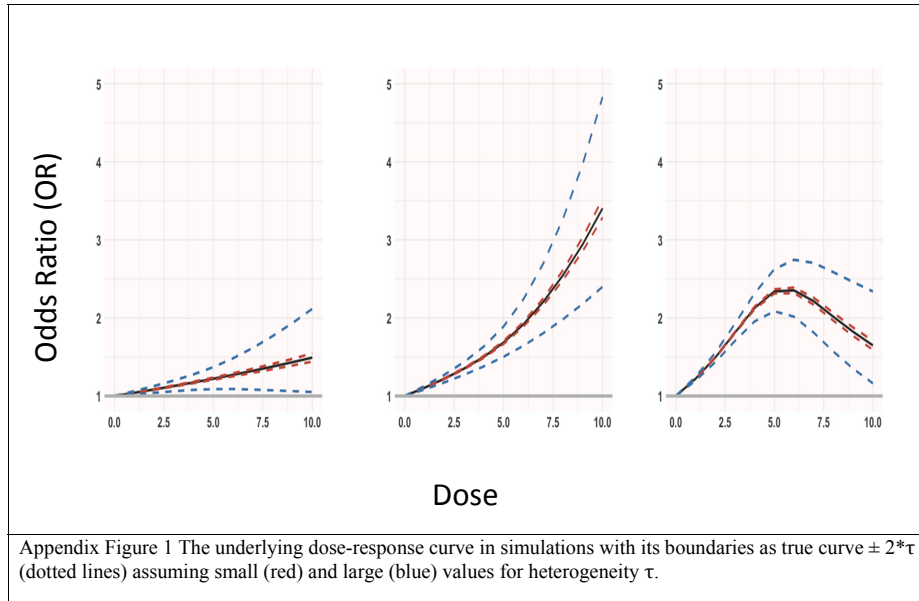# A Bayesian dose-response meta-analysis model: supplementary material
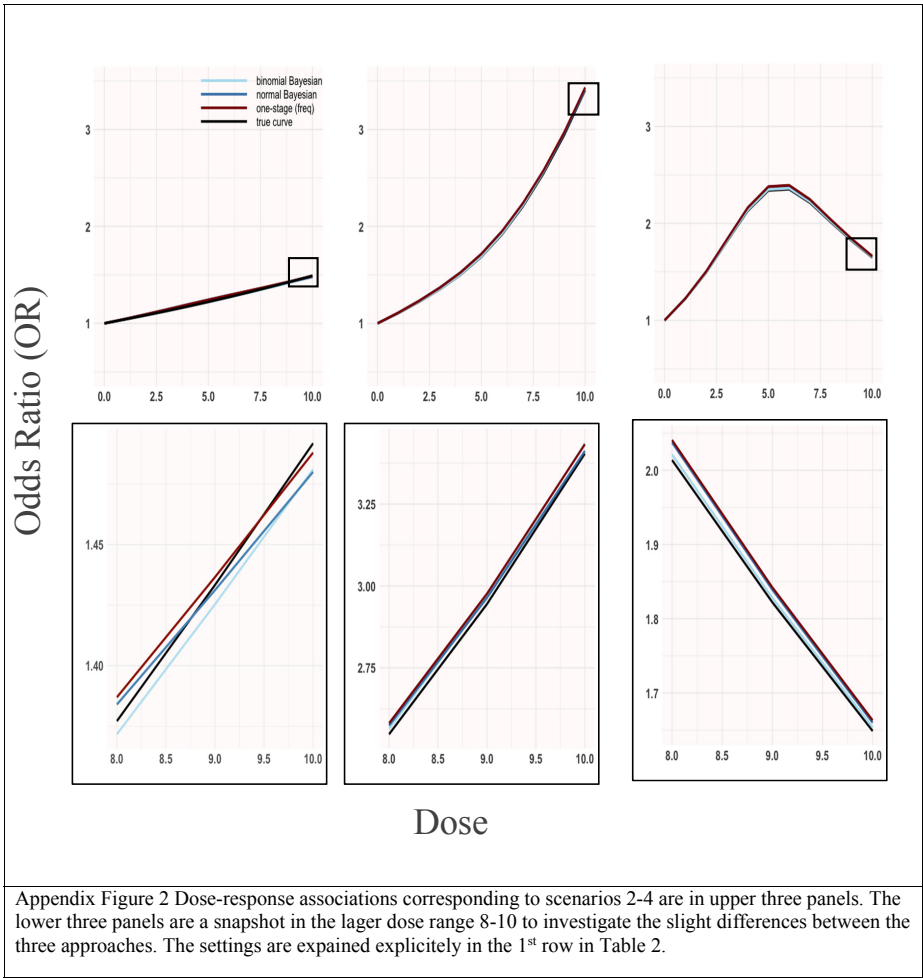
Tasnim Hamza[1], Andrea Cipriani[2], Toshi A. Furukawa[3], Matthias Egger[1], Nicola Orsini[4], Georgia Salanti[1].
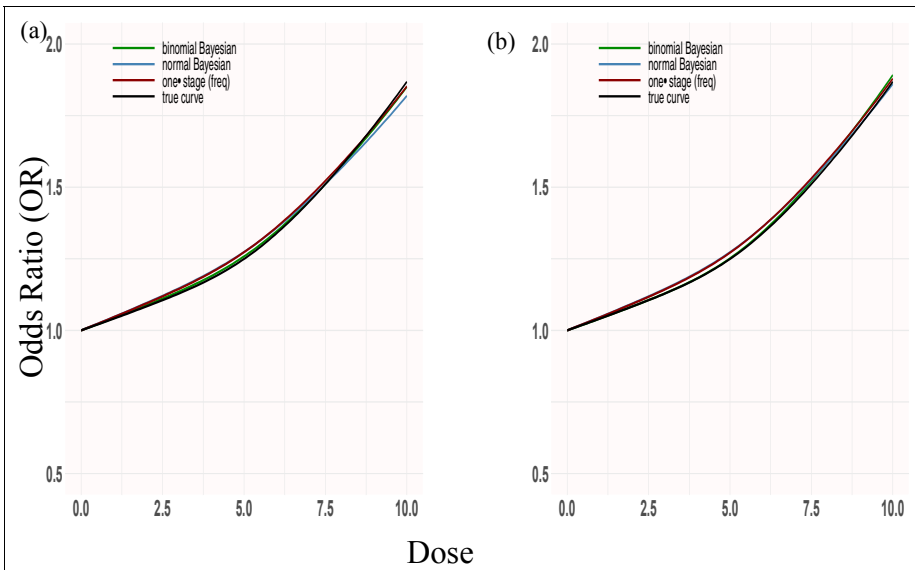
[1]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [2]Department of Psychiatry, University of Oxford. [3]Department of Health Promotion and Human Behavior, and Department of Clinical Epidemiology, Graduate School of Medicine/School of Public Health, Kyoto University, Kyoto, Japan. [4]Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden.

1. Additional results from simulations on OR

Appendix Figure 1 The underlying dose-response curve in simulations with its boundaries as true curve ± 2*τ (dotted lines) assuming small (red) and large (blue) values for heterogeneity τ.

Appendix Figure 2 Dose-response associations corresponding to scenarios 2-4 are in upper three panels. The lower three panels are a snapshot in the lager dose range 8-10 to investigate the slight differences between the three approaches. The settings are expained explicitely in the 1st row in Table 2.

(a) and (b) dose-response plots with legends: binomial Bayesian, normal Bayesian, one-stage (freq), true curve.
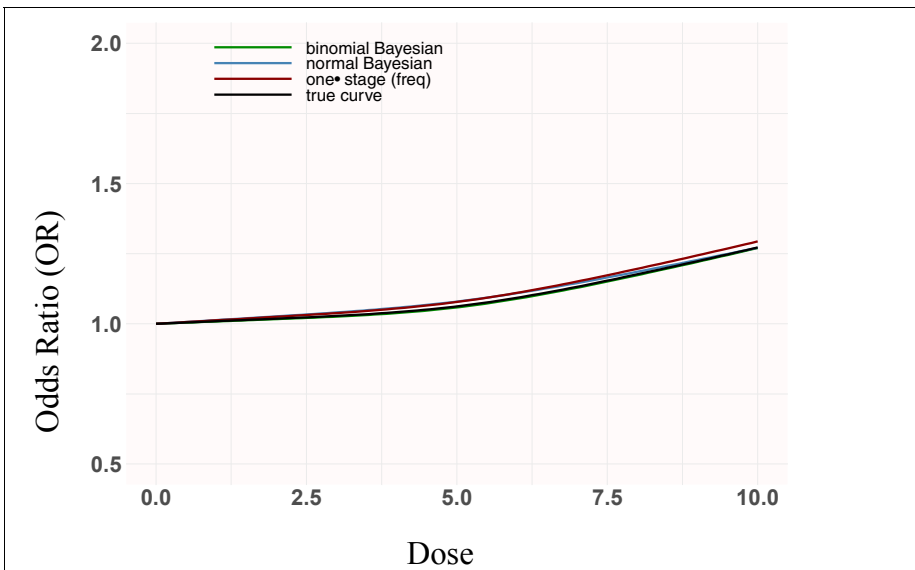
Appendix Figure 333 Dose-response associations corresponding to the fourth simulation setting in Table 2. In that setting, we generated data with (a) 8 and (b) 16 trials.
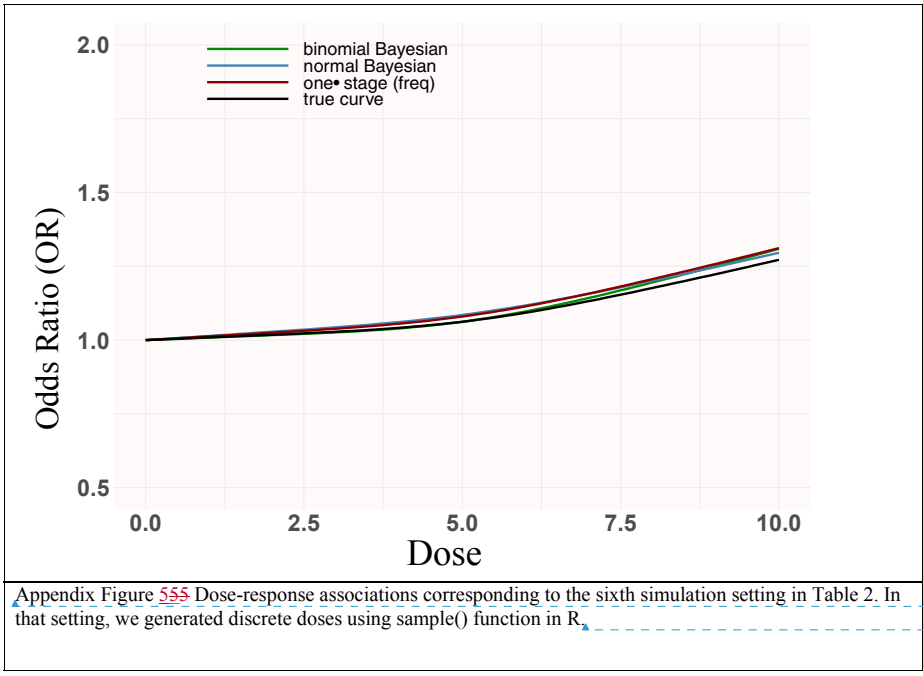
Dose-response plot with legend: binomial Bayesian, normal Bayesian, one-stage (freq), true curve.

Appendix Figure 444 Dose-response associations corresponding to the fifth simulation setting in Table 2. In that setting, we generated the doses of half of the studies from Unif(1,6) and in the other half from Unif(4,10).

Appendix Figure 555 Dose-response associations corresponding to the sixth simulation setting in Table 2. In that setting, we generated discrete doses using sample() function in R.
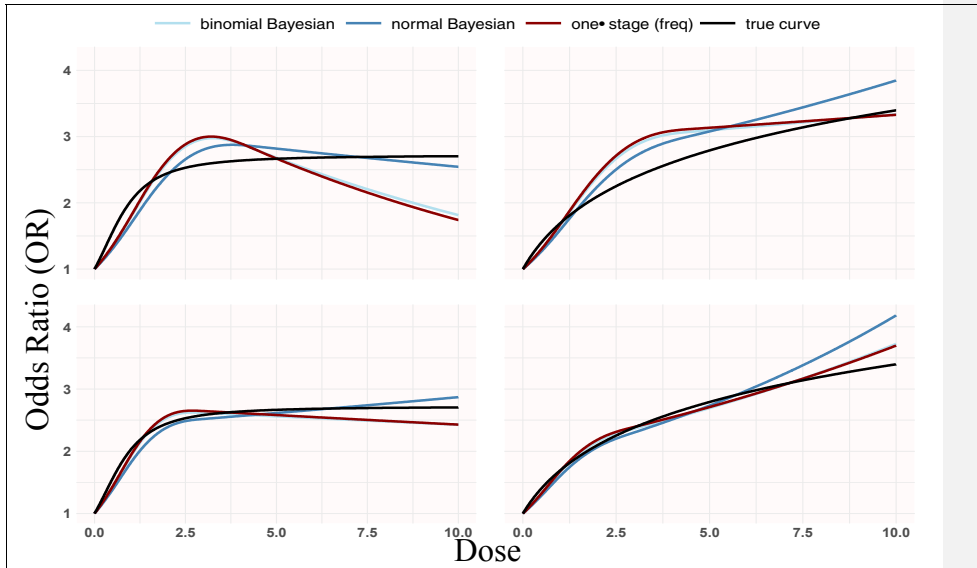
Simulation results for the half-sigmoid model (a,c) and the log-dose model (b,d) as the true dose-response curve (black) and the three estimated dose-response curves using restricted cubic splines (see Table 1). Knots are placed in 10%, 50% and 90% quantiles (doses 0.2, 1.3 and 4.3) in panels a and b and and at doses 0, 1, 3 in panels c and d. The doses are generated from $\chi^2(2)$.

Appendix Table 1 Assuming odds ratio (OR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assume 40 trials reporting aggregated-level data with three dose-levels each. The results for the linear coefficient B_1.

True B_1		0	0.04	0.1	0.2	0	0.04	0.1	0.2
True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
Bias	binomial Bayesian	0.0001	0.0002	0.0004	0.001	0.0004	0.0008	0.0009	0.002
	normal Bayesian	0.0055	0.0049	0.0045	0.0038	0.0058	0.0056	0.0048	0.0046
	one-stage (frequentist)	0.0048	0.0043	0.004	0.0041	0.0052	0.005	0.0044	0.0049
Coverage	binomial Bayesian	0.954	0.964	0.944	0.953	0.96	0.951	0.954	0.951
	normal Bayesian	0.937	0.95	0.921	0.943	0.939	0.925	0.944	0.935
	one-stage (frequentist)	0.95	0.959	0.936	0.953	0.949	0.936	0.954	0.947
MSE	binomial Bayesian	0.0002	0.0002	0.0002	0.0001	0.0002	0.0002	0.0002	0.0001
	normal Bayesian	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
	one-stage (frequentist)	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
Power	binomial Bayesian	-	0.872	1	1	-	0.851	1	1
	normal Bayesian	-	0.926	1	1	-	0.923	1	1
	one-stage (frequentist)	-	0.914	1	1	-	0.893	1	1
Se2mean	binomial Bayesian	0.0002	0.0002	0.0002	0.0001	0.0002	0.0002	0.0002	0.0001
	normal Bayesian	0.0002	0.0002	0.0002	0.0001	0.0002	0.0002	0.0002	0.0001
	one-stage (frequentist)	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
MCse (bias)	binomial Bayesian	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004
	normal Bayesian	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004
	one-stage (frequentist)	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004	0.0004
$\sqrt{\hat{R}}$	binomial Bayesian	1.0082	1.0088	1.0083	1.0073	1.0069	1.0068	1.0075	1.0063
	normal Bayesian	1.0052	1.0055	1.0052	1.0045	1.0047	1.0046	1.0047	1.0039

Appendix Table 2 Assuming odds ratio (OR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assume 40 trials reporting aggregated-level data with three dose-levels each. The results for the spline coefficient B_2.

True B_2		0	0	0.03	-0.2	0	0	0.03	-0.2
True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
Bias	binomial Bayesian	-0.0003	-0.0012	0.0007	-0.0009	-0.0008	0.0004	0	-0.0026
	normal Bayesian	-0.0071	-0.0075	-0.0057	-0.0042	-0.0078	-0.0064	-0.0063	-0.0057
	one-stage (frequentist)	-0.005	-0.0061	-0.0043	-0.0043	-0.006	-0.0048	-0.0048	-0.0059
Coverage	binomial Bayesian	0.952	0.956	0.955	0.961	0.953	0.954	0.95	0.955
	normal Bayesian	0.946	0.945	0.947	0.954	0.948	0.952	0.948	0.938
	one-stage (frequentist)	0.959	0.952	0.96	0.961	0.955	0.957	0.954	0.945
MSE	binomial Bayesian	0.0008	0.0007	0.0006	0.0005	0.0009	0.0007	0.0006	0.0005
	normal Bayesian	0.0008	0.0007	0.0006	0.0005	0.0009	0.0007	0.0006	0.0006
	one-stage (frequentist)	0.0008	0.0007	0.0006	0.0005	0.0009	0.0007	0.0006	0.0006
Power	binomial Bayesian	-	-	0.275	1	-	-	0.248	1
	normal Bayesian	-	-	0.204	1	-	-	0.194	1
	one-stage (frequentist)	-	-	0.201	1	-	-	0.197	1
Se2mean	binomial Bayesian	0.0009	0.0007	0.0006	0.0005	0.0009	0.0007	0.0006	0.0006
	normal Bayesian	0.0009	0.0007	0.0006	0.0006	0.0009	0.0007	0.0006	0.0006
	one-stage (frequentist)	0.0009	0.0008	0.0007	0.0006	0.0009	0.0008	0.0007	0.0006
MCse (bias)	binomial Bayesian	0.0009	0.0008	0.0008	0.0007	0.0009	0.0008	0.0008	0.0007
	normal Bayesian	0.0009	0.0008	0.0007	0.0007	0.0009	0.0008	0.0008	0.0007
	one-stage (frequentist)	0.0009	0.0008	0.0008	0.0007	0.0009	0.0008	0.0008	0.0008
$\sqrt{\hat{R}}$	binomial Bayesian	1.01	1.0102	1.0095	1.0086	1.0081	1.0079	1.0085	1.0074
	normal Bayesian	1.0066	1.007	1.0064	1.0056	1.0059	1.0055	1.0057	1.0048

Appendix Table 3 Assuming odds ratio (OR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assume 40 trials reporting aggregated-level data with three dose-levels each. The results for the common heterogeneity τ.

True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
True B_2		0	0	0.03	-0.2	0	0	0.03	-0.2
True B_1		0	0.04	0.1	0.2	0	0.04	0.1	0.2
Bias	binomial Bayesian	0.0124	0.0118	0.0105	0.0108	0.0051	0.0044	0.0033	0.0037
	normal Bayesian	0.013	0.0126	0.0116	0.0117	0.0055	0.0051	0.0041	0.0047
Coverage	binomial Bayesian	0.938	0.934	0.956	0.942	0.982	0.977	0.975	0.986
	normal Bayesian	0.914	0.906	0.907	0.906	0.981	0.975	0.971	0.964
MSE	binomial Bayesian	0.0002	0.0002	0.0001	0.0001	0.0001	0.0001	0	0
	normal Bayesian	0.0002	0.0002	0.0002	0.0002	0.0001	0.0001	0.0001	0.0001
Power	binomial Bayesian	0.078	0.082	0.065	0.068	0.149	0.162	0.169	0.17
	normal Bayesian	0.109	0.116	0.127	0.129	0.161	0.2	0.215	0.234
Se2mean	binomial Bayesian	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
	normal Bayesian	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
MCse (bias)	binomial Bayesian	0.0002	0.0002	0.0001	0.0001	0.0002	0.0002	0.0002	0.0002
	normal Bayesian	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
$\sqrt{\hat{R}}$	binomial Bayesian	1.0208	1.0215	1.0199	1.0204	1.0198	1.0199	1.0211	1.0209
	normal Bayesian	1.0147	1.015	1.0149	1.0155	1.0161	1.0148	1.0151	1.0171

Appendix Table 4 Assuming odds ratio (OR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assumed 20 trials reporting aggregated-level data with three dose-levels each, where sample size is generated from Unif(20, 100). The results for the linear coefficient B_1.
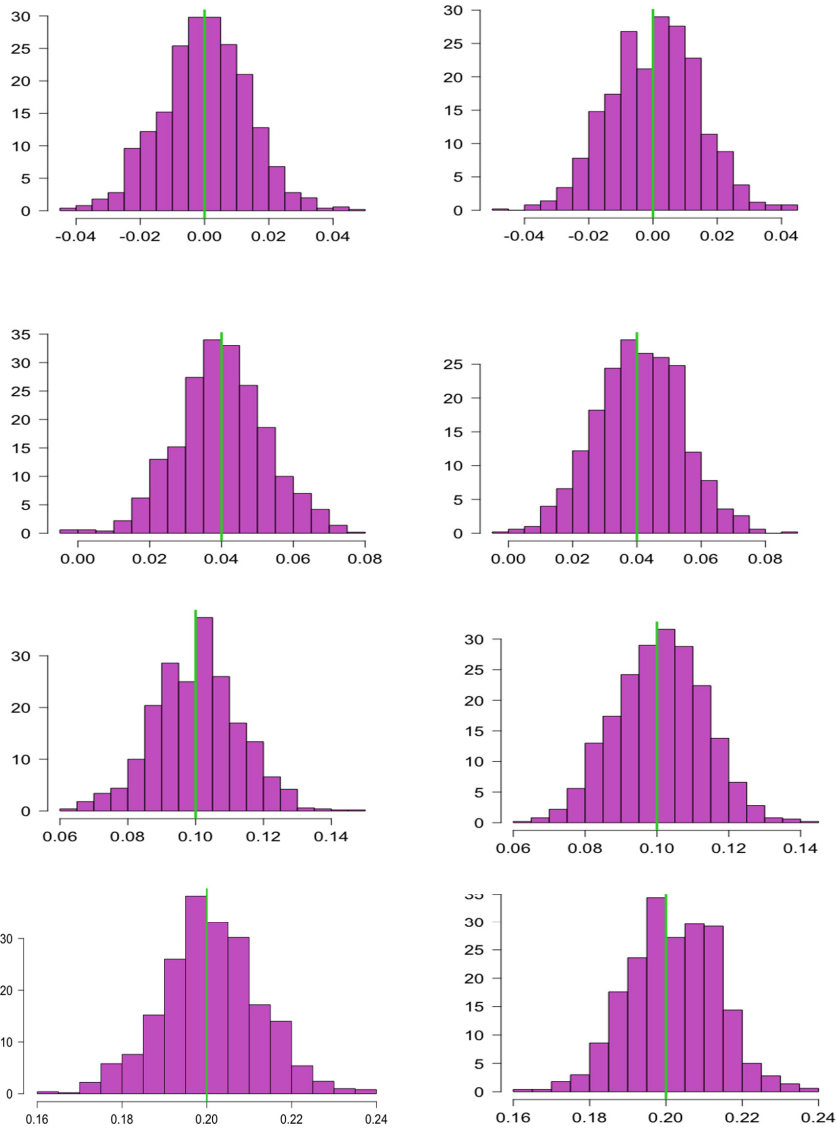
True B_1		0	0.04	0.1	0.2	0	0.04	0.1	0.2
True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
Bias	binomial Bayesian	0.0021	0.0017	0.0021	0.0039	0.0022	0.0043	0.0045	0.0042
	normal Bayesian	0.0237	0.0214	0.0203	0.0134	0.0247	0.0246	0.0217	0.0145
	one-stage (frequentist)	0.022	0.0201	0.0189	0.0172	0.0231	0.0233	0.0202	0.0176
Coverage	binomial Bayesian	0.958	0.964	0.962	0.976	0.968	0.959	0.951	0.962
	normal Bayesian	0.911	0.916	0.909	0.94	0.915	0.894	0.879	0.919
	one-stage (frequentist)	0.927	0.937	0.947	0.941	0.938	0.918	0.908	0.929
MSE	binomial Bayesian	0.0013	0.0012	0.0011	0.0009	0.0012	0.0012	0.0012	0.001
	normal Bayesian	0.0019	0.0018	0.0017	0.0013	0.0019	0.002	0.0019	0.0015
	one-stage (frequentist)	0.0019	0.0019	0.0017	0.0015	0.0019	0.0021	0.0019	0.0017
Power	binomial Bayesian	-	0.215	0.844	0.999	-	0.236	0.867	1
	normal Bayesian	-	0.388	0.92	0.999	-	0.404	0.93	1
	one-stage (frequentist)	-	0.315	0.882	0.999	-	0.343	0.894	1
Se2mean	binomial Bayesian	0.0014	0.0013	0.0012	0.0011	0.0015	0.0013	0.0012	0.0011
	normal Bayesian	0.0015	0.0014	0.0012	0.0011	0.0015	0.0014	0.0012	0.0011
	one-stage (frequentist)	0.0018	0.0017	0.0015	0.0014	0.0018	0.0017	0.0015	0.0014
MCse (bias)	binomial Bayesian	0.0011	0.0011	0.0011	0.0009	0.0011	0.0011	0.0011	0.001
	normal Bayesian	0.0012	0.0011	0.0011	0.0011	0.0011	0.0012	0.0012	0.0012
	one-stage (frequentist)	0.0012	0.0012	0.0012	0.0011	0.0012	0.0012	0.0012	0.0012
$\sqrt{\hat{R}}$	binomial Bayesian	1.0049	1.0049	1.005	1.005	1.0048	1.0051	1.0051	1.0049
	normal Bayesian	1.0031	1.0029	1.0028	1.0028	1.003	1.0028	1.0027	1.0025

Appendix Table 5 Assuming odds ratio (OR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assumed 20 trials reporting aggregated-level data with three dose-levels each where sample size is generated from $Unif(20, 100)$. The results for the spline coefficient B_2.

True B_2		0	0	0.03	-0.2	0	0	0.03	-0.2
True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
Bias	binomial Bayesian	-0.0075	-0.0025	0.0022	-0.0032	-0.0057	-0.0059	-0.0047	-0.0023
	normal Bayesian	-0.0358	-0.031	-0.0283	-0.0122	-0.0357	-0.0345	-0.0326	-0.0144
	one-stage (frequentist)	-0.0301	-0.027	-0.0226	-0.0196	-0.0307	-0.0298	-0.0269	-0.0204
Coverage	binomial Bayesian	0.964	0.972	0.96	0.965	0.975	0.961	0.961	0.963
	normal Bayesian	0.937	0.947	0.93	0.956	0.953	0.926	0.909	0.942
	one-stage (frequentist)	0.954	0.969	0.948	0.957	0.964	0.938	0.936	0.946
MSE	binomial Bayesian	0.006	0.0052	0.0044	0.0036	0.006	0.0063	0.0048	0.0043
	normal Bayesian	0.007	0.0063	0.0058	0.0045	0.0069	0.0078	0.0066	0.0055
	one-stage (frequentist)	0.0075	0.0072	0.0062	0.0052	0.0078	0.009	0.0067	0.0063
Power	binomial Bayesian	-	-	0.076	0.861	-	-	0.064	0.859
	normal Bayesian	-	-	0.049	0.875	-	-	0.064	0.87
	one-stage (frequentist)	-	-	0.045	0.869	-	-	0.054	0.851
Se2mean	binomial Bayesian	0.007	0.0062	0.0049	0.0047	0.0071	0.0061	0.0049	0.0046
	normal Bayesian	0.0069	0.0063	0.005	0.0049	0.0071	0.0063	0.0051	0.0048
	one-stage (frequentist)	0.0084	0.008	0.0063	0.0061	0.0087	0.0077	0.0061	0.0059
MCse (bias)	binomial Bayesian	0.0024	0.0023	0.0021	0.0019	0.0025	0.0025	0.0022	0.0021
	normal Bayesian	0.0024	0.0023	0.0022	0.0021	0.0024	0.0026	0.0024	0.0023
	one-stage (frequentist)	0.0026	0.0025	0.0024	0.0022	0.0026	0.0029	0.0024	0.0024
$\sqrt{\hat{R}}$	binomial Bayesian	1.0061	1.0059	1.0058	1.0058	1.0058	1.0061	1.006	1.0058
	normal Bayesian	1.0039	1.0036	1.0033	1.0034	1.0037	1.0034	1.0033	1.003

Appendix Table 6 Assuming odds ratio (OR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assume 20 trials reporting aggregated-level data with three dose-levels each where sample size is generated from $Unif(20, 100)$. The results for the common heterogeneity τ.

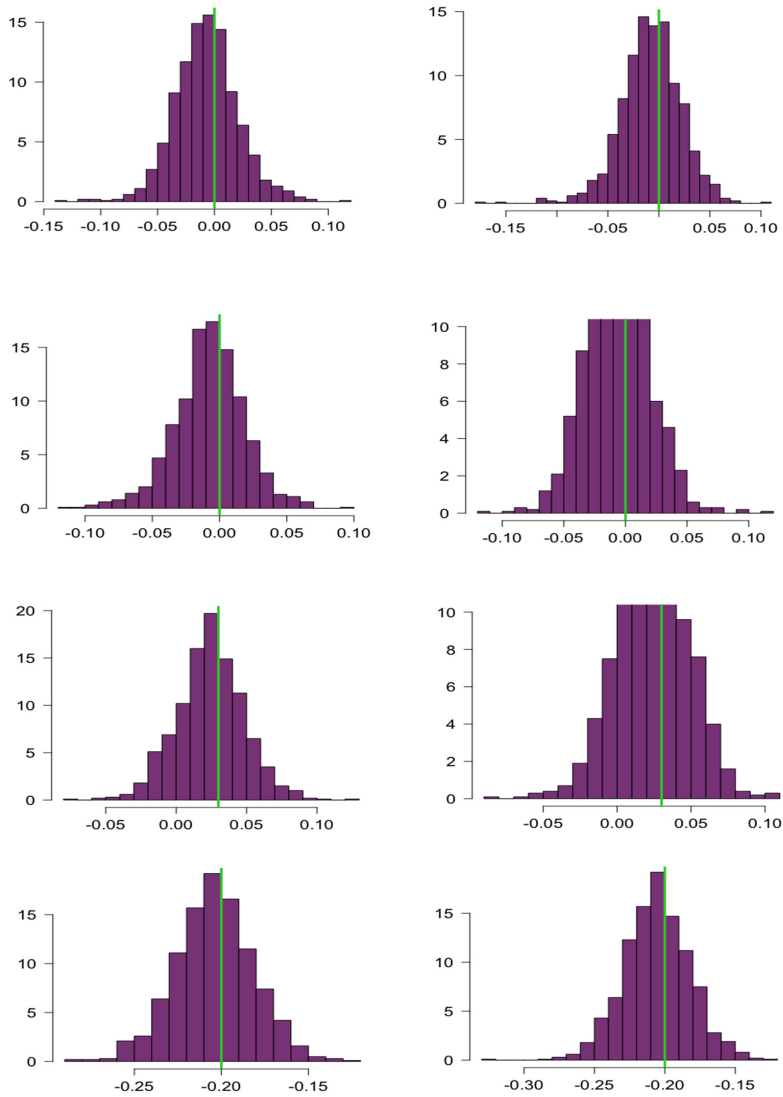| True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
True B_2		0	0	0.03	-0.2	0	0	0.03	-0.2
True B_1		0	0.04	0.1	0.2	0	0.04	0.1	0.2
Bias	binomial Bayesian	0.0124	0.0118	0.0105	0.0108	0.0051	0.0044	0.0033	0.0037
	normal Bayesian	0.013	0.0126	0.0116	0.0117	0.0055	0.0051	0.0041	0.0047
Coverage	binomial Bayesian	0.938	0.934	0.956	0.942	0.982	0.977	0.975	0.986
	normal Bayesian	0.914	0.906	0.907	0.906	0.981	0.975	0.971	0.964
MSE	binomial Bayesian	0.0002	0.0002	0.0001	0.0001	0.0001	0.0001	0	0
	normal Bayesian	0.0002	0.0002	0.0002	0.0002	0.0001	0.0001	0.0001	0.0001
Power	binomial Bayesian	0.078	0.082	0.065	0.068	0.149	0.162	0.169	0.17
	normal Bayesian	0.109	0.116	0.127	0.129	0.161	0.2	0.215	0.234
Se2mean	binomial Bayesian	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
	normal Bayesian	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001
MCse (bias)	binomial Bayesian	0.0002	0.0002	0.0001	0.0001	0.0002	0.0002	0.0002	0.0002
	normal Bayesian	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002	0.0002
$\sqrt{\hat{R}}$	binomial Bayesian	1.0208	1.0215	1.0199	1.0204	1.0198	1.0199	1.0211	1.0209
	normal Bayesian	1.0147	1.015	1.0149	1.0155	1.0161	1.0148	1.0151	1.0171

Appendix Figure 776 Histogram for $\widehat{B}_1$ in a simulation study based on odds ratio (OR) for the binomial dose-response meta-analysis model of restricted cubic spline in various scenarios for true $B_2=$ (a) 0 (b) 0 (c) 0.03 (d) -0.2 and true $B_1=$ (a) 0 (b) 0.04 (c) 0.1 (d)0.2 (green line) where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$, respectively.
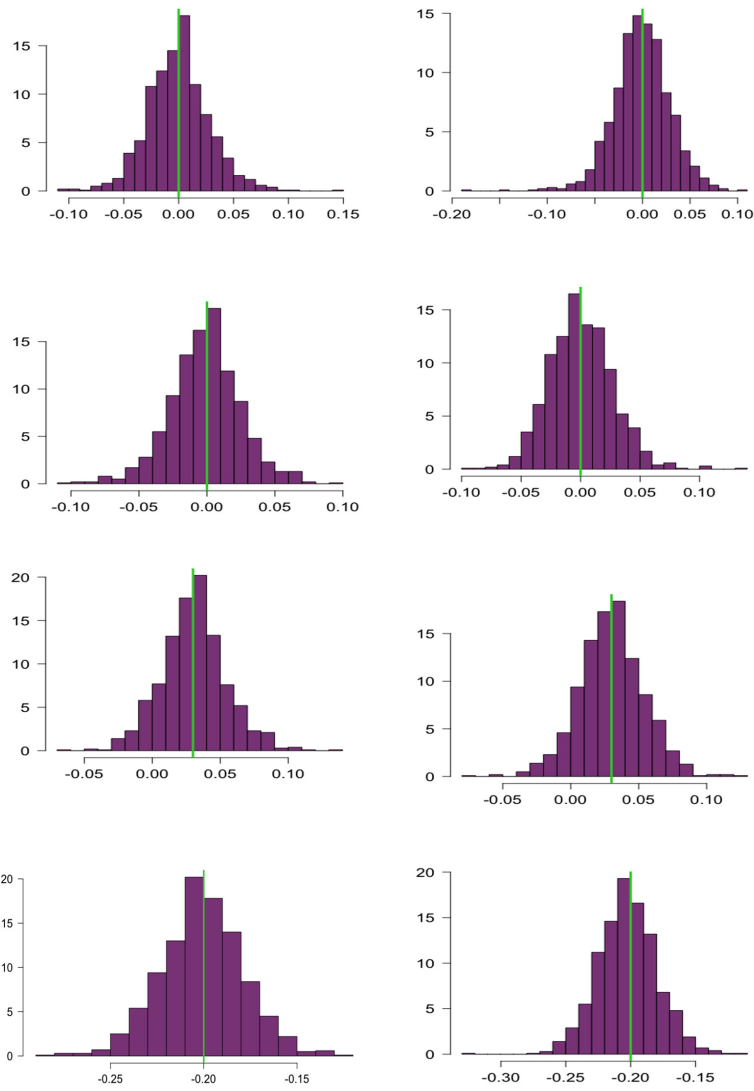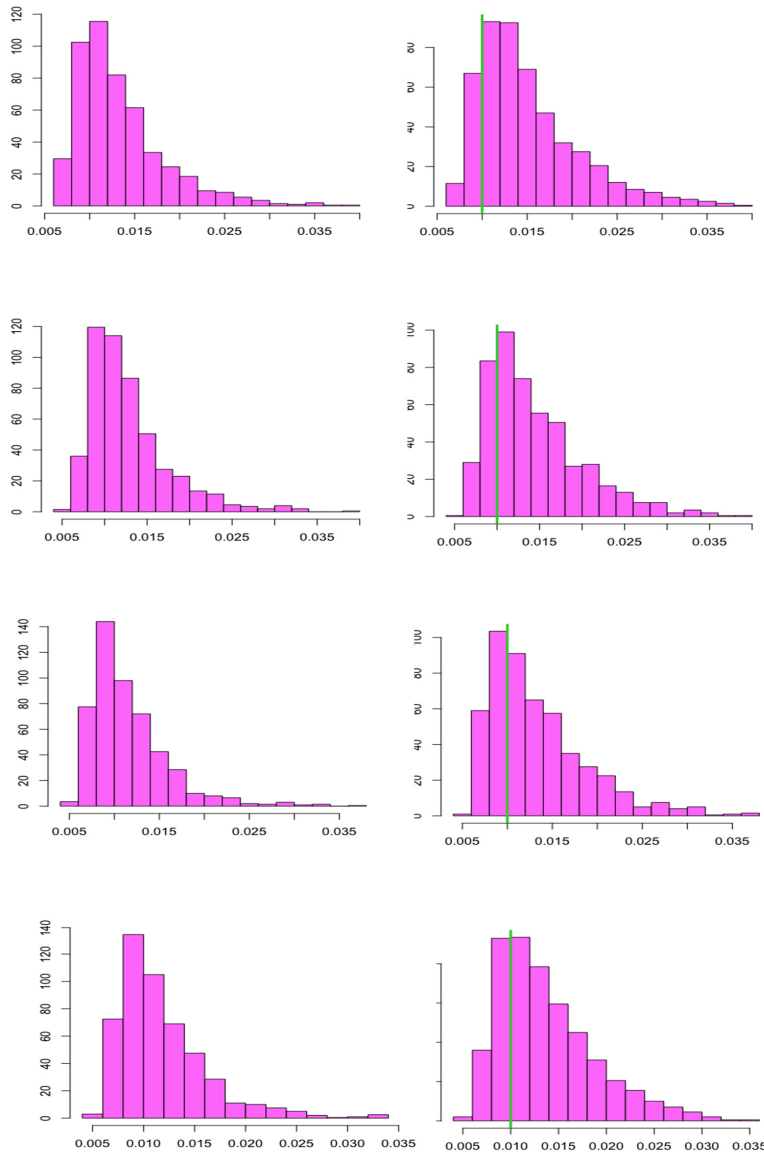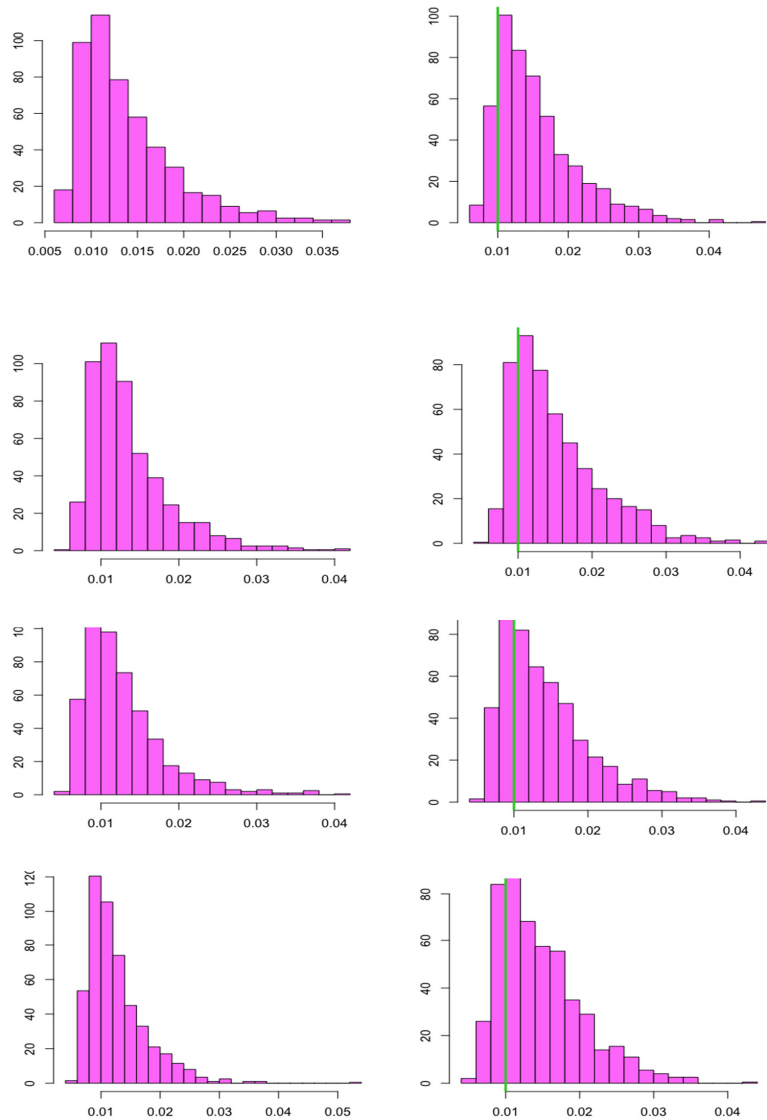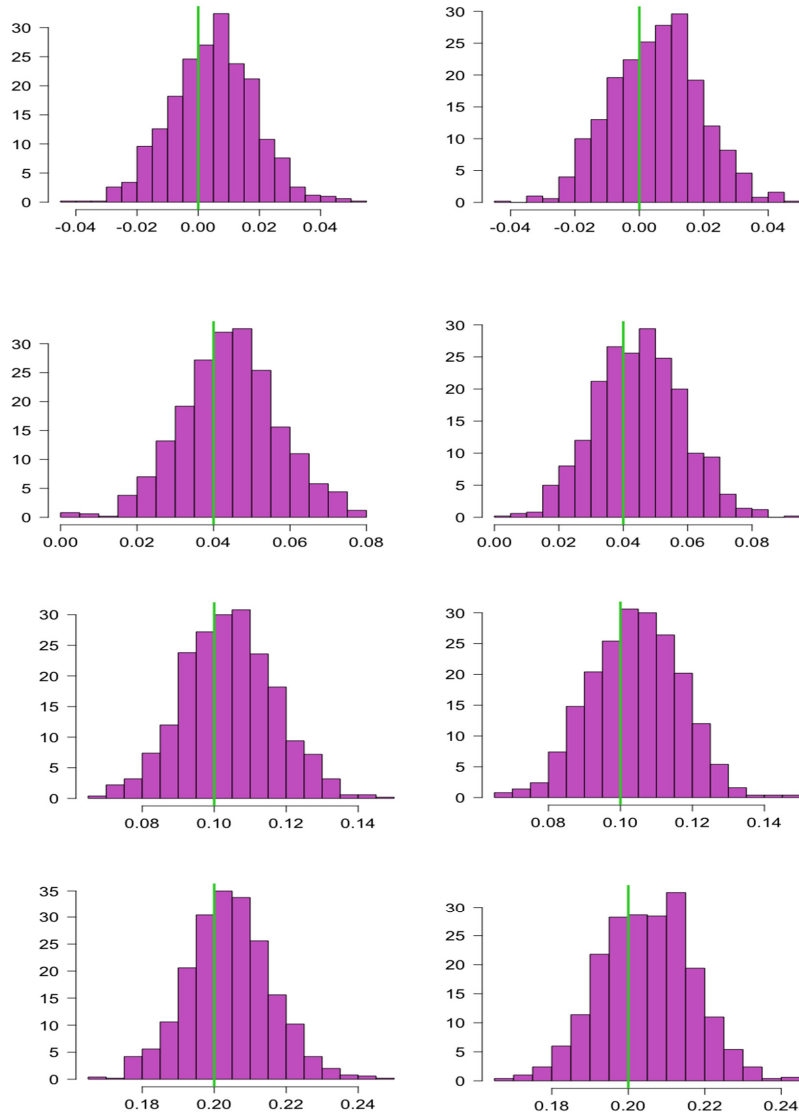
Appendix Figure 887 Histogram for $\widehat{B}_2$ in a simulation study based on odds ratio (OR) for the binomial dose-response meta-analysis model of restricted cubic spline in various scenarios for true B_2= (a) 0 (b) 0 (c) 0.03 (d) -0.2 (green line) and true B_1= (a) 0 (b) 0.04 (c) 0.1 (d)0.2 where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$, respectively.
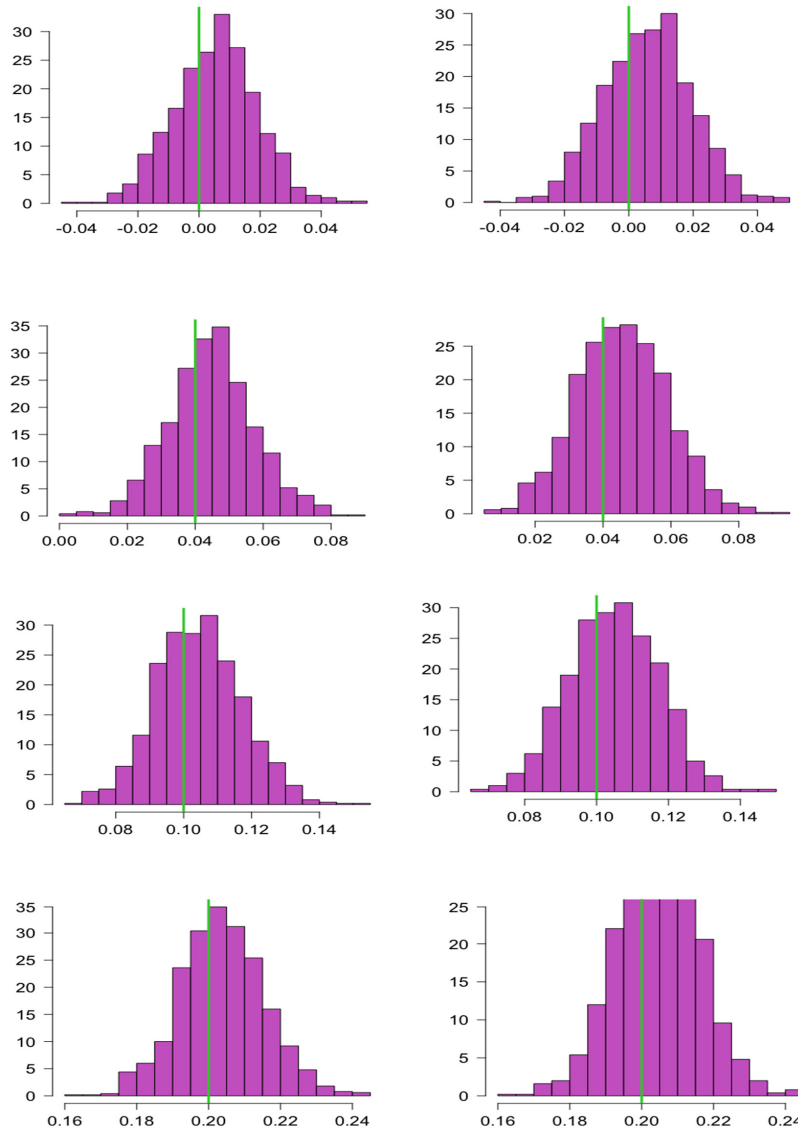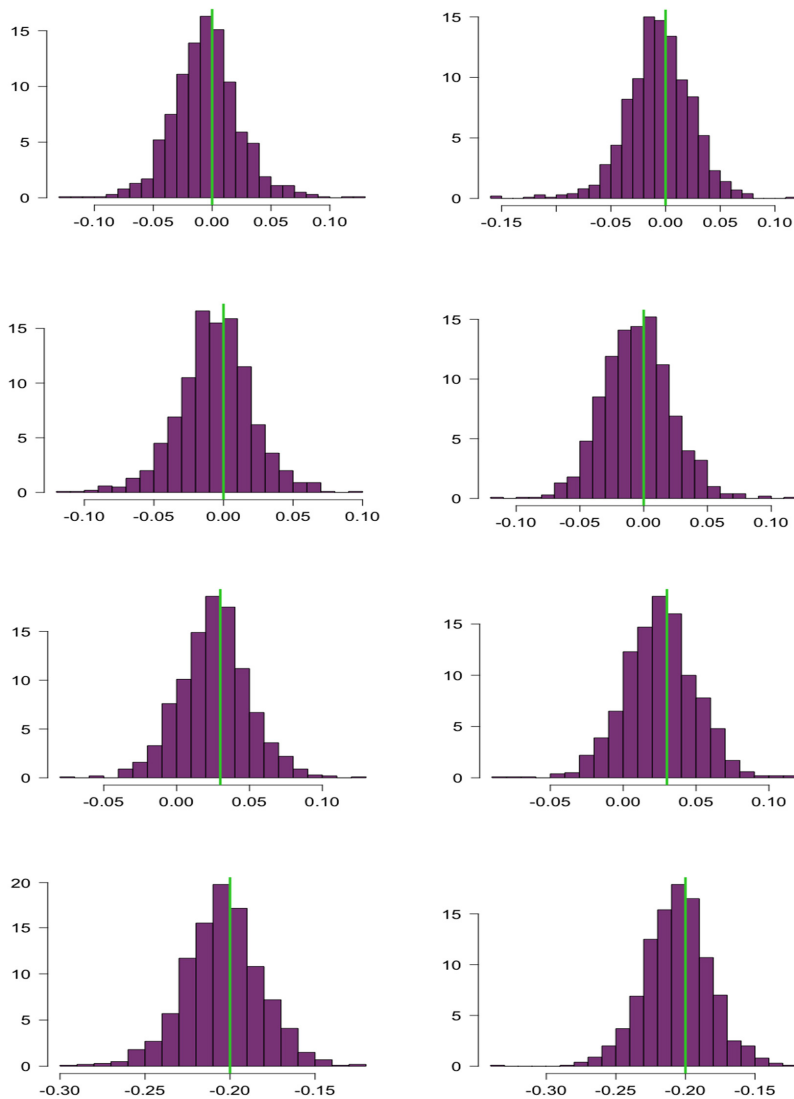
Appendix Figure 998 Histogram for $\widehat{B}_1$ in a simulation study based on odds ratio (OR) for the normal dose-response meta-analysis model of restricted cubic spline in various scenarios for true B_2= (a) 0 (b) 0 (c) 0.03 (d) -0.2 and true B_1= (a) 0 (b) 0.04 (c) 0.1 (d)0.2 (green line) where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$, respectively.

Appendix Figure 10109 Histogram for $\hat{B}_2$ in a simulation study based on odds ratio (OR) for the normal dose-response meta-analysis model of restricted cubic spline in various scenarios for true B_2= (a) 0 (b) 0 (c) 0.03 (d) -0.2 (green line) and true B_1= (a) 0 (b) 0.04 (c) 0.1 (d)0.2 where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$, respectively.

Appendix Figure 11~~1110~~ Histogram for τ̂ in a simulation study based on odds ratio (OR) for the binomial dose-response meta-analysis model of restricted cubic spline in various scenarios for true B_2= (a) 0 (b) 0 (c) 0.03 (d) -0.2 and true B_1= (a) 0 (b) 0.04 (c) 0.1 (d)0.2 where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$ (green line), respectively.

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Appendix Figure 121211 Histogram for τ̂ in a simulation study based on odds ratio (OR) for the normal dose-response meta-analysis model of restricted cubic spline in various scenarios for true B_2= (a) 0 (b) 0 (c) 0.03 (d) -0.2 and true B_1= (a) 0 (b) 0.04 (c) 0.1 (d)0.2 where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$ (green line), respectively.

Appendix Figure 131312 Histogram for $\hat{B}_1$ in a simulation study based on odds ratio (OR) for the one-stage (frequentist) dose-response meta-analysis model of restricted cubic spline in various scenarios for true $B_2=$ (a) 0 (b) 0 (c) 0.03 (d) -0.2 and true $B_1=$ (a) 0 (b) 0.04 (c) 0.1 (d)0.2 (green line) where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$, respectively.

Appendix Figure 141413 Histogram for $\hat{B}_2$ in a simulation study based on odds ratio (OR) for the one-stage (frequentist) dose-response meta-analysis model of restricted cubic spline in various scenarios for true $B_2 =$ (a) 0 (b) 0 (c) 0.03 (d) -0.2 (green line) and true $B_1 =$ (a) 0 (b) 0.04 (c) 0.1 (d)0.2 where in the first and the second columns the true heterogeneity is set as $\tau = 0.001$ and $\tau = 0.01$, respectively.

2.   Results from simulations on RR
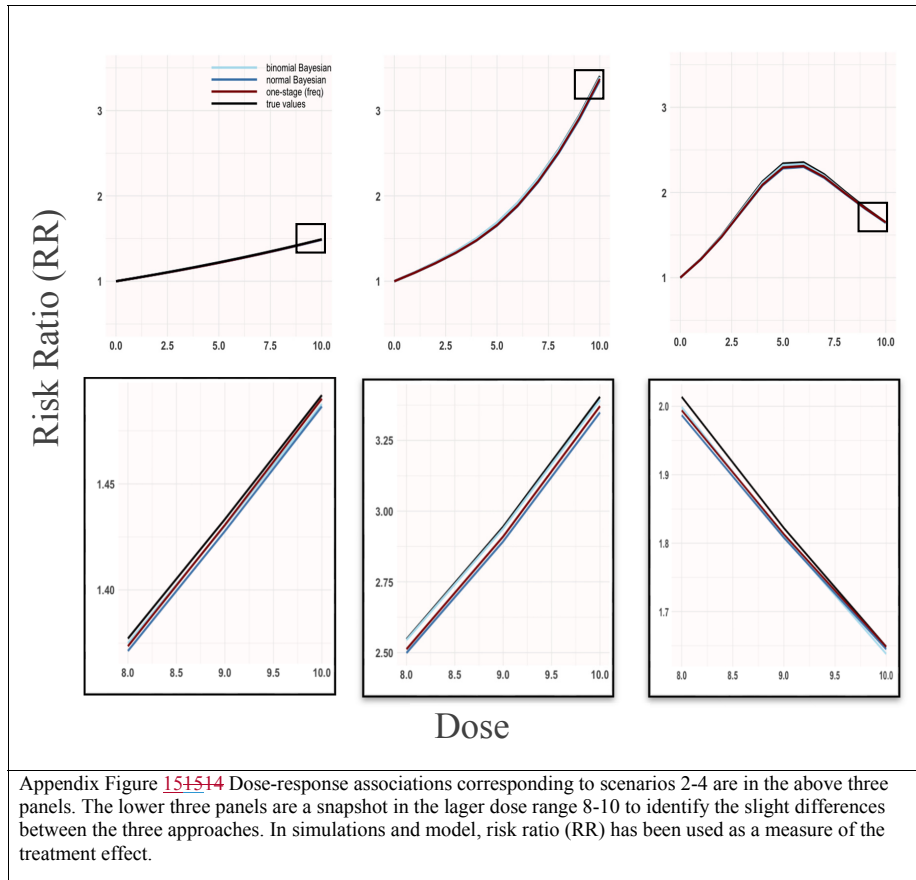
Appendix Figure 151514 Dose-response associations corresponding to scenarios 2-4 are in the above three panels. The lower three panels are a snapshot in the lager dose range 8-10 to identify the slight differences between the three approaches. In simulations and model, risk ratio (RR) has been used as a measure of the treatment effect.

Appendix Table 7 Assuming risk ratio (RR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assume 40 trials reporting aggregated-level data with three dose-levels each. The results for the linear coefficient B_1.

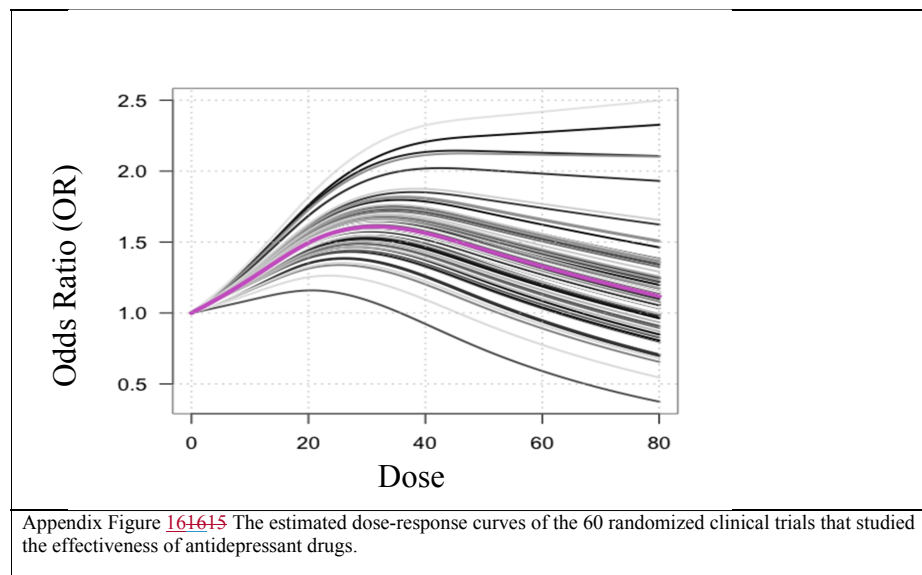| True B_1		0	0.04	0.1	0.2	0	0.04	0.1	0.2
True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
Bias	binomial Bayesian	0	0.0001	0.0005	-0.0018	0.0006	0	0.0008	0.0004
	normal Bayesian	0.0001	-0.001	-0.0047	-0.006	0.0002	-0.0017	-0.0067	-0.0059
	one-stage (frequentist)	0	-0.001	-0.004	-0.0049	0.0002	-0.0015	-0.0055	-0.0044
Coverage	binomial Bayesian	0.952	0.952	0.932	0.913	0.943	0.948	0.962	0.96
	normal Bayesian	0.904	0.908	0.853	0.79	0.915	0.904	0.866	0.815
	one-stage (frequentist)	0.95	0.939	0.9	0.857	0.938	0.927	0.916	0.896
MSE	binomial Bayesian	0	0	0.0001	0.0001	0	0	0.0001	0
	normal Bayesian	0	0	0.0001	0.0001	0	0.0001	0.0002	0.0001
	one-stage (frequentist)	0	0	0.0001	0.0001	0	0.0001	0.0002	0.0001
Power	binomial Bayesian	-	1	1	1	-	1	1	1
	normal Bayesian	-	1	1	1	-	0.996	1	1
	one-stage (frequentist)	-	1	1	1	-	0.993	1	1
Se2mean	binomial Bayesian	0	0	0.0001	0	0	0	0.0001	0
	normal Bayesian	0	0	0.0001	0	0	0.0001	0.0001	0.0001
	one-stage (frequentist)	0	0	0.0001	0.0001	0	0.0001	0.0001	0.0001
MCse (bias)	binomial Bayesian	0.0001	0.0002	0.0003	0.0003	0.0002	0.0002	0.0003	0.0002
	normal Bayesian	0.0002	0.0002	0.0004	0.0003	0.0002	0.0003	0.0004	0.0003
	one-stage (frequentist)	0.0002	0.0002	0.0003	0.0003	0.0002	0.0003	0.0004	0.0003
$\sqrt{\hat{R}}$	binomial Bayesian	1.0078	1.009	1.0086	1.0074	1.0036	1.0049	1.0066	1.0042
	normal Bayesian	1.0021	1.0026	1.0026	1.0018	1.0018	1.0021	1.0023	1.0016

Appendix Table 8 Assuming risk ratio (RR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assume 40 trials reporting aggregated-level data with three dose-levels each. The results for the spline coefficient B_2.

True B_2		0	0	0.03	-0.2	0	0	0.03	-0.2
True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
Bias	binomial Bayesian	-0.0003	-0.0005	-0.0011	0.0015	-0.0004	0.0004	-0.0002	0
	normal Bayesian	-0.0004	0.0009	0.0041	0.0077	0	0.0019	0.0073	0.0094
	one-stage (frequentist)	0.0001	0.0011	0.0041	0.0065	0.0001	0.0021	0.0064	0.0076
Coverage	binomial Bayesian	0.957	0.957	0.953	0.911	0.941	0.955	0.964	0.954
	normal Bayesian	0.825	0.809	0.789	0.708	0.849	0.838	0.807	0.719
	one-stage (frequentist)	0.914	0.922	0.907	0.872	0.921	0.909	0.909	0.879
MSE	binomial Bayesian	0.0001	0.0001	0.0002	0.0002	0.0001	0.0002	0.0003	0.0002
	normal Bayesian	0.0002	0.0003	0.0008	0.0006	0.0003	0.0005	0.001	0.0009
	one-stage (frequentist)	0.0002	0.0003	0.0008	0.0005	0.0003	0.0004	0.001	0.0008
Power	binomial Bayesian	-	-	0.544	1	-	-	0.424	1
	normal Bayesian	-	-	0.544	0.998	-	-	0.487	0.999
	one-stage (frequentist)	-	-	0.402	1	-	-	0.312	0.995
Se2mean	binomial Bayesian	0.0001	0.0001	0.0002	0.0001	0.0001	0.0002	0.0003	0.0002
	normal Bayesian	0.0001	0.0001	0.0003	0.0002	0.0002	0.0002	0.0004	0.0003
	one-stage (frequentist)	0.0002	0.0002	0.0006	0.0004	0.0003	0.0004	0.0008	0.0005
MCse (bias)	binomial Bayesian	0.0003	0.0003	0.0005	0.0004	0.0004	0.0004	0.0006	0.0004
	normal Bayesian	0.0005	0.0006	0.0009	0.0007	0.0006	0.0007	0.001	0.0009
	one-stage (frequentist)	0.0005	0.0005	0.0009	0.0007	0.0006	0.0007	0.001	0.0009
$\sqrt{\hat{R}}$	binomial Bayesian	1.0094	1.0104	1.0096	1.0086	1.0043	1.0055	1.0074	1.0048
	normal Bayesian	1.0026	1.0031	1.003	1.0021	1.0021	1.0025	1.0027	1.0018

Appendix Table 9 Assuming risk ratio (RR) as a measure of the treatment effect, 8 scenarios are simulated for a spline dose-response association with random effects coefficients. We assume 40 trials reporting aggregated-level data with three dose-levels each. The results for the common heterogeneity τ.
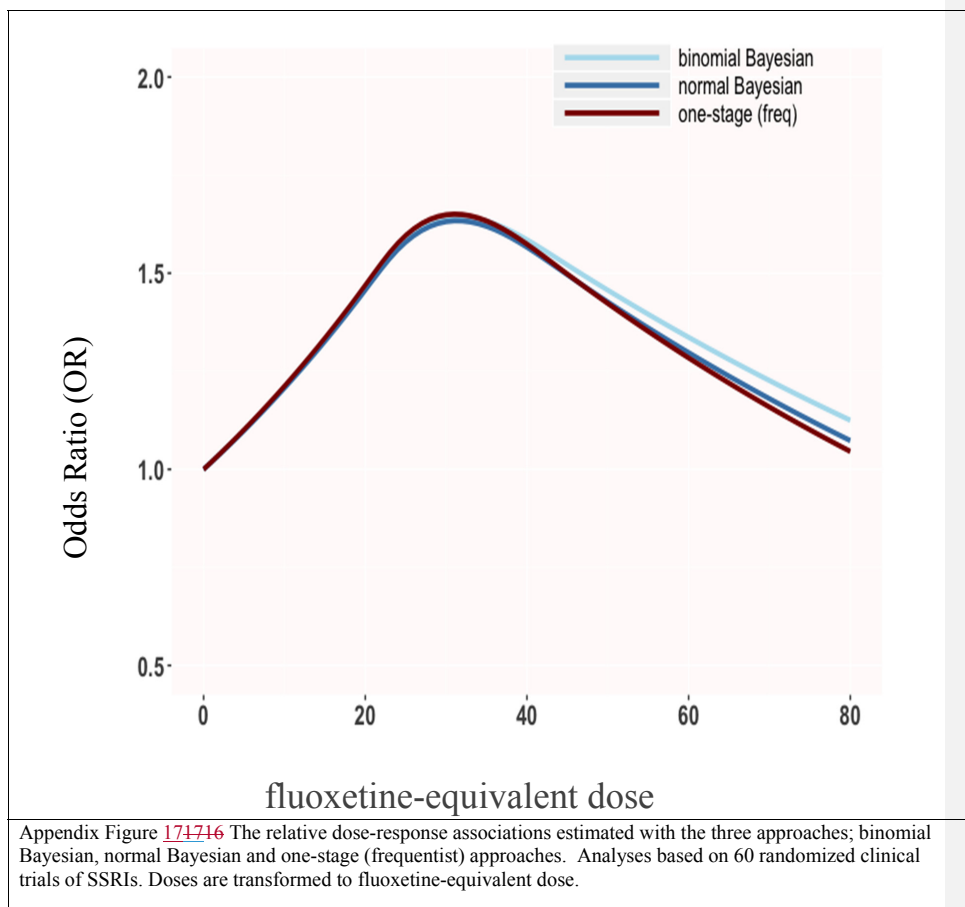
True τ		0.001	0.001	0.001	0.001	0.01	0.01	0.01	0.01
True B_2		0	0	0.03	-0.2	0	0	0.03	-0.2
True B_1		0	0.04	0.1	0.2	0	0.04	0.1	0.2
Bias	binomial Bayesian	0.0032	0.004	0.0063	0.0051	-0.0002	-0.0001	0.0015	0.0003
	normal Bayesian	0.0086	0.0096	0.0158	0.0154	0.0041	0.0049	0.0106	0.0107
Coverage	binomial Bayesian	0.969	0.966	0.963	0.919	0.967	0.967	0.991	0.974
	normal Bayesian	0.369	0.468	0.372	0.212	0.836	0.801	0.683	0.544
MSE	binomial Bayesian	0	0	0	0.0001	0	0	0	0
	normal Bayesian	0.0001	0.0001	0.0003	0.0003	0	0.0001	0.0002	0.0002
Power	binomial Bayesian	0.08	0.078	0.071	0.129	0.616	0.44	0.267	0.47
	normal Bayesian	0.716	0.622	0.687	0.828	0.834	0.752	0.707	0.889
Se2mean	binomial Bayesian	0	0	0	0	0	0	0	0
	normal Bayesian	0	0	0	0	0	0	0.0001	0
MCse (bias)	binomial Bayesian	0	0.0001	0.0001	0.0002	0.0001	0.0001	0.0001	0.0001
	normal Bayesian	0.0001	0.0001	0.0002	0.0002	0.0002	0.0002	0.0003	0.0002
$\sqrt{\hat{R}}$	binomial Bayesian	1.0202	1.0205	1.0178	1.019	1.0204	1.0202	1.0211	1.0221
	normal Bayesian	1.0163	1.0171	1.0164	1.014	1.0141	1.0154	1.016	1.0102

3. Further results for dose-response meta-analysis analysis of antidepressants.

Appendix Table 10 Results of the three approaches regarding the estimation of linear and spline coefficients B_1 and B_2, respectively, in addition to their common heterogeneity τ. These results are based on simulated antidepressant dataset from restricted cubic spline dose-response meta-analysis model, the coefficients are set as the frequentist estimation that are displayed in Table 3.

	True	binomial Bayesian		normal Bayesian		One-stage (frequentist)	
		Mean	SD	Mean	SD	Mean	SE
B_1	0.0209	0.0212	0.0022	0.0215	0.0022	0.0214	0.0023
B_2	-0.0376	-0.0375	0.0051	-0.0376	0.0050	-0.0374	0.0052
τ	0.0071	0.0073	0.0014	0.0070	0.0014	-	-

Appendix Figure 16 The estimated dose-response curves of the 60 randomized clinical trials that studied the effectiveness of antidepressant drugs.

Appendix Figure 17~~1716~~ The relative dose-response associations estimated with the three approaches; binomial Bayesian, normal Bayesian and one-stage (frequentist) approaches. Analyses based on 60 randomized clinical trials of SSRIs. Doses are transformed to fluoxetine-equivalent dose.

# 4.   CODA for dose-response meta-analysis of antidepressants

In R, *coda* package is used to perform MCMC convergence diagnosis and produce the proceeding results.

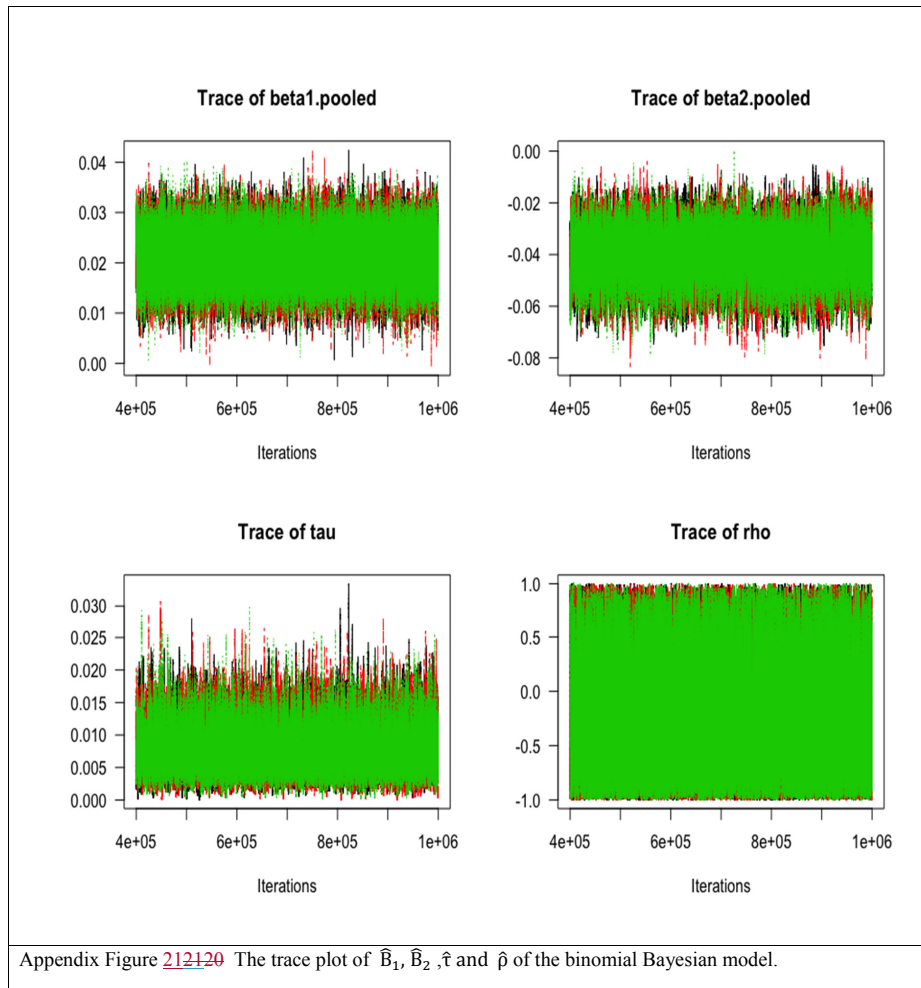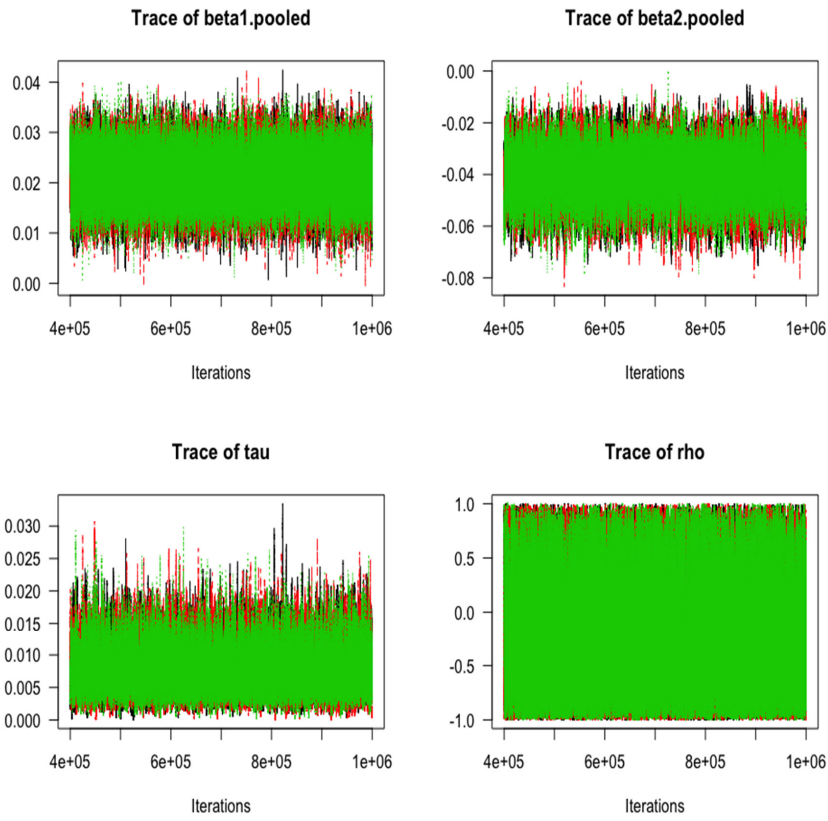**Histogram:** it presents the density of the estimated parameters.

Appendix Figure 181817 The distribution of $\widehat{B}_1$, $\widehat{B}_2$, $\hat{\tau}$ and $\hat{\rho}$ of the binomial Bayesian model.
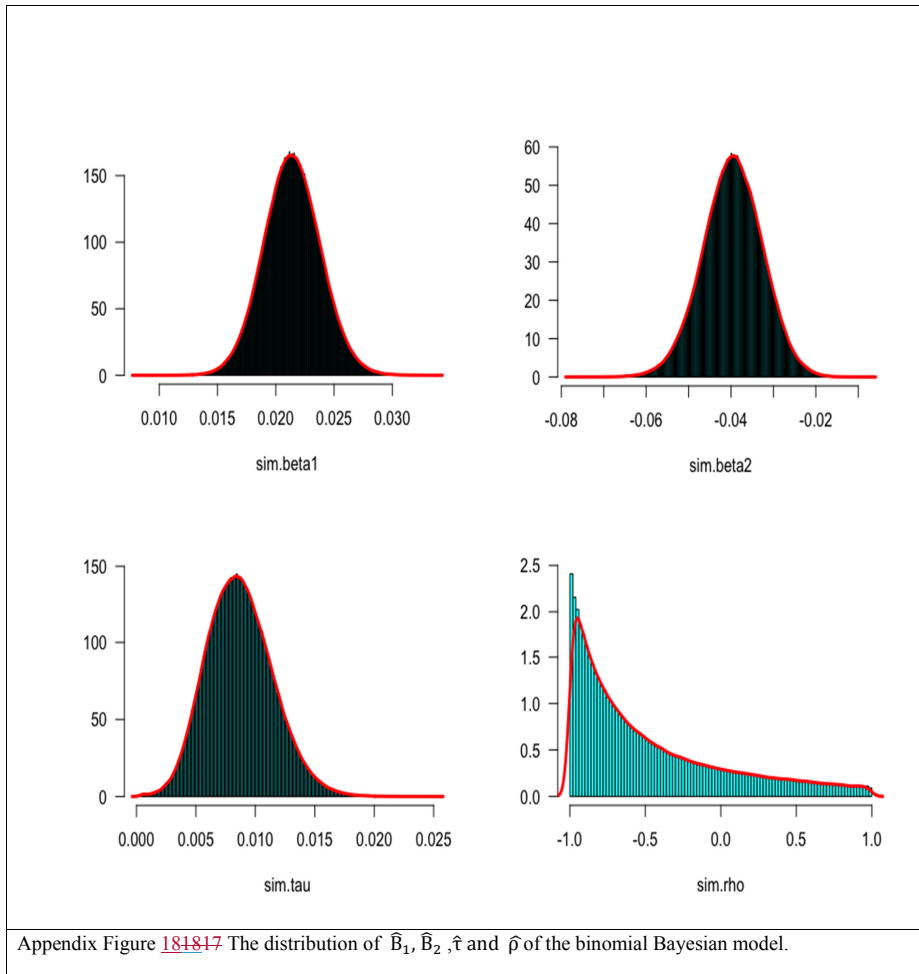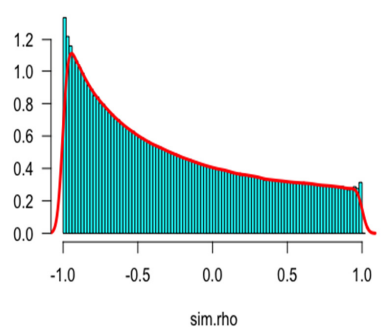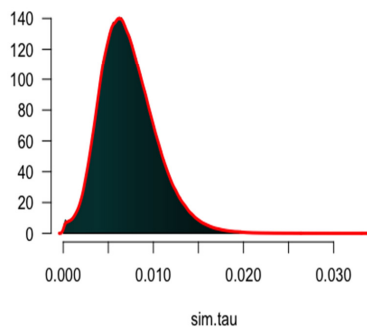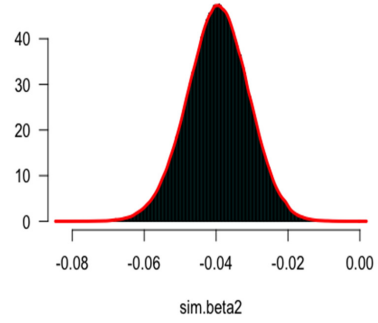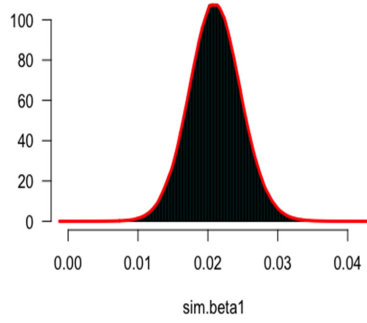
Appendix Figure 191918 The distribution of $\hat{B}_1$, $\hat{B}_2$, $\hat{\tau}$ and $\hat{\rho}$ of the normal Bayesian model.
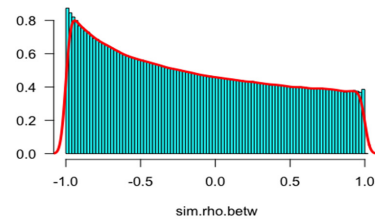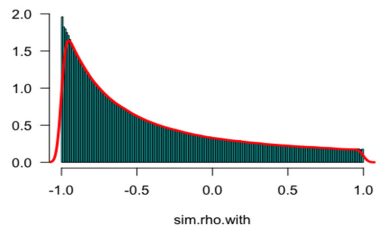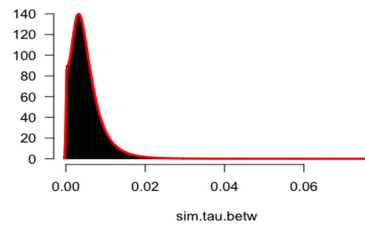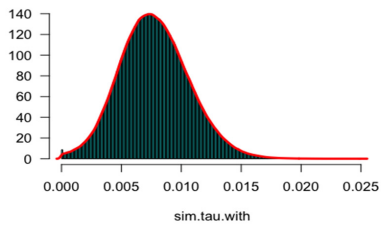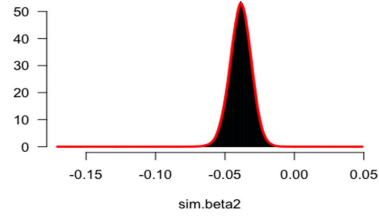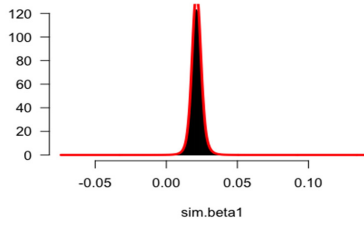
Appendix Figure 202019 The distribution of $\hat{B}_1$, $\hat{B}_2$, $\hat{\tau}_{within}$, $\hat{\tau}_{between}$, $\hat{\rho}_{within}$ and $\hat{\rho}_{between}$ of the binomial Bayesian model with drug-specific class.

Trace plots: this plot is used to diagnose the convergence and mixing of MCMC. We notice that, as iterations increase, the estimations depart from the starting value. Additionally, the different chains are well mixed (overlapped). For SSRIs, the MCMC satisfy convergence and chains are well mixed.
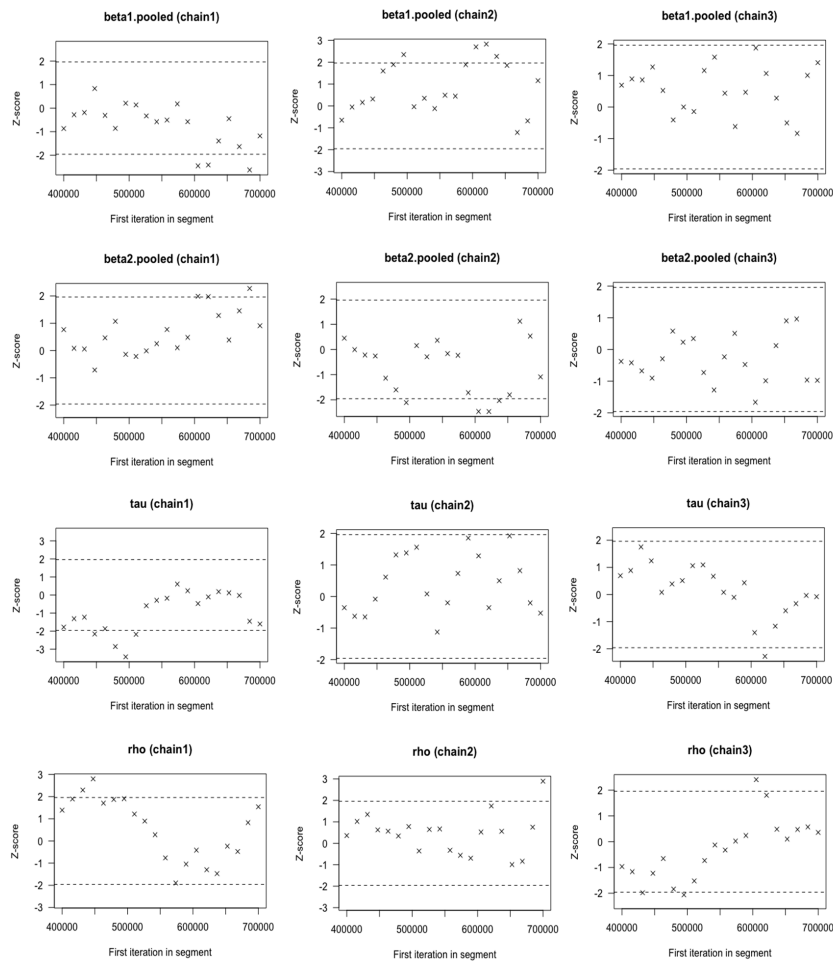

Appendix Figure 212120 The trace plot of $\hat{B}_1$, $\hat{B}_2$,$\hat{\tau}$ and $\hat{\rho}$ of the binomial Bayesian model.

Appendix Figure 232321 The trace plot of $\hat{\beta}_1$, $\hat{\beta}_2$, $\hat{\tau}$, and $\hat{\rho}_{within}$, $\hat{\rho}_{between}$ $\hat{\rho}_{within}$ and $\hat{\rho}_{between}$ of the normal Bayesian model of the binomial Bayesian model with drug-specific class.

Geweke plot: it is used to examine the stationary property of every chain. To do that, it is started by divide the chain into two parts; first and last part, then compare the means in both parts. In the plot, in the x-axis, the number of iterations in the first part is varied. In y-axis, the Z-score is displayed as the standard normal score which quantify the difference in means in the two parts. The chain is stationary if the difference in means is 'statistically' equal zero. In other words, in 5% level of significance, if the points lay within -1.96 and 1.96 (the dashed lines) then there is no evidence that means are different. In SSRIs analysis, we notice that most of dots lay within the dash lines, this means that, overall, no evidence of differences in means and thus the chains are stationary.
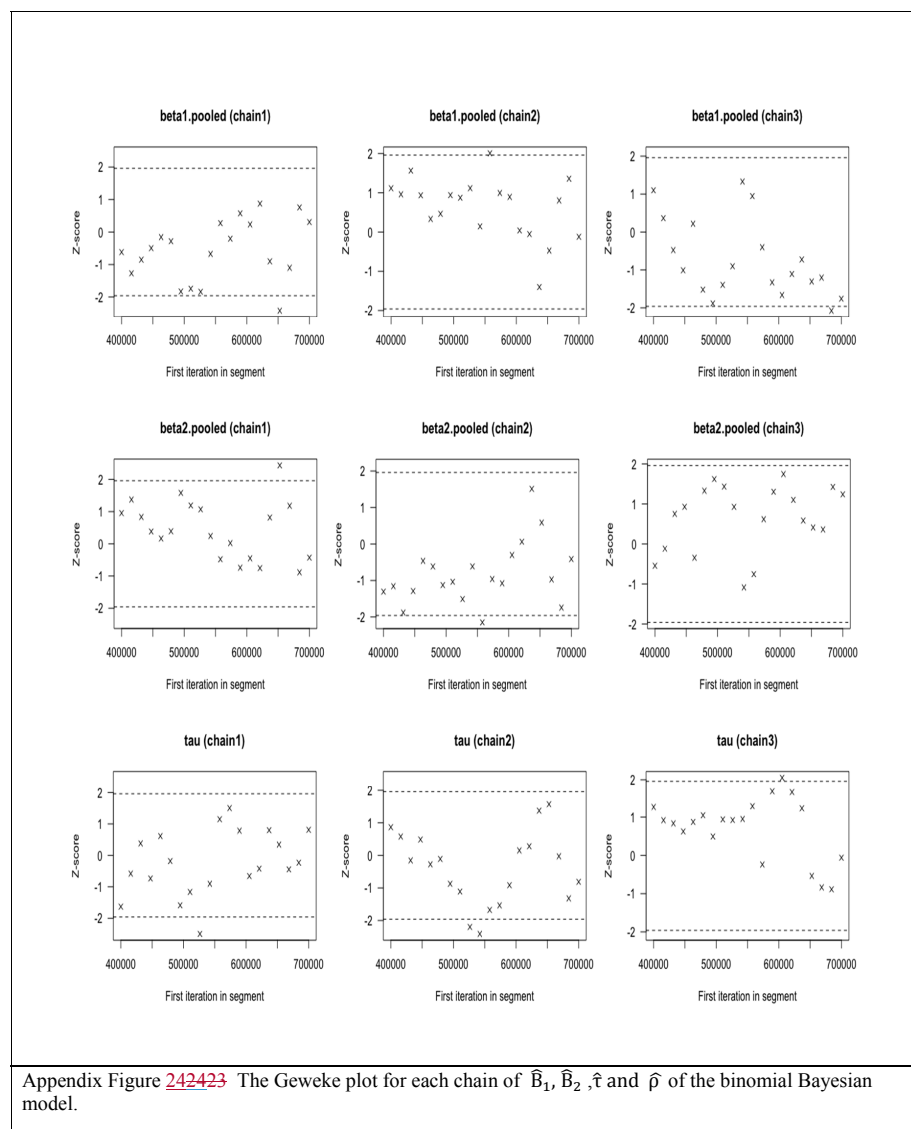
Appendix Figure ~~2424~~23 The Geweke plot for each chain of $\widehat{B}_1$, $\widehat{B}_2$,$\widehat{\tau}$ and $\widehat{\rho}$ of the binomial Bayesian model.

Appendix Figure 252524 The Geweke plot for each chain of $\widehat{B}_1$, $\widehat{B}_2$, $\widehat{\tau}$ and $\widehat{\rho}$ of the normal Bayesian model.
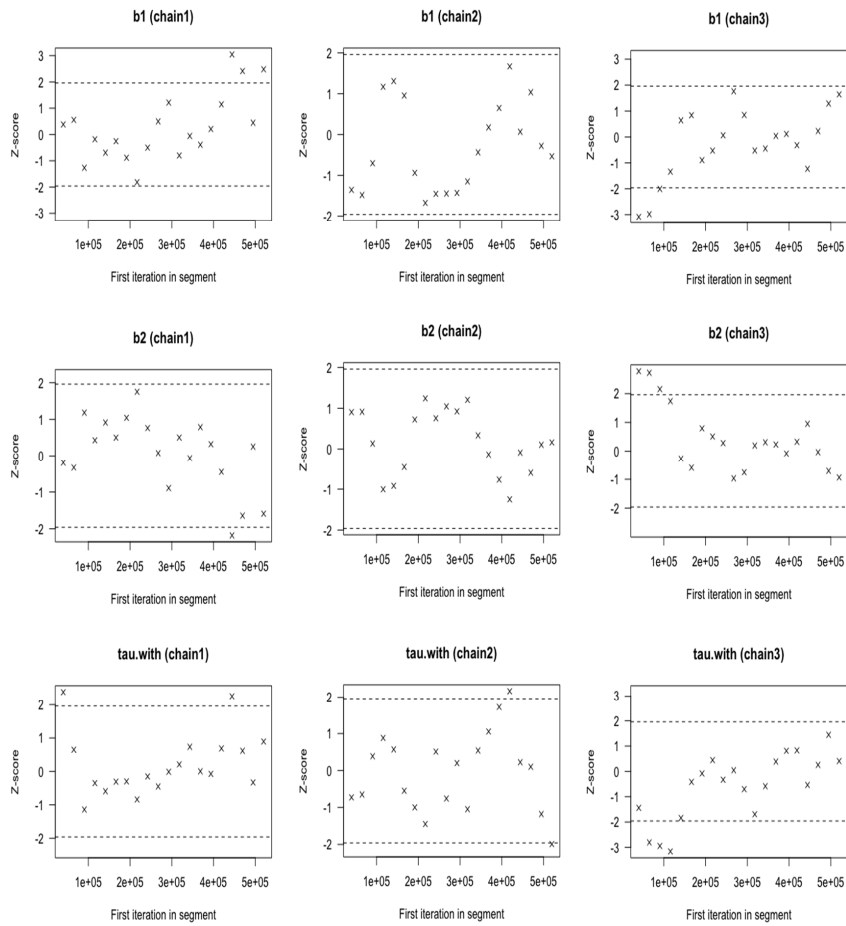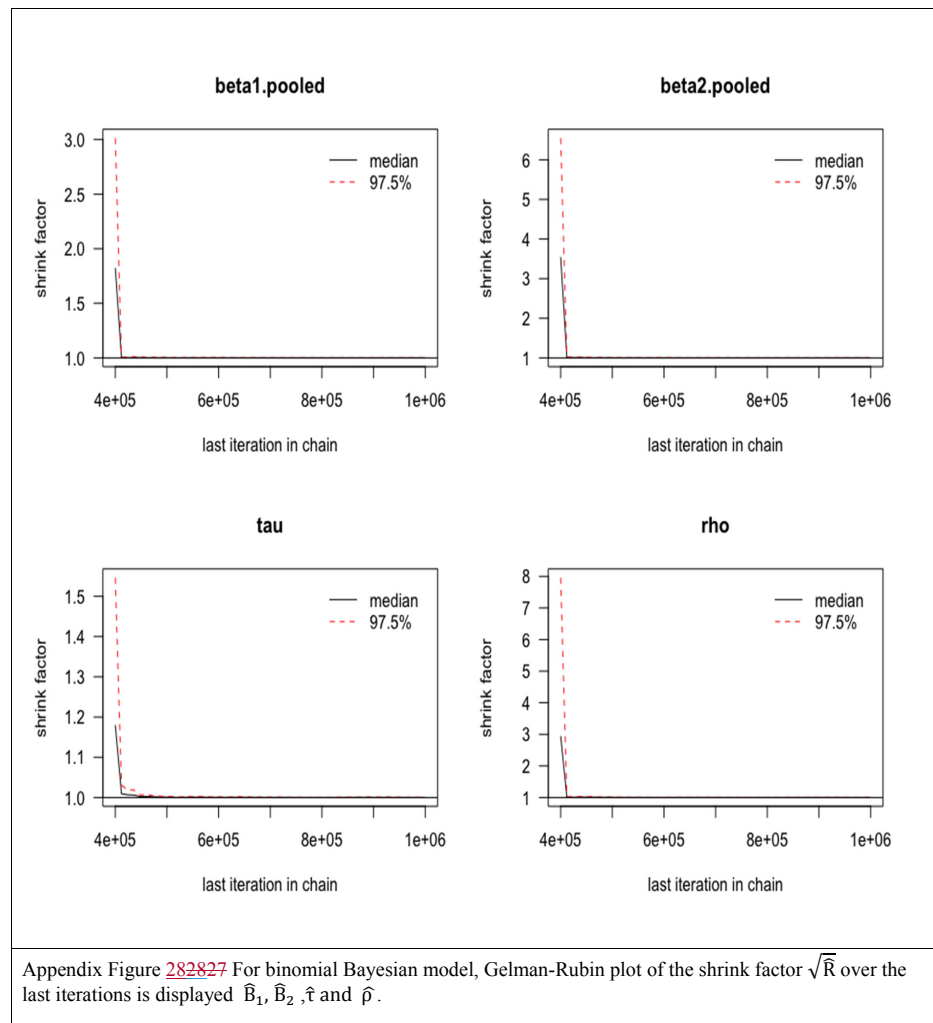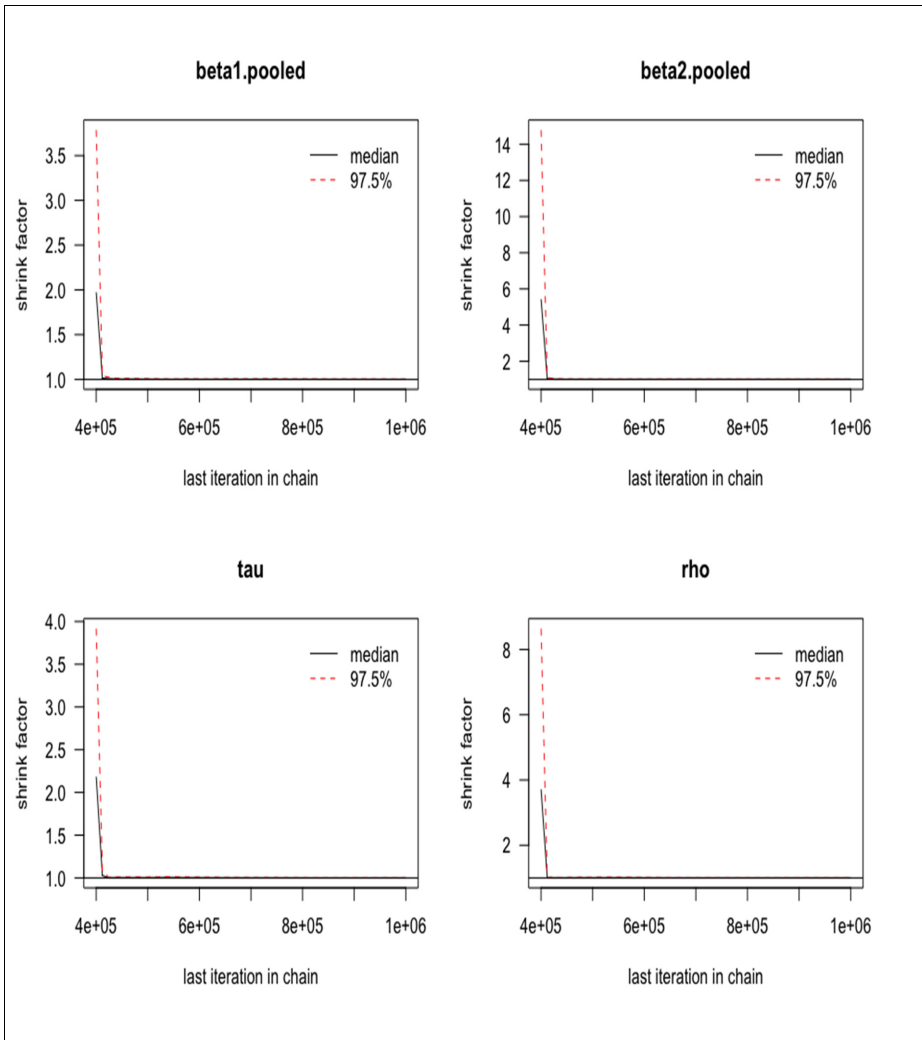
Appendix Figure 262625 The Geweke plot for each chain of $\widehat{B}_1$, $\widehat{B}_2$ and $\widehat{\tau}_{within}$ of the binomial Bayesian model with drug-specific class.
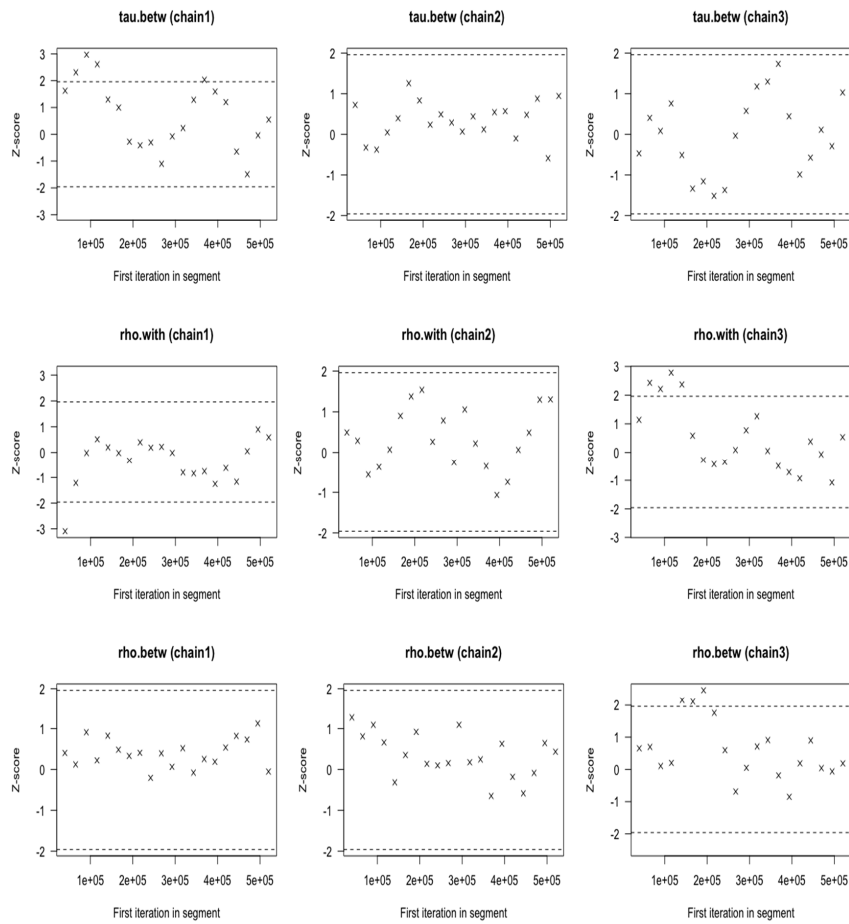
Appendix Figure 272726 The Geweke plot for each chain $\hat{\tau}_{between}$, $\hat{\rho}_{within}$ and $\hat{\rho}_{between}$ of the binomial Bayesian model with drug-specific class.

Gelman-Rubin plot: The shrink factor($\sqrt{\bar{R}}$) is the ratio between the within- and between-chains variances. In y-axis, the 50% and 97.5% quantiles of the shrink factor empirical distribution is presented. In x-axis, the number of iterations that are used in the estimation in the last part of the chain is set. The convergence of MCMC is satisfied when $\sqrt{\bar{R}}$ approaches 1 as number of iterations increase. In our SSRIs analysis, overall, the shrink factor converges to 1, thus the convergence is satisfied.

Appendix Figure ~~2828~~27 For binomial Bayesian model, Gelman-Rubin plot of the shrink factor $\sqrt{R}$ over the last iterations is displayed $\hat{B}_1$, $\hat{B}_2$,$\hat{\tau}$ and $\hat{\rho}$.

Appendix Figure ~~29~~~~29~~28 For normal Bayesian model, Gelman-Rubin plot of the shrink factor $\sqrt{\hat{R}}$ over the last iterations is displayed $\hat{B}_1$, $\hat{B}_2$, $\hat{\tau}$ and $\hat{\rho}$.
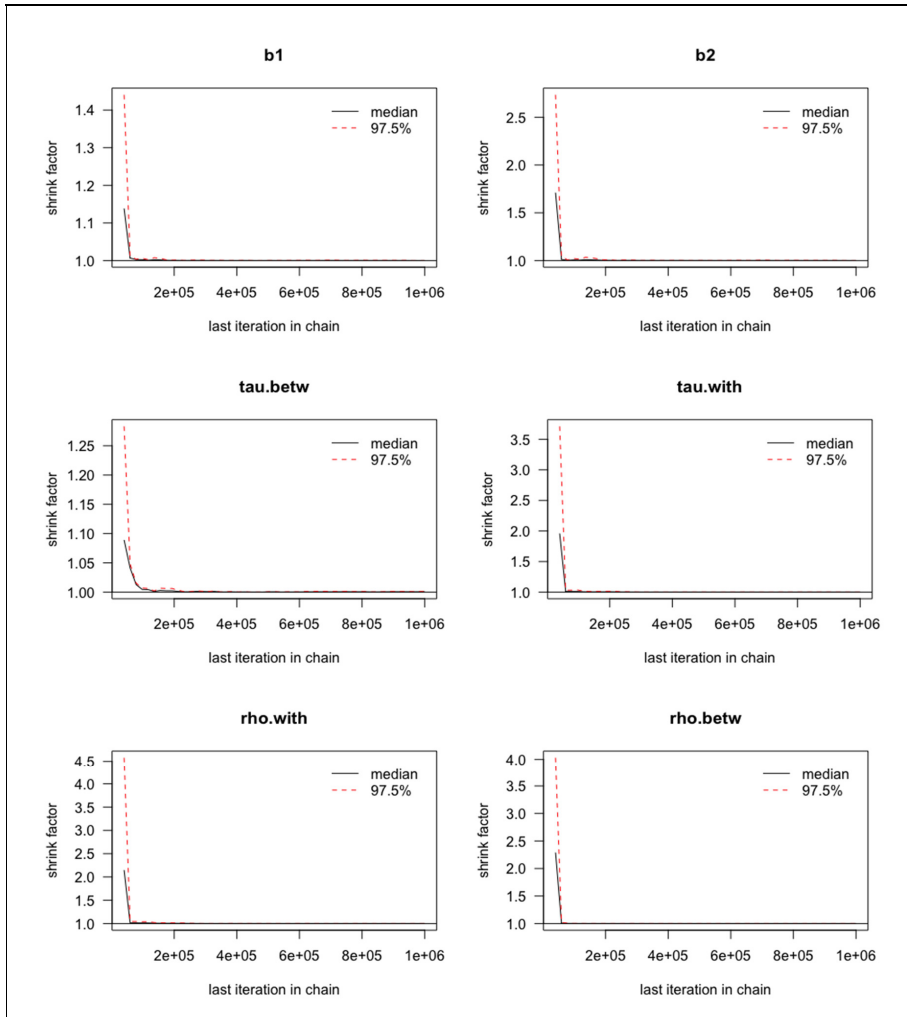
Appendix Figure 303029 For binomial Bayesian model with drug-specific class, Gelman-Rubin plot of the shrink factor $\sqrt{\hat{R}}$ over the iterations is displayed for $\hat{B}_1$, $\hat{B}_2$, $\hat{\tau}_{within}$, $\hat{\tau}_{between}$, $\hat{\rho}_{within}$ and $\hat{\rho}_{between}$.

Raftery and Lewis: the approach is used to estimate the least number of iterations and number of burn-in that are required to estimate the corresponding parameter within specific precision, say %95. Additionally, the dependence factor I is computed which measures how many times the number of iterations need to be increased to achieve the convergence. Larger values of I reflects large within chain correlations. For SSRIs analysis, to meet the least estimated numbers, we have run 1'000'000 iterations with 400'000 burn-in.

Appendix Table 11 For binomial Bayesian model, the estimated number of burn-in, number of iterations and I factor on each chain is presented

	Chain 1			Chain 2			Chain 3		
	n. burn-in	n. iter	I factor	n. burn-in	n. iter	I factor	n. burn-in	n. iter	I factor
B_1	66	98758	26.4	69	101085	27	75	101875	27.2
B_2	195	219297	58.5	170	193324	51.6	190	220894	59
τ	276	320666	85.6	328	371214	99.1	280	312240	83.4
ρ	315	354555	94.6	441	535248	143	315	347625	92.8

Appendix Table 12 For normal Bayesian model, the estimated number of burn-in, number of iterations and I factor on each chain is presented.

	Chain 1			Chain 2			Chain 3		
	n. burn-in	n. iter	I factor	n. burn-in	n. iter	I factor	n. burn-in	n. iter	I factor
B_1	148	175602	46.9	204	248268	66.3	132	154440	41.2
B_2	228	264024	70.5	320	347968	92.2	282	329893	88.1
τ	576	640064	171	704	797544	213	490	515529	138
ρ	392	463981	124	399	442776	118	376	389019	104

Appendix Table 13 For binomial Bayesian model with drug-specific class, the estimated number of burn-in, number of iterations and I factor on each chain is presented.

	Chain 1			Chain 2			Chain 3		
	n. burn-in	n. iter	I factor	n. burn-in	n. iter	I factor	n. burn-in	n. iter	I factor
B_1	63	86814	23.2	69	93840	25.1	90	124020	33.1
B_2	284	360609	96.3	290	348638	93.1	255	286671	76.5
τ_{within}	952	1003289	268	945	1084125	289	558	583358	156
$\tau_{between}$	258	283370	75.5	255	326706	87.2	228	242592	64.8
ρ_{within}	441	468090	125	364	421564	113	406	479428	128
$\rho_{between}$	81	117909	31.5	64	75136	20.1	51	79203	21.1

Heidelberger and Welch: this approach employ two tests, first, it tests the stationarity of MCMC, i.e H_0: stationarity *holds*, based on Cramer-von-Mises statistic. The iterations are discarded gradually from the estimation and each time the test is performed until the null hypothesis is rejected and the chain passes the test. Second, the resulted stationarity chain, then, passed to the halfwidth test. If the statistic of the halfwidth test is less than a specific limit, say 0.1, this means that the succeeded sample provide a posterior mean estimate with sufficient precision. For SSRIs analysis, the stationarity and the halfwidth test have been passed by all chains of the parameters. The estimated posterior means are very close to our presented estimate in Table 3.

Appendix Table 14 For binomial Bayesian model, the p-value of the stationarity test and halfwidth test and the estimated posterior mean of the stationary part of chain is displayed.

	Chain 1			Chain 2			Chain 3		
	stationarity test (p-value)	halfwidth test (p-value)	mean	stationarity test (p-value)	halfwidth test (p-value)	mean	stationarity test (p-value)	halfwidth test (p-value)	mean
B_1	0.435	4.89e-05	0.0214	0.277	4.75e-05	0.0214	0.354	4.81e-05	0.0215
B_2	0.477	0.000219	-0.0396	0.14	0.000208	-0.0395	0.621	0.000212	-0.0398
τ	0.198	7.15e-05	0.00869	0.526	7.46e-05	0.0087	0.123	7.43e-05	0.00866
ρ	0.542	0.0176	-0.458	0.486	0.018	-0.469	0.4	0.019	-0.444

Appendix Table 15 For normal Bayesian model, the p-value of the stationarity test and halfwidth test and the estimated posterior mean of the stationary part of chain is displayed.

	Chain 1			Chain 2			Chain 3		
	stationarity test (p-value)	halfwidth test (p-value)	mean	stationarity test (p-value)	halfwidth test (p-value)	mean	stationarity test (p-value)	halfwidth test (p-value)	mean
B_1	0.229	0.000105	0.0209	0.112	0.000108	0.021	0.541	0.000108	0.0211
B_2	0.354	0.000332	-0.0394	0.173	0.000341	-0.0395	0.829	0.000344	-0.0398
τ	0.0715	9.55e-05	0.00724	0.769	9.74e-05	0.00726	0.48	8.94e-05	0.00724
ρ	0.105	0.0199	-0.246	0.529	0.0197	-0.252	0.292	0.0202	-0.245

Appendix Table 16 For binomial Bayesian model with drug-specific class, the p-value of the stationarity test and halfwidth test and the estimated posterior mean of the stationary part of chain is displayed.

	Chain 1			Chain 2			Chain 3		
	stationarity test (p-value)	halfwidth test (p-value)	mean	stationarity test (p-value)	halfwidth test (p-value)	mean	stationarity test (p-value)	halfwidth test (p-value)	mean
B_1	0.101	5.49e-05	0.0214	0.659	5.41e-05	0.0214	0.1	5.51e-05	0.0213
B_2	0.233	0.000248	-0.0388	0.886	0.00025	-0.0388	0.108	0.000254	-0.0386
τ_{within}	0.337	7.18e-05	0.00778	0.924	7.28e-05	0.00774	0.0666	7.36e-05	0.00773
$\tau_{between}$	0.129	6.78e-05	0.00507	0.498	6.6e-05	0.00504	0.761	6.84e-05	0.0051
ρ_{within}	0.23	0.0157	-0.402	0.821	0.0154	-0.395	0.0609	0.0148	-0.387
$\rho_{between}$	0.806	0.00667	-0.129	0.342	0.00668	-0.128	0.166	0.00662	-0.132