{10}$BF	33.38	34.50	-2.37	-0.84	3.62	24.34	52.62	99.66	142.34	171.82
		-$\log_{10}$PPNA	34.89	34.48	0.05	0.74	5.11	25.83	54.11	101.15	143.83	173.31
		-$\log_{10}$ASTpv	9.94	4.87	0.38	3.28	6.09	9.52	12.93	18.91	23.68	25.43
2,1	0.3	$\log_{10}$BF	60.31	39.41	-2.07	4.80	29.29	56.15	84.89	131.91	170.04	201.46
		-$\log_{10}$PPNA	61.80	39.41	0.10	6.29	30.79	57.64	86.38	133.40	171.53	202.95
		-$\log_{10}$ASTpv	23.01	9.65	1.95	8.48	16.03	22.08	29.42	40.06	47.69	56.17
	0.1	$\log_{10}$BF	30.24	31.41	-2.60	-1.22	3.58	21.99	47.77	90.33	129.23	188.29
		-$\log_{10}$PPNA	31.76	31.39	0.03	0.46	5.07	23.48	49.26	91.82	130.72	189.78
		-$\log_{10}$ASTpv	9.67	4.47	0.51	3.36	6.25	9.22	12.39	17.44	21.33	27.02
4,0	0.3	$\log_{10}$BF	95.17	48.22	-0.33	24.89	59.37	91.99	128.33	179.22	214.40	245.43
		-$\log_{10}$PPNA	96.66	48.22	1.19	26.38	60.86	93.48	129.82	180.71	215.89	246.92
		-$\log_{10}$ASTpv	31.10	11.45	3.93	13.73	22.87	30.59	39.11	50.95	58.48	67.47
	0.1	$\log_{10}$BF	56.83	46.68	-2.16	0.80	19.87	48.05	80.55	146.62	213.33	234.68
		-$\log_{10}$PPNA	58.32	46.68	0.08	2.30	21.36	49.54	82.04	148.12	214.82	236.17
		-$\log_{10}$ASTpv	13.50	5.62	1.01	5.64	9.36	12.71	16.70	24.19	28.88	33.48
2,2	0.3	$\log_{10}$BF	88.32	44.33	0.31	23.17	55.83	86.42	114.73	168.46	192.95	224.88
		-$\log_{10}$PPNA	89.81	44.33	1.81	24.66	57.32	87.91	116.22	169.95	194.44	226.37
		-$\log_{10}$ASTpv	30.90	11.07	5.90	14.24	22.88	30.45	37.58	51.09	55.65	65.78
	0.1	$\log_{10}$BF	51.67	41.90	-1.73	0.39	17.85	43.79	77.10	127.42	176.04	257.33
		-$\log_{10}$PPNA	53.16	41.89	0.20	1.88	19.34	45.28	78.59	128.91	177.53	258.83
		-$\log_{10}$ASTpv	12.96	5.06	1.70	5.38	9.37	12.67	16.02	21.63	25.04	37.98

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with no overlapping subjects, the uncorrelated version of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S5: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **10 non-overlapping** case-control studies. Here **2** and **4** among **10** traits are associated.

						quantile						
K_1^+,K_1^-	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
2,0	0.3	$\log_{10}$BF	27.15	25.74	-4.30	-2.69	5.25	21.92	43.93	75.80	101.52	129.36
		-$\log_{10}$PPNA	30.19	25.70	0.02	0.49	8.26	24.93	46.94	78.81	104.53	132.37
		-$\log_{10}$ASTpv	13.69	7.69	0.30	2.76	7.79	12.76	18.96	27.45	33.79	41.97
	0.1	$\log_{10}$BF	11.17	21.28	-4.34	-3.79	-2.10	1.72	15.69	63.79	86.82	112.94
		-$\log_{10}$PPNA	14.30	21.20	0.02	0.07	0.96	4.73	18.70	66.80	89.83	115.95
		-$\log_{10}$ASTpv	5.54	3.90	0.00	0.79	2.57	4.72	7.63	13.72	16.25	19.99
1,1	0.3	$\log_{10}$BF	29.01	27.54	-4.18	-2.55	6.54	24.33	46.85	81.66	117.15	138.98
		-$\log_{10}$PPNA	32.06	27.50	0.03	0.59	9.55	27.34	49.86	84.67	120.16	141.99
		-$\log_{10}$ASTpv	13.48	7.47	0.56	2.75	7.71	13.09	18.61	26.26	34.03	40.35
	0.1	$\log_{10}$BF	11.73	21.45	-4.25	-3.85	-2.22	2.19	18.41	63.34	88.81	122.15
		-$\log_{10}$PPNA	14.88	21.35	0.02	0.06	0.85	5.20	21.42	66.35	91.82	125.16
		-$\log_{10}$ASTpv	5.25	3.54	0.05	0.61	2.67	4.77	6.98	12.29	15.35	19.13
4,0	0.3	$\log_{10}$BF	89.89	47.02	-3.04	17.36	56.24	88.18	117.85	174.97	214.41	257.88
		-$\log_{10}$PPNA	92.90	47.02	0.29	20.37	59.25	91.19	120.86	177.98	217.41	260.89
		-$\log_{10}$ASTpv	28.90	10.95	2.45	12.23	21.61	28.34	35.62	48.58	59.27	64.09
	0.1	$\log_{10}$BF	48.12	44.63	-3.91	-2.02	9.87	38.46	72.24	133.95	162.01	208.74
		-$\log_{10}$PPNA	51.15	44.62	0.05	1.03	12.88	41.47	75.25	136.96	165.02	211.75
		-$\log_{10}$ASTpv	11.54	5.42	0.99	3.44	7.58	11.01	15.03	21.23	24.74	28.48
2,2	0.3	$\log_{10}$BF	85.65	45.24	-3.28	14.94	52.11	84.36	117.50	161.07	188.45	227.38
		-$\log_{10}$PPNA	88.66	45.24	0.19	17.95	55.12	87.37	120.51	164.08	191.46	230.39
		-$\log_{10}$ASTpv	28.33	10.51	2.58	12.07	20.62	27.62	34.88	46.53	52.30	58.24
	0.1	$\log_{10}$BF	43.43	44.04	-4.13	-2.32	7.47	32.08	67.89	136.26	172.62	215.32
		-$\log_{10}$PPNA	46.45	44.02	0.03	0.77	10.48	35.09	70.90	139.27	175.63	218.33
		-$\log_{10}$ASTpv	10.80	5.12	0.09	3.64	7.04	10.20	14.12	20.77	24.02	27.71

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with no overlapping subjects, the uncorrelated version of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S6: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **10 non-overlapping** case-control studies. Here **6** and **8** among **10** traits are associated.

						quantile						
K_1^+, K_1^-	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
6,0	0.3	$\log_{10}$BF	147.42	56.38	-2.28	59.44	108.43	147.16	181.30	247.10	284.08	300.00
		-$\log_{10}$PPNA	150.42	56.36	0.81	62.45	111.44	150.17	184.31	250.11	287.09	302.01
		-$\log_{10}$ASTpv	43.75	13.70	4.92	23.89	33.58	42.92	51.90	66.37	78.13	100.85
	0.1	$\log_{10}$BF	101.47	63.28	-2.37	4.40	54.63	99.43	139.34	212.69	266.31	300.00
		-$\log_{10}$PPNA	104.48	63.26	0.73	7.41	57.64	102.44	142.35	215.70	269.32	300.00
		-$\log_{10}$ASTpv	18.21	6.92	2.45	7.46	13.29	17.83	22.36	30.50	35.63	39.72
3,3	0.3	$\log_{10}$BF	155.54	61.70	6.09	61.82	109.56	153.34	199.97	259.31	300.00	306.79
		-$\log_{10}$PPNA	158.49	61.57	9.10	64.83	112.57	156.35	202.98	262.32	300.00	300.00
		-$\log_{10}$ASTpv	43.29	13.66	10.44	22.95	33.37	42.07	52.78	64.85	75.52	107.79
	0.1	$\log_{10}$BF	97.35	67.35	-3.44	5.99	44.30	85.84	141.52	226.59	288.29	300.00
		-$\log_{10}$PPNA	100.33	67.26	0.14	9.00	47.31	88.85	144.53	229.60	291.27	300.00
		-$\log_{10}$ASTpv	17.17	6.66	2.14	7.99	12.28	16.12	21.33	28.82	35.29	44.07
8,0	0.3	$\log_{10}$BF	220.79	62.53	-2.96	111.95	174.89	220.83	282.06	300.00	306.07	308.16
		-$\log_{10}$PPNA	223.15	61.70	0.33	114.95	177.90	223.84	285.07	300.00	303.24	305.75
		-$\log_{10}$ASTpv	59.89	16.60	6.50	34.85	48.36	57.74	71.32	90.44	99.24	116.55
	0.1	$\log_{10}$BF	166.21	77.32	-2.73	40.09	108.27	161.28	223.77	300.00	301.56	308.02
		-$\log_{10}$PPNA	169.02	76.98	0.46	43.10	111.28	164.29	226.78	300.00	302.10	304.80
		-$\log_{10}$ASTpv	25.39	8.28	2.97	13.27	19.34	24.44	30.72	39.65	46.85	66.42
4,4	0.3	$\log_{10}$BF	223.58	62.88	5.44	109.97	177.21	226.38	284.23	300.00	303.46	307.82
		-$\log_{10}$PPNA	225.99	62.17	8.45	112.98	180.22	229.39	287.24	300.00	305.37	308.10
		-$\log_{10}$ASTpv	58.72	16.15	12.15	34.11	47.51	56.49	68.94	87.91	97.65	107.58
	0.1	$\log_{10}$BF	167.13	78.46	-2.65	37.36	108.28	161.39	228.15	300.00	305.07	307.48
		-$\log_{10}$PPNA	169.86	77.98	0.52	40.37	111.29	164.40	231.16	300.00	300.00	308.08
		-$\log_{10}$ASTpv	24.25	7.62	4.21	13.03	18.68	23.23	29.24	37.93	44.33	50.27

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with no overlapping subjects, the uncorrelated version of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S7: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **15 non-overlapping** case-control studies. Here 3, 6, and 9 among 15 traits are associated.

						quantile						
K_1^+,K_1^-	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
3,0	0.3	$\log_{10}$BF	55.17	41.68	-5.35	-0.51	23.33	51.13	81.53	132.41	168.25	256.16
		-$\log_{10}$PPNA	59.69	41.68	0.06	4.01	27.85	55.64	86.05	136.92	172.77	260.68
		-$\log_{10}$ASTpv	20.09	10.16	1.57	5.88	12.41	19.06	26.12	38.63	48.88	66.07
	0.1	$\log_{10}$BF	27.28	34.09	-5.48	-4.48	0.77	16.30	42.46	103.17	136.60	146.95
		-$\log_{10}$PPNA	31.83	34.05	0.05	0.32	5.29	20.82	46.98	107.69	141.12	151.46
		-$\log_{10}$ASTpv	7.84	4.49	0.22	1.69	4.49	7.31	10.18	16.73	20.07	22.00
2,1	0.3	$\log_{10}$BF	51.39	37.55	-5.32	0.31	21.42	48.76	73.17	120.28	154.40	185.80
		-$\log_{10}$PPNA	55.91	37.54	0.06	4.82	25.94	53.27	77.68	124.79	158.91	190.31
		-$\log_{10}$ASTpv	19.12	9.31	1.60	5.86	12.04	18.38	25.13	35.86	44.07	51.10
	0.1	$\log_{10}$BF	25.10	31.59	-5.58	-4.74	-0.81	12.28	44.58	84.75	119.30	167.94
		-$\log_{10}$PPNA	29.67	31.54	0.04	0.20	3.71	16.79	49.09	89.27	123.82	172.45
		-$\log_{10}$ASTpv	7.07	4.19	0.14	1.31	3.80	6.46	10.06	14.46	19.37	24.86
6,0	0.3	$\log_{10}$BF	150.85	64.62	2.07	50.34	100.90	149.05	196.66	265.13	300.00	301.07
		-$\log_{10}$PPNA	155.29	64.46	6.58	54.86	105.41	153.57	201.17	269.64	300.00	305.59
		-$\log_{10}$ASTpv	42.15	14.59	11.11	20.04	31.75	40.78	51.27	67.53	80.81	96.92
	0.1	$\log_{10}$BF	93.93	64.16	-3.85	2.17	42.78	84.86	135.96	216.35	261.75	294.71
		-$\log_{10}$PPNA	98.44	64.16	0.75	6.69	47.29	89.38	140.48	220.87	266.26	299.22
		-$\log_{10}$ASTpv	16.90	6.52	4.34	7.10	12.14	16.19	20.84	28.50	33.52	35.63
3,3	0.3	$\log_{10}$BF	148.37	62.97	7.85	53.78	102.07	146.29	186.63	261.24	298.32	306.15
		-$\log_{10}$PPNA	152.84	62.85	12.37	58.29	106.58	150.81	191.15	265.75	300.00	303.71
		-$\log_{10}$ASTpv	40.80	13.42	11.36	21.27	30.75	40.37	49.04	64.17	71.31	98.25
	0.1	$\log_{10}$BF	87.73	64.91	-4.57	0.54	36.33	78.09	124.58	215.44	266.81	302.95
		-$\log_{10}$PPNA	92.24	64.88	0.28	5.05	40.84	82.61	129.09	219.95	271.33	307.46
		-$\log_{10}$ASTpv	15.30	6.04	3.00	6.59	10.96	14.70	18.84	26.57	32.37	35.26
9,0	0.3	$\log_{10}$BF	246.57	56.94	49.23	139.33	202.60	261.84	300.00	300.00	305.87	307.81
		-$\log_{10}$PPNA	249.49	55.45	53.74	143.85	207.11	266.36	300.00	300.00	303.63	308.15
		-$\log_{10}$ASTpv	65.43	17.91	21.04	39.79	52.46	64.45	76.44	97.32	111.35	132.49
	0.1	$\log_{10}$BF	181.55	81.36	-1.88	48.93	114.80	185.53	247.14	300.00	300.62	305.66
		-$\log_{10}$PPNA	185.47	80.49	2.63	53.45	119.31	190.04	251.66	300.00	303.71	307.81
		-$\log_{10}$ASTpv	26.31	8.63	6.98	13.68	20.04	25.99	31.70	41.36	49.88	57.39
5,4	0.3	$\log_{10}$BF	244.60	56.81	41.08	138.93	206.04	260.15	300.00	300.00	302.91	307.72
		-$\log_{10}$PPNA	247.74	55.48	45.60	143.44	210.56	264.66	300.00	300.00	305.56	308.16
		-$\log_{10}$ASTpv	63.44	16.19	20.03	38.69	50.97	61.76	74.80	90.39	104.75	127.61
	0.1	$\log_{10}$BF	176.98	81.15	1.87	40.71	116.37	173.77	243.61	300.00	303.21	308.20
		-$\log_{10}$PPNA	180.93	80.29	6.39	45.22	120.88	178.29	248.13	300.00	301.91	307.71
		-$\log_{10}$ASTpv	24.89	7.76	4.96	12.84	19.11	24.29	30.06	38.86	42.55	52.72

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with no overlapping subjects, the uncorrelated version of CPBayes is implemented. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S8: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **5 overlapping** case-control studies. Here **1** and **2** among **5** traits are associated.

							quantile						
K_1^+,K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
1,0	0.3	0.4%	$\log_{10}$BF	6.95	10.32	-3.10	-2.61	-0.84	3.21	11.81	28.04	37.84	58.48
			-$\log_{10}$PPNA	8.62	10.16	0.01	0.03	0.74	4.70	13.30	29.53	39.33	59.97
			-$\log_{10}$ASTpv	6.10	4.83	0.00	0.36	2.14	4.96	9.13	15.12	19.45	25.38
	0.1	0.8%	$\log_{10}$BF	2.02	7.16	-2.90	-2.76	-2.03	-0.52	2.19	17.23	32.78	43.58
			-$\log_{10}$PPNA	3.86	6.96	0.02	0.02	0.11	1.02	3.68	18.72	34.27	45.07
			-$\log_{10}$ASTpv	2.58	2.39	0.00	0.11	0.69	1.87	3.75	7.36	9.46	14.57
2,0	0.3	0.6%	$\log_{10}$BF	21.94	21.25	-2.68	-1.15	4.03	16.66	34.84	61.40	89.90	101.77
			-$\log_{10}$PPNA	23.46	21.22	0.03	0.50	5.52	18.15	36.33	62.90	91.40	103.26
			-$\log_{10}$ASTpv	9.24	5.13	0.29	2.15	5.27	8.86	12.38	19.15	22.07	26.72
	0.1	0.8%	$\log_{10}$BF	9.77	16.91	-2.83	-2.23	-0.54	1.63	14.19	47.50	70.04	129.58
			-$\log_{10}$PPNA	11.39	16.82	0.02	0.07	1.00	3.12	15.68	48.99	71.53	131.07
			-$\log_{10}$ASTpv	4.07	2.76	0.03	0.58	2.02	3.51	5.63	9.26	11.86	19.98
1,1	0.3	0.6%	$\log_{10}$BF	29.20	23.09	-2.27	0.44	11.06	25.75	43.96	74.31	96.00	115.74
			-$\log_{10}$PPNA	30.70	23.07	0.07	1.94	12.55	27.24	45.45	75.80	97.49	117.23
			-$\log_{10}$ASTpv	11.97	6.28	0.67	3.05	7.22	11.58	16.14	23.73	27.73	32.93
	0.1	4.6%	$\log_{10}$BF	16.22	18.96	-2.66	-1.77	0.50	9.03	26.47	51.73	75.19	95.58
			-$\log_{10}$PPNA	17.77	18.91	0.03	0.18	1.99	10.52	27.96	53.22	76.68	97.07
			-$\log_{10}$ASTpv	4.86	2.86	0.04	0.89	2.57	4.49	6.91	10.03	12.34	13.67

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with overlapping subjects, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S9: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **5 overlapping** case-control studies. Here **3** and **4** among **5** traits are associated.

							quantile						
K_1^+, K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
3,0	0.3	0.4%	$\log_{10}$BF	34.94	28.81	-2.55	0.14	12.46	28.52	51.75	87.75	119.47	161.65
			-$\log_{10}$PPNA	36.45	28.80	0.04	1.64	13.95	30.01	53.24	89.24	120.96	163.15
			-$\log_{10}$ASTpv	11.64	5.40	0.78	3.71	7.81	10.96	15.17	21.38	25.35	31.84
	0.1	0.8%	$\log_{10}$BF	15.32	22.10	-2.73	-2.04	-0.10	5.92	23.74	60.50	88.52	139.69
			-$\log_{10}$PPNA	16.90	22.03	0.02	0.11	1.41	7.41	25.23	61.99	90.01	141.18
			-$\log_{10}$ASTpv	5.08	2.98	0.03	1.05	2.94	4.59	6.77	10.77	13.30	16.52
2,1	0.3	2.2%	$\log_{10}$BF	52.74	31.83	-2.01	7.77	28.42	49.47	72.46	112.17	141.18	156.62
			-$\log_{10}$PPNA	54.24	31.83	0.12	9.27	29.91	50.96	73.95	113.66	142.67	158.11
			-$\log_{10}$ASTpv	15.68	6.63	1.21	5.67	10.92	15.00	20.00	27.83	33.05	35.93
	0.1	5.8%	$\log_{10}$BF	32.79	29.50	-2.78	-0.93	6.50	26.35	52.58	88.01	113.65	122.83
			-$\log_{10}$PPNA	34.30	29.48	0.02	0.66	8.00	27.84	54.08	89.50	115.14	124.33
			-$\log_{10}$ASTpv	6.45	3.21	0.02	2.00	3.93	6.16	8.59	11.99	14.84	16.27
4,0	0.3	1	$\log_{10}$BF	40.37	32.14	-2.32	0.74	14.01	35.31	59.80	98.97	127.94	169.53
			-$\log_{10}$PPNA	41.87	32.13	0.06	2.24	15.50	36.80	61.29	100.46	129.43	171.03
			-$\log_{10}$ASTpv	13.67	5.53	0.76	5.38	9.76	12.96	17.49	23.38	28.23	31.19
	0.1	3.6	$\log_{10}$BF	14.98	24.90	-2.65	-1.94	-0.29	3.55	21.02	69.20	105.87	151.60
			-$\log_{10}$PPNA	16.56	24.84	0.03	0.13	1.23	5.05	22.51	70.69	107.36	153.09
			-$\log_{10}$ASTpv	5.94	3.19	0.35	1.54	3.61	5.56	7.85	12.20	14.84	17.87
2,2	0.3	1	$\log_{10}$BF	82.12	37.92	-0.81	24.63	53.20	78.45	109.34	143.83	178.97	195.74
			-$\log_{10}$PPNA	83.61	37.92	0.76	26.12	54.70	79.95	110.83	145.32	180.46	197.24
			-$\log_{10}$ASTpv	19.07	6.56	2.14	8.70	14.05	18.80	23.69	30.08	33.76	37.17
	0.1	6.8	$\log_{10}$BF	53.77	35.96	-1.82	0.89	25.71	49.63	78.00	123.01	135.74	151.22
			-$\log_{10}$PPNA	55.26	35.95	0.17	2.39	27.20	51.12	79.49	124.50	137.23	152.71
			-$\log_{10}$ASTpv	7.74	3.03	0.80	3.17	5.54	7.29	9.91	12.92	15.16	16.92

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with overlapping subjects, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S10: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **10 overlapping** case-control studies. Here **2** and **4** among **10** traits are associated.

							quantile						
K_1^+, K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
2,0	0.3	0.2%	$\log_{10}$BF	22.76	22.21	-4.25	-2.54	4.48	17.93	37.13	65.19	87.68	113.37
			-$\log_{10}$PPNA	25.80	22.17	0.02	0.60	7.49	20.94	40.14	68.20	90.69	116.38
			-$\log_{10}$ASTpv	7.93	4.91	0.00	0.99	4.12	7.38	11.04	16.83	21.79	26.42
	0.1	2.4%	$\log_{10}$BF	9.70	17.03	-4.32	-3.86	-2.07	3.30	15.21	47.44	72.03	93.28
			-$\log_{10}$PPNA	12.84	16.92	0.02	0.06	0.99	6.31	18.22	50.45	75.04	96.29
			-$\log_{10}$ASTpv	2.92	2.57	0.00	0.03	0.91	2.38	4.24	7.53	12.19	14.01
1,1	0.3	1%	$\log_{10}$BF	27.39	22.87	-4.08	-2.22	8.91	23.86	41.70	71.44	87.53	117.80
			-$\log_{10}$PPNA	30.43	22.84	0.04	0.85	11.92	26.87	44.71	74.45	90.54	120.81
			-$\log_{10}$ASTpv	10.07	6.08	0.02	1.18	5.12	9.55	13.97	21.60	24.71	29.81
	0.1	3.8%	$\log_{10}$BF	13.86	19.58	-4.39	-3.75	-1.16	6.53	22.99	52.39	82.73	105.61
			-$\log_{10}$PPNA	16.97	19.49	0.02	0.07	1.86	9.54	26.00	55.40	85.74	108.62
			-$\log_{10}$ASTpv	3.28	2.58	0.00	0.07	1.22	2.78	4.92	8.47	10.73	12.49
4,0	0.3	0.6%	$\log_{10}$BF	57.66	38.31	-3.66	3.74	28.53	53.68	81.07	132.47	157.92	183.85
			-$\log_{10}$PPNA	60.67	38.31	0.09	6.75	31.54	56.69	84.08	135.48	160.93	186.85
			-$\log_{10}$ASTpv	11.73	5.22	0.34	4.46	8.02	11.03	14.89	21.50	25.96	30.74
	0.1	3.6%	$\log_{10}$BF	25.97	31.75	-3.81	-2.76	0.36	14.82	40.68	93.18	122.71	161.92
			-$\log_{10}$PPNA	29.01	31.73	0.06	0.44	3.37	17.83	43.69	96.19	125.72	164.93
			-$\log_{10}$ASTpv	4.41	2.84	0.02	0.72	2.28	4.03	5.88	9.77	13.47	15.66
2,2	0.3	4.8%	$\log_{10}$BF	77.81	40.39	-1.34	18.29	50.34	72.52	100.73	152.82	172.32	199.91
			-$\log_{10}$PPNA	80.82	40.39	1.68	21.30	53.35	75.53	103.74	155.83	175.33	202.92
			-$\log_{10}$ASTpv	16.80	6.35	1.63	6.71	12.27	16.17	21.39	28.00	30.75	32.92
	0.1	12.4%	$\log_{10}$BF	46.82	36.71	-3.32	-1.54	18.64	39.66	70.42	114.56	141.42	179.66
			-$\log_{10}$PPNA	49.84	36.69	0.17	1.48	21.65	42.67	73.43	117.57	144.43	182.67
			-$\log_{10}$ASTpv	5.88	2.76	0.08	1.56	3.76	5.71	7.80	10.59	12.33	14.16

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with overlapping subjects, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S11: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **10 overlapping** case-control studies. Here **6** and **8** among **10** traits are associated.

							quantile						
K_1^+, K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
6,0	0.3	3%	$\log_{10}$BF	83.92	49.08	-3.71	12.94	48.13	79.33	116.43	170.26	224.05	265.78
			-$\log_{10}$PPNA	86.93	49.08	0.08	15.95	51.14	82.34	119.44	173.27	227.06	268.79
			-$\log_{10}$ASTpv	14.06	5.37	0.94	6.58	10.02	13.72	17.25	24.07	27.59	34.60
	0.1	8.6%	$\log_{10}$BF	35.46	42.51	-3.52	-2.38	3.21	21.12	53.48	122.70	162.39	261.30
			-$\log_{10}$PPNA	38.48	42.50	0.12	0.72	6.22	24.13	56.49	125.71	165.40	264.31
			-$\log_{10}$ASTpv	5.41	3.03	0.03	1.52	3.07	4.91	7.07	11.41	14.02	17.92
3,3	0.3	6.8%	$\log_{10}$BF	139.07	53.94	8.81	55.16	101.18	135.69	173.47	230.87	289.54	300.51
			-$\log_{10}$PPNA	142.07	53.90	11.82	58.17	104.19	138.70	176.48	233.88	292.55	303.52
			-$\log_{10}$ASTpv	21.21	6.49	5.19	11.23	16.48	20.85	25.65	32.16	36.14	39.79
	0.1	14.8%	$\log_{10}$BF	97.04	57.63	-2.57	4.98	53.47	92.07	136.05	200.53	234.69	280.41
			-$\log_{10}$PPNA	100.05	57.63	0.58	7.99	56.48	95.08	139.06	203.54	237.70	283.42
			-$\log_{10}$ASTpv	7.84	3.02	0.92	3.21	5.69	7.69	9.84	12.86	15.05	18.50
8,0	0.3	6.4%	$\log_{10}$BF	90.62	59.51	-3.79	11.84	45.35	79.68	123.46	205.05	266.41	300.00
			-$\log_{10}$PPNA	93.63	59.49	0.07	14.85	48.36	82.69	126.47	208.06	269.42	300.00
			-$\log_{10}$ASTpv	16.28	5.76	0.77	8.38	12.13	15.56	19.73	26.55	32.47	34.89
	0.1	21.8%	$\log_{10}$BF	39.87	52.80	-3.99	-2.85	-0.56	19.04	65.18	143.11	222.08	301.12
			-$\log_{10}$PPNA	42.91	52.78	0.04	0.39	2.45	22.05	68.19	146.12	225.09	304.13
			-$\log_{10}$ASTpv	6.41	3.40	0.05	1.88	3.81	5.84	8.43	12.73	15.66	18.32
4,4	0.3	7%	$\log_{10}$BF	201.68	59.53	30.89	103.30	159.75	200.35	245.62	300.00	303.97	308.11
			-$\log_{10}$PPNA	204.45	59.13	33.90	106.31	162.76	203.36	248.63	300.00	303.90	307.17
			-$\log_{10}$ASTpv	24.99	6.41	5.69	14.63	20.24	25.42	29.21	35.53	39.73	43.02
	0.1	23.4%	$\log_{10}$BF	153.58	75.61	-2.99	25.13	98.67	157.58	208.83	279.24	300.00	304.04
			-$\log_{10}$PPNA	156.52	75.48	0.31	28.14	101.68	160.59	211.84	282.25	300.00	307.05
			-$\log_{10}$ASTpv	9.49	3.05	1.02	4.55	7.33	9.46	11.69	14.54	16.51	17.63

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with overlapping subjects, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S12: Summary of measures for the evidence of the overall pleiotropic association when a subset of traits are associated for **15 overlapping** case-control studies. Here 3,6, and 9 among 15 traits are associated.

							quantile						
K_1^+, K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
3,0	0.3	2%	$\log_{10}$BF	40.22	30.92	-5.56	-1.62	15.82	35.76	58.47	99.67	123.13	144.36
			-$\log_{10}$PPNA	44.75	30.91	0.04	2.89	20.34	40.27	62.99	104.19	127.65	148.88
			-$\log_{10}$ASTpv	9.06	4.79	0.00	1.84	5.87	8.65	11.75	17.76	21.93	27.17
	0.1	3.6%	$\log_{10}$BF	19.65	26.51	-5.70	-4.71	-2.00	10.42	31.76	72.91	106.83	151.34
			-$\log_{10}$PPNA	24.22	26.46	0.03	0.21	2.51	14.94	36.27	77.42	111.34	155.86
			-$\log_{10}$ASTpv	3.00	2.58	0.00	0.01	1.08	2.50	4.08	7.83	11.60	16.89
2,1	0.3	5%	$\log_{10}$BF	47.03	32.44	-5.39	2.96	23.44	41.37	66.60	110.51	132.43	153.69
			-$\log_{10}$PPNA	51.55	32.44	0.05	7.47	27.96	45.89	71.11	115.02	136.94	158.20
			-$\log_{10}$ASTpv	11.83	6.32	0.00	2.74	6.86	11.11	16.08	23.60	27.04	30.20
	0.1	11%	$\log_{10}$BF	24.17	28.34	-5.64	-4.58	0.24	16.58	41.62	76.20	112.88	147.56
			-$\log_{10}$PPNA	28.73	28.30	0.03	0.27	4.76	21.10	46.14	80.72	117.39	152.07
			-$\log_{10}$ASTpv	3.26	2.56	0.00	0.04	1.11	2.90	5.05	7.78	10.58	12.66
6,0	0.3	3.2%	$\log_{10}$BF	98.03	51.34	-4.30	22.72	61.20	92.73	132.10	186.17	226.55	249.79
			-$\log_{10}$PPNA	102.55	51.34	0.42	27.23	65.71	97.25	136.62	190.69	231.07	254.31
			-$\log_{10}$ASTpv	13.00	5.03	1.41	5.77	9.33	12.38	16.18	22.16	27.71	29.63
	0.1	7.4%	$\log_{10}$BF	50.67	48.04	-5.20	-3.52	11.23	38.68	79.61	143.06	190.66	228.90
			-$\log_{10}$PPNA	55.20	48.03	0.08	1.04	15.74	43.20	84.12	147.57	195.17	233.42
			-$\log_{10}$ASTpv	4.40	2.87	0.00	0.85	2.40	3.88	5.78	10.21	13.85	18.72
3,3	0.3	9.6%	$\log_{10}$BF	131.30	55.63	2.77	40.71	94.71	124.78	167.57	228.71	254.75	300.00
			-$\log_{10}$PPNA	135.81	55.60	7.28	45.23	99.22	129.29	172.09	233.23	259.26	300.00
			-$\log_{10}$ASTpv	19.19	6.29	2.98	8.81	14.82	18.85	23.33	30.05	32.90	39.04
	0.1	18%	$\log_{10}$BF	88.17	56.96	-4.76	2.81	43.27	81.75	128.31	192.61	238.06	280.95
			-$\log_{10}$PPNA	92.69	56.95	0.20	7.32	47.78	86.26	132.83	197.13	242.58	285.47
			-$\log_{10}$ASTpv	6.20	2.80	0.42	1.88	4.13	6.06	8.13	10.84	12.86	14.86
9,0	0.3	3%	$\log_{10}$BF	138.27	67.50	5.60	38.98	88.00	129.53	176.81	269.42	300.00	304.92
			-$\log_{10}$PPNA	142.66	67.19	10.11	43.50	92.52	134.04	181.33	273.93	300.00	306.17
			-$\log_{10}$ASTpv	15.23	5.37	3.73	8.09	11.41	14.08	18.47	25.55	30.46	34.76
	0.1	13%	$\log_{10}$BF	63.42	64.23	-5.03	-3.23	13.52	48.72	96.29	201.05	284.78	303.37
			-$\log_{10}$PPNA	67.91	64.09	0.11	1.31	18.04	53.23	100.80	205.57	289.25	307.89
			-$\log_{10}$ASTpv	5.36	3.19	0.07	1.31	3.09	4.81	7.03	11.85	15.46	17.46
5,4	0.3	12.4%	$\log_{10}$BF	215.86	60.21	34.66	111.91	172.70	217.38	266.32	300.00	301.70	307.35
			-$\log_{10}$PPNA	219.77	59.38	39.17	116.43	177.22	221.90	270.83	300.00	303.80	307.01
			-$\log_{10}$ASTpv	23.88	5.96	8.05	14.39	19.81	23.71	28.19	33.76	38.67	40.10
	0.1	26.2%	$\log_{10}$BF	162.58	75.70	-3.20	34.04	106.51	161.99	219.54	298.60	300.00	305.56
			-$\log_{10}$PPNA	166.90	75.34	1.34	38.56	111.02	166.50	224.06	300.00	302.77	306.51
			-$\log_{10}$ASTpv	8.18	2.85	1.57	3.71	6.25	8.13	10.16	12.84	15.23	16.42

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote – $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For multiple studies with overlapping subjects, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S13: Summary of measures for the evidence of the overall pleiotropic association for a **cohort** study with **5** binary phenotypes. Here 1, 2, and 3 among 5 traits are associated.

							quantile						
K_1^+, K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
1,0	0.3	0.4%	$\log_{10}$BF	2.35	5.71	-2.60	-1.95	-0.68	0.30	3.18	13.14	25.07	36.20
			-$\log_{10}$PPNA	3.94	5.64	0.03	0.13	0.87	1.80	4.67	14.63	26.56	37.69
			-$\log_{10}$ASTpv	3.28	1.80	0.14	0.90	1.94	3.03	4.41	6.41	8.54	9.60
	0.1	0.8%	$\log_{10}$BF	5.58	13.62	-2.56	-1.84	-0.60	0.31	5.62	31.54	61.89	134.17
			-$\log_{10}$PPNA	7.15	13.58	0.04	0.16	0.95	1.81	7.11	33.03	63.38	135.67
			-$\log_{10}$ASTpv	2.94	1.59	0.22	0.79	1.82	2.68	3.86	5.97	7.59	9.02
2,0	0.3	0.4%	$\log_{10}$BF	16.93	20.10	-2.49	-1.30	0.49	8.88	29.37	56.92	70.49	144.78
			-$\log_{10}$PPNA	18.46	20.06	0.04	0.40	1.99	10.37	30.86	58.41	71.98	146.27
			-$\log_{10}$ASTpv	5.92	2.65	0.42	2.15	4.05	5.74	7.39	10.80	12.73	15.19
	0.1	0.6%	$\log_{10}$BF	37.24	44.95	-2.39	-0.98	0.70	20.95	57.70	134.10	172.37	260.25
			-$\log_{10}$PPNA	38.76	44.93	0.05	0.63	2.19	22.44	59.19	135.59	173.86	261.74
			-$\log_{10}$ASTpv	5.24	2.25	0.18	2.04	3.57	5.12	6.59	9.31	11.24	13.47
1,1	0.3	1%	$\log_{10}$BF	28.69	25.32	-2.30	-0.05	8.70	23.34	43.06	75.65	104.41	131.11
			-$\log_{10}$PPNA	30.19	25.32	0.06	1.46	10.19	24.83	44.55	77.15	105.90	132.60
			-$\log_{10}$ASTpv	6.87	2.63	0.46	3.05	5.04	6.77	8.49	11.44	13.71	17.00
	0.1	1.4%	$\log_{10}$BF	75.35	57.50	-1.77	0.88	29.54	66.54	110.21	193.99	242.63	270.47
			-$\log_{10}$PPNA	76.84	57.50	0.18	2.37	31.04	68.03	111.70	195.49	244.12	271.96
			-$\log_{10}$ASTpv	6.82	2.54	1.20	3.03	5.02	6.59	8.28	11.60	13.07	15.80
3,0	0.3	0.6%	$\log_{10}$BF	29.04	32.40	-2.15	-1.04	1.24	17.90	47.42	96.83	130.47	157.60
			-$\log_{10}$PPNA	30.56	32.38	0.09	0.58	2.73	19.39	48.91	98.32	131.96	159.09
			-$\log_{10}$ASTpv	8.24	3.29	1.32	3.59	5.76	7.84	10.32	14.16	16.41	19.55
	0.1	0.6%	$\log_{10}$BF	66.73	70.53	-2.29	-0.76	5.17	43.91	110.55	204.88	285.55	305.56
			-$\log_{10}$PPNA	68.23	70.48	0.06	0.80	6.66	45.40	112.04	206.37	287.04	307.05
			-$\log_{10}$ASTpv	7.44	2.92	0.89	3.37	5.22	7.14	9.15	13.09	15.32	18.67
2,1	0.3	0.4%	$\log_{10}$BF	60.72	36.96	-0.05	8.79	31.84	58.14	83.58	122.86	149.41	225.07
			-$\log_{10}$PPNA	62.21	36.96	1.46	10.28	33.33	59.63	85.08	124.35	150.91	226.56
			-$\log_{10}$ASTpv	9.64	2.96	3.58	5.21	7.51	9.36	11.55	14.86	16.86	20.40
	0.1	0.2%	$\log_{10}$BF	144.11	78.84	0.47	23.29	84.36	139.72	203.80	300.00	300.00	305.28
			-$\log_{10}$PPNA	145.54	78.71	1.96	24.78	85.85	141.21	205.29	300.00	300.00	306.77
			-$\log_{10}$ASTpv	9.37	2.69	3.52	5.27	7.42	9.27	11.18	13.93	16.43	20.06

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For a cohort study, since the summary statistics are correlated, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S14: Summary of measures for the evidence of the overall pleiotropic association for a **cohort** study with **10** binary phenotypes. Here 2, 4, and 6 among 10 traits are associated.

							quantile						
K_1^+, K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
2,0	0.3	1.4%	$\log_{10}$BF	15.43	22.86	-3.84	-2.83	-0.96	6.94	23.85	64.26	94.62	141.25
			-$\log_{10}$PPNA	18.47	22.83	0.06	0.40	2.05	9.95	26.86	67.27	97.63	144.26
			-$\log_{10}$ASTpv	4.42	2.22	0.21	1.32	2.82	4.09	5.69	8.65	9.98	14.28
	0.1	2%	$\log_{10}$BF	39.56	52.79	-3.65	-2.65	-0.73	17.77	61.14	150.17	208.91	300.00
			-$\log_{10}$PPNA	42.59	52.74	0.09	0.52	2.28	20.78	64.15	153.18	211.92	300.00
			-$\log_{10}$ASTpv	3.83	1.94	0.32	0.90	2.47	3.54	5.04	7.19	9.34	10.46
1,1	0.3	2.4%	$\log_{10}$BF	25.82	24.81	-3.56	-1.85	5.20	19.64	39.79	74.28	98.89	120.00
			-$\log_{10}$PPNA	28.84	24.80	0.11	1.18	8.21	22.65	42.80	77.29	101.90	123.01
			-$\log_{10}$ASTpv	4.88	2.42	0.18	1.58	3.06	4.63	6.24	9.40	11.67	15.97
	0.1	2.2%	$\log_{10}$BF	53.73	49.08	-3.88	-0.92	17.83	40.63	76.23	145.13	224.11	306.52
			-$\log_{10}$PPNA	56.72	48.95	0.06	2.10	20.84	43.64	79.24	148.14	227.12	305.48
			-$\log_{10}$ASTpv	4.93	2.41	0.06	1.74	3.25	4.56	6.36	9.42	11.40	17.14
4,0	0.3	2.2%	$\log_{10}$BF	56.33	54.33	-3.51	-1.89	6.75	46.66	86.96	169.80	215.64	244.32
			-$\log_{10}$PPNA	59.35	54.32	0.12	1.15	9.76	49.67	89.97	172.81	218.65	247.33
			-$\log_{10}$ASTpv	8.47	3.36	0.93	3.89	5.94	7.89	10.38	14.76	18.33	20.98
	0.1	3.8%	$\log_{10}$BF	119.80	100.88	-3.34	-1.95	23.09	104.41	193.24	300.00	304.52	308.12
			-$\log_{10}$PPNA	122.52	100.33	0.17	1.09	26.10	107.42	196.25	300.00	300.01	308.03
			-$\log_{10}$ASTpv	7.23	2.92	1.29	3.07	5.24	6.92	8.79	12.70	15.48	17.78
2,2	0.3	3.8%	$\log_{10}$BF	99.93	46.20	-2.36	26.66	66.67	99.40	130.90	176.83	216.07	254.43
			-$\log_{10}$PPNA	102.94	46.20	0.74	29.67	69.68	102.41	133.91	179.84	219.08	257.44
			-$\log_{10}$ASTpv	10.42	2.98	3.39	5.87	8.26	10.36	12.27	15.42	18.26	21.29
	0.1	4.4%	$\log_{10}$BF	227.05	78.66	-2.35	71.00	171.94	249.85	300.00	300.00	303.33	307.17
			-$\log_{10}$PPNA	229.08	77.75	0.75	74.01	174.95	252.86	300.00	300.00	302.47	306.32
			-$\log_{10}$ASTpv	10.63	3.30	1.40	5.53	8.25	10.43	12.64	16.28	18.50	26.30
6,0	0.3	5.6%	$\log_{10}$BF	88.10	77.83	-3.57	-1.81	17.54	73.16	144.29	232.21	300.00	302.61
			-$\log_{10}$PPNA	91.09	77.73	0.11	1.23	20.55	76.17	147.30	235.22	300.00	305.62
			-$\log_{10}$ASTpv	11.59	4.12	1.83	5.67	8.64	11.23	13.91	19.29	22.88	29.19
	0.1	4.8%	$\log_{10}$BF	174.39	115.88	-3.43	-1.72	66.20	181.02	300.00	300.00	301.73	306.12
			-$\log_{10}$PPNA	176.49	114.88	0.14	1.31	69.20	184.03	300.00	300.00	303.51	307.87
			-$\log_{10}$ASTpv	10.22	3.52	1.83	5.29	7.76	9.89	12.26	16.74	20.79	23.54
3,3	0.3	5.2%	$\log_{10}$BF	202.10	57.94	32.55	100.05	165.63	204.42	245.35	300.00	302.67	305.65
			-$\log_{10}$PPNA	204.94	57.66	35.56	103.06	168.64	207.43	248.36	300.00	302.39	307.74
			-$\log_{10}$ASTpv	15.67	3.58	6.08	10.05	13.19	15.49	17.99	21.41	25.39	27.98
	0.1	4%	$\log_{10}$BF	295.46	22.55	93.92	277.38	300.00	300.00	300.00	300.00	300.00	305.60
			-$\log_{10}$PPNA	295.64	21.98	96.93	280.39	300.00	300.00	300.00	300.00	300.00	304.24
			-$\log_{10}$ASTpv	15.89	3.57	7.36	10.46	13.71	15.67	18.22	21.72	24.68	32.26

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For a cohort study, since the summary statistics are correlated, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S15: Summary of measures for the evidence of the overall pleiotropic association for a **cohort** study with **15** binary phenotypes. Here 3, 6, and 9 among 15 traits are associated.

							quantile						
K_1^+, K_1^-	m	uncor%		mean	sd	min	5%	25%	50%	75%	95%	99%	max
3,0	0.3	2.8%	$\log_{10}$BF	35.52	38.84	-5.03	-3.62	3.13	23.84	59.72	109.93	156.95	206.75
			-$\log_{10}$PPNA	40.05	38.82	0.12	0.95	7.65	28.35	64.24	114.45	161.46	211.26
			-$\log_{10}$ASTpv	5.42	2.53	0.36	1.89	3.65	5.07	6.95	9.68	12.78	16.67
	0.1	1.6%	$\log_{10}$BF	91.59	85.98	-5.06	-3.10	10.53	79.47	148.50	259.71	300.00	305.64
			-$\log_{10}$PPNA	96.01	85.70	0.11	1.43	15.05	83.99	153.02	264.22	300.00	307.76
			-$\log_{10}$ASTpv	4.68	2.23	0.01	1.69	3.04	4.40	5.98	8.61	11.66	13.06
2,1	0.3	4.8%	$\log_{10}$BF	50.99	38.85	-4.91	-2.40	17.71	45.66	75.27	119.05	157.58	188.70
			-$\log_{10}$PPNA	55.51	38.85	0.15	2.12	22.23	50.17	79.78	123.56	162.09	193.22
			-$\log_{10}$ASTpv	5.58	2.48	0.41	2.03	3.79	5.37	6.98	10.15	12.31	14.73
	0.1	4%	$\log_{10}$BF	127.84	80.25	-4.47	7.71	63.09	123.28	182.87	276.54	300.00	306.77
			-$\log_{10}$PPNA	132.20	79.92	0.33	12.23	67.60	127.79	187.39	281.05	300.00	305.14
			-$\log_{10}$ASTpv	5.40	2.37	0.01	1.74	3.64	5.31	6.91	9.23	11.28	15.27
6,0	0.3	4.8%	$\log_{10}$BF	103.39	80.43	-4.47	-2.86	36.27	95.49	154.95	250.77	294.16	300.00
			-$\log_{10}$PPNA	107.88	80.34	0.32	1.67	40.78	100.00	159.46	255.29	298.67	300.35
			-$\log_{10}$ASTpv	9.90	3.53	2.06	4.70	7.34	9.65	11.96	16.32	19.38	22.77
	0.1	5.8%	$\log_{10}$BF	197.13	110.97	-4.91	-2.45	99.53	236.02	300.00	300.00	300.00	307.61
			-$\log_{10}$PPNA	199.83	109.28	0.15	2.07	104.04	240.53	300.00	300.00	302.37	304.28
			-$\log_{10}$ASTpv	8.57	3.06	0.76	4.22	6.37	8.37	10.34	13.81	17.21	21.96
3,3	0.3	4%	$\log_{10}$BF	190.67	61.02	14.94	88.20	152.24	192.81	231.43	300.00	300.00	304.60
			-$\log_{10}$PPNA	194.93	60.57	19.45	92.71	156.75	197.33	235.94	300.00	300.00	306.52
			-$\log_{10}$ASTpv	13.37	3.51	4.33	7.93	11.07	13.20	15.49	19.59	22.10	25.72
	0.1	7.6%	$\log_{10}$BF	292.98	28.66	10.06	249.35	300.00	300.00	300.00	300.00	301.12	307.81
			-$\log_{10}$PPNA	293.42	27.66	14.58	253.87	300.00	300.00	300.00	300.00	300.00	307.89
			-$\log_{10}$ASTpv	13.49	3.58	3.94	8.35	10.89	13.18	15.67	19.83	22.81	25.69
9,0	0.3	8.2%	$\log_{10}$BF	137.39	110.59	-4.67	-3.30	25.92	131.91	236.19	300.00	302.61	307.78
			-$\log_{10}$PPNA	141.24	109.60	0.23	1.25	30.44	136.43	240.70	300.00	303.51	308.00
			-$\log_{10}$ASTpv	13.51	4.81	3.76	7.28	9.76	12.87	16.43	22.69	27.08	34.57
	0.1	8.4%	$\log_{10}$BF	216.47	113.62	-4.69	-2.90	120.36	300.00	300.00	300.00	300.00	305.19
			-$\log_{10}$PPNA	218.47	111.75	0.22	1.62	124.87	300.00	300.00	300.00	300.01	301.90
			-$\log_{10}$ASTpv	11.88	4.25	3.98	5.69	8.93	11.44	14.25	19.82	23.76	30.41
5,4	0.3	7.6%	$\log_{10}$BF	287.14	31.28	87.96	215.08	298.03	300.00	300.00	300.00	303.78	308.20
			-$\log_{10}$PPNA	288.29	29.91	92.48	219.60	300.00	300.00	300.00	300.00	304.74	307.64
			-$\log_{10}$ASTpv	19.61	3.85	8.76	13.22	17.16	19.35	22.16	25.80	29.35	33.71
	0.1	9.2%	$\log_{10}$BF	300.00	0.16	297.25	300.00	300.00	300.00	300.00	300.00	300.00	302.15
			-$\log_{10}$PPNA	300.02	0.35	300.00	300.00	300.00	300.00	300.00	300.00	300.00	306.66
			-$\log_{10}$ASTpv	19.41	3.96	9.27	13.56	16.56	19.19	21.81	26.19	30.74	31.58

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association), -$\log_{10}$(ASTpv): -$\log_{10}$(ASSET p-value). For a cohort study, since the summary statistics are correlated, the combined strategy of CPBayes is implemented. Of note, uncor% denotes the percentage of replications in which the combined strategy of CPBayes used the uncorrelated version of CPBayes. Different summary measures obtained across 500 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Figure S2: Comparison of the accuracy of selection of associated traits by CPBayes and ASSET for cohort study. The total number of phenotypes/studies is denoted by K and m denotes the minor allele frequency at the risk SNP.

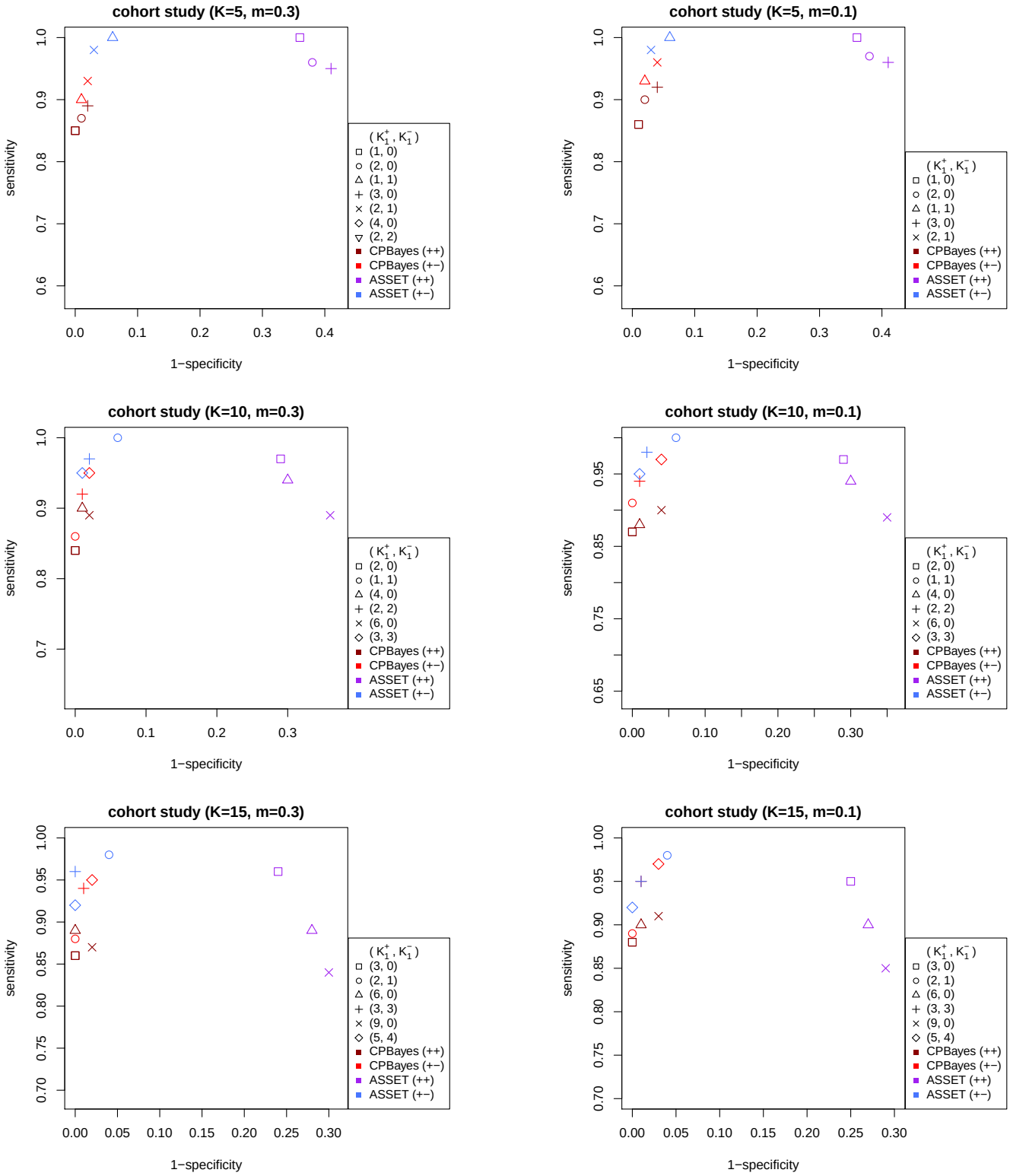


Table S16: Simulation study for **50** traits. Summary of measures for the evidence of the overall pleiotropic association for **50** overlapping case-control studies. Here 0, 5, and 10 among 50 traits are associated.

						quantile						
K_1^+, K_1^-	m		mean	sd	min	5%	25%	50%	75%	95%	99%	max
0,0	0.3	$\log_{10}$BF	-16.43	0.11	-16.61	-16.56	-16.50	-16.44	-16.38	-16.25	-16.08	-15.83
		-$\log_{10}$PPNA	0.02	0.006	0.01	0.01	0.02	0.02	0.02	0.03	0.04	0.07
	0.1	$\log_{10}$BF	-16.18	0.25	-16.42	-16.38	-16.30	-16.24	-16.15	-15.83	-15.51	-13.96
		-$\log_{10}$PPNA	0.04	0.08	0.02	0.02	0.02	0.03	0.03	0.07	0.13	1.12
5,0	0.3	$\log_{10}$BF	80.75	49.38	-10.03	9.21	45.43	74.39	107.94	170.54	216.63	240.42
		-$\log_{10}$PPNA	95.80	49.38	5.02	24.26	60.48	89.44	123.00	185.60	231.68	255.47
	0.1	$\log_{10}$BF	44.74	48.08	-15.93	-14.86	1.51	38.10	74.46	124.66	164.88	205.38
		-$\log_{10}$PPNA	59.82	48.05	0.05	0.41	16.56	53.15	89.51	139.71	179.94	220.43
3,2	0.3	$\log_{10}$BF	90.92	52.29	-8.18	19.74	51.37	85.36	120.45	192.00	224.04	235.20
		-$\log_{10}$PPNA	105.97	52.29	6.87	34.80	66.42	100.41	135.50	207.05	239.10	250.25
	0.1	$\log_{10}$BF	49.80	55.62	-15.27	-14.33	3.45	34.91	81.20	161.52	196.32	221.93
		-$\log_{10}$PPNA	64.86	55.60	0.21	0.80	18.51	49.96	96.25	176.58	211.37	236.98
10,0	0.3	$\log_{10}$BF	199.00	67.19	25.03	96.56	146.74	201.41	249.66	300.00	300.01	307.05
		-$\log_{10}$PPNA	212.35	64.74	40.08	111.61	161.79	216.46	264.71	300.00	305.53	306.50
	0.1	$\log_{10}$BF	130.40	89.63	-15.33	-12.20	58.70	128.76	189.76	285.52	300.02	306.13
		-$\log_{10}$PPNA	144.74	88.29	0.18	2.85	73.75	143.81	204.81	300.00	300.16	305.42
5,5	0.3	$\log_{10}$BF	226.35	61.43	86.31	122.24	179.19	232.38	288.33	300.00	303.86	307.56
		-$\log_{10}$PPNA	237.90	57.39	101.36	137.29	194.24	247.43	300.00	300.00	305.03	306.94
	0.1	$\log_{10}$BF	159.54	83.40	-14.64	21.29	98.02	158.45	222.71	300.00	301.30	308.25
		-$\log_{10}$PPNA	173.33	81.33	0.56	36.34	113.07	173.50	237.76	300.00	302.45	305.23

Legend: m - allele frequency at the risk SNP; $m = 0.3, 0.1$. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. Hence the total number of associated traits is $K_1 = K_1^+ + K_1^-$. The following abbreviations denote − $\log_{10}$BF: $\log_{10}$(Bayes factor), -$\log_{10}$PPNA: -$\log_{10}$(posterior probability of null association). For multiple studies with overlapping subjects, the combined strategy of CPBayes is implemented. Different summary measures obtained across 200 replications are provided: mean, standard deviation (sd), minimum (min), 5% quantile, 25% quantile, 50% quantile, 75% quantile, 95% quantile, 99% quantile, and maximum (max).

Table S17: Simulation study for 50 traits. Accuracy in selection of associated traits by CPBayes for 50 overlapping case-control studies. The number of positively and negatively associated traits are denoted by K_1^+ and K_1^-, respectively. And m denotes the minor allele frequency at the risk SNP.

K_1^+, K_1^-	m	specificity	sensitivity
5,0	0.3	1.00	0.81
	0.1	1.00	0.61
3,2	0.3	1.00	0.81
	0.1	1.00	0.59
10,0	0.3	1.00	0.83
	0.1	1.00	0.62
5,5	0.3	1.00	0.82
	0.1	1.00	0.62

Table S18: Name of 22 phenotypes in the Kaiser GERA cohort analyzed by CPBayes and ASSET.

GERA cohort phenotypes			
Asthma	Type 2 Diabetes	Iron Deficiency	Peptic Ulcer
Allergic Rhinitis	Dyslipidemia	Irritable Bowel Syndrome	Psychiatric disorders
Cardiovascular Disease	Hypertension	Macular Degeneration	Stress Disorders
Cancers	Hemorrhoids	Osteoarthritis	Varicose Veins
Depressive Disorder	Abdominal Hernia	Osteoporosis	
Dermatophytosis	Insomnia	Peripheral Vascular Disease	

Table S19: Independent pleiotropic SNPs identified by CPBayes for which one phenotype was selected.

rsID	chrom band	CPBayes $\log_{10}$BF	CPBayes PPNA	Associated trait	PPA_j	Direction	Univariate p-values
rs2300430	1q31.3	300.00	1.00E-300	Macular Degeneration	100%	negative	2.57E-77
rs35505017	1q31.3	213.91	2.92E-221	Macular Degeneration	100%	negative	3.14E-14
rs77394225	1q31.3	76.74	4.33E-84	Macular Degeneration	100%	negative	6.04E-16
rs4658043	1q31.3	15.56	6.62E-23	Macular Degeneration	100%	negative	4.61E-08
rs77795056	1p36.23	9.50	7.47E-17	Iron Deficiency	100%	negative	5.13E-05
rs79032519	1q43	8.80	3.76E-16	Peptic Ulcer	100%	negative	2.14E-05
rs481069	2p24.1	46.16	1.64E-53	Dyslipidemia	100%	positive	2.89E-30
rs1367117	2p24.1	38.25	1.34E-45	Dyslipidemia	100%	negative	5.26E-43
rs7604788	2p24.1	26.91	2.95E-34	Dyslipidemia	100%	positive	1.19E-13
rs17398765	2p24.1	17.46	8.33E-25	Dyslipidemia	100%	negative	2.11E-15
rs11709077	3p25.2	9.86	3.29E-17	Type 2 Diabetes	100%	positive	1.26E-09
rs115946033	3q25.32	8.59	6.07E-16	Type 2 Diabetes	100%	positive	3.83E-07
rs75081018	5q34	16.24	1.37E-23	Iron Deficiency	100%	positive	1.06E-05
rs183671	5p13.2	13.00	2.37E-20	Cancers	100%	positive	4.13E-09
rs12916	5q13.3	8.32	1.15E-15	Dyslipidemia	100%	negative	1.46E-22
rs12203592	6p25.3	77.46	8.27E-85	Cancers	100%	negative	2.36E-48
rs4151672	6p21.33	40.39	9.64E-48	Macular Degeneration	100%	positive	1.01E-08
rs2300051	7q31.1	113.86	3.28E-121	Peptic Ulcer	100%	negative	3.93E-07
rs849135	7p15.1	7.66	5.22E-15	Type 2 Diabetes	100%	positive	1.79E-14
rs17321515	8q24.13	10.81	3.73E-18	Dyslipidemia	100%	positive	1.19E-24
rs74580577	9q22.33	14.09	1.95E-21	Peptic Ulcer	100%	negative	1.81E-05
rs61871745	10q26.13	300.00	1.00E-300	Macular Degeneration	100%	negative	1.96E-75
rs2292627	10q26.13	84.13	1.75E-91	Macular Degeneration	100%	negative	8.23E-21
rs2253755	10q26.13	51.81	3.65E-59	Macular Degeneration	100%	negative	2.94E-21
rs2672589	10q26.13	22.96	2.60E-30	Macular Degeneration	100%	positive	3.36E-16
rs75799135	10q26.13	17.07	2.04E-24	Macular Degeneration	100%	negative	1.95E-13
rs76517520	10p13	13.60	5.95E-21	Peptic Ulcer	100%	negative	1.39E-05
rs7079711	10q25.2	8.22	1.45E-15	Type 2 Diabetes	100%	positive	6.74E-12
rs1799963	11p11.2	41.52	7.13E-49	Peripheral Vascular Disease	100%	negative	1.19E-08
rs964184	11q23.3	32.15	1.68E-39	Dyslipidemia	100%	negative	5.49E-28
rs55975204	11q13.2	11.43	8.91E-19	Osteoporosis	100%	negative	2.00E-09
rs74836424	16q24.3	12.39	9.69E-20	Cancers	100%	negative	1.14E-12
rs1801689	17q24.2	8.78	3.93E-16	Dyslipidemia	100%	negative	4.80E-09
rs8092654	18p11.31	12.24	1.39E-19	Peripheral Vascular Disease	100%	negative	4.18E-06
rs56289821	19p13.2	151.61	5.81E-159	Dyslipidemia	100%	positive	2.09E-62
rs28399654	19q13.32	54.76	4.12E-62	Dyslipidemia	100%	positive	2.79E-17
rs76075198	19q13.31	41.56	6.53E-49	Dyslipidemia	100%	positive	5.29E-11
rs34095326	19q13.32	40.41	9.18E-48	Dyslipidemia	100%	negative	4.03E-25
rs2927472	19q13.32	16.99	2.42E-24	Dyslipidemia	100%	positive	1.56E-21
rs2230199	19p13.3	7.58	6.28E-15	Macular Degeneration	100%	negative	4.42E-09

Table S20: Independent pleiotropic signals detected by ASSET for chromosome 1-2

rsID	chrom band	ASTpv	Subset of associated traits	Univariate p-values
rs2300430	1q31.3	1.52E-72	Allergic Rhinitis	0.34
			Depressive Disorder	0.18
			Dermatophytosis	0.09
			Hemorrhoids	0.36
			Insomnia	0.47
			Macular Degeneration	2.57E-77
			Osteoporosis	0.09
			Peptic Ulcer	0.74
rs10494745	1q31.3	1.05E-14	Cancers	0.04
			Dermatophytosis	0.27
			Type 2 Diabetes	0.13
			Insomnia	0.03
			Iron Deficiency	0.28
			Macular Degeneration	6.15E-21
			Peripheral Vascular Disease	0.24
			Peptic Ulcer	0.35
rs6025	1q24.2	1.38E-11	Dermatophytosis	0.0018
			Hemorrhoids	0.0014
			Iron Deficiency	0.0004
			Osteoporosis	0.0002
			Peripheral Vascular Disease	6.81E-14
rs77394225	1q31.3	6.84E-10	Dermatophytosis	0.62
			Dyslipidemia	0.47
			Abdominal Hernia	0.65
			Macular Degeneration	6.04E-16
			Osteoarthritis	0.30
			Osteoporosis	0.34
			Peptic Ulcer	0.46
			Psychiatric disorders	0.39
			Stress Disorders	0.32
rs35505017	1q31.3	3.18E-08	Dermatophytosis	0.56
			Dyslipidemia	0.40
			Macular Degeneration	3.14E-14
			Peptic Ulcer	0.63
			Stress Disorders	0.21
rs1367117	2p24.1	5.19E-34	Depressive Disorder	0.61
			Dyslipidemia	5.26E-43
			Hemorrhoids	0.67
			Abdominal Hernia	0.34
			Macular Degeneration	0.50
			Peptic Ulcer	0.57
			Varicose Veins	0.70
rs562338	2p24.1	3.15E-27	Cardiovascular Disease	0.26
			Dyslipidemia	3.43E-35
			Abdominal Hernia	0.18
			Peptic Ulcer	0.04
			Psychiatric disorders	0.22
rs79281791	2p24.1	9.75E-10	Dyslipidemia	4.91E-17
			Insomnia	0.007
			Iron Deficiency	0.04
			Macular Degeneration	0.17
			Peptic Ulcer	0.31
			Varicose Veins	0.13
rs3791679	2p16.1	3.73E-09	Type 2 Diabetes	0.35
			Abdominal Hernia	2.66E-14
			Insomnia	0.25
			Peripheral Vascular Disease	0.25
			Psychiatric disorders	0.11
			Stress Disorders	0.24
			Varicose Veins	0.002

Table S21: Independent pleiotropic signals detected by ASSET for chromosome 3-7

rsID	chrom band	ASTpv	Subset of associated traits	Univariate p-values
rs3846662	5q13.3	8.84E-16	Depressive Disorder	0.18
			Type 2 Diabetes	0.02
			Dyslipidemia	2.29E-22
			Iron Deficiency	0.48
			Irritable Bowel Syndrome	0.49
			Macular Degeneration	0.18
			Peptic Ulcer	0.34
rs12203592	6p25.3	7.70E-42	Cancers	2.36E-48
			Dyslipidemia	0.13
			Hypertension	0.006
			Osteoarthritis	0.10
			Peptic Ulcer	0.08
			Psychiatric disorders	0.02
rs78825896	6p21.32	7.32E-13	Asthma	0.003
			Allergic Rhinitis	0.06
			Cancers	1.92E-07
			Dyslipidemia	2.20E-13
			Hemorrhoids	0.03
			Iron Deficiency	0.46
			Irritable Bowel Syndrome	0.43
			Peptic Ulcer	0.45
rs10455872	6q25.3	5.49E-11	Allergic Rhinitis	0.07
			Cardiovascular Disease	6.14E-05
			Dyslipidemia	6.97E-15
			Insomnia	0.37
			Iron Deficiency	0.57
			Irritable Bowel Syndrome	0.34
			Osteoarthritis	0.12
			Peripheral Vascular Disease	0.0002
rs522162	6p21.33	3.16E-09	Hypertension	0.16
			Hemorrhoids	0.13
			Macular Degeneration	1.02E-15
			Osteoarthritis	0.26
			Peptic Ulcer	0.62
			Varicose Veins	0.07
rs2395182	6p21.32	1.87E-08	Asthma	0.009
			Allergic Rhinitis	0.05
			Cancers	0.001
			Dermatophytosis	0.016
			Type 2 Diabetes	1.36E-05
			Dyslipidemia	9.65E-06
			Insomnia	0.09
			Iron Deficiency	0.49
			Macular Degeneration	0.08
			Osteoporosis	0.39
			Peripheral Vascular Disease	0.13
			Peptic Ulcer	0.30
			Psychiatric disorders	0.36
rs864745	7p15.1	2.52E-09	Asthma	1.25E-05
			Cancers	0.30
			Type 2 Diabetes	4.19E-14
			Hemorrhoids	0.52
			Macular Degeneration	0.33
			Peripheral Vascular Disease	0.23

Table S22: Independent pleiotropic signals detected by ASSET for chromosome 8-10

rsID	chrom band	ASTpv	Subset of associated traits	Univariate p-values
rs2001945	8q24.13	4.01E-19	Asthma	0.43
			Allergic Rhinitis	0.26
			Depressive Disorder	0.39
			Dyslipidemia	1.86E-25
			Abdominal Hernia	0.37
			Iron Deficiency	0.61
			Macular Degeneration	0.07
			Osteoporosis	0.39
			Stress Disorders	0.30
rs651007	9q34.2	3.09E-16	Depressive Disorder	0.09
			Dyslipidemia	2.89E-15
			Hypertension	0.03
			Hemorrhoids	0.17
			Abdominal Hernia	0.34
			Peripheral Vascular Disease	9.55E-08
			Peptic Ulcer	0.03
			Varicose Veins	0.0027
rs61871745	10q26.13	6.99E-69	Depressive Disorder	0.04
			Hemorrhoids	0.05
			Insomnia	0.16
			Macular Degeneration	1.96E-75
			Stress Disorders	0.01
rs4506565	10q25.2	1.48E-46	Asthma	0.18
			Type 2 Diabetes	2.02E-55
			Irritable Bowel Syndrome	0.37
			Peptic Ulcer	0.63
			Varicose Veins	0.36
rs2292627	10q26.13	9.71E-15	Type 2 Diabetes	0.06
			Hemorrhoids	0.34
			Insomnia	0.29
			Irritable Bowel Syndrome	0.54
			Macular Degeneration	8.23E-21
			Peptic Ulcer	0.54
			Stress Disorders	0.36
			Varicose Veins	0.65
rs2253755	10q26.13	3.65E-14	Allergic Rhinitis	0.18
			Cardiovascular Disease	0.29
			Dermatophytosis	0.37
			Type 2 Diabetes	0.14
			Macular Degeneration	2.94E-21
			Psychiatric disorders	0.26
			Stress Disorders	0.39
rs2672589	10q26.13	1.70E-10	Iron Deficiency	0.17
			Irritable Bowel Syndrome	0.29
			Macular Degeneration	3.36E-16
			Peptic Ulcer	0.058
			Stress Disorders	0.019
rs75799135	10q26.13	2.45E-08	Depressive Disorder	0.04
			Type 2 Diabetes	0.029
			Hemorrhoids	0.088
			Insomnia	0.037
			Macular Degeneration	1.95E-13
			Stress Disorders	0.19

Table S23: Independent pleiotropic signals detected by ASSET for chromosome 11-22

rsID	chrom band	ASTpv	Subset of associated traits	Univariate p-values
rs964184	11q23.3	5.36E-21	Asthma	0.32
			Allergic Rhinitis	0.16
			Dyslipidemia	5.49E-28
			Insomnia	0.39
			Iron Deficiency	0.11
			Irritable Bowel Syndrome	0.42
			Macular Degeneration	0.24
			Osteoarthritis	0.23
			Osteoporosis	0.077
			Peripheral Vascular Disease	0.46
			Peptic Ulcer	0.13
rs3764261	16q13	1.32E-09	Depressive Disorder	0.09
			Dyslipidemia	7.51E-13
			Irritable Bowel Syndrome	0.27
			Macular Degeneration	8.58E-05
			Osteoarthritis	0.0029
			Osteoporosis	0.023
			Peripheral Vascular Disease	0.14
			Peptic Ulcer	0.2
			Stress Disorders	0.24
rs56289821	19p13.2	1.17E-52	Asthma	0.44
			Allergic Rhinitis	0.35
			Dermatophytosis	0.47
			Dyslipidemia	2.09E-62
			Osteoarthritis	0.54
			Stress Disorders	0.69
			Varicose Veins	0.48
rs34095326	19q13.32	7.53E-20	Cancers	0.045
			Type 2 Diabetes	0.018
			Dyslipidemia	4.03E-25
			Irritable Bowel Syndrome	0.25
			Macular Degeneration	0.096
			Osteoporosis	0.016
			Peptic Ulcer	0.60
rs2927472	19q13.32	1.20E-13	Cancers	0.14
			Dyslipidemia	1.56E-21
			Hemorrhoids	0.055
			Macular Degeneration	0.51
			Peptic Ulcer	0.29
rs28399654	19q13.32	1.37E-09	Allergic Rhinitis	0.40
			Depressive Disorder	0.43
			Dermatophytosis	0.62
			Dyslipidemia	2.79E-17
			Macular Degeneration	0.51
			Peripheral Vascular Disease	0.65
			Peptic Ulcer	0.65

Table S24: Pair-wise trait-trait correlation matrix in the GERA cohort.

	astm	alrg	card	canc	dprs	drmt	dia2	dysl	hypr	hemr	hern	insm	iron	irrb	mcdg	osta	ostp	pvd	pept	psyc	strs	vrvn
astm	1.00	0.27	0.06	0.00	0.09	0.03	0.05	0.04	0.06	0.03	0.03	0.05	0.05	0.06	0.02	0.08	0.02	0.05	0.02	0.09	0.08	0.02
alrg	0.27	1.00	0.02	0.00	0.08	0.05	0.01	0.03	0.03	0.04	0.02	0.06	0.02	0.09	0.01	0.08	0.02	0.02	0.02	0.09	0.09	0.03
card	0.06	0.02	1.00	0.16	0.01	0.08	0.16	0.27	0.32	0.05	0.12	0.06	0.09	0.02	0.14	0.18	0.07	0.22	0.09	0.03	0.02	0.03
canc	0.00	0.00	0.16	1.00	-0.02	0.07	0.05	0.10	0.14	0.06	0.10	0.03	0.05	0.01	0.10	0.11	0.07	0.14	0.04	-0.01	0.00	0.03
dprs	0.09	0.08	0.01	-0.02	1.00	0.03	0.03	0.02	0.01	0.03	0.00	0.13	0.04	0.09	0.00	0.06	0.01	0.03	0.02	0.35	0.17	0.01
drmt	0.03	0.05	0.08	0.07	0.03	1.00	0.08	0.06	0.07	0.04	0.06	0.04	0.03	0.02	0.04	0.10	0.01	0.07	0.02	0.03	0.04	0.05
dia2	0.05	0.01	0.16	0.05	0.03	0.08	1.00	0.26	0.28	0.01	0.04	0.01	0.07	-0.01	0.05	0.08	-0.03	0.08	0.04	0.01	0.03	0.00
dysl	0.04	0.03	0.27	0.10	0.02	0.06	0.26	1.00	0.36	0.06	0.07	0.04	0.04	0.01	0.07	0.16	0.04	0.12	0.05	0.02	0.03	0.01
hypr	0.06	0.03	0.32	0.14	0.01	0.07	0.28	0.36	1.00	0.05	0.09	0.04	0.07	0.02	0.13	0.21	0.05	0.15	0.06	0.02	0.04	0.02
hemr	0.03	0.04	0.05	0.06	0.03	0.04	0.01	0.06	0.05	1.00	0.06	0.04	0.05	0.07	0.02	0.06	0.01	0.04	0.03	0.04	0.03	0.02
hern	0.03	0.02	0.12	0.10	0.00	0.06	0.04	0.07	0.09	0.06	1.00	0.02	0.08	0.01	0.05	0.07	0.00	0.09	0.06	0.00	-0.01	0.02
insm	0.05	0.06	0.06	0.03	0.13	0.04	0.01	0.04	0.04	0.04	0.02	1.00	0.04	0.08	0.03	0.08	0.04	0.06	0.03	0.15	0.10	0.02
iron	0.05	0.02	0.09	0.05	0.04	0.03	0.07	0.04	0.07	0.05	0.08	0.04	1.00	0.03	0.04	0.06	0.03	0.09	0.10	0.04	0.03	0.02
irrb	0.06	0.09	0.02	0.01	0.09	0.02	-0.01	0.01	0.02	0.07	0.01	0.08	0.03	1.00	0.02	0.07	0.05	0.01	0.03	0.14	0.11	0.02
mcdg	0.02	0.01	0.14	0.10	0.00	0.04	0.05	0.07	0.13	0.02	0.05	0.03	0.04	0.02	1.00	0.11	0.09	0.10	0.03	0.00	0.00	0.02
osta	0.08	0.08	0.18	0.11	0.06	0.10	0.08	0.16	0.21	0.06	0.07	0.08	0.06	0.07	0.11	1.00	0.11	0.13	0.06	0.04	0.07	0.07
ostp	0.02	0.02	0.07	0.07	0.01	0.01	-0.03	0.04	0.05	0.01	0.00	0.04	0.03	0.05	0.09	0.11	1.00	0.08	0.02	0.03	0.03	0.04
pvd	0.05	0.02	0.22	0.14	0.03	0.07	0.08	0.12	0.15	0.04	0.09	0.06	0.09	0.01	0.10	0.13	0.08	1.00	0.06	0.03	0.02	0.04
pept	0.02	0.02	0.09	0.04	0.02	0.02	0.04	0.05	0.06	0.03	0.06	0.03	0.10	0.03	0.03	0.06	0.02	0.06	1.00	0.02	0.01	0.01
psyc	0.09	0.09	0.03	-0.01	0.35	0.03	0.01	0.02	0.02	0.04	0.00	0.15	0.04	0.14	0.00	0.04	0.03	0.03	0.02	1.00	0.24	0.02
strs	0.08	0.09	0.02	0.00	0.17	0.04	0.03	0.03	0.04	0.03	-0.01	0.10	0.03	0.11	0.00	0.07	0.03	0.02	0.01	0.24	1.00	0.03
vrvn	0.02	0.03	0.03	0.03	0.01	0.05	0.00	0.01	0.02	0.02	0.02	0.02	0.02	0.02	0.02	0.07	0.04	0.04	0.01	0.02	0.03	1.00

Legend: Phenotypes are abbreviated as: astm - Asthma, alrg - Allergic Rhinitis, card - Cardiovascular Disease, canc - Cancers, dprs - Depressive Disorder, drmt - Dermatophytosis, dia2 - Type 2 Diabetes, dysl - Dyslipidemia, hypr - Hypertension, hemr - Hemorrhoids, hern - Abdominal Hernia, insm - Insomnia, iron - Iron Deficiency, irrb - Irritable Bowel Syndrome, mcdg - Macular Degeneration, osta - Osteoarthritis, ostp - Osteoporosis, pvd - Peripheral Vascular Disease, pept - Peptic Ulcer, psyc - Psychiatric disorders, strs - Stress Disorders, vrvn - Varicose Veins.

10 Comparison between the continuous spike and Dirac spike

We carried out simulation study to compare the selection accuracy of two different type of spikes. We chose the same set-up of multiple overlapping case-control studies considered while comparing CPBayes and ASSET in the main simulation study. We implemented the Gibbs sampling algorithm for the Dirac spike described in Algorithm 2. Since the summary statistics are correlated, we implemented the combined strategy for the Dirac spike as well as for the continuous spike. The slab variance for the Dirac spike (b^2) is considered to vary in $0.8 - 1.2$ (the same as that for the continuous spike). We compute the mean specificity and sensitivity across 200 replications. The results are provided in Figure S3 (see the next page).

We observe that the Dirac spike produces less specificity than the continuous spike. The Dirac spike suffers from reduced specificity more for larger number of associated traits (K_1). The continuous spike consistently yields very good level of specificity across different scenarios. The Dirac spike offers higher sensitivity, but at the expense of lower specificity compared to the continuous spike. For example, for $K = 10,\ K_1^+ = 4$ & $K_1^- = 4$ ($K_1 = 8$), and $m = 0.1$, the Dirac spike produced a mean specificity of 64% and sensitivity of 87%, whereas the continuous spike gave a mean specificity of 97% and sensitivity of 72%. Similarly, for $K = 15,\ K_1^+ = 5$ & $K_1^- = 4$ ($K_1 = 9$), and $m = 0.1$, the Dirac spike gave 65% specificity and 85% sensitivity, whereas the continuous spike produced 99% specificity and 69% sensitivity.

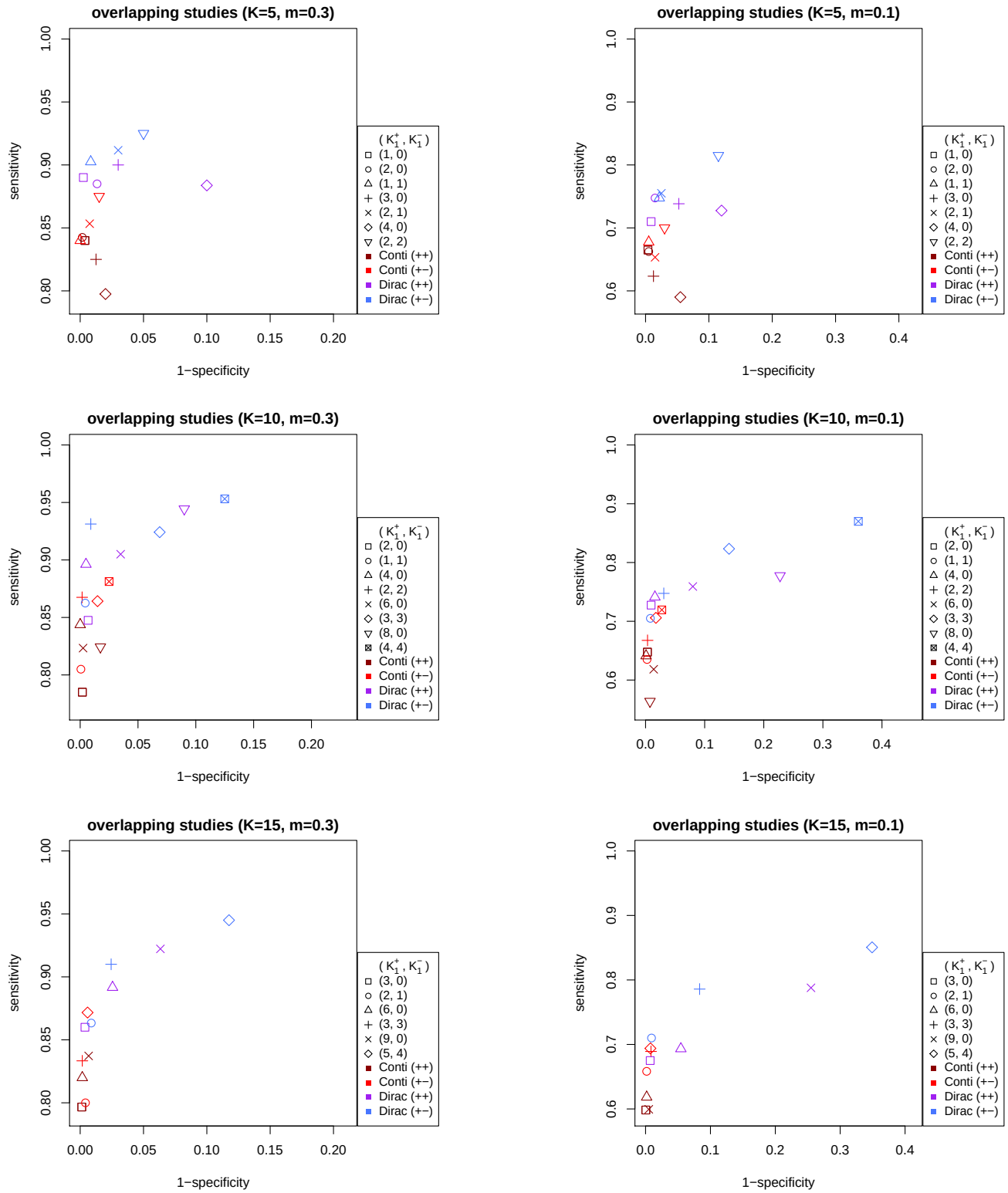



Figure S3: Comparison of the accuracy of selection of associated traits by the continuous and the Dirac spike for multiple overlapping case-control studies. The total number of phenotypes/studies is denoted by K and m denotes the minor allele frequency at the risk SNP.