Supplementary material for: Profile-likelihood Bayesian model averaging for two-sample summary data Mendelian randomization in the presence of horizontal pleiotropy

Chin Yang Shapland*[1,2], Qingyuan Zhao[3], and Jack Bowden[4,1,2]

[1] *MRC Integrative Epidemiology Unit at the University of Bristol, U.K.*
[2] *Population Health Sciences, University of Bristol, U.K.*
[3] *Department of Pure Mathematics and Mathematical Statistics at the University of Cambridge, U.K.*
[4] *College of Medicine and Health at the University of Exeter, U.K.*

*Correspondence to chinyang.shapland@bristol.ac.uk

Appendix 1: Bias from violation of InSIDE assumption

Suppose we are estimating the causal parameter from instruments that violate the InSIDE assumption using the IVW approach. Its estimand will equal:

$$\hat{\beta}_{IVW} = \frac{\sum_{j=1}^{L} \hat{\Gamma}_j \hat{\gamma}_j}{\sum_{j=1}^{L} \hat{\gamma}_j^2} \tag{1}$$

as the $N \to \infty$, $\hat{\Gamma}_j \to \Gamma_j$ and $\hat{\gamma}_j \to \gamma_j$, so that asymptotically, the IVW estimate tends towards the following

$$= \frac{\widehat{Cov}(\Gamma_j, \gamma_j) + \bar{\Gamma}\bar{\gamma}}{\widehat{Var}(\gamma_j) + \bar{\gamma}^2} \tag{2}$$

$$= \frac{\widehat{Cov}(\alpha_j + \beta\gamma_j, \gamma_j) + (\bar{\alpha} + \beta\bar{\gamma})\bar{\gamma}}{\widehat{Var}(\gamma_j) + \bar{\gamma}^2} \tag{3}$$

$$= \frac{\widehat{Cov}(\alpha_j, \gamma_j) + \beta\widehat{Var}(\gamma_j) + \bar{\alpha}\bar{\gamma} + \beta\bar{\gamma}^2}{\widehat{Var}(\gamma_j) + \bar{\gamma}^2} \tag{4}$$

$$= \beta + \underbrace{\frac{\widehat{Cov}(\alpha_j, \gamma_j) + \bar{\alpha}\bar{\gamma}}{\widehat{Var}(\gamma_j) + \bar{\gamma}^2}}_{\text{bias term}} \tag{5}$$

When InSIDE is perfectly violated ($\alpha_j = \gamma_j$) the numerator and denominator of the bias term in equation (5) are equal. Therefore, $\beta_{IVW} = \beta + 1$

Appendix 2: Metropolis-Hastings algorithm for the one-parameter causal model

The full Bayesian implementation

- **Update** β

  1. Sample $\beta^* \sim \beta_i + h_\beta N(0,1)$, where h_β is a user defined tuning constant.
  2. Accept $\beta_{i+1} = \beta^*$ with probability:

  $$prob = \min\left\{1, \frac{P(\beta^*, Prec_i, I_i)}{P(\beta_i, Prec_i, I_i)}\right\}$$

  otherwise set $\beta_{i+1} = \beta_i$.

- **Update** $Prec$ **(**$\tau^2 = 1/Prec$**)**

  1. Sample

  $$\begin{aligned} &Prec^* \sim U(\mathrm{LB}_{Prec^*}, \mathrm{UB}_{Prec^*}) \\ &\mathrm{LB}_{Prec^*} = \max(\mathrm{LL}, Prec_i - h_{Prec}) \\ &\mathrm{UB}_{Prec^*} = \min(\mathrm{UL}, Prec_i + h_{Prec}) \end{aligned}$$

  where $U(,)$ is the proposal density in the form of a uniform distribution. LL and UL is user defined lower and upper limit for $Prec$ respectively, and h_{Prec} is a user defined tuning constant.
  2. Accept $Prec_{i+1} = Prec^*$ with probability:

  $$prob = \min\left\{1, \frac{U(\mathrm{LB}_{Prec_i}, \mathrm{UB}_{Prec_i})P(\beta_{i+1}, Prec^*, I_i)}{U(\mathrm{LB}_{Prec^*}, \mathrm{UB}_{Prec^*})P(\beta_{i+1}, Prec_i, I_i)}\right\}$$

  Otherwise set $Prec_{i+1} = Prec_i$.

- **Update** I

  1. Generate a random number between 1 and L from $P(I_L)$, define it as I_q^*, which is the qth element of I^*.
  2. Set $I_d^* = I_{id}$ for all $d \neq q$.

3. Set $I_q^* = (I_{iq} - 1)^2$ (this defines the proposed and current model to differ by one instrument).
4. If $\sum_{j=1}^{L} I_j \geq 5$ is true, continue to the next step, otherwise repeat step 1 (ensures there is enough IVs for estimation).
5. Accept $I_{i+1} = I^*$ with probability:

$$prob = \min\left\{1, \frac{P(\beta_{i+1}, Prec_{i+1}, I^*)}{P(\beta_{i+1}, Prec_{i+1}, I_i)}\right\}$$

otherwise set $I_{i+1} = I_i$.

The h_β and h_{Prec} acts as tuning parameters for the acceptance rate. That is, the proportion of iterations that θ^* is accepted as θ_{i+1}. Acceptance rates are recommended to be between 0.25 and 0.45 for the random walk M-H algorithm [1]. We follow this guidance in our implementation of the approach in simulations and applied data settings.

The DL implementation

- **Update** β

1. Sample $\beta^* \sim \beta_i + h_\beta N(0, 1)$, where h_β is a user defined tuning constant.
2. Accept $\beta_{i+1} = \beta^*$ with probability:

$$prob = \min\left\{1, \frac{P(\beta^*, \hat{\tau}_i^2, I_i)}{P(\beta_i, \hat{\tau}_i^2, I_i)}\right\}$$

where $\hat{\tau}^2$ is calculated from DerSimonian-Laird estimate [2]. Otherwise set $\beta_{i+1} = \beta_i$.

- **Update** L

1. Generate a random number between 1 and L from $P(I_L)$, define it as I_q^*, which is the qth element of I^*.
2. Set $I_d^* = I_{id}$ for all $d \neq q$.
3. Set $I_q^* = (I_{iq} - 1)^2$.
4. If $\sum_{j=1}^{L} I_j \geq 5$ is true, continue to the next step, otherwise repeat step 1 (ensures there is enough IVs for estimation).

5. Accept $I_{i+1} = I^*$ with probability:

$$prob = \min \left\{ 1, \frac{P(\beta_{i+1}, \hat{\tau}^{2*}, I^*)}{P(\beta_{i+1}, \hat{\tau}_i^2, I_i)} \right\}$$

where $\hat{\tau}^2$ and $\hat{\tau}^{2*}$ is calculated from DerSimonian-Laird estimate [2] with I_i and I^* respectively. Otherwise set $I_{i+1} = I_i$.

Appendix 3: Simulations under the one-parameter model

Convergence

Convergence is an important aspect to Bayesian analysis when implemented using MCMC methods, as it is an iterative process, different possible values are explored at each iteration. To investigate convergence, we run 5 short chains, each with random starting values, 50,000 iterations and 10,000 burn-ins. We also run one long chain with 500,000 iterations and 100,000 burn-ins.

We tested convergence on 3 different types of instruments; (1) Scenario 1 and (2) Scenario 2 without invalid instruments, and (3) Scenario 1 with 30% invalid instruments.

Table 1 demonstrates evidence for convergence with 50,000 iterations and 10,000 burn in. The mean, standard deviation and 95% credible interval of the posterior distribution for β are similar between long and shorts chains, in all 3 scenarios. The difference shown between long and short chains are the standard error and the time-series standard error (adjusted for auto-correlation). This is expected as the accuracy for the posterior mean of β increases with number of iterations. The trace plot is another diagnostic tool; it is a continuous line that shows the values a parameter has against the iteration number. A "catepillar" shaped trace plot, and similarities between long and short chains, supports evidence for convergence (Figure 1 and 2).

Table 1: *Convergence diagnostic of Scenario 1 and 2 without invalid, and with 30% invalid instruments by comparing a long and 5 short chains. Each short chain have 50,000 iterations with 5,000 burn-ins and the long chain have 500,000 iterations and 100,000 burn-ins. True β is 0.05. SD, standard deviation; SE, standard error; CI, credible interval; inst., instrument(s).*

Inst. scenario	**chain**	**mean β**	**SD**	**SE**	**Time-series SE**	**Lower 95% CI**	**Upper 95% CI**
	DL estimate						
	1	0.0485	0.0080	0.00004	0.00014	0.0332	0.0640
	2	0.0488	0.0081	0.00004	0.00014	0.0330	0.0643
	3	0.0485	0.0079	0.00004	0.00014	0.0333	0.0643
	4	0.0484	0.0081	0.00004	0.00014	0.0324	0.0645
	5	0.0485	0.0081	0.00004	0.00014	0.0325	0.0642
Strong	Long	0.0485	0.0081	0.00001	0.00005	0.0327	0.0645
and valid	**Full Bayesian**						
	1	0.0486	0.0082	0.00004	0.00014	0.0323	0.0647
	2	0.0489	0.0080	0.00004	0.00013	0.0331	0.0646
	3	0.0487	0.0082	0.00004	0.00014	0.0324	0.0647
	4	0.0487	0.0083	0.00004	0.00013	0.0327	0.0650
	5	0.0491	0.0083	0.00004	0.00015	0.0325	0.0653
	Long	0.0488	0.0083	0.00001	0.00005	0.0326	0.0652
	DL estimate						
	1	0.0485	0.0083	0.00004	0.00016	0.0328	0.0652
	2	0.0482	0.0083	0.00004	0.00015	0.0323	0.0648
	3	0.0480	0.0083	0.00004	0.00015	0.0324	0.0649
	4	0.0484	0.0083	0.00004	0.00014	0.0329	0.0652
	5	0.0484	0.0083	0.00004	0.00016	0.0329	0.0648
Weak	Long	0.0482	0.0083	0.00001	0.00005	0.0323	0.0650
and valid	**Full Bayesian**						
	1	0.0483	0.0084	0.00004	0.00014	0.0319	0.0653
	2	0.0481	0.0085	0.00004	0.00015	0.0320	0.0656
	3	0.0485	0.0083	0.00004	0.00015	0.0324	0.0652
	4	0.0485	0.0084	0.00004	0.00016	0.0330	0.0657
	5	0.0480	0.0086	0.00004	0.00015	0.0318	0.0655
	Long	0.0484	0.0085	0.00001	0.00005	0.0322	0.0658
	DL estimate						
	1	0.0578	0.0094	0.00005	0.00020	0.0397	0.0768
Strong	2	0.0580	0.0097	0.00005	0.00024	0.0396	0.0776
with	3	0.0575	0.0094	0.00005	0.00020	0.0389	0.0767
30%	4	0.0573	0.0094	0.00005	0.00024	0.0395	0.0767
invalid	5	0.0584	0.0098	0.00005	0.00026	0.0401	0.0789
	Long	0.0576	0.0095	0.00002	0.00008	0.0391	0.0766

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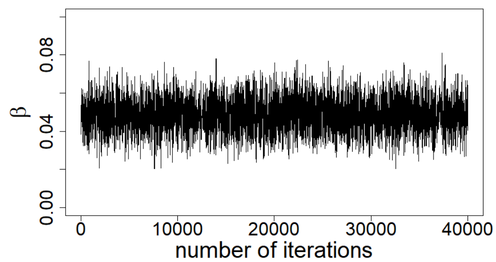
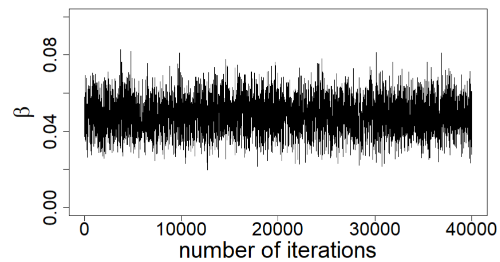
Table 1 – continued from previous page

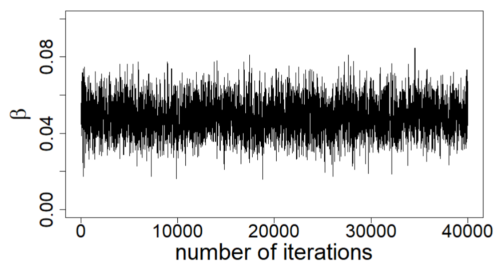
Inst. scenario	**chain**	**mean β**	**SD**	**SE**	**Time-series SE**	**Lower 95% CI**	**Upper 95% CI**
	Full Bayesian						
	1	0.0574	0.0097	0.00005	0.00023	0.0384	0.0768
	2	0.0580	0.0096	0.00005	0.00022	0.0394	0.0769
	3	0.0574	0.0097	0.00005	0.00021	0.0385	0.0767
	4	0.0576	0.0096	0.00005	0.00023	0.0394	0.0768
	5	0.0574	0.0096	0.00005	0.00021	0.0384	0.0765
	Long	0.0576	0.0095	0.00001	0.00007	0.0392	0.0764



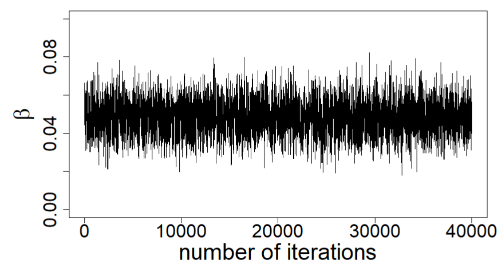
(a) Strong and valid: short



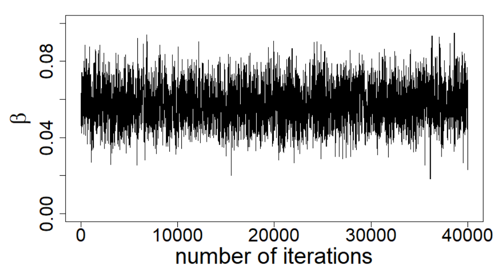
(b) Strong and valid: long



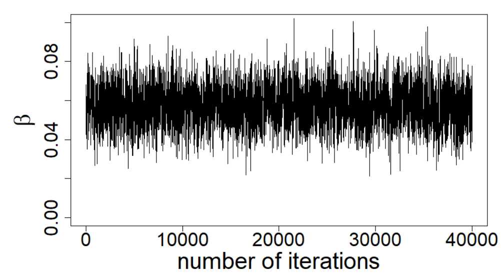
(c) Weak and valid: short



(d) Weak and valid: long

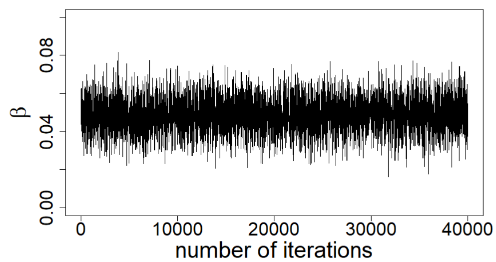


(e) Strong with 30% invalid: short

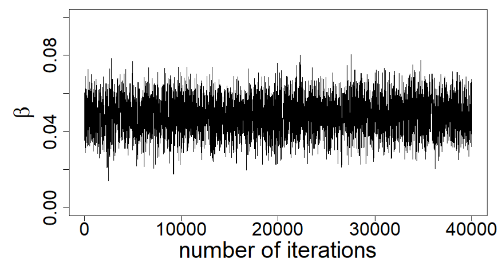


(f) Strong with 30% invalid: long

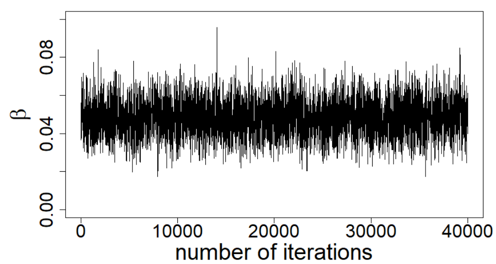
Figure 1: *Trace plot of the causal effect estimate (β) from DL approach with 3 different instrument scenarios; (a, b) strong valid, (c, d) weak valid instruments only and (e, f) strong with 30% invalid instruments. Short and long chain consist of 50,000 and 500,000 iterations with 10,000 and 100,000 burn-in respectively*



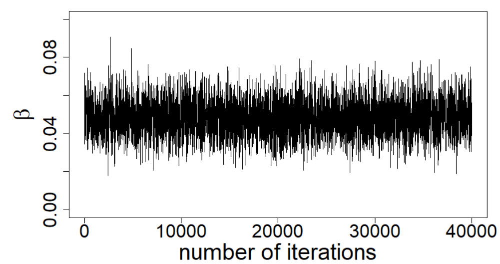
(a) Strong and valid: short



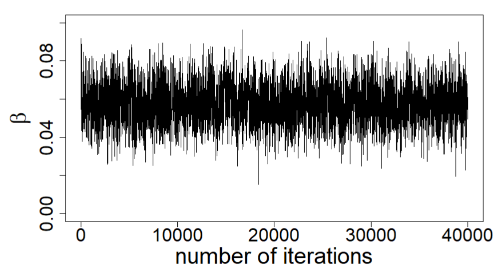
(b) Strong and valid: long



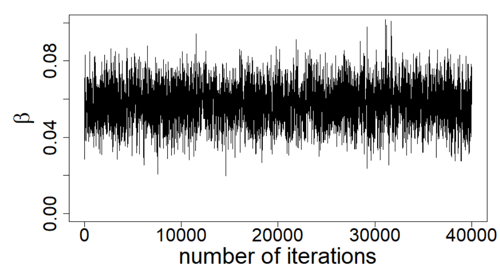
(c) Weak and valid: short



(d) Weak and valid: long



(e) Strong with 30% invalid: short



(f) Strong with 30% invalid: long

Figure 2: *Trace plot of the causal effect estimate (β) from full Bayesian approach with 3 different instrument scenarios; (1) strong valid (Scenario 1), (2) weak valid instruments only (Scenario 2) and (3) strong with 30% invalid instruments (Scenario 1). Short and long chain consist of 50,000 and 500,000 iterations with 10,000 and 100,000 burn-in respectively*

Weaker instruments

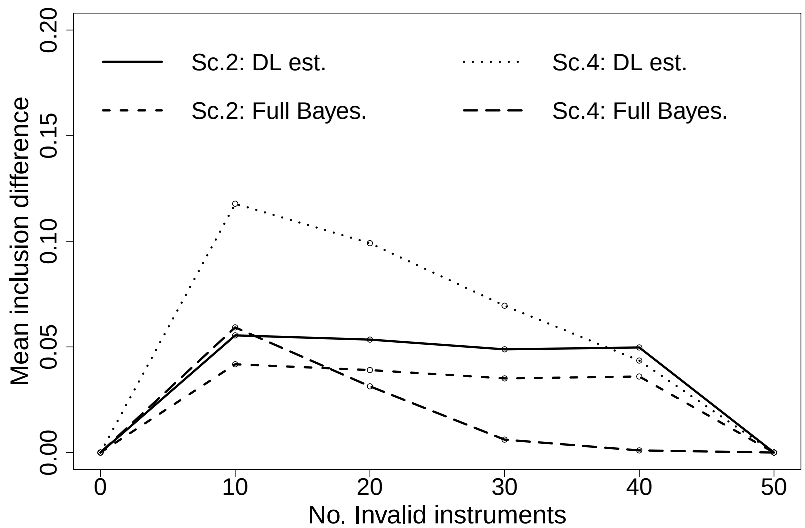


Figure 3: *The difference in mean inclusion probability between valid and invalid instruments for weaker instruments. Instruments have mean F-statistics of 10. As shown by the legend: solid and short dashed lines are Scenario 2 for DL estimate and full Bayesian respectively. Dotted and long dashed lines are Scenario 4 for DL estimate and full Bayesian respectively.*

Many weak instruments

Many weak instruments were simulated under scenario 1, but with 100 instruments. We experimented with 2 different mean F-statistics; 5 and 10. Table 2 gives the bias and coverage. Figure 4 shows the difference in mean inclusion probability between valid and invalid instruments.

Table 2: *Evaluation criteria with many weak instruments. 100 instruments in total. True β is 0.05. No. inv., Number of invalid instrument(s); Q, Q-statistics with exact weights; bias, mean bias; DL est., DL estimate; Full Bayes., Full Bayesian; $\bar{F}$, mean F-statistics.*

No. inv.	***Q***	**IVW**		**DL est.**		**Full Bayes.**		**MR-APS**		**MR-RAPS**	
$\bar{F} = 10$											
bias(i); coverage(ii)		i	ii	i	ii	i	ii	i	ii	i	ii
0	98.0	-0.019	9.30	-0.001	96.40	0.000	94.90	-0.000	93.70	0.000	93.10
20	109.3	-0.019	13.80	-0.001	96.30	0.003	92.90	0.003	90.10	0.002	91.50
40	120.2	-0.019	14.10	-0.000	96.70	0.006	89.50	0.007	84.10	0.006	85.90
60	131.0	-0.019	21.20	0.000	95.90	0.008	81.40	0.009	72.00	0.009	74.20
80	139.5	-0.019	21.10	0.000	96.40	0.012	73.20	0.012	62.10	0.011	65.10
100	149.4	-0.019	29.10	0.002	94.10	0.016	62.40	0.016	49.70	0.016	50.00
$\bar{F} = 5$											
bias(i); coverage(ii)		i	ii	i	ii	i	ii	i	ii	i	ii
0	97.8	-0.038	0.00	-0.006	94.30	0.001	90.40	0.000	93.20	0.000	93.10
20	104.8	-0.039	0.00	-0.005	95.40	0.004	87.80	0.003	92.40	0.003	92.30
40	110.7	-0.038	0.00	-0.004	94.60	0.009	83.00	0.009	87.40	0.008	89.30
60	116.8	-0.038	0.00	-0.001	97.60	0.012	74.20	0.013	80.00	0.013	81.80
80	121.2	-0.038	0.00	0.001	96.30	0.016	68.90	0.015	74.50	0.016	74.40
100	125.7	-0.038	0.00	0.003	97.10	0.021	55.20	0.022	59.30	0.022	59.90

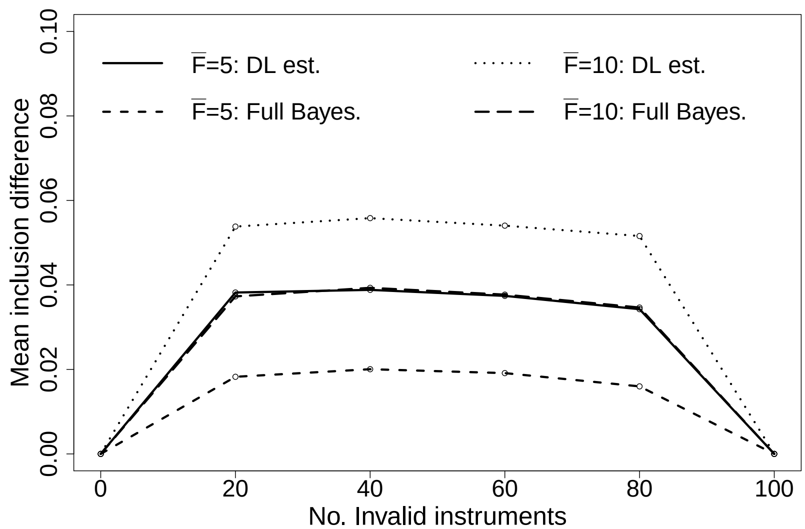


Figure 4: *The difference in mean inclusion probability between valid and invalid instruments for many weak instruments. As shown by the legend: solid and short dashed lines are when instruments have mean F-statistics* ($\bar{F}$) *of 5 for DL estimate and full Bayesian respectively. Dotted and long dashed lines are* $\bar{F}$ *of 10 for DL estimate and full Bayesian respectively.*

Sensitivity to strengths of heterogeneity

We can use Q-statistics to monitor the heterogeneity between the causal effect estimate from each of the instruments [3]. This section investigates our approaches' sensitivity to the change in Q-statistics. From Bowden *et al.* [3],

$$Var(\beta_j) = \frac{\beta^2\sigma_{xj}^2 + \sigma_{yj}^2}{\hat{\gamma_j^2}} \tag{6}$$

$$Q = \sum_{j=1}^{L} w_j(\beta)(\hat{\beta}_j - \beta)^2 \tag{7}$$

where $w_j(\beta) = 1/Var(\beta_j)$. And $\hat{\beta}_j = \beta + \dfrac{\alpha_j + \epsilon_j}{\gamma_j}$. We can then write down the expected value of the true Q-statistic as;

$$\text{E[Q]} = \sum_{j=1}^{L} \frac{\alpha_j^2}{\beta^2\sigma_{xj}^2 + \sigma_{yj}^2} + (L-1) \tag{8}$$

and using the χ^2 distribution for $L-1$ degrees of freedom, we could fix α_j^2 to give p-values for different levels of heterogeneity. We considered 2 forms of Q-statistics; (1) the true Q-statistics in total for 20% invalid instruments are 85, 75, 66 and 62 to give p-value of 0.001, 0.01, 0.05 and 0.1 respectively. (2) Each invalid instruments have true Q-statistics of 11, 7, 4 and 3 to give p-value of 0.001, 0.01, 0.05 and 0.1 respectively. But in total, it is borderline evidence for heterogeneity (Q-statistic p-value=0.05), hence, the number of invalid instruments increases with the Q-statistics. See Table 3 for a summary.

Our results demonstrate three facts:

1. Increasing heterogeneity with same number of invalid instruments does not affect the overall performance of the estimators, but only the inclusion probability of the instruments.

2. Increasing the number of invalid instruments whilst fixing the total heterogeneity does not affect the overall performance of the estimators.

3. When the pleiotropy parameters are small and exchangeable, the probability of inclusion is approximately constant across SNPs

Table 3: *Summary of Q-statistics (Q) simulation. The p-value for overall and individual Q is from χ^2 distribution of $L-1$ and 1 degrees of freedom respectively. Total number of instruments is 50. Ind., individual.*

Scenario	**No. invalid**	**Overall Q (p-value)**	**Individual Q (p-value)**
Sum Q	10	85 (0.001)	8.5 (0.01)
	10	75 (0.01)	7.5 (0.01)
	10	66 (0.05)	6.6 (0.01)
	10	62 (0.1)	6.2 (0.01)
Ind. Q	6	66 (0.05)	11 (0.001)
	10	66 (0.05)	7 (0.01)
	17	66 (0.05)	4 (0.05)
	25	66 (0.05)	3 (0.1)

Table 4: *Evaluation criteria for varying Q-statistics. 50 instruments with mean F-statistics of 100. True β is 0.05. No. inv., Number of invalid instrument(s); Q exact, estimated Q-statistics for all instruments with exact weights; Ind., individual.*

Scenario	**No. inv.**	**Overall Q**	**Ind. Q**	**Q exact**	**DL est.**		**Full Bayes.**	
		bias(i);coverage(ii)			i	ii	i	ii
Sum Q	10	85	8.5	134.5	0.001	94.90	0.001	92.30
	10	75	7.5	124.2	0.000	97.00	0.000	94.40
	10	66	6.6	115.3	0.001	96.10	0.001	93.60
	10	62	6.2	111.0	0.000	96.60	0.001	94.90
		bias(i);coverage(ii)			i	ii	i	ii
Ind. Q	6	66	11	113.8	0.000	96.80	0.000	95.90
	10	66	7	115.4	0.001	96.60	0.001	94.00
	17	66	4	113.7	-0.001	95.90	0.000	91.70
	25	66	3	116.7	-0.001	96.00	0.000	87.60

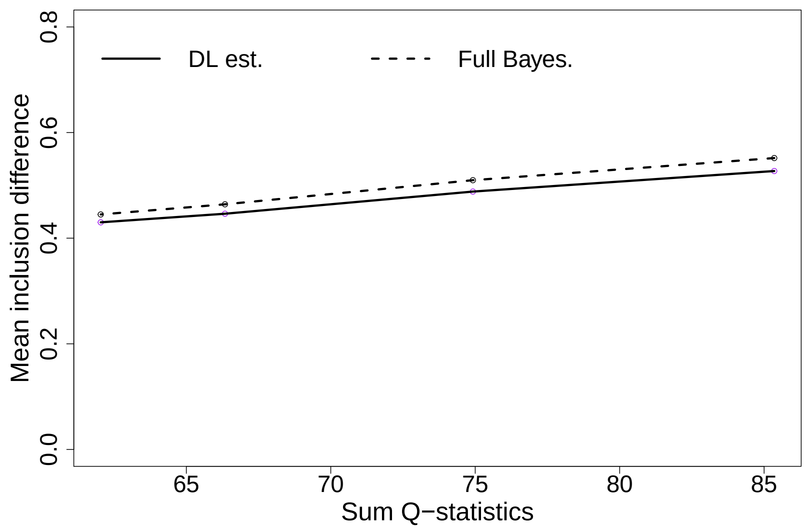


Figure 5: *The difference in mean inclusion probability against sum Q of all invalid instruments. As shown by legend: solid and short dashed lines are Scenario 1 for DL estimate and full Bayesian respectively.*

Appendix 4: Modified Metropolis-Hastings algorithm for InSIDE violating pleiotropy

The updating algorithm for β_1, β_2, τ_1^2 and τ_2^2 is the same as β and τ^2 in the one-parameter model respectively (Appendix 2).

- **Update** I_1

  1. Generate a random number between 1 and L, define it as I_{1q}^* from $P(I_L)$, which is the qth element of I_1^*
  2. Set $I_{1d}^* = I_{i1d}$ for all $d \neq q$, if $I_{i2q} \neq 1$, otherwise repeat step 1.
  3. Set $I_{1q}^* = (I_{i1q} - 1)^2$.
  4. If $\sum_{j=1}^{L} I_{1j} \geq 5$ is true, proceed to next step, otherwise repeat step 1.
  5. Accept $I_{1i+1} = I_1^*$ with probability:

  $$prob = \min\left\{1, \frac{P(\beta_{1i+1}, \tau_{1i+1}^2, \beta_{2i+1}, \tau_{2i+1}^2, I_1^*, I_{2i})}{P(\beta_{1i+1}, \tau_{1i+1}^2, \beta_{2i+1}, \tau_{2i+1}^2, I_{1i}, I_{2i})}\right\}$$

  otherwise set $I_{1i+1} = I_{1i}$.

- **Update** I_2

  1. Generate a random number between 1 and L, define it as I_{2q}^* from $P(I_L)$, which is the qth element of I_2^*
  2. Set $I_{2d}^* = I_{i2d}$ for all $d \neq q$, if $I_{i1q} \neq 1$, otherwise repeat step 1.
  3. Set $I_{2q}^* = (I_{i2q} - 1)^2$.
  4. If $\sum_{j=1}^{L} I_{2j} \geq 5$ is true, proceed to next step, otherwise repeat step 1.
  5. Accept $I_{2i+1} = I_2^*$ with probability:

  $$prob = \min\left\{1, \frac{P(\beta_{1i+1}, \tau_{1i+1}^2, \beta_{2i+1}, \tau_{2i+1}^2, I_{1i+1}, I_2^*)}{P(\beta_{1i+1}, \tau_{1i+1}^2, \beta_{2i+1}, \tau_{2i+1}^2, I_{1i+1}, I_{2i})}\right\}$$

  otherwise set $I_{2i+1} = I_{2i}$.

Step 2 in **Update** I_1 and **Update** I_2 restricts the new jump to be conditional on I_2 and I_1 respectively, this will stop the case of $(I_{1j} = 1, I_{2j} = 1)$. Model space including both $(I_{1j} = 1, I_{2j} = 1)$ and $(I_{1j} = 0, I_{2j} = 0)$ is equivalent to giving model that consists of outlying instruments higher probability then models where instruments have to be designated to either I_1 or I_2.

Appendix 5: Weak instruments in the two-parameter model

We reduced the strength of instrument of scenario 6 to have mean F-statistics of 10; σ_{Xj} are generated from a Uniform $U(0.06, 1)$ distribution for both S_1 and S_2. Table 5 gives the bias and coverage. Figure 6 shows the difference in mean inclusion probability between valid and invalid instruments.

Table 5: *Evaluation criteria for estimating two causal parameter from instruments with mean F-statistic of 10. 50 instruments in total. The true β is 0.05. Est., estimator; Inst., instrument(s); Q, exact Q-statistics; DL est., DL estimate; Full Bayes., Full Bayesian. β_1 is estimating β and β_2 for $\beta+1$.*

Est.	**Inst.**	***Q***		**mean bias**		**median bias**		**coverage**	
	$S_1 : S_2$	S_1	S_2	β_1	β_2	β_1	β_2	β_1	β_2
	40:10	58.8	51.2	-0.004	-0.988	-0.003	-0.990	98.7	0.2
	30:20	43.5	118.9	0.026	-0.870	0.014	-0.974	98.4	18.3
DL est.	25:25	35.4	153.2	0.051	-0.532	0.020	-0.511	95.9	60.4
	20:30	28.0	205.5	0.027	-0.252	0.012	-0.185	94.8	86.8
	10:40	12.8	278.5	0.252	-0.143	0.178	-0.118	75.3	93.9
	40:10	58.8	51.2	-0.236	-0.478	-0.002	-0.050	81.4	70.3
	30:20	43.5	118.9	-0.395	-0.364	-0.009	0.064	65.9	69.8
Full Bayes.	25:25	35.4	153.2	0.551	-1.420	0.973	-1.025	30.1	41.4
	20:30	28.0	205.5	0.500	-1.566	1.062	-1.816	19.0	42.4
	10:40	12.8	278.5	0.258	-2.332	1.087	-3.133	1.9	27.2

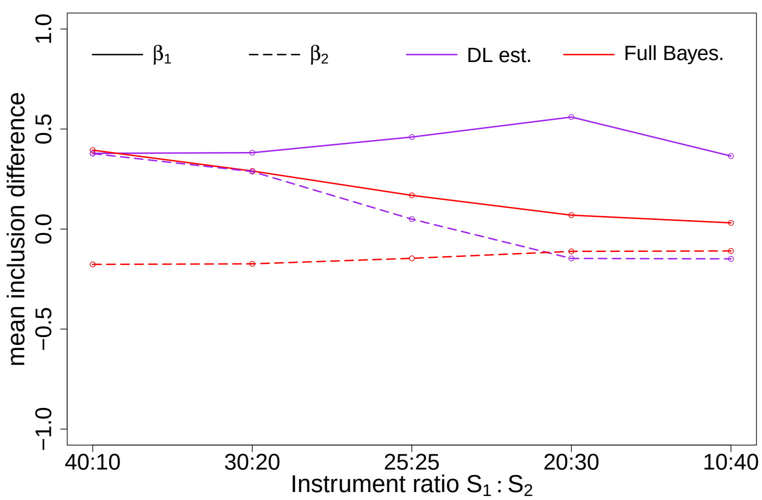


Figure 6: *Mean difference in the inclusion probability between S_1 and S_2 as a function of the true ratio S_1:S_2 for weak instruments (mean F-statistic of 10).*

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