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Mendelian randomization informs shared genetic etiology underlying exposure and outcome by interrogating correlated horizontal pleiotropy

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Abstract

Mendelian randomization (MR) harnesses genetic variants as instrumental variables (IVs) to study the causal effect of exposure on trait/disease using summary statistics from genome-wide association studies. Classic MR assumptions are violated when IVs are associated with unmeasured confounders, i.e., when correlated horizontal pleiotropy (CHP) arises. Such confounders could be a shared gene or inter-connected pathways underlying exposure and outcome. We propose MR-CUE (MR with Correlated horizontal pleiotropy Unraveling shared Etiology and confounding), for estimating causal effect while identifying IVs with CHP and accounting for estimation uncertainty. For those IVs, we map their cis-associated genes and enriched pathways to inform shared genetic etiology underlying exposure and outcome. We apply MR-CUE to study the effects of interleukin 6 on multiple traits/diseases and identify several *S100* genes involved in cross-traits etiology. We assess the effects of multiple exposures on type 2 diabetes across European and East Asian populations.

Introduction

In the post-genome-wide association study (GWAS) era, many efforts were made to step beyond genetic associations towards causation and mechanistic examinations. Mendelian randomization (MR) assesses the causal effect of potential risk exposures on outcome traits and diseases by leveraging genetic variants as instrument variables (IV) and integrating existing GWAS summary statistics¹. MR has been widely applied to study the relationships among complex traits and

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diseases, and have achieved numerous successes in providing causal evaluations and suggesting disease prevention and therapeutic strategies².

Two-sample MR methods take as input two sets of summary statistics, IV-to-exposure and IV-to-outcome association statistics, to estimate the causal effect of exposure on outcome. Since genotypes are ‘Mendelian randomized’ during meiosis, they are generally unrelated to the external unmeasured confounding factors. Classic MR methods imposed strong assumptions on the validity of IVs. They assumed IVs to be associated with the exposure (“relevance”); to affect the outcome only through the exposure (“exclusion restriction”); and to be unconfounded (“exchangeability”). Fig. 1a illustrated the classic assumptions. However, those assumptions are often challenged by the pervasiveness of horizontal pleiotropy — genetic variants affecting outcome via other pathways independent of exposure. The presence of horizontal pleiotropy can bias the estimation and confound the causal inference if not properly handled. Specifically, the ‘uncorrelated horizontal pleiotropy (UHP)’ is a phenomenon where a genetic variant affects outcome via other pathways not through exposure, and ‘correlated horizontal pleiotropy (CHP)’ is a phenomenon where a genetic variant affects both exposure and outcome through a heritable shared factor, i.e., an IV being associated with unmeasured confounders. In the recent literature, many robust MR methods were proposed to relax IV assumptions and allow for IVs with UHP either by treating those IVs as outliers^{3,4}, or by modeling their UHP effects in a joint model^{5–8}. More recently, other MR methods^{9,10}, were developed to estimate and adjust for both uncorrelated and correlated horizontal pleiotropy. As a stepwise method, CAUSE⁹ first identifies the IVs with CHP effects, and subsequently estimates the causal effect of exposure on outcome by fixing the parameters related to CHP. The method cML-MA¹⁰ used a constrained maximum likelihood to draw causal inference by excluding IVs with either UHP or CHP. Both methods allowed only IVs in weak or no linkage disequilibrium (LD).

Correlated horizontal pleiotropy is a challenging phenomenon to address, yet frequently arises in MR analyses. Many complex traits/diseases are polygenic, i.e., affected by multiple genes and pathways, and some common genes/pathways may be shared between exposure and outcome. When a genetic variant being associated with the genes/pathways is selected as an IV, CHP is present and it builds a confounded relationship between exposure and outcome. Fig. 1b-c shows an example in which correlated horizontal pleiotropy is present between body mass index (BMI) and triglycerides (TG). Without properly identifying and accounting for CHP, the effect of exposure on outcome could be confounded and the estimated causal effect of outcome on exposure is also non-zero, i.e., reverse causation may occur. To properly study causation and identify the effect of CHP, as illustrated in Fig. 1d right panel we propose that the effect of confounders on outcome (α_k) can be decomposed into two parts: the first part is the shared confounding effect across all IVs with CHP and is proportional to the confounders’ effect on exposure induced by each IV; and the second part ($\tilde{\alpha}_k$) captures how IV-specific perturbation to confounders (a variant’s unique effect on a set of confounder genes/pathways) may affect outcome, and is orthogonal to the first part. Existing methods^{9,10} considered only the first part and implicitly assumed that IVs with CHP affect the confounders via a deterministic common mechanism. In contrast, our method also allows for IV-specific perturbations to confounder sets, and can capture more complicated CHP effects when multiple underlying pathways and confounders exist. When estimating the effect from exposure on outcome, CHP induces a bias, $\delta = E(\frac{\delta\gamma_k + \alpha_k}{\gamma_k})$. The bias is equal to the shared CHP effect parameter on outcome, δ . When

IVs with CHP have bi-directional effects and the effects are balanced with a mean of zero, the bias is zero. If unbalanced CHP is present ($\delta \neq 0$) and unadjusted, the effect of exposure on outcome is given by $\beta_2 = \beta_1 + \delta$, and is non-zero even if the true causal effect β_1 is zero. False positives may arise or power may be reduced. As a side note, IVs with CHP tend to be involved in inter-connected pathways and be associated with common drivers in the pathways. Their correlations to those common drivers may further lead to a non-zero genetic correlation that describes the relationship between two traits/diseases. Therefore, a non-zero genetic correlation¹¹ between two traits/diseases may reflect the extent of pleiotropic genes/pathways rather than a true causal relationship¹².

Properly accounting for CHP induced genetic confounding is of utmost importance in making valid causal inference in MR analyses, though the task is often not easy. It is commonly assumed in the literature that not all selected IVs are affected by genetic confounding. Thus, selected IVs can be partitioned into two sets as depicted in Fig. 1d. Variants in IV Set 1 (left panel, only UHP) are not associated with unmeasured confounders while variants in IV Set 2 (right panel, with CHP) are associated with the unknown confounding gene(s)/pathway(s). Existing method⁹ first deconvolutes the normal mixture distribution of pleiotropic effects and identifies the IV ‘membership’ (from Set 1 or 2) for each IV, and then estimates the causal effect. In this work, we propose a MR method, MR-CUE (MR with Correlated horizontal pleiotropy Unraveling shared Etiology and confounding). MR-CUE also allows all IVs to have potential non-zero UHP effects. It builds a Bayesian hierarchical model to estimate the causal effect while simultaneously quantifying the probability of each IV being affected by CHP. Since CHP effects could be highly or moderately sparse, the quantification of estimation uncertainty by MR-CUE allows us to identify IVs with CHP at different levels of confidence and make precise causal inference with the proper control of statistical significance.

Another major innovation is that we propose to further study sets of IVs with CHP and examine their cis-associated genes and involved pathways. Through two examples, we illustrate that the estimated IVs/variants with CHP can suggest genes and pathways that are suspected sources of genetic confounding. Those genes and pathways may shed light on the shared genetic etiology for traits and diseases affected by a common exposure, or may reveal relevant pathways and mechanisms underlying different causal exposures for a complex disease outcome. Those disease-relevant common confounders and pathways could inform concerted mechanisms and etiologies across populations and ethnic groups.

[Figure 1 about here.]

Results

MR-CUE examines causal effects by delineating correlated and un-correlated horizontal pleiotropic effects

We propose MR-CUE to estimate the causal effect from exposure (X) on outcome (Y) while accounting for both uncorrelated and correlated horizontal pleiotropy. As illustrated in Fig. 1d, we model the IV-to-outcome effect of the k -th IV ($k = 1, \dots, p$), Γ_k , as a function of IV-to-exposure effect, γ_k , and pleiotropic effects:

$$\Gamma_k = \beta_1 \gamma_k + \theta_k + \alpha_k, \quad k = 1, \dots, p. \quad (1)$$

where β_1 is the causal effect of exposure on outcome; θ_k is the UHP effect, and α_k is the CHP effect of the k -th IV; and both the IV-to-outcome and IV-to-exposure effects, Γ_k and γ_k , respectively, can be obtained from GWASs. We assume that all IVs may have UHP effects, θ_k , while only a proportion of IVs may also have CHP effects. As illustrated in Fig. 1d right panel, we also assume that for an IV with CHP, it affects the exposure and confounder proportionally, and γ_k is the sum of IV-to-exposure effect via and not via confounders. We rescale the IV-to-confounder effect to be 1 and the effect of confounders on exposure is then γ_k . In Fig. 1d, the line representing the direct effect from IV to exposure is omitted to avoid over-parameterization since it is assumed to change proportionally with IV-to-confounder effect. By definition, the CHP effect, α_k , is correlated with IV-to-exposure effect γ_k . Different than existing method⁹ assuming CHP effect being always proportional to γ_k , here we argue that different IVs may perturb the confounders (U , a gene, a gene set, or multiple pathways) in slightly different ways and may lead to different CHP effects. Therefore, for an IV k with a non-zero CHP effect, we decompose the effect into two components, $\alpha_k = \delta \gamma_k + \tilde{\alpha}_k$. The first component ($\delta \gamma_k$) is the IV-shared confounding effect, and is proportional to IV-strength, γ_k . The second component, $\tilde{\alpha}_k$, describes how the IV-specific perturbation on confounders (i.e., the unique effect of the IV on the confounders) may affect outcome, and is independent of γ_k . We reparametrize our model as

$$\Gamma_k = \begin{cases} \beta_1 \gamma_k + \theta_k, & \text{if } k \in \text{IV Set 1 with no CHP} \\ \beta_2 \gamma_k + \theta_k + \tilde{\alpha}_k, & \text{if } k \in \text{IV Set 2 with CHP,} \end{cases} \quad (2)$$

where β_1 is the causal effect of interest and can be estimated using IVs without CHP. The parameter $\beta_2 = \beta_1 + \delta$ is a nuisance parameter capturing both β_1 and δ , where δ is the IV-shared confounding parameter due to CHP. MR-CUE is built on a Bayesian hierarchical model that estimates the parameters from the above model and obtains inference via Gibbs sampling.

In Fig. 1b, we illustrate our model using a real data example to assess the causal effect of BMI on TG. When plotting IV-to-BMI effects against IV-to-TG effects in Fig. 1b, there is a positive causal relationship for some IVs (blue) while there are a few other IVs entailing a different pattern with an opposite slope (red). The proposed MR-CUE model identifies the IVs affected by CHP (red dots), and estimates the causal effect from BMI on TG using IVs not affected by CHP (blue dots). The unconfounded causal effect is estimated to be significant and positive, $\hat{\beta}_{1(\text{BMI} \rightarrow \text{TG})} = 0.262$. For IVs affected by CHP, their estimated causal effects is significant and negative, $\hat{\beta}_{2(\text{BMI} \rightarrow \text{TG})} = -0.655$, due to the large and negative confounding bias δ . As further illustrated in Fig. 1c, MR-CUE reduces false positive findings due to reverse causation by identifying the IVs affected by CHP and quantifying the uncertainty in the estimation/identification. Without properly handling CHP, one may obtain a crude sum of effect estimates combining the unconfounded and the confounded effects. In the BMI-TG example, we observe that the compound effects (red), $\hat{\beta}_2$'s, for both BMI-to-TG and TG-to-BMI are significant and negative, due to the shared confounding. While the unconfounded effect is only significant from BMI to TG, not the reverse. In the presence of unadjusted CHP, one

may suffer from a reduced power or an inflated type I error rate depending on the direction of confounding effect.

In practice, there is often no clear cut for IVs unaffected or affected by CHP due to trait polygenicity and LD. The uncertainty of each variant belonging to either IV Set 1 or Set 2 can be accounted for by modeling a latent variable, η_k . MR-CUE imposes a spike-slab prior^{13,14} for $\tilde{\alpha}_k$, with a spike (mass density) at zero and a slab spreading over a wide range of plausible values. MR-CUE quantifies the probability of each variant being affected by CHP. Different than existing methods, MR-CUE provides the flexibility for selecting IVs likely from Set I for causal effect estimation while considering selection/estimation uncertainty, and it can account for CHP effects at different levels of confidence. To further allow IVs in LD, MR-CUE partitions the whole genome into independent blocks and introduce a group latent variable, η_l , for IVs in same blocks (see Methods). By quantifying the uncertainty in latent IV status, MR-CUE not only provides unbiased causal effect estimates but also works as a useful tool for further examining the potential shared genetic components underlying the exposure and outcome. The IVs estimated to have CHP and their cis-associated genes may imply common genes and genetic pathways associated with both exposure and outcome.

MR-CUE identifies IVs with CHP effects, estimates the causal effects and reduces false positives

We conducted simulation studies to evaluate the performance of MR-CUE and compare with existing MR methods in a variety of scenarios. We first generated genotype matrices from different LD patterns (see Methods). Both exposure and outcome were simulated based on polygenic architecture as shown in Eqn. (15). All IVs ($p=1,000$) contributed a total heritability of 0.1 to exposure, while the heritability for outcome can be decomposed as variation through the causal effect (β_1), variation contributed by UHP (θ) and variation attributable to CHP (α). We controlled the combinatorial values for heritability due to UHP and CHP, denoted as h_θ^2 and h_α^2 , respectively. As discussed earlier, we assumed that CHP is due to shared genetic components between exposure and outcome traits and only a proportion of IVs have nonzero CHP effects. We performed single-variant association tests to obtain the summary statistics for both IV-to-exposure and IV-to-outcome associations as input for MR analyses.

We compared MR-CUE with eight other methods, including CAUSE⁹, cML-MA¹⁰, MR-Corr²¹⁵, MR-LDP⁸, GSMR³, RAPS⁶, IVW¹⁶, and MR-Egger⁵. For cML-MA, we evaluated its performance using its two default versions, i.e., cML-MA-BIC and cML-MA-BIC-DP. Among those methods, MR-LDP, RAPS, IVW, MR-Egger, and GSMR assumed that no IV/variant is affected by correlated horizontal pleiotropy, but allowed IVs to have uncorrelated horizontal pleiotropic effects. The proposed MR-CUE and two other methods, CAUSE and cML-MA, allowed IVs to have both uncorrelated and correlated horizontal pleiotropy. Among all competing methods, MR-CUE, MR-LDP, and MR-Corr², can handle variants in moderate-to-strong LD, and two methods, CAUSE and GSMR, allowed for variants in weak LD.

First, we evaluated the performance of MR-CUE in selection/identification for IVs with CHP effects. Note that MR-CUE provided a quantitative metric for this purpose. We considered two prior distributions, i.e., the default prior (a Beta distribution with shape parameters being 2 and L , the number of LD blocks) and the non-informative prior, Beta(1,1). Here, we considered

$h_{\theta}^2 = 0.02$ or 0.05 , $h_{\alpha}^2 = 0.05$ or 0.1 , and the correlation between α_k and γ_k being $\rho_{\alpha\gamma} = 0.2$.
 Note that when $\rho_{\alpha\gamma} = 0$, only UHP is present. We also considered moderate and strong LD structure ($r = 0.4, 0.8$) with autoregressive correlation. Fig. 2a showed the false discovery rate (FDR) for identifying IVs with CHP effects and Fig. S3a (Supplementary Materials) showed the corresponding area under the curve (AUC) of the receiver operating characteristic (ROC) curve. MR-CUE with the default prior can control the FDR at the nominal level of 0.1 while achieving a high level of AUC. Next, we evaluated the performance of type I error rate control (Fig. 2b) for all competing methods. MR-CUE could control type I error rates in all settings while CAUSE was generally conservative. cML-MA-BIC suffered from inflated type I error rates while its data perturbation version, cML-MA-BIC-DP, could control the type I error rate at the expenses of power reduction (Fig. 2c). Since MR-Corr² accounts for only CHP effects, it could control the type I error rates better than MR-LDP, which does not allow for IVs with CHP effects. Simulations for CAUSE, GSMR, RAPS, IVW and MR-Egger were all based on independent IVs after SNP clumping, since those methods were initially proposed using IVs in weak-to-moderate LD. With independent IVs, RAPS, IVW and MR-Egger could generally control the type I error rates, up to some slight inflation. We also performed simulations with a larger number of IVs ($p=2,000$) and a stronger correlation between IV-to-exposure and CHP effects, $\rho_{\alpha\gamma}$. The results were largely similar and additional details were provided in Fig. S1 - S4 (Supplementary Materials). When the correlation in CHP ($\rho_{\alpha\gamma}$) was stronger, RAPS, IVW and MR-Egger suffered from increased levels of inflation in type I error rate.

We compared the power of each method by varying h_{γ}^2 (Fig. 2c) while fixing $h_{\theta}^2 = 0.1$, $h_{\alpha}^2 = 0.05$, $r = 0.4$, and $\rho_{\alpha\gamma} = 0.2$. MR-CUE achieved the highest power among the methods that could control the type I error rates. CAUSE, as a conservative method, was under-powered⁹. Although cML-MA-BIC had a high power, its type I error rate was inflated. Its data perturbation version, cML-MA-BIC-DP, was less powerful than MR-CUE. We also considered other simulation settings with different h_{θ}^2 , h_{α}^2 , autoregressive coefficient r for LD, and correlation $\rho_{\alpha\gamma}$ in CHP. Results were similar, and additional details were provided in Fig. S5 - S8 (Supplementary Materials).

Next, we evaluated whether MR-CUE could distinguish causal relationship from reverse causality. Reverse causality occurs when there exist IVs affecting the exposure and outcome traits through some shared confounding factors. Since MR-CUE is capable of identifying IVs with CHP effects, it is expected to identify the direction of true causal effect and reduce false positive findings due to reverse causality. To examine this, we simulated data with a causal effect from a trait A on a trait B ($\beta_{A \rightarrow B} \neq 0$), and tested for a reverse causal effect from B on A ($B \rightarrow A$) using MR-CUE and other methods. The simulation details were provided in the Methods Section. In all scenarios, we fixed the heritability for exposure and outcome at 0.3 and 0.25, respectively. For each simulation replicate, we applied the above MR methods for assessing the causal effects in both directions. We evaluated and compared the powers for detecting the true causal effect of exposure A on outcome B, while also compared the type I error rates for the reverse causal effect of outcome B on exposure A. Fig. 2d showed the ROC curves using 100 simulated replicates at varying significance thresholds. MR-CUE, CAUSE and cML-MA-BIC-DP could distinguish causal effects from reverse causation in all simulations, while other methods cannot.

[Figure 2 about here.]

Additionally, we evaluated the performance of MR-CUE and other methods using real data with negative and positive controls¹⁷, with varying IV selection thresholds. In the analyses of negative control outcomes, we used self-reported tanning ability and hair color as outcome, since both traits were largely determined at birth and were unlikely to be affected by other traits we considered¹⁸. We considered 16 complex traits and diseases (Table S4, Supplementary Materials) as exposure to evaluate the control of type I error rates for MR-CUE and other MR methods. For each method, we applied five different IV selection thresholds to evaluate the sensitivity of different methods to IV selection criteria. Fig. 2e showed the quantile-quantile (QQ) plot of negative log base 10 of p -values for MR-CUE and other methods when IV selection threshold was 5×10^{-4} . MR-CUE and some existing MR methods including MR-LDP, RAPS, IVW and MR-Egger can well control type I error rates, with p -values falling within the 95% confidence band of the null distribution. Note that in the analyses of negative control outcomes, MR methods without considering CHP performed well. This was probably because that the outcomes considered were not polygenic and there was no CHP effects. On the other hand, MR-Corr² and GSMR had inflated p -values while CAUSE had deflated p -values. MR-Corr² had inflated type I error rates possibly because it only considered CHP but not UHP. In the analyses of positive controls, we selected 100 established pairs of traits and diseases with causal relationships supported by exiting literature. The pairs of exposure and outcome were listed in Supplementary Table S5. We also applied different IV selection thresholds to evaluate the sensitivity of results to IV selection. Fig. 2f showed the QQ plots of negative log base 10 of p -values using 5×10^{-4} as the IV selection threshold. The QQ plots using other thresholds were provided in the Supplementary Fig. S9 - S10. In all scenarios, MR-CUE had the highest power. GSMR also had high powers but suffered from inflated type I error rates as shown in both simulations and negative control analyses.

Examining the effects of interleukin 6 on multiple traits/diseases implies shared genes and pathways as sources of CHP

Interleukin 6 (IL-6) is a key inflammatory cytokine, and has both pro- and anti-inflammatory properties. It plays an important role in immune-related processes and pathways¹⁹. Here we applied MR-CUE and other MR methods to evaluate the causal effects of IL-6 on 27 complex traits and diseases (Table S6, Supplementary Materials). The soluble IL-6 receptor (sIL6R), a negative regulator of IL-6 signaling, has been suggested to affect many complex traits and diseases including lipid levels (e.g., high density lipoprotein cholesterol, HDL-c), both severity and susceptibility of COVID-19, heart diseases (e.g., atrial fibrillation, AF), autoimmune diseases (e.g., Crohn’s disease, CD), and others^{19,20}. We analyzed those complex traits/diseases and other diseases that may not be affected by IL-6. Supplementary Tables S1 and S9 summarized the p -values and the estimated causal effects for MR-CUE and other methods.

[Figure 3 about here.]

IL-6 is a multifunctional cytokine and is highly polygenic with a heritability estimate of up to 61%²¹. In addition to estimating the causal effects of IL-6, we further obtained the posterior probabilities of IVs having CHP effects on each of the 27 outcomes, $\Pr(\eta_l = 1|\text{data})$,

from each chromosome clustered in blocks. In Fig. 3a right panel, we plotted the strengths of CHP effects for IVs across all chromosomes for 27 outcomes, with estimated causal effects shown in the very right column. In Fig. 3a left panel, we also plotted the genetic correlations among 27 outcome traits estimated by LDSC¹¹. From the heatmap, we observed that traits in high genetic correlations tend to have similar or dependent estimated causal effects of IL-6, e.g., COVID19 severity and susceptibility; any stroke (AS), any ischemic stroke (AIS) and cardio-embolic stroke (CES). Those outcomes also presented similar patterns of CHP effects. On the other hand, traits in mild-to-moderate genetic correlations, e.g., bone mass density (BMD), blood urea nitrogen (BUN), major depressive disorder (MDD), bipolar disorder (BIP), and schizophrenia (SCZ), may not share causal effect estimates but could still share CHP effect patterns. CHP effects could be present when there are no causal effects.

We further identified the IVs with significant CHP effects, $\Pr(\eta_i = 1 | \text{data}) > 0.8$, and examined the genes in cis (1MB distance) and being associated with those IVs (p -value < 0.05). The identified genes and gene sets may shed light on the shared pathways between IL-6 and the examined complex outcomes. In Fig. 3b, we plotted the heatmap of selected cis-genes associated with at least one IV affected by CHP across multiple outcomes, with color indicating the strength of the most significant association of the gene and its cis-IVs with CHP. There were many genes involved in the same pathways and being identified as IV-associated shared factors across multiple outcomes. Those shared genes may partially explain the observed genetic correlations among those 27 traits/diseases in Fig 3a (left panel). Specifically, MR-CUE identified 13 *S100* genes encoding S100 proteins located in the chromosome 1q21 region. The S100 proteins belong to a family of calcium-binding cytosolic proteins and have a broad range of intracellular and extracellular functions. The extracellular S100 proteins play a crucial role in the regulation of immune homeostasis, post-traumatic injury, and inflammation²². S100 proteins trigger inflammation through their interactions with receptors for *RAGE* and *TLR4*²³. *S100A12* has been shown to induce the production of pro-inflammatory cytokine IL-6 and IL-8 in both a dose-dependent and time-dependent manner²². Additionally, S100 proteins play a significant role to the development of chronic inflammatory and auto-inflammatory diseases^{24,25}. MR-CUE also identified some genes in cornified envelope pathway, *SPRR* family and *IVL*. These genes together with *S100* genes constituted the epidermal differentiation complex that are essential for epidermal differentiation, building the first-line defense against external assaults and protecting our bodies from dehydration²⁶. Genes in ATPase complex were identified to play a shared role as well. Existing literature²⁷ reported that the overexpression of *KAT5* gene potentiated transcription of downstream antiviral genes including *IL-6*. Other works²⁸ reported that histone methyltransferase *ASH1L* suppresses *TLR*-induced *IL-6* production.

The above analysis also showed that different IVs with CHP effects may be involved in multiple pathways entailed by multiple sources of genetic confounding. The confounding effect on outcome could be IV-specific. MR-CUE allows the estimation of an overall CHP effect while accounting for IV-specific variation/perturbation to confounders and improves the estimation of CHP. By closely examining the IVs with CHP effects and their cis-associated genes, we identified genes and gene sets that were highly inter-connected as suggested sources of genetic confounding and further informed potential shared genetic etiology among the traits examined.

MR-CUE informs type 2 diabetes-related pathways for multiple risk factors across two populations

We applied MR-CUE and other MR methods to test for causal effects of potential risk exposures for T2D in the European and East Asian populations. Type 2 diabetes (T2D) is a form of diabetes characterized by high blood sugar, insulin resistance, and relative lack of insulin²⁹. T2D is high polygenic and has a complex etiology^{30,31}. Examining multiple potential risk exposures for T2D may reveal common patterns in the etiology for related factors while also presenting unique characteristics for different types of factors. Established risk factors for T2D include both lifestyle factors, such as overweight and obesity, and medical conditions³². We also considered other exposure traits, including lipid levels, e.g., TG and high-density lipoprotein cholesterol (HDL-c), blood cell parameters, e.g., counts for red blood cells (RBC) and white blood cells (WBC), insulin-resistance-related factors, e.g., fasting insulin (FI), fasting glucose (FG) and HbA1c, and others. We examined 29 and 14 exposures for T2D in European and East Asian populations, respectively. The full list of exposure traits/diseases was provided in the Supplementary Tables S7 - S8. Tables S2 - S3 and S10 - S11 (Supplementary Materials) summarized the p -values and the estimated causal effects for MR-CUE and other methods. We further used MR-CUE to examine T2D-related pathways among multiple risk factors in both populations.

Some exposures for T2D are significant in both populations, such as obesity and blood cell parameters. Obesity is a well-known risk factor for T2D and the associations of blood cell parameters and T2D were also reported in many studies³³⁻³⁵. HbA1c was also identified by MR-CUE in both populations and its association with hypoglycemia was reported in a previous study³⁶. Some established T2D risk factors, including insulin resistance, insulin-resistance-related factors, and other obesity factors, have genetic-association summary statistics in only the European population, and thus the cross-population comparison was not presented. MR-CUE reported significant causal effects for those factors in the European population. Cross-populations analyses using summary statistics from different populations and ethnic groups still present many challenges due to the substantially varying linkage disequilibrium (LD) patterns, difficulties in data harmonization, study heterogeneity and others. Moreover, only a proportion of the causal variants and genes for complex traits/diseases might be shared across populations, and the risk exposures for a complex disease could also differ by population. MR-CUE is robust in cross-population analyses as it offers two layers of inference – it obtains the causal effect estimation using IVs not affected by genetic confounding, while also maps the underlying genes and pathways for IVs affected by confounding.

To further investigate the shared genetic pathways for the 29 and 14 traits in the European and East Asian populations, we obtained the IVs with significant CHP effects, $\Pr(\eta_l = 1 | \text{data}) > 0.8$. In Fig. 4a & b, we plotted the strengths of CHP effects for IVs across chromosomes for both European and East Asian populations, respectively. In general, exposures with higher polygenicity tend to have more IVs with CHP. We further performed pathway analysis based on those IVs using SNPnexus³⁷ and obtained their enriched pathways, shown in Fig. 4c & d for European and East Asian populations, respectively. The significant causal risk factors identified by MR-CUE are similar in both populations, and the enriched pathways presented some cross-population similarity as well. MR-CUE identified both metabolism and immune response

361 pathways for multiple exposures and T2D in both populations. T2D itself is an inflammatory
 362 disease triggered by disordered metabolism³⁸. MR-CUE identified many metabolic-related
 363 factors, including glycine, fasting glucose, and fasting insulin, having shared genetic components
 364 in metabolism pathway with T2D. Dysregulation of lipid metabolism triggers *NLRP3* activation
 365 leading to obesity-induced inflammation and insulin resistance^{39,40}. Moreover, HbA1c that is
 366 chemically linked to a sugar was used as a screening tool to detect early T2D⁴¹. Fasting glucose
 367 and HbA1c shared many common pathways in European population (Fig. 4c) while pathways
 368 for HbA1c were similar in both populations. A recent work⁴² reported that genetic variants
 369 in glutamate cysteine ligase conferred protection against T2D, while glycine was considered
 370 a promising amino acid for improving metabolic health⁴³. Glutamate and glycine are both
 371 metabolites, and they play critical roles in the metabolism pathway. Glycine was reported to
 372 improve immunity and treat metabolic disorders in diabetes⁴⁴, while glutamate was found to
 373 be a key immunomodulator in the initiation and development of T-cell-mediated immunity⁴⁵.
 374 We also observed that many exposures share the signal transduction pathway with T2D in
 375 both populations. Signal transduction pathway plays an important role in both red blood cell⁴⁶
 376 and T2D^{47,48}. Biologically, signal transduction contains insulin receptor signaling pathway that
 377 may mediate the development of T2D by endoplasmic reticulum stress⁴⁹.

378 [Figure 4 about here.]

379 Discussion

380 In this work, we propose MR-CUE, a principled MR method that accounts for both uncorrelated
 381 and correlated horizontal pleiotropy. Horizontal pleiotropy arises when a genetic variant as an
 382 instrumental variable is associated with outcome not via exposure and may bias the estimation
 383 of MR inference. Correlated horizontal pleiotropy occurs when an IV is associated with
 384 unmeasured confounders, such as a shared genetic pathways underlying exposure and outcome.
 385 CHP is particularly challenging to address due to the complexity of unknown genetic pathways,
 386 yet it is frequently encountered when studying polygenic complex traits/diseases as exposure
 387 and/or outcome. MR-CUE allows all IVs to have potential uncorrelated horizontal pleiotropy,
 388 and some IVs to have CHP. MR-CUE characterizes the IVs with CHP, estimates the causal
 389 effect of exposure on outcome using the IVs not affected by CHP, and simultaneously accounts
 390 for estimation uncertainty in a Bayesian hierarchical model. MR-CUE further examines the IVs
 391 with CHP effects and their cis-associated genes for potential shared genes/pathways/mechanisms
 392 underlying exposure and outcome. With simulation studies and analyses of negative control
 393 outcomes and positive controls, we demonstrated that MR-CUE can reduce false positives due
 394 to reverse causation, control the type I error rates, and improve power and estimation precision;
 395 MR-CUE is insensitive to IV selection threshold and allow for correlated IVs; and MR-CUE
 396 identifies IVs with CHP at the desired confidence levels.

397 We studied the causal effects of IL-6 on multiple outcomes. By further examining the IVs
 398 with significant CHP effects and their cis-associated genes, we highlighted multiple genes that
 399 may be shared (also served as confounders) between IL-6 and some examined traits/diseases.
 400 Those suggested genes included multiple *S100* genes and genes in the cornified envelope pathway,
 401 shedding light on the shared genetic etiology. In another analysis, we applied MR-CUE to

study the effects of multiple putative exposures on T2D risks in both European and East Asian populations. A cross-population analysis and comparison of multiple risk exposures showed consistent causal effect estimates in both populations. We further examined the IVs with CHP effects and their enriched pathways. In both populations, it was suggested that metabolism and immune response pathways play a central role in the shared etiologies among multiple putative exposures and T2D.

MR-CUE paved the way for future cross-population MR analyses to reduce disparity. Cross-populations MR analyses using summary statistics from different populations is still challenging due to varying LD patterns, difficulties in data harmonization, study heterogeneity and others. MR-CUE is robust in cross-population analyses as it provides double layers of inference for cross-population comparisons – it estimates the causal effect of exposure using IVs not affected by genetic confounding, while also maps the underlying genes and pathways for IVs affected by confounding.

MR-CUE has some caveats that may require further explorations. First, MR-CUE works for a single exposure and a single outcome. When the exposure is known to be highly correlated with other exposures, or when multiple outcomes may often co-occur, multi-variable MR methods accounting for both CHP and UHP may be considered. Second, MR-CUE requires multiple (at least dozens of) IVs to identify and delineate CHP effects and is not suitable for analyzing molecular risk exposures such as gene expression levels. Third, MR-CUE identifies the IVs with significant CHP effects, though the mapping of cis-associated genes/pathways from those identified IVs is still not an automated process. We are working on improving the automation of this step.

When using MR to infer causation, caution should always be exercised. By leveraging GWAS summary statistics from large genetic consortia or biobank-sized studies, MR analysis is empowered. On the other hand, insights are still limited regarding potential subgroup effects, indirect effects from different mediators between exposure and outcome, and potential exposure-mediator interactions. Further integration of MR with mediation analyses could be valuable for the development of prevention and treatment strategies towards precision medicine.

Method

MR-CUE model for independent IVs

To estimate the causal effect in the MR-CUE model, we use the marginal effect size and standard error estimates from GWASs for exposure (X) and outcome (Y) diseases/traits as input. Let $\{\widehat{\gamma}_k, \widehat{s}_{\gamma_k}\}$ denote the IV-to-exposure effect size and its standard error for IV k . Let $\{\widehat{\Gamma}_k, \widehat{s}_{\Gamma_k}\}$ denote the IV-to-outcome effect size and standard error. Let γ_k and Γ_k be the true marginal effect size of IV k for traits X and Y , respectively. For independent IVs, we model the distribution for the estimated effect sizes in both exposure and outcome diseases/traits using the following independently and identically distributed (*i.i.d.*) normal distributions,

$$\widehat{\gamma}_k \sim \mathcal{N}(\gamma_k, \widehat{s}_{\gamma_k}^2), \text{ and } \widehat{\Gamma}_k \sim \mathcal{N}(\Gamma_k, \widehat{s}_{\Gamma_k}^2). \quad (3)$$

The proposed MR-CUE models the IV-to-outcome effect as a function of IV-to-exposure, and uncorrelated and correlated horizontal pleiotropic effects:

$$\Gamma_k = \beta_1 \gamma_k + \theta_k + \alpha_k, \quad k = 1, \dots, p,$$

where θ_k and α_k capture UHP and CHP effects, respectively. The UHP effect is *i.i.d.* as $\theta_k \sim \mathcal{N}(0, \sigma_\theta^2)$. The IV-to-exposure effect (γ_k) and the CHP effect (α_k) are correlated, and *i.i.d.* with a bivariate normal distribution:

$$\begin{pmatrix} \gamma_k \\ \alpha_k \end{pmatrix} \sim \mathcal{N}\left(\mathbf{0}, \begin{pmatrix} \sigma_\gamma^2 & \rho_{\alpha\gamma} \sigma_\gamma \sigma_{\alpha_0} \\ \rho_{\alpha\gamma} \sigma_\gamma \sigma_{\alpha_0} & \sigma_{\alpha_0}^2 \end{pmatrix}\right), \quad (4)$$

where $\rho_{\alpha\gamma}$ is the correlation between γ_k and α_k .

The decomposition of CHP effects From Eqn. (4), we reparameterize γ_k and α_k as follows

$$\begin{aligned} \gamma_k &\sim \mathcal{N}(0, \sigma_\gamma^2), \\ \alpha_k &= \rho_{\alpha\gamma} \cdot \frac{\sigma_{\alpha_0}}{\sigma_\gamma} \cdot \gamma_k + \sqrt{1 - \rho_{\alpha\gamma}^2} \cdot \sigma_{\alpha_0} \cdot Z_k \stackrel{\text{def}}{=} \delta \cdot \gamma_k + \widetilde{\alpha}_k, \end{aligned} \quad (5)$$

where Z_k follows a standard normal distribution, $Z_k \sim \mathcal{N}(0, 1)$ and $Z_k \perp \gamma_k$, and $\delta = \rho_{\alpha\gamma} \frac{\sigma_{\alpha_0}}{\sigma_\gamma}$. Eqn. (5) decomposes the CHP effect α_k into two parts, with one being proportional to γ_k and the other part being independent of γ_k , i.e., $\widetilde{\alpha}_k \perp \gamma_k$. The decomposition in Eqn. (5) can also be viewed as a linear regression of α_k regressed on γ_k with $\widetilde{\alpha}_k$ being the residuals. Let $\widetilde{\alpha}_k \sim \mathcal{N}(0, \sigma_\alpha^2)$. We call $\widetilde{\alpha}_k$ as the orthogonal projection of CHP. We can further parameterize the effect size of IV-to-outcome for IV k as in Eqn. (2). Therefore, identifying the IVs with CHP effects in Eqn. (4) is equivalent to identifying the IVs with non-zero projected CHP, namely $\widetilde{\alpha}_k \neq 0$, in Eqn. (2). The estimation of causal effect β_1 is based on IVs with $\widetilde{\alpha}_k = 0$.

We further introduce a latent indicator η_k for each IV k , with $\eta_k = 1$ for IVs with non-zero CHP effects. We impose the following spike-slab prior^{13, 50} on $\widetilde{\alpha}_k$:

$$\widetilde{\alpha}_k \sim \begin{cases} \mathcal{N}(0, \sigma_\alpha^2), & \eta_k = 1 \\ \delta_0(\alpha_k), & \eta_k = 0, \end{cases} \quad (6)$$

where δ_0 denotes the Dirac delta function at zero, and η_k follows a Bernoulli distribution with $\eta_k \sim \omega^{\eta_k} (1 - \omega)^{1 - \eta_k}$. Then, Eqn. (2) can be written as

$$\Gamma_k | \beta_1, \beta_2, \gamma_k, \eta_k, \tau_1^2, \tau_2^2 \sim \begin{cases} \mathcal{N}(\beta_1 \gamma_k, \tau_1^2), & \eta_k = 0 \\ \mathcal{N}(\beta_2 \gamma_k, \tau_2^2), & \eta_k = 1 \end{cases}, \quad (7)$$

where $\tau_1^2 = \sigma_\theta^2$ and $\tau_2^2 = \sigma_\theta^2 + \sigma_\alpha^2$. To promote the computational efficiency in low-signal-noise-ratio regime, we expand the original distribution (7) as follows^{51,52}:

$$\Gamma_k | \beta_1, \beta_2, \gamma_k, \eta_k, \tau_1^2, \tau_2^2, \xi^2 \sim \begin{cases} \mathcal{N}(\beta_1 \gamma_k, \xi^2 \tau_1^2), & \eta_k = 0 \\ \mathcal{N}(\beta_2 \gamma_k, \tau_2^2), & \eta_k = 1 \end{cases}, \quad (8)$$

where ξ^2 is an expanded parameter. By combining Eqns. (3) and (8), we build the Bayesian hierarchical model with conjugate priors for hyper parameters, $\sigma_\gamma^2 \sim \mathcal{IG}(a_\gamma, b_\gamma)$, $\tau_1^2 \sim \mathcal{IG}(a_{\tau_1}, b_{\tau_1})$, $\tau_2^2 \sim \mathcal{IG}(a_{\tau_2}, b_{\tau_2})$, and $\omega \sim \text{Beta}(a, b)$.

Accounting for LD

We expand the MR-CUE model to allow for correlated IVs by modeling their LD structure. We model the estimated effect sizes in both exposure and outcome diseases/traits with approximated multivariate normal distributions⁵³ as follows,

$$\begin{aligned} \hat{\gamma} | \gamma, \hat{\mathbf{R}}, \hat{\mathbf{S}}_\gamma &\sim \mathcal{N}(\hat{\mathbf{S}}_\gamma \hat{\mathbf{R}} \hat{\mathbf{S}}_\gamma^{-1} \gamma, \hat{\mathbf{S}}_\gamma \hat{\mathbf{R}} \hat{\mathbf{S}}_\gamma), \\ \hat{\Gamma} | \Gamma, \hat{\mathbf{R}}, \hat{\mathbf{S}}_\Gamma &\sim \mathcal{N}(\hat{\mathbf{S}}_\Gamma \hat{\mathbf{R}} \hat{\mathbf{S}}_\Gamma^{-1} \Gamma, \hat{\mathbf{S}}_\Gamma \hat{\mathbf{R}} \hat{\mathbf{S}}_\Gamma), \end{aligned} \quad (9)$$

where $\hat{\gamma} = [\hat{\gamma}_1, \dots, \hat{\gamma}_p]^T$ and $\hat{\Gamma} = [\hat{\Gamma}_1, \dots, \hat{\Gamma}_p]^T$ are vectors for the marginal effect sizes in exposure and outcome diseases/traits, respectively; $\hat{\mathbf{S}}_\gamma = \text{diag}([\hat{s}_{\gamma_1}, \dots, \hat{s}_{\gamma_p}])$ and $\hat{\mathbf{S}}_\Gamma = \text{diag}([\hat{s}_{\Gamma_1}, \dots, \hat{s}_{\Gamma_p}])$ are the corresponding diagonal matrices for standard errors; and $\hat{\mathbf{R}} \in \mathbb{R}^{p \times p}$ is the estimated correlation matrix among all selected IVs. In the approximated distributions in Eqn. (9), all quantities except for $\hat{\mathbf{R}}$ can be obtained from summary-level GWAS results while $\hat{\mathbf{R}}$ is estimated using an independent reference panel data.

Estimating LD matrix from a reference panel

To estimate the LD matrix, we used independent reference panel data from the following sources: UK10K Project (Avon Longitudinal Study of Parents and Children, ALSPAC⁵⁴, and TwinsUK⁵⁵) merged with European-ancestry samples in 1000 Genome Project Phase 3⁵⁶. There are 4,284 individuals in total. We conducted strict quality control for the reference data using PLINK⁵⁷ and GCTA⁵⁸. We removed the individuals with genotype missing rates greater than 5%, and further removed one pair of individuals that have genetic relatedness larger than 0.05. Since both ALSPAC and TwinsUK cohorts contain non-European samples, we further performed the principal components analysis (PCA)⁵⁹ followed by the analysis of hierarchical clustering on principal components (HCPC)⁶⁰ to extract and restrict the analysis to samples from European ancestries. After data pre-processing, roughly 3,700 samples were retained as the reference panel data.

Often it is useful to define approximately independent LD blocks a priori. Here we used LDetect⁶¹ based on an efficient signal processing approach for choosing segment boundaries between

486 blocks. Consequently, LDetect partitioned the entire genome into 1,703 and 1,445 independent
 487 blocks for European and Asian populations, respectively ([http://bitbucket.org/nygcresearch/ldetect-](http://bitbucket.org/nygcresearch/ldetect-data)
 488 [data](http://bitbucket.org/nygcresearch/ldetect-data)). For each LD block, we calculated the empirical correlation matrix and further applied a
 489 simple shrinkage correlation estimator⁶² to obtain

$$\widehat{\mathbf{R}}^{(l)} = \lambda \widehat{\mathbf{R}}_{\text{emp}}^{(l)} + (1 - \lambda) \widehat{\mathbf{I}}^{(l)}, \quad (10)$$

490 where $\widehat{\mathbf{R}}_{\text{emp}}^{(l)} \in \mathbb{R}^{p_l \times p_l}$ was the empirical correlation matrix for the l -th block in the panel data
 491 and $\lambda \geq 0$ was a shrinkage parameter. By obtaining all $\widehat{\mathbf{R}}^{(l)}$ s, $l = 1, \dots, L$, we could further ob-
 492 tain $\widehat{\mathbf{R}} = \text{diag}(\widehat{\mathbf{R}}^{(l)}) \in \mathbb{R}^{p \times p}$ with $\sum_{l=1}^L p_l = p$. Here we fixed the shrinkage parameter λ at 0.85⁸.

493
 494 *A group spike-slab prior* For IVs in moderate-to-strong LD, if there is a single variant k
 495 with a nonzero CHP effect, the CHP effect for other nearby variants in the block would be
 496 also nonzero. In our analyses, genetic variants across the genome can be partitioned into
 497 independent blocks. IVs from different blocks could be roughly taken as independent. Thus,
 498 the projected $\tilde{\alpha}_k$ is estimated in a group manner. We introduce a group-level latent status
 499 η_l , indicating whether IVs within the l -th block having nonzero CHP effects and assigning a
 500 group-level spike-slab prior as follows:

$$\tilde{\alpha}_{lk} \sim \begin{cases} \mathcal{N}(0, \sigma_\alpha^2), & \eta_l = 1 \\ \delta_0(\alpha_{lk}), & \eta_l = 0, \end{cases} \quad (11)$$

501 where $\eta_l = 1$ implies the IVs within the l -th block having nonzero projected CHP effects and
 502 $\eta_l = 0$ means the projected CHP effects being all zero for IVs in the block. Here, η_l is a
 503 Bernoulli random variable with probability ω being 1, $\eta_l \sim \omega^{\eta_l} (1 - \omega)^{1 - \eta_l}$.

504 Considering IVs in LD, we have the following mixture distribution for Γ_{lk} that is similar to
 505 Eqn. (8):

$$\Gamma_{lk} | \beta_1, \beta_2, \gamma_{lk}, \eta_l, \tau_1^2, \tau_2^2, \xi^2 \sim \begin{cases} \mathcal{N}(\beta_1 \gamma_{lk}, \xi^2 \tau_1^2), & \text{if } \eta_l = 0 \\ \mathcal{N}(\beta_2 \gamma_{lk}, \tau_2^2), & \text{if } \eta_l = 1. \end{cases} \quad (12)$$

506 Accounting for sample overlap

507 When IV-to-exposure and IV-to-outcome summary statistics are taken from biobank-sized or
 508 consortia-based GWASs with potential overlapping samples, we need to account for the potential
 509 additional correlations. To allow overlapping samples in GWAS for both diseases/traits, we
 510 could rewrite the distribution for summary statistics in Eqn. (9) as the following matrix normal
 511 distribution for Z -score

$$\widehat{\mathbf{z}} = [\widehat{\mathbf{z}}_\gamma, \widehat{\mathbf{z}}_\Gamma] \sim \mathcal{MN}([\widehat{\mathbf{R}} \widehat{\mathbf{S}}_\gamma^{-1} \boldsymbol{\gamma}, \widehat{\mathbf{R}} \widehat{\mathbf{S}}_\Gamma^{-1} \boldsymbol{\Gamma}], \widehat{\mathbf{R}}, \mathbf{R}_e),$$

512 where $\widehat{\mathbf{z}}_\gamma = \widehat{\mathbf{S}}_\gamma^{-1} \widehat{\boldsymbol{\gamma}}$, $\widehat{\mathbf{z}}_\Gamma = \widehat{\mathbf{S}}_\Gamma^{-1} \widehat{\boldsymbol{\Gamma}}$, and $\mathbf{R}_e = \begin{bmatrix} 1 & \rho_e \\ \rho_e & 1 \end{bmatrix}$ is the correlation matrix that accounts
 513 for sample overlap. Here, the correlation due to sample overlap ρ_e can be estimated using
 514 summary statistics among independent variants with no associations to both exposure and
 515 outcome diseases/traits.

516 We propose the following Bayesian hierarchical model for correlated IVs with overlapping
517 samples,

$$\begin{aligned}
\widehat{\mathbf{z}} &= [\widehat{\mathbf{z}}_\gamma, \widehat{\mathbf{z}}_\Gamma] \sim \mathcal{MN}([\widehat{\mathbf{R}}\widehat{\mathbf{S}}_\gamma^{-1}\boldsymbol{\gamma}, \widehat{\mathbf{R}}\widehat{\mathbf{S}}_\Gamma^{-1}\boldsymbol{\Gamma}], \widehat{\mathbf{R}}, \widehat{\mathbf{R}}_e), \\
\Gamma_{lk}|\beta_1, \beta_2, \gamma_{lk}, \eta_l, \tau_1^2, \tau_2^2, \xi^2 &\stackrel{iid}{\sim} \{ \mathcal{N}(\beta_1\gamma_{lk}, \xi^2\tau_1^2) \}^{(1-\eta_l)} \{ \mathcal{N}(\beta_2\gamma_{lk}, \tau_2^2) \}^{\eta_l}, \\
\gamma_{lk}|\sigma_\gamma^2 &\stackrel{iid}{\sim} \mathcal{N}(0, \sigma_\gamma^2), \quad \tilde{\alpha}_{lk}|\sigma_\alpha^2 \stackrel{iid}{\sim} \mathcal{N}(0, \sigma_\alpha^2), \quad \eta_l|\omega \stackrel{iid}{\sim} \omega^{\eta_l}(1-\omega)^{1-\eta_l}, \\
\sigma_\gamma^2 &\sim \mathcal{IG}(a_\gamma, b_\gamma), \quad \tau_1^2 \sim \mathcal{IG}(a_{\tau_1}, b_{\tau_1}), \quad \tau_2^2 \sim \mathcal{IG}(a_{\tau_2}, b_{\tau_2}), \\
\Pr(\xi^2) &\propto \frac{1}{\xi^2}, \quad \eta_l|\omega \stackrel{iid}{\sim} \omega^{\eta_l}(1-\omega)^{1-\eta_l}, \quad \omega \sim \text{Beta}(a, b).
\end{aligned} \tag{13}$$

518 Since the estimated LD matrix is block-diagonal, the resulting Gibbs sampler can be performed
519 in a parallel manner for each block. The algorithmic details are given in the Supplementary
520 Materials.

521 Generation of summary statistics in the simulation studies

522 We generated the summary statistics using simulated individual-level data. We first simulated
523 genotypes $\mathbf{G}_x \in \mathbb{R}^{n_x \times p}$, $\mathbf{G}_y \in \mathbb{R}^{n_y \times p}$ and $\mathbf{G}_r \in \mathbb{R}^{n_r \times p}$ for both exposure and outcome as well as
524 for an independent reference data, respectively, where n_x , n_y , and n_r were the corresponding
525 sample sizes and p was the total number of IVs. We set the number of blocks L to be 100 or
526 200, and the number of IVs within a block to be 10, respectively. Correspondingly, the number
527 of IVs was either 1,000 or 2,000. For all simulations, we considered $n_x = 50,000$, $n_y = 50,000$
528 and $n_r = 4,000$.

529 We then generated a data matrix from a multivariate normal distribution $\mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}(r))$,
530 where $r \in \{0.4, 0.8\}$ represented the autoregressive correlation among IVs. We simulated
531 genotype matrix by categorizing data matrices into dosage values $\{0, 1, 2\}$ according to minor
532 allele frequency that is uniformly distributed in $[0.05, 0.5]$. We then considered the following
533 structural model to generate individual-level data

$$\mathbf{x} = \mathbf{G}_x\boldsymbol{\gamma} + \mathbf{U}_x\boldsymbol{\psi}_x + \boldsymbol{\epsilon}_x, \quad \mathbf{y} = \beta_1\mathbf{x} + \mathbf{G}_y\boldsymbol{\alpha} + \mathbf{G}_y\boldsymbol{\theta} + \mathbf{U}_y\boldsymbol{\psi}_y + \boldsymbol{\epsilon}_y, \tag{14}$$

534 where $\mathbf{U}_x \in \mathbb{R}^{n_x \times q}$ and $\mathbf{U}_y \in \mathbb{R}^{n_y \times q}$ are the matrices for q confounders for exposure and
535 outcome, respectively; $\boldsymbol{\psi}_x \in \mathbb{R}^{q \times 1}$ and $\boldsymbol{\psi}_y \in \mathbb{R}^{q \times 1}$ are the corresponding vector of coefficients;
536 $\boldsymbol{\epsilon}_x \in \mathbb{R}^{n_x \times 1}$ and $\boldsymbol{\epsilon}_y \in \mathbb{R}^{n_y \times 1}$ are the random errors; and β_1 is the causal effect of interest. In all
537 simulations, we considered $q = 50$ and each column of $\mathbf{U}_x$ and $\mathbf{U}_y$ was sampled from a standard
538 normal distribution. The coefficients of these confounders, $\boldsymbol{\psi}_x$ and $\boldsymbol{\psi}_y$, were sampled from a
539 bivariate normal distribution $\mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}_\psi)$, where $\boldsymbol{\Sigma}_\psi$ was a two-by-two matrix with diagonal
540 elements of 1 and off-diagonal elements of 0.8. For CHP effects, we assumed γ_k and α_k following
541 a bivariate normal distribution $\mathcal{N}(\mathbf{0}, \boldsymbol{\Sigma}(\rho_{\alpha\gamma}))$. We considered α_k to be sparse, i.e., only 10% of
542 α_k was sampled from the bivariate normal distribution and the others were zero. For UHP, we
543 assumed θ_k to be dense and follow an independent normal distribution, $\mathcal{N}(0, \sigma_\theta^2)$.

544 We further performed the single-variant analysis to obtain summary statistics, $\{\widehat{\gamma}_k, \widehat{\mathbf{s}}_{\gamma_k}\}$
545 and $\{\widehat{\Gamma}_k, \widehat{\mathbf{s}}_{\Gamma_k}\}$, $\forall k = 1, \dots, p$, for both exposure and outcome, respectively. In the simulation
546 study, we controlled the magnitudes for $\boldsymbol{\gamma}$, $\boldsymbol{\alpha}$ and $\boldsymbol{\theta}$ using $h_\gamma^2 = \frac{\text{var}(\beta_1\mathbf{G}_1\boldsymbol{\gamma})}{\text{var}(\mathbf{y})}$, $h_\alpha^2 = \frac{\text{var}(\mathbf{G}_2\boldsymbol{\alpha})}{\text{var}(\mathbf{y})}$
547 and $h_\theta^2 = \frac{\text{var}(\mathbf{G}_2\boldsymbol{\theta})}{\text{var}(\mathbf{y})}$, respectively. We considered $h_\gamma^2 = 0.1$ and varied $h_\theta^2 \in \{0.02, 0.05\}$ and

548 $h_\alpha^2 \in \{0.05, 0.1\}$ to evaluate the performance of MR-CUE in selecting/identifying IVs with
 549 CHP effects and in the control of type I error rates. To further examine the power, we varied
 550 h_γ^2 in a sequence of values from 0 to 0.1 while fixing other parameters.

551 **Generation of summary statistics for reverse causation analysis**

552 We considered the following structural model to generate individual-level data that is similar
 553 to existing work⁹:

$$\mathbf{x} = \mathbf{G}_1\boldsymbol{\gamma} + \mathbf{e}_1, \quad \mathbf{y} = \beta_1\mathbf{x} + \mathbf{G}_2\boldsymbol{\theta} + \mathbf{e}_2, \quad (15)$$

554 where $\boldsymbol{\gamma}$ and $\boldsymbol{\theta}$ are from two independent normal distributions. In this simulation, we first
 555 controlled the heritability of exposure and outcome, denoted as h_x^2 and h_y^2 , respectively. We
 556 further assumed that 20% of the outcome heritability, h_y^2 , can be explained by the causal effect
 557 (β_1) of exposure on outcome. Thus, we have three quantities below

$$h_x^2 \stackrel{\text{def}}{=} \frac{\text{var}(\mathbf{G}_1\boldsymbol{\gamma})}{\text{var}(\mathbf{x})}, \quad h_y^2 \stackrel{\text{def}}{=} \frac{\text{var}(\beta_1\mathbf{G}_2\boldsymbol{\gamma} + \mathbf{G}_2\boldsymbol{\theta})}{\text{var}(\mathbf{y})} \quad \text{and} \quad \frac{\text{var}(\beta_1\mathbf{G}_2\boldsymbol{\gamma})}{\text{var}(\mathbf{y})} = \frac{h_y^2}{5}.$$

558 We set $h_y^2 = 0.25$, $h_x^2 = 0.3$, and only 5% of $\boldsymbol{\gamma}$ being nonzero. We fixed $r = 0.4, p = 2000$,
 559 and $\rho_{\alpha\gamma} = 0.2$. To examine reverse causality, we applied MR-CUE and other methods to
 560 assess the causal effects in both directions for 100 simulated replicates. By varying significance
 561 thresholds, we obtained the ROC curves for true positives vs. false positives averaged over the
 562 100 replicates.

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Figure 1: (a) The causal diagram by classic MR methods. Classic MR methods assume IV to affect outcome through only exposure. (b) An illustrative example of estimating the causal effect of BMI on TG in the presence of CHP. (c) The reverse causation estimation of TG on BMI confounded by CHP. When estimating the effect of BMI on TG, some IVs (red) are affected by CHP. Adjusting those IVs would lead to a significant effect estimate of BMI on TG, $\hat{\beta}_1(\text{BMI} \rightarrow \text{TG}) = 0.262$, and an insignificant reverse causal effect estimate from TG to BMI, $\hat{\beta}_1(\text{TG} \rightarrow \text{BMI}) = 0.008$. In this example, CHP would induce genetic confounding and introduce a significant and negative bias. Using estimated IVs with CHP, one may obtain significant causal and reverse causal effect estimates, $\hat{\beta}_2(\text{BMI} \rightarrow \text{TG}) = -0.655$, and $\hat{\beta}_2(\text{TG} \rightarrow \text{BMI}) = -0.443$. (d) An illustration of the MR-CUE model. MR-CUE decomposes IVs into two sets, those not affected by CHP (left, $\eta_k = 0$) and those affected by CHP (right, $\eta_k = 1$). MR-CUE allows all IVs to have potential non-zero UHP effect, θ_k . In (d) right panel, we assume that the IV affects the exposure and confounder proportionally, with a sum of IV-to-exposure effect of γ_k . We rescale the IV-to-confounder effect to be 1 and the effect of confounders on exposure is then γ_k (yellow line). The line representing the direct effect from IV to exposure is omitted since it is assumed to change proportionally with IV-to-confounder effect. The red line represents the decomposed and projected confounder-to-outcome effect and is also proportional to IV-strength, γ_k . The IV-specific perturbation of confounders may induce an IV-specific bias, $\tilde{\alpha}_k$, which has a mean of zero.

Figure 2: (a) False discovery rates for IVs identified with CHP under combinatorial settings for h_θ^2 and h_α^2 with $\rho_{\alpha\gamma} = 0.2$ and $p = 1,000$. (b) Type I error rates for MR-CUE and other methods under combinatorial settings for h_θ^2 and h_α^2 with $\rho_{\alpha\gamma} = 0.2$ and $p = 1,000$. (c) Powers for MR-CUE and other methods under the setting: $h_\theta^2 = 0.1$, $h_\alpha^2 = 0.05$, $p = 1,000$, $r = 0.4$ and $\rho_{\alpha\gamma} = 0.2$. (d) ROC curves for evaluation of causation and reverse causality among all methods. (e) QQ plots of $-\log_{10}(p\text{-values})$ for all methods under the null from analyses of negative controls. (f) QQ plots of $-\log_{10}(p\text{-values})$ for all methods from analyses of positive controls.

Figure 3: (a) The heatmap of the estimated genetic correlations among the 27 examined outcomes (left panel) with IL-6 as exposure; the heatmap of the estimated strengths of CHP, $-\log_{10}(1 - \Pr(\eta_l = 1))$, for selected IVs across all chromosomes for the 27 outcomes (right panel). (b) The heatmap of a partial list of cis-genes that were significantly associated with at least one IV affected by CHP across multiple outcomes, with color indicating the strength of the most significant association for each gene. Cis-associations were assessed using blood tissue samples from the Genotype-Tissue Expression (GTEx) project for IVs with estimated CHP effect.

(a) Heatmap for European population

(b) Heatmap for Asian population

(c) Pathway for European population

(d) Pathway for Asian population

Figure 4: (a) & (b) The heatmaps of the estimated strengths of CHP, $-\log_{10}(1 - \Pr(\eta_l = 1))$, for selected IVs across all chromosomes for 29 and 14 exposures for T2D in the European and East Asian populations, respectively. (c) & (d) The heatmaps of enriched pathways for identified IVs with CHP by exposure in the European and East Asian populations, respectively.

Supplementary Files

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