Web appendices for "The role of covariate heterogeneity in meta-analysis of gene-environment interactions on quantitative traits" by Li *et. al.* (2014)

Appendix A: Appendix Figures and Tables

Figure 1: Comparison of the proposed meta-analytical methods (in terms of power) under different scenarios of susceptibility models and covariate heterogeneity through a simulation study. *Setting (a), under both assumptions 1 and 2*.

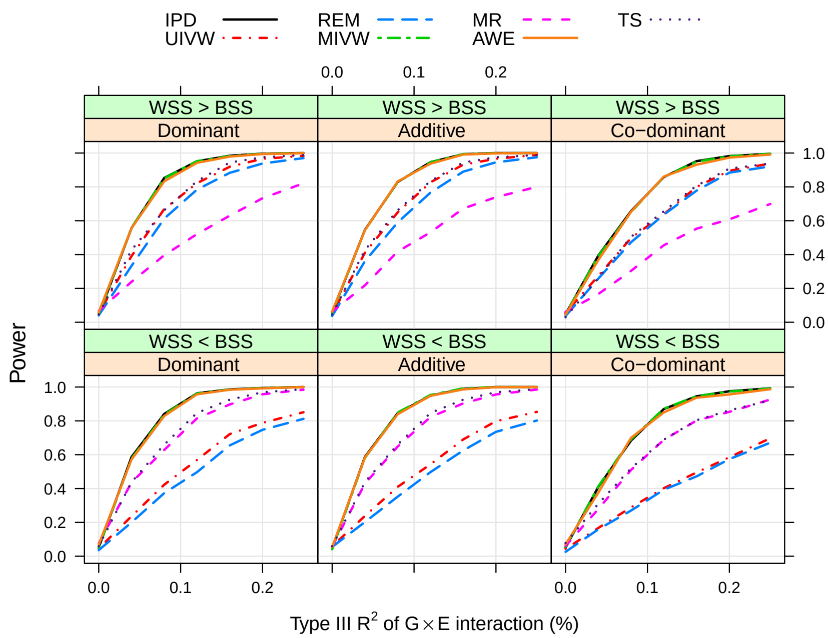

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Figure 2: Comparison of the proposed meta-analytical methods (in terms of power) under different scenarios of susceptibility models and covariate heterogeneity through a simulation study. *Setting (b), under assumption 1 but not 2.*

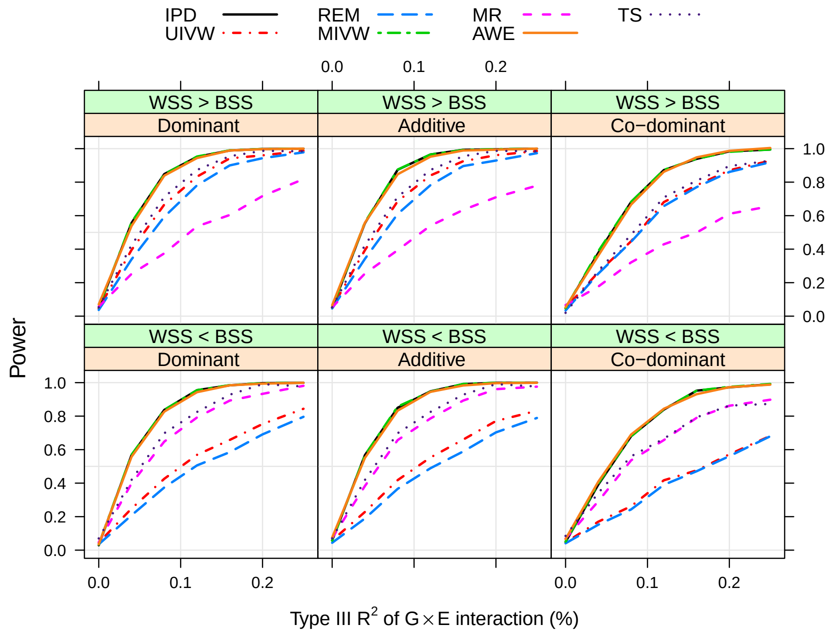

Figure 3: Comparison of the proposed meta-analytical methods (in terms of power) under different scenarios of susceptibility models and covariate heterogeneity through a simulation study. *Setting (c), under assumption 2 but not 1.*

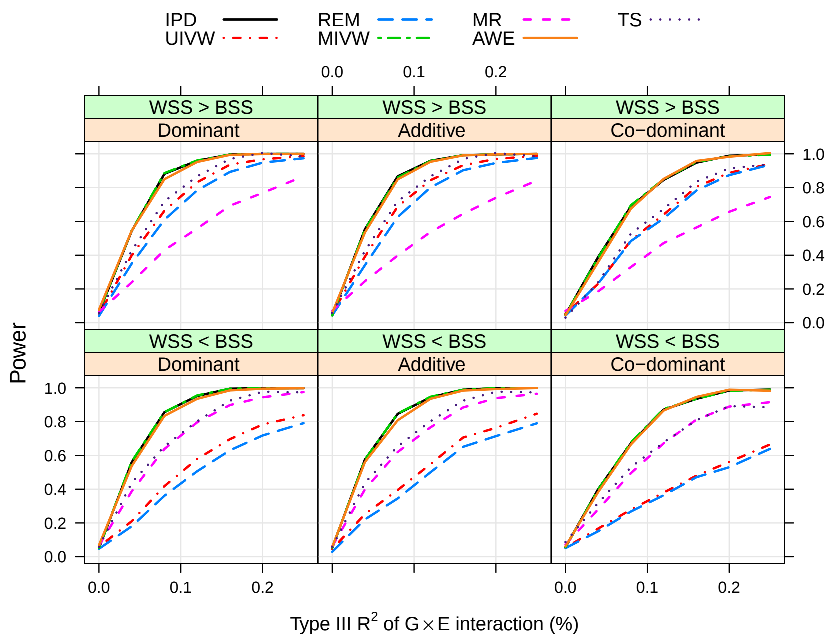

Figure 4: Comparison of the proposed meta-analytical methods (in terms of power) under different scenarios of susceptibility models and covariate heterogeneity through a simulation study, for the situation of lack of common set of covariates across studies. *Setting (a), under both assumptions 1 and 2.*

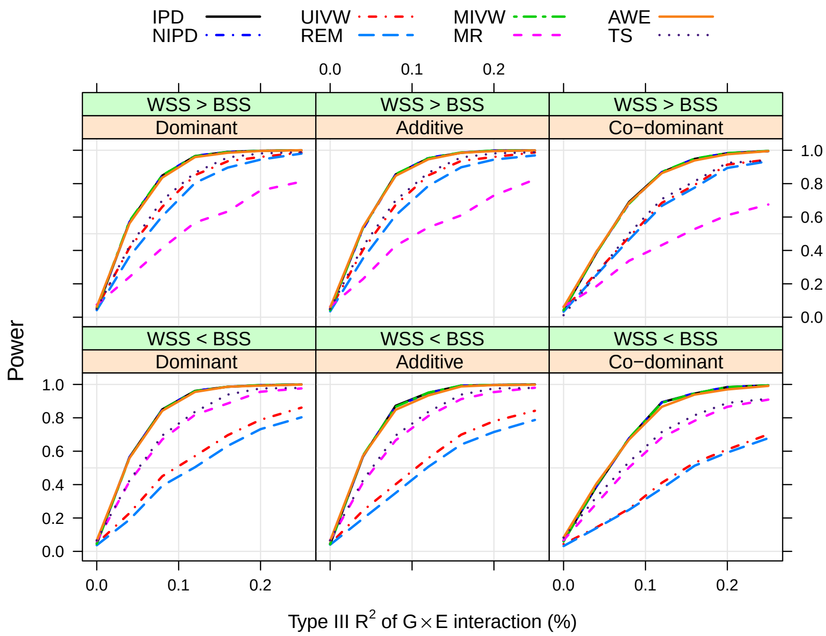

Figure 5: Comparison of the proposed meta-analytical methods (in terms of power) under different scenarios of susceptibility models and covariate heterogeneity through a simulation study, for the situation of lack of common set of covariates across studies. *Setting (b), under assumption 1 but not 2.*

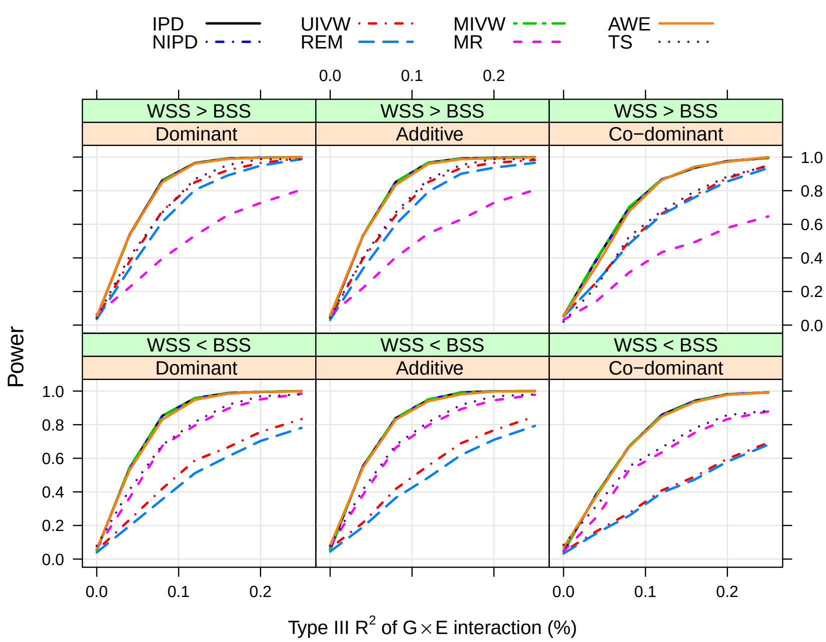

Figure 6: Comparison of the proposed meta-analytical methods (in terms of power) under different scenarios of susceptibility models and covariate heterogeneity through a simulation study, for the situation of lack of common set of covariates across studies. *Setting (c), under assumption 2 but not 1*.

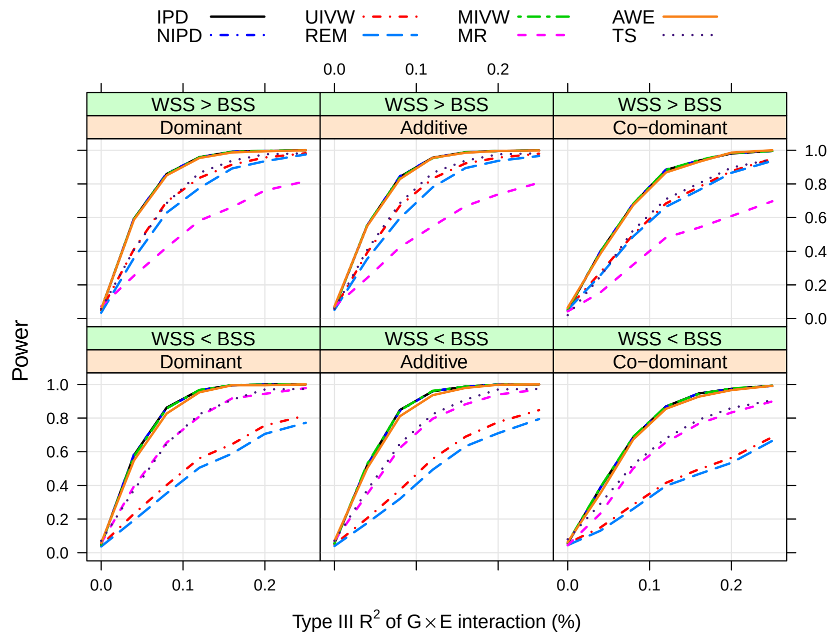

Figure 7: Power curves under misspecified susceptibility models (dominant/additive), where the generating co-dominant model has $\delta^{AA} = 1.5\delta^{Aa}$, and no assumption of gene-environment independence or homogeneity in allele frequencies is assumed.

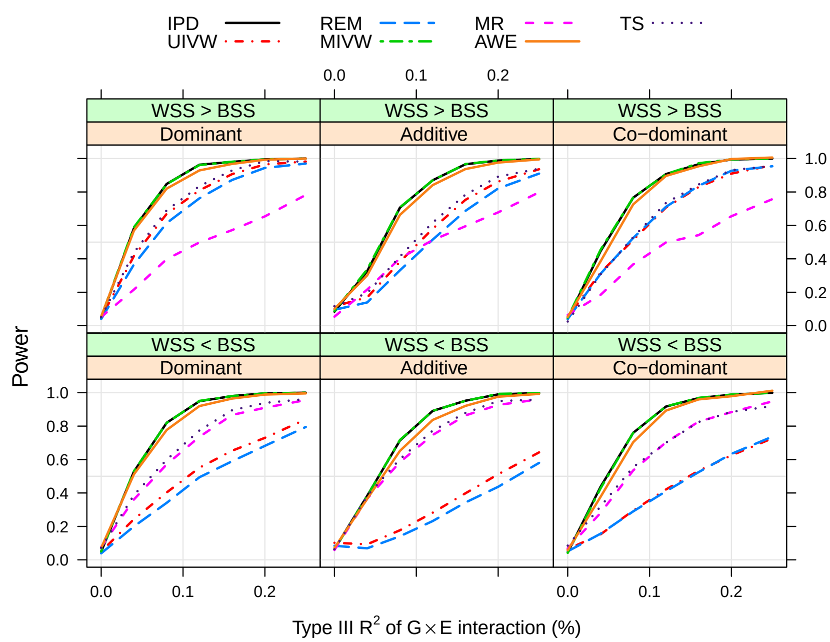

Figure 8: Marginal SNP (rs1121980) effect against mean covariate values of age and BMI across cohorts in the Type 2 Diabetes example. Solid line: Meta-regression line; Dashed line: Meta-regression line without outlier (cohort FUSION for age and cohort DPS for BMI).

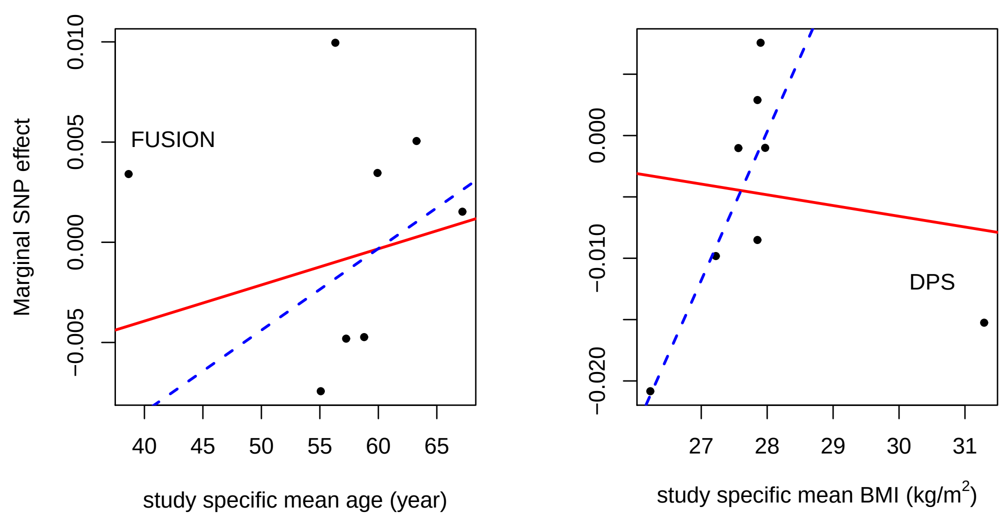

Figure 9: Absolute relative bias of $\hat{\delta}^{\mathrm{MR}}$ and $\hat{\delta}^{\mathrm{AWE}}$ as a function of the ratio BSS/TSS, when G-E correlation is strong ($\rho = 0.8$).

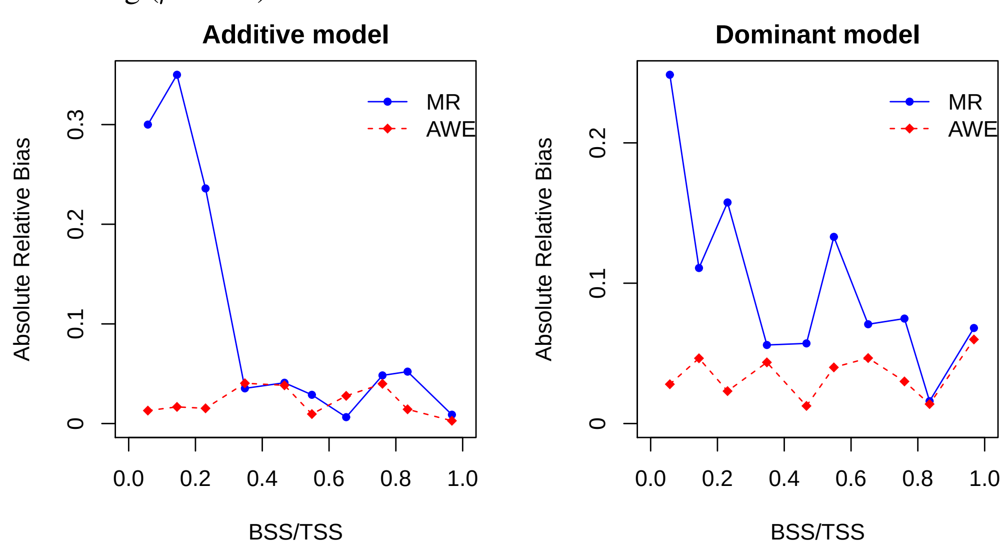

Table 1: Comparison of the proposed meta-analytical methods under different scenarios of susceptibility models and covariate heterogeneity through a simulation study. *Setting (a): under both assumptions 1 and 2*.

			wss/bss=2					bss/wss=2				
(%)	Method[a]		RB[b](%)	MV[b]	EV[b]	MSE[b]	Power	RB (%)	MV	EV	MSE	Power
R^2=0	Dominant	IPD		1.14	1.12	1.12	0.04		1.15	1.12	1.12	0.05
		UIVW		1.73	1.71	1.71	0.05		3.39	3.46	3.46	0.05
		REM		2.08	1.78	1.78	0.04		4.07	3.58	3.57	0.04
		MIVW		1.13	1.12	1.12	0.05		1.15	1.12	1.12	0.05
		MR		3.91	4.06	4.06	0.07		1.95	1.82	1.82	0.08
		AWE		1.13	1.19	1.19	0.06		1.16	1.19	1.19	0.07
	Additive	IPD		0.75	0.75	0.75	0.06		0.76	0.68	0.68	0.05
		UIVW		1.15	1.11	1.11	0.05		2.25	2.39	2.38	0.06
		REM		1.38	1.15	1.15	0.04		2.69	2.44	2.44	0.06
		MIVW		0.75	0.75	0.75	0.06		0.76	0.68	0.68	0.04
		MR		2.62	2.55	2.55	0.06		1.25	1.24	1.25	0.06
		AWE		0.75	0.79	0.79	0.06		0.76	0.72	0.72	0.05
R^2= 0.05	Dominant	IPD	0.44	1.14	1.15	1.15	0.56	-1.78	1.13	1.29	1.29	0.59
		UIVW	1.60	1.71	1.75	1.75	0.39	0.11	3.31	3.28	3.28	0.24
		REM	1.67	2.06	1.79	1.79	0.33	0.02	3.98	3.42	3.42	0.20
		MIVW	0.42	1.13	1.15	1.15	0.56	-1.78	1.13	1.29	1.29	0.58
		MR	0.27	4.05	4.20	4.20	0.24	-2.14	1.90	2.01	2.01	0.44
		AWE	0.50	1.13	1.21	1.21	0.56	-1.90	1.13	1.36	1.36	0.57
	Additive	IPD	0.64	0.75	0.76	0.76	0.55	-0.81	0.75	0.79	0.79	0.59
		UIVW	-0.85	1.14	1.14	1.14	0.41	2.12	2.19	2.35	2.35	0.24
		REM	-0.52	1.34	1.17	1.16	0.36	2.11	2.60	2.38	2.38	0.20
		MIVW	0.71	0.75	0.76	0.76	0.54	-0.66	0.75	0.80	0.80	0.58
		MR	5.59	2.64	2.89	2.90	0.22	-1.25	1.26	1.24	1.24	0.43
		AWE	1.15	0.75	0.81	0.81	0.54	-0.59	0.75	0.83	0.83	0.58
R^2= 0.15	Dominant	IPD	1.29	1.11	1.26	1.26	0.98	-0.28	1.14	1.44	1.44	0.99
		UIVW	1.22	1.69	1.78	1.78	0.92	-1.14	3.31	3.38	3.38	0.72
		REM	1.62	2.01	1.84	1.84	0.88	-1.50	4.00	3.52	3.53	0.66
		MIVW	1.33	1.10	1.26	1.26	0.98	-0.34	1.14	1.44	1.44	0.98
		MR	1.50	3.95	4.57	4.57	0.63	0.02	1.95	2.46	2.46	0.90
		AWE	1.47	1.11	1.34	1.34	0.98	-0.29	1.14	1.53	1.53	0.98
	Additive	IPD	-0.20	0.73	0.76	0.76	0.99	-0.32	0.75	0.95	0.95	0.99
		UIVW	0.33	1.12	1.10	1.10	0.93	0.09	2.20	2.46	2.46	0.69
		REM	0.58	1.33	1.14	1.14	0.89	0.27	2.68	2.58	2.58	0.62
		MIVW	-0.18	0.73	0.76	0.76	0.99	-0.30	0.75	0.96	0.96	0.99
		MR	-2.43	2.59	2.61	2.61	0.67	0.06	1.30	1.45	1.45	0.90
		AWE	-0.39	0.74	0.81	0.81	0.99	-0.36	0.76	1.02	1.02	0.99
R^2= 0.25	Dominant	IPD	0.44	1.11	1.30	1.30	1.00	0.66	1.11	1.71	1.71	1.00
		UIVW	0.36	1.68	1.97	1.97	0.98	0.12	3.28	3.79	3.79	0.85
		REM	0.30	1.97	2.00	2.00	0.97	-0.00	3.93	4.02	4.02	0.81
		MIVW	0.47	1.11	1.30	1.30	1.00	0.70	1.11	1.72	1.72	1.00
		MR	0.20	4.02	4.31	4.31	0.82	0.75	1.90	2.48	2.48	0.98
		AWE	0.50	1.12	1.37	1.37	1.00	0.73	1.12	1.79	1.79	1.00
	Additive	IPD	0.13	0.74	0.87	0.86	1.00	-0.30	0.74	1.02	1.02	1.00
		UIVW	-0.34	1.12	1.22	1.22	0.99	-0.31	2.18	2.49	2.48	0.85
		REM	-0.40	1.31	1.26	1.26	0.97	-0.42	2.67	2.60	2.60	0.80
		MIVW	0.12	0.73	0.87	0.87	1.00	-0.27	0.74	1.03	1.02	1.00
		MR	0.48	2.73	2.79	2.79	0.80	0.02	1.25	1.59	1.58	0.98
		AWE	-0.01	0.75	0.89	0.89	1.00	-0.03	0.74	1.07	1.07	1.00

[a] IPD: individual patient data analysis; UIVW: univariate inverse-variance weighted estimator; REM: random effect model; MIVW: multivariate inverse-variance weighted estimator; MR: Meta-regression; AWE: adaptively weighted estimator.

[b] RB: relative bias; MV: mean of model based variance; EV: empirical variance; MSE: mean squared error. (MV, EV and MSE have been multiplied by 100.)

Table 2: Comparison of the proposed meta-analytical methods under different scenarios of susceptibility models and covariate heterogeneity through a simulation study. *Setting (b): under assumption 1 but not 2*.

			wss/bss=2					bss/wss=2				
(%)	Method[a]		RB[b](%)	MV[b]	EV[b]	MSE[b]	Power	RB (%)	MV	EV	MSE	Power
R^2= 0	Dominant	IPD		1.16	1.21	1.21	0.05		1.18	1.04	1.04	0.03
		UIVW		1.79	1.89	1.88	0.04		3.49	3.35	3.36	0.04
		REM		2.09	1.92	1.92	0.04		4.15	3.42	3.43	0.04
		MIVW		1.16	1.21	1.21	0.05		1.17	1.04	1.04	0.03
		MR		4.18	4.20	4.20	0.06		1.96	1.78	1.78	0.05
		AWE		1.19	1.28	1.28	0.07		1.18	1.08	1.08	0.04
	Additive	IPD		0.75	0.75	0.75	0.05		0.77	0.81	0.81	0.06
		UIVW		1.17	1.18	1.18	0.05		2.28	2.50	2.50	0.06
		REM		1.37	1.19	1.19	0.05		2.75	2.56	2.56	0.04
		MIVW		0.75	0.75	0.75	0.05		0.77	0.81	0.81	0.06
		MR		2.70	2.54	2.54	0.05		1.32	1.31	1.31	0.07
		AWE		0.77	0.81	0.81	0.06		0.78	0.86	0.86	0.07
R^2= 0.05	Dominant	IPD	-0.13	1.15	1.15	1.15	0.56	-1.93	1.16	1.23	1.23	0.57
		UIVW	0.88	1.78	1.86	1.86	0.40	-2.00	3.45	3.65	3.65	0.25
		REM	0.89	2.13	1.91	1.91	0.34	-1.88	4.15	3.74	3.74	0.21
		MIVW	-0.13	1.15	1.16	1.16	0.56	-1.95	1.16	1.23	1.23	0.57
		MR	-0.80	4.11	4.00	4.00	0.25	-2.55	2.00	2.02	2.02	0.40
		AWE	0.45	1.17	1.26	1.26	0.54	-2.03	1.19	1.30	1.30	0.56
	Additive	IPD	-0.78	0.75	0.79	0.79	0.56	-1.15	0.76	0.83	0.83	0.57
		UIVW	0.05	1.16	1.22	1.21	0.39	-0.10	2.27	2.40	2.39	0.23
		REM	0.06	1.39	1.28	1.28	0.34	1.20	2.72	2.51	2.51	0.19
		MIVW	-0.84	0.75	0.80	0.80	0.56	-1.24	0.76	0.83	0.83	0.57
		MR	-3.05	2.72	2.79	2.79	0.25	-1.25	1.29	1.34	1.34	0.38
		AWE	-0.98	0.77	0.86	0.86	0.56	-0.81	0.77	0.87	0.87	0.55
R^2= 0.15	Dominant	IPD	-0.00	1.14	1.16	1.16	0.99	0.82	1.15	1.51	1.51	0.98
		UIVW	-1.33	1.75	1.67	1.68	0.94	0.28	3.42	3.73	3.73	0.66
		REM	-1.15	2.10	1.73	1.73	0.90	0.41	4.09	3.81	3.81	0.58
		MIVW	-0.02	1.13	1.17	1.17	0.99	0.80	1.15	1.52	1.52	0.98
		MR	2.56	4.23	3.95	3.96	0.60	0.99	2.02	2.25	2.25	0.89
		AWE	-0.13	1.17	1.24	1.24	0.99	0.90	1.17	1.56	1.56	0.98
	Additive	IPD	-0.65	0.74	0.82	0.82	0.99	0.57	0.75	0.97	0.96	0.99
		UIVW	-0.81	1.15	1.23	1.23	0.92	1.35	2.24	2.34	2.34	0.66
		REM	-0.90	1.37	1.26	1.26	0.90	1.30	2.71	2.44	2.44	0.59
		MIVW	-0.73	0.74	0.82	0.82	0.99	0.57	0.75	0.97	0.97	0.99
		MR	-0.29	2.76	2.58	2.58	0.63	-0.05	1.32	1.51	1.51	0.89
		AWE	-0.63	0.77	0.87	0.87	0.99	0.36	0.77	1.01	1.01	0.98
R^2= 0.25	Dominant	IPD	-0.38	1.13	1.18	1.18	1.00	-0.32	1.13	1.75	1.75	1.00
		UIVW	-0.95	1.74	1.85	1.85	0.99	-0.33	3.38	4.08	4.07	0.84
		REM	-1.08	2.06	1.91	1.91	0.98	-0.48	4.07	4.17	4.16	0.80
		MIVW	-0.35	1.12	1.19	1.19	1.00	-0.39	1.13	1.76	1.76	1.00
		MR	-0.58	4.08	4.39	4.39	0.82	-0.92	1.97	2.57	2.57	0.98
		AWE	-0.59	1.15	1.28	1.28	1.00	-0.43	1.17	1.86	1.86	1.00
	Additive	IPD	0.77	0.74	0.84	0.84	1.00	1.17	0.74	1.15	1.15	1.00
		UIVW	0.07	1.15	1.24	1.24	0.99	1.71	2.22	2.69	2.70	0.83
		REM	0.16	1.37	1.26	1.26	0.97	1.55	2.67	2.72	2.72	0.79
		MIVW	0.81	0.74	0.84	0.84	1.00	1.10	0.74	1.15	1.15	1.00
		MR	2.13	2.76	2.86	2.87	0.78	0.88	1.28	1.81	1.81	0.98
		AWE	0.74	0.77	0.90	0.90	1.00	1.34	0.76	1.20	1.21	1.00

[a] IPD: individual patient data analysis; UIVW: univariate inverse-variance weighted estimator; REM: random effect model; MIVW: multivariate inverse-variance weighted estimator; MR: Meta-regression; AWE: adaptively weighted estimator.

[b] RB: relative bias; MV: mean of model based variance; EV: empirical variance; MSE: mean squared error. (MV, EV and MSE have been multiplied by 100.)

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			wss/bss=2					bss/wss=2				
(%)	Method[a]		RB[b](%)	MV[b]	EV[b]	MSE[b]	Power	RB (%)	MV	EV	MSE	Power
R^2= 0	Dominant	IPD		1.21	1.30	1.30	0.06		1.19	1.24	1.24	0.05
		UIVW		1.92	1.98	1.98	0.05		3.76	3.95	3.96	0.06
		REM		2.28	2.03	2.03	0.04		4.56	4.13	4.14	0.05
		MIVW		1.21	1.30	1.30	0.06		1.19	1.24	1.24	0.05
		MR		4.01	3.82	3.82	0.06		2.05	1.97	1.97	0.07
		AWE		1.22	1.41	1.41	0.08		1.24	1.41	1.41	0.07
	Additive	IPD		0.76	0.73	0.73	0.04		0.76	0.75	0.75	0.05
		UIVW		1.18	1.17	1.17	0.06		2.30	2.24	2.24	0.05
		REM		1.40	1.20	1.20	0.04		2.78	2.26	2.25	0.03
		MIVW		0.76	0.73	0.73	0.04		0.76	0.75	0.75	0.05
		MR		2.61	2.56	2.56	0.07		1.37	1.44	1.44	0.06
		AWE		0.76	0.79	0.79	0.06		0.80	0.83	0.83	0.06
R^2= 0.05	Dominant	IPD	2.60	1.20	1.34	1.34	0.54	1.44	1.17	1.20	1.20	0.56
		UIVW	0.14	1.90	1.99	1.98	0.40	4.08	3.73	3.74	3.74	0.21
		REM	0.09	2.28	2.05	2.05	0.35	3.14	4.46	3.84	3.84	0.18
		MIVW	2.68	1.19	1.35	1.35	0.55	1.34	1.17	1.20	1.20	0.56
		MR	6.78	3.99	4.18	4.20	0.24	0.55	2.09	2.20	2.19	0.39
		AWE	2.25	1.21	1.39	1.39	0.54	1.06	1.24	1.36	1.36	0.54
	Additive	IPD	1.66	0.75	0.78	0.78	0.55	-1.80	0.76	0.86	0.86	0.58
		UIVW	2.22	1.16	1.24	1.24	0.39	-5.26	2.28	2.30	2.30	0.25
		REM	2.64	1.38	1.25	1.25	0.34	-4.94	2.73	2.38	2.39	0.22
		MIVW	1.85	0.75	0.78	0.78	0.55	-1.73	0.75	0.86	0.86	0.57
		MR	2.33	2.67	2.83	2.83	0.25	0.72	1.36	1.40	1.40	0.40
		AWE	2.56	0.76	0.85	0.85	0.54	-1.42	0.80	0.96	0.96	0.56
R^2= 0.15	Dominant	IPD	-0.20	1.18	1.20	1.20	1.00	-0.93	1.19	1.63	1.63	0.99
		UIVW	-0.32	1.86	1.85	1.85	0.94	-1.91	3.66	4.26	4.26	0.70
		REM	-0.10	2.23	1.93	1.93	0.89	-1.68	4.42	4.35	4.35	0.63
		MIVW	-0.17	1.18	1.20	1.20	1.00	-0.95	1.18	1.62	1.62	0.99
		MR	-0.78	4.09	3.86	3.85	0.69	-0.52	2.19	2.67	2.67	0.90
		AWE	-0.11	1.21	1.26	1.26	0.99	-0.82	1.26	1.72	1.72	0.98
	Additive	IPD	0.10	0.74	0.76	0.76	0.99	-0.39	0.76	1.08	1.08	0.99
		UIVW	0.12	1.14	1.15	1.15	0.93	-1.12	2.23	2.35	2.35	0.71
		REM	-0.01	1.36	1.19	1.19	0.90	-1.13	2.72	2.48	2.48	0.65
		MIVW	0.12	0.74	0.77	0.77	0.99	-0.34	0.76	1.08	1.08	0.99
		MR	-0.29	2.69	2.65	2.65	0.64	-0.19	1.43	1.83	1.83	0.88
		AWE	-0.26	0.75	0.80	0.80	0.99	-0.34	0.81	1.19	1.19	0.98
R^2= 0.25	Dominant	IPD	-0.66	1.15	1.35	1.35	1.00	-0.70	1.13	1.77	1.77	1.00
		UIVW	-0.51	1.84	2.09	2.09	0.99	-1.03	3.60	4.24	4.24	0.84
		REM	-0.29	2.16	2.15	2.15	0.97	-1.43	4.31	4.34	4.35	0.79
		MIVW	-0.71	1.15	1.36	1.36	1.00	-0.70	1.12	1.79	1.79	1.00
		MR	-1.69	3.94	4.03	4.04	0.87	-1.01	1.99	2.61	2.62	0.97
		AWE	-1.10	1.18	1.49	1.49	1.00	-1.19	1.20	1.94	1.95	1.00
	Additive	IPD	-1.31	0.73	0.88	0.89	1.00	0.93	0.73	1.04	1.04	1.00
		UIVW	-1.19	1.13	1.27	1.27	0.99	1.15	2.21	2.49	2.49	0.85
		REM	-1.29	1.35	1.31	1.31	0.98	1.20	2.67	2.56	2.56	0.79
		MIVW	-1.36	0.72	0.89	0.89	1.00	0.90	0.72	1.04	1.04	1.00
		MR	-2.50	2.56	2.84	2.85	0.84	0.26	1.38	1.71	1.71	0.96
		AWE	-1.68	0.74	0.95	0.96	1.00	0.46	0.79	1.19	1.19	1.00

[a] IPD: individual patient data analysis; UIVW: univariate inverse-variance weighted estimator; REM: random effect model; MIVW: multivariate inverse-variance weighted estimator; MR: Meta-regression; AWE: adaptively weighted estimator.

[b] RB: relative bias; MV: mean of model based variance; EV: empirical variance; MSE: mean squared error. (MV, EV and MSE have been multiplied by 100.)

Table 4: Comparison of the proposed meta-analytical methods under different scenarios of susceptibility models and covariate heterogeneity through a simulation study. *Setting (d): without assumption 1 or 2*.

			wss/bss=2					bss/wss=2				
(%)	Method[a]		RB[b](%)	MV[b]	EV[b]	MSE[b]	Power	RB (%)	MV	EV	MSE	Power
R^2= 0	Dominant	IPD		1.23	1.21	1.21	0.04		1.22	1.16	1.16	0.04
		UIVW		1.99	2.08	2.08	0.06		3.89	4.02	4.02	0.05
		REM		2.40	2.13	2.13	0.04		4.68	4.18	4.18	0.04
		MIVW		1.22	1.22	1.22	0.04		1.22	1.16	1.16	0.04
		MR		4.05	4.13	4.13	0.07		2.12	2.05	2.06	0.06
		AWE		1.26	1.35	1.35	0.05		1.29	1.33	1.33	0.06
	Additive	IPD		0.76	0.74	0.74	0.05		0.78	0.76	0.75	0.04
		UIVW		1.20	1.21	1.21	0.05		2.35	2.42	2.42	0.06
		REM		1.43	1.24	1.24	0.04		2.84	2.48	2.48	0.04
		MIVW		0.76	0.74	0.74	0.04		0.77	0.75	0.75	0.04
		MR		2.67	2.66	2.66	0.07		1.38	1.35	1.35	0.06
		AWE		0.78	0.84	0.84	0.05		0.81	0.85	0.85	0.06
R^2= 0.05	Dominant	IPD	-2.87	1.21	1.21	1.21	0.59	0.54	1.21	1.34	1.34	0.55
		UIVW	-3.68	1.95	2.11	2.12	0.42	1.82	3.81	4.03	4.03	0.23
		REM	-3.78	2.34	2.18	2.19	0.37	1.18	4.66	4.12	4.12	0.19
		MIVW	-2.96	1.20	1.22	1.22	0.59	0.51	1.21	1.35	1.34	0.56
		MR	0.19	4.17	4.03	4.02	0.26	-0.59	2.16	2.45	2.45	0.40
		AWE	-3.18	1.25	1.32	1.32	0.57	0.04	1.29	1.46	1.46	0.53
	Additive	IPD	0.23	0.75	0.80	0.80	0.55	-0.16	0.77	0.83	0.83	0.57
		UIVW	1.14	1.18	1.22	1.22	0.37	0.85	2.31	2.46	2.46	0.23
		REM	1.40	1.40	1.27	1.27	0.33	1.21	2.80	2.52	2.52	0.19
		MIVW	0.35	0.75	0.81	0.81	0.55	-0.18	0.77	0.84	0.84	0.57
		MR	0.93	2.67	2.96	2.95	0.24	-0.10	1.44	1.35	1.35	0.37
		AWE	0.84	0.77	0.86	0.86	0.54	-0.15	0.82	0.93	0.93	0.54
R^2= 0.15	Dominant	IPD	0.52	1.19	1.25	1.25	0.99	0.09	1.17	1.51	1.51	0.98
		UIVW	1.30	1.92	2.00	2.01	0.91	0.03	3.75	4.13	4.13	0.65
		REM	1.18	2.28	2.08	2.08	0.87	0.16	4.50	4.21	4.21	0.59
		MIVW	0.58	1.18	1.26	1.26	0.99	0.14	1.17	1.52	1.52	0.98
		MR	-0.82	4.04	4.28	4.28	0.67	-0.31	2.07	2.45	2.45	0.90
		AWE	0.62	1.23	1.36	1.36	0.99	0.01	1.25	1.63	1.63	0.98
	Additive	IPD	0.85	0.74	0.78	0.78	0.99	0.74	0.75	0.86	0.86	0.99
		UIVW	0.40	1.17	1.24	1.24	0.92	1.29	2.27	2.28	2.28	0.67
		REM	0.63	1.41	1.29	1.28	0.87	1.40	2.73	2.36	2.37	0.59
		MIVW	0.85	0.74	0.78	0.78	0.99	0.73	0.75	0.86	0.86	0.99
		MR	1.62	2.70	2.56	2.56	0.65	0.05	1.40	1.60	1.60	0.87
		AWE	0.78	0.76	0.86	0.86	0.98	0.87	0.80	0.95	0.95	0.97
R^2= 0.25	Dominant	IPD	-0.54	1.18	1.36	1.36	1.00	-0.04	1.16	1.62	1.62	1.00
		UIVW	0.09	1.90	2.17	2.17	0.98	-0.13	3.75	4.32	4.32	0.82
		REM	0.15	2.23	2.19	2.19	0.97	-0.21	4.54	4.45	4.45	0.77
		MIVW	-0.54	1.18	1.37	1.37	1.00	-0.05	1.15	1.63	1.63	1.00
		MR	-1.68	4.22	4.43	4.43	0.83	0.18	2.04	2.66	2.66	0.98
		AWE	-0.63	1.23	1.51	1.51	1.00	0.19	1.24	1.82	1.82	1.00
	Additive	IPD	-1.22	0.74	0.85	0.85	1.00	-0.28	0.74	1.13	1.13	1.00
		UIVW	-0.98	1.15	1.22	1.22	0.99	-0.50	2.28	2.73	2.73	0.83
		REM	-0.98	1.38	1.27	1.27	0.97	-0.65	2.74	2.75	2.75	0.80
		MIVW	-1.26	0.73	0.85	0.85	1.00	-0.28	0.74	1.14	1.14	1.00
		MR	-2.67	2.73	3.00	3.02	0.83	0.32	1.41	1.84	1.84	0.96
		AWE	-1.23	0.76	0.93	0.93	1.00	-0.12	0.81	1.25	1.25	1.00

[a] IPD: individual patient data analysis; UIVW: univariate inverse-variance weighted estimator; REM: random effect model; MIVW: multivariate inverse-variance weighted estimator; MR: Meta-regression; AWE: adaptively weighted estimator.

[b] RB: relative bias; MV: mean of model based variance; EV: empirical variance; MSE: mean squared error. (MV, EV and MSE have been multiplied by 100.)

Table 5: Comparison of power and Type-I error corresponding to the proposed methods, where the GEI effects are heterogeneous across studies (under the additive model). *Setting (d): without assumption 1 or 2*.

		wss/bss=2	bss/wss=2
(%)	Method[a]	Power (%)	Power (%)
R^2= 0	IPD	5	5
	UIVW	6	4
	MIVW	4	5
	MR	5	6
	AWE	5	5
R^2= 0.05	IPD	81	84
	UIVW	58	36
	MIVW	80	85
	MR	43	61
	AWE	81	82
R^2= 0.10	IPD	93	94
	UIVW	85	57
	MIVW	93	94
	MR	47	70
	AWE	93	88
R^2= 0.15	IPD	98	99
	UIVW	92	72
	MIVW	98	99
	MR	61	83
	AWE	96	97

[a] IPD: individual patient data analysis; UIVW: univariate inverse-variance weighted estimator; MIVW: multivariate inverse-variance weighted estimator; MR: Meta-regression; AWE: adaptively weighted estimator.

Table 6: Relative bias of $\hat{\delta}^{\mathrm{MR}}$ and $\hat{\delta}^{\mathrm{AWE}}$ across the whole spectrum of BSS/TSS values, when G-E correlation is strong $\rho = 0.8$. (These numerical results corresponded to Appendix Figure 9)

	Additive		Dominant	
	MR	AWE	MR	AWE
BSS/TSS	RB	RB	RB	RB
0.05	0.30	0.01	0.25	0.03
0.14	0.35	0.02	0.11	-0.05
0.23	0.24	0.02	0.16	0.02
0.35	0.04	-0.04	-0.06	-0.04
0.47	-0.04	-0.04	-0.06	-0.01
0.55	-0.03	-0.01	0.13	0.04
0.65	-0.01	-0.03	-0.07	0.05
0.76	-0.05	-0.04	-0.07	0.03
0.84	-0.05	-0.01	0.02	0.01
0.97	-0.01	0.00	0.07	0.06

[a] MR: Meta-regression; AWE: adaptively weighted estimator; RB: relative bias.

Appendix B: Technical Details

Appendix B.1: Proof of Lemma 1 and Theorem 1

(1) Proof of Lemma 1: Let $\boldsymbol{X}_1 = (X_1, ..., X_p)$ and $\boldsymbol{X}_2 = (X_{p+1}, ..., X_{p+q})$. Then $\hat{\boldsymbol{\lambda}} = (\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top \boldsymbol{Y}$

$$\text{and} \quad \begin{pmatrix} \hat{\boldsymbol{\beta}}_1 \\ \hat{\boldsymbol{\beta}}_2 \end{pmatrix} = \begin{pmatrix} \boldsymbol{X}_1^\top \boldsymbol{X}_1 & \boldsymbol{X}_1^\top \boldsymbol{X}_2 \\ \boldsymbol{X}_2^\top \boldsymbol{X}_1 & \boldsymbol{X}_2^\top \boldsymbol{X}_2 \end{pmatrix}^{-1} \begin{pmatrix} \boldsymbol{X}_1^\top \boldsymbol{Y} \\ \boldsymbol{X}_2^\top \boldsymbol{Y} \end{pmatrix}.$$

Let $\boldsymbol{A} = \boldsymbol{I} - \boldsymbol{X}_1(\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top$, then $\hat{\boldsymbol{\beta}}_2$ can be written as $(\boldsymbol{X}_2^\top \boldsymbol{A}\boldsymbol{X}_2)^{-1}\boldsymbol{X}_2^\top \boldsymbol{A}\boldsymbol{Y}$. We have

$$\begin{aligned} Cov(\hat{\boldsymbol{\lambda}}, \hat{\boldsymbol{\beta}}_2) &= Cov\{(\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top \boldsymbol{Y}, \quad (\boldsymbol{X}_2^\top \boldsymbol{A}\boldsymbol{X}_2)^{-1}\boldsymbol{X}_2^\top \boldsymbol{A}\boldsymbol{Y}\} \\ &= (\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top Cov(\boldsymbol{Y}, \boldsymbol{Y})\boldsymbol{A}^\top \boldsymbol{X}_2(\boldsymbol{X}_2^\top \boldsymbol{A}\boldsymbol{X}_2)^{-1} \\ &= (\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top Cov(\boldsymbol{Y}, \boldsymbol{Y})\{\boldsymbol{I} - \boldsymbol{X}_1(\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top\}\boldsymbol{X}_2(\boldsymbol{X}_2^\top \boldsymbol{A}\boldsymbol{X}_2)^{-1} \\ &= Var(Y_i)\{(\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top - (\boldsymbol{X}_1^\top \boldsymbol{X}_1)^{-1}\boldsymbol{X}_1^\top\}\boldsymbol{X}_2(\boldsymbol{X}_2^\top \boldsymbol{A}\boldsymbol{X}_2)^{-1} \\ &= 0 \end{aligned}$$

Because the MLEs $\hat{\boldsymbol{\lambda}}$ and $\hat{\boldsymbol{\beta}}_2$ are jointly asymptotically normal, the fact that $\hat{\boldsymbol{\lambda}}$ and $\hat{\boldsymbol{\beta}}_2$ have asymptotic covariance zero implies that they are asymptotically independent.

(2) Theorem 1 establishes that with the particular choice of weights as given in 2.1, $\hat{\delta}^{\text{AWE}}$ has the maximal precision within the class of weighted estimators of the form $\hat{\delta}^{\text{AWE}}(w) = w\hat{\delta}^{\text{UIVW}} + (1 - w)\hat{\delta}^{\text{MR}}$, $0 \leq w \leq 1$.

Theorem 1. *For the class of weighted estimators* $\hat{\delta}^{\text{AWE}}(w) = w\hat{\delta}^{\text{UIVW}} + (1 - w)\hat{\delta}^{\text{MR}}$, $0 \leq w \leq 1$, $\mathbf{v}(\hat{\delta}^{\text{AWE}}(w))^{-1}$ *attains its maximum at* $\mathbf{v}(\hat{\delta}^{\text{UIVW}})^{-1} + \mathbf{v}(\hat{\delta}^{\text{MR}})^{-1}$ *if and only if the weight* $w = \mathbf{v}(\hat{\delta}^{\text{MR}})/\{\mathbf{v}(\hat{\delta}^{\text{UIVW}}) + \mathbf{v}(\hat{\delta}^{\text{MR}})\}$.

Proof of Theorem 1: Following lemma 1, $\hat{\delta}_k$ and $\hat{\lambda}_{Gk}$ are asymptotically independent because they come from two nested linear regression models (1) and (2). So $cov(\hat{\delta}_k, \hat{\lambda}_{Gk}) = 0$. We also have $cov(\hat{\delta}_j, \hat{\lambda}_{Gk}) = 0$ for $j \neq k$ among the K independent studies. Under the standard condition, $\hat{\delta}^{\text{UIVW}}$ is a linear combination of $\hat{\delta}_k$ and $\hat{\delta}^{\text{MR}}$ is a linear combination of $\hat{\lambda}_{Gk}$, it follows $cov(\hat{\delta}^{\text{UIVW}}, \hat{\delta}^{\text{MR}}) = 0$.

For $\hat{\delta}^{\text{AWE}}(w) = w\hat{\delta}^{\text{UIVW}} + (1 - w)\hat{\delta}^{\text{MR}}$, $0 \leq w \leq 1$, we have $\mathbf{v}(\hat{\delta}^{\text{AWE}}(w)) = w^2\mathbf{v}(\hat{\delta}^{\text{UIVW}}) + (1 - w)^2\mathbf{v}(\hat{\delta}^{\text{MR}}) + 2w(1 - w)cov(\hat{\delta}^{\text{UIVW}}, \hat{\delta}^{\text{MR}}) = w^2\mathbf{v}(\hat{\delta}^{\text{UIVW}}) + (1 - w)^2\mathbf{v}(\hat{\delta}^{\text{MR}}) = \{\mathbf{v}(\hat{\delta}^{\text{UIVW}}) + \mathbf{v}(\hat{\delta}^{\text{MR}})\}[w - \mathbf{v}(\hat{\delta}^{\text{MR}})/\{\mathbf{v}(\hat{\delta}^{\text{UIVW}}) + \mathbf{v}(\hat{\delta}^{\text{MR}})\}]^2 + \mathbf{v}(\hat{\delta}^{\text{UIVW}})\mathbf{v}(\hat{\delta}^{\text{MR}})/\{\mathbf{v}(\hat{\delta}^{\text{UIVW}}) + \mathbf{v}(\hat{\delta}^{\text{MR}})\}$. So $\mathbf{v}(\hat{\delta}^{\text{AWE}}(w))$ reaches its minimum if and only if $w = \mathbf{v}(\hat{\delta}^{\text{MR}})/\{\mathbf{v}(\hat{\delta}^{\text{UIVW}}) + \mathbf{v}(\hat{\delta}^{\text{MR}})\}$. With this choice of w, $\mathbf{v}(\hat{\delta}^{\text{AWE}})^{-1} = \mathbf{v}(\hat{\delta}^{\text{UIVW}})^{-1} + \mathbf{v}(\hat{\delta}^{\text{MR}})^{-1}$.

Appendix B.2: Proof of Proposition 1

(1) Proof of Proposition 1: Assumption 1 implies that the distributions $P(E|G = g)$ are the same for $g = 0, 1, 2$ (corresponding to (aa, Aa, AA) respectively), within each study as well as for the

whole population. Let $n_{gk} = \sum_{i:G_{ki}=g} 1$, $\overline{G}_k = \sum_{i=1}^{n_k} G_{ki}/n_k$, $m_{gk} = \sum_{i:G_{ki}=g} E_{ki}/n_{gk}$; and $\mu_{gk} = E(E_{ki}|G_{ki} = g, \text{study} = k)$, $\mu_k = E(E_{ki}|\text{study} = k)$. Assumption 1 implies: (i) $\mu_{gk} = \mu_k$; (ii) $\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)E_{ki} \to 0$ as $n_k \to \infty$; and (iii)

$$\frac{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}E_{ki}}{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}} = \frac{\sum_{g=1,2}\{\sum_{i:\,G_{ki}=g}(g - \overline{G}_k)gE_{ki}\}}{\sum_{g=1,2}\{\sum_{i:\,G_{ki}=g}(g - \overline{G}_k)g\}} = \frac{\sum_{g=1,2}\{(g - \overline{G}_k)gn_{gk}m_{gk}\}}{\sum_{g=1,2}\{(g - \overline{G}_k)gn_{gk}\}} \to \mu_k,$$

as $n_{gk} \to \infty$. From model (2), we have $\hat{\lambda}_{Gk} = \sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)Y_{ki}/\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}$. So

$$\begin{aligned} E(\hat{\lambda}_{Gk}) &= \beta_{0k}\frac{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)}{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}} + \beta_G + \beta_E\frac{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)E_{ki}}{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}} + \delta\frac{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}E_{ki}}{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}} \\ &\to \beta_G + \delta\mu_k, \quad \text{as } n_{gk} \to \infty \end{aligned}$$

So $\hat{\delta}^{\text{MR}}$ is asymptotically unbiased for δ under assumption 1. The above calculation holds for dominant, recessive and additive genetic susceptibility models. For co-dominant model, the calculation holds for AA and Aa respectively.

(2) Unbiasness of MR when assumption 1 is relaxed: If assumption 1 is relaxed, unbiased estimator of δ can still be found through different MR models for different susceptibility model. For example, under dominant model,

$$E(\hat{\lambda}_{Gk}) = \beta_G + \beta_E(\frac{n_{1k}m_{1k} + n_{2k}m_{2k}}{n_{1k} + n_{2k}} - m_{0k}) + \delta(\frac{n_{1k}m_{1k} + n_{2k}m_{2k}}{n_{1k} + n_{2k}});$$

under additive model,

$$E(\hat{\lambda}_{Gk}) = \beta_G + \beta_E\frac{-\overline{G}_k n_{0k}m_{0k} + (1 - \overline{G}_k)n_{1k}m_{1k} + (2 - \overline{G}_k)n_{2k}m_{2k}}{(1 - \overline{G}_k)n_{1k} + 2(2 - \overline{G}_k)n_{2k}} + \delta\frac{(1 - \overline{G}_k)n_{1k}m_{1k} + 2(2 - \overline{G}_k)n_{2k}m_{2k}}{(1 - \overline{G}_k)n_{1k} + 2(2 - \overline{G}_k)n_{2k}}.$$

(3) Bias of $\hat{\delta}^{\text{MR}}$ in terms of bss/tss: For simplicity, we derive the bias of $\hat{\delta}^{\text{MR}}$ under assumption 2 for a dominant model. Let the sample mean of E for the carrier (non-carrier) group be m_{1k} (m_{0k}) for the k-th study. We have

$$E(\hat{\delta}^{\text{MR}}) = \{\sum_k w_k(m_k - \overline{m})^2\}^{-1}\{\sum_k w_k(m_k - \overline{m})E(\hat{\lambda}_{Gk})\},$$

where $w_k = n_k^{-1}n_{1k}n_{0k}$, $\overline{m} = (\sum_k n_k^{-1}n_{1k}n_{0k}m_k)/(\sum_k n_k^{-1}n_{1k}n_{0k})$ and $E(\hat{\lambda}_{Gk}) = \beta_G + \beta_E(m_{1k} - m_{0k}) + \delta m_{1k}$. We have $n_{1k}/n_k \to p$, $m_k \xrightarrow{p} \mu_k$, $\overline{m} \xrightarrow{p} \mu$, $s_{Ek}^2 \xrightarrow{p} \sigma_{Ek}^2$, as $n_k \to \infty$. Suppose $n_k/N \to \varrho_k \in (0, 1)$ as $N \to \infty$. Then

$$E(\hat{\delta}^{\text{MR}}) \xrightarrow{p} \{\sum_k \varrho_k(\mu_k - \mu)^2\}^{-1}\sum_k \varrho_k(\mu_k - \mu)\{\beta_E(\mu_{1k} - \mu_{0k}) + \delta\mu_{1k}\}.$$

Denote the sample Pearson correlation coefficient between G and E in study k as

$$\hat{\rho}_k = \frac{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)E_{ki}}{\{\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}\}^{\frac{1}{2}}\{n_k s_{Ek}^2\}^{\frac{1}{2}}},$$

then we can write

$$m_{1k} - m_k \ = \ n_k^{-1} n_{0k}(m_{1k} - m_{0k}) = n_k^{-1} n_{0k} \frac{\sum_{i=1}^{n_k} (G_{ki} - \overline{G}_k) E_{ki}}{\sum_{i=1}^{n_k} (G_{ki} - \overline{G}_k) G_{ki}} = n_k^{-1} n_{0k} \hat{\rho}_k \{ \frac{n_k s_{Ek}^2}{n_k^{-1} n_{0k} n_{1k}} \}^{\frac{1}{2}}.$$

Asymptotically, $\mu_{1k} - \mu_k = (1-p)(\mu_{1k} - \mu_{0k}) = (1-p)\rho_k[\sigma_{Ek}^2 / \{p(1-p)\}]^{\frac{1}{2}}$. The bias of $\hat{\delta}^{\text{MR}}$

$$\begin{aligned} E(\hat{\delta}^{\text{MR}}) - \delta &\xrightarrow{p} \{\sum_k \varrho_k (\mu_k - \mu)^2\}^{-1} \sum_k \varrho_k (\mu_k - \mu) \{\beta_E (\mu_{1k} - \mu_{0k}) + \delta(\mu_{1k} - \mu_k + \mu)\} \\ &= \{p(1-p)\}^{-\frac{1}{2}} \{\sum_k \varrho_k (\mu_k - \mu)^2\}^{-1} \sum_k \varrho_k (\mu_k - \mu) \sigma_{Ek} [\beta_E \rho_k + \delta(1-p)\rho_k]. \end{aligned}$$

Clearly, if assumption 1 holds (implying $\rho_k = 0$, for $k = 1, ..., K$), $E(\hat{\delta}^{\text{MR}}) - \delta \xrightarrow{p} 0$. If not, we have $0 \leq \beta_E \rho_k + \delta(1-p)\rho_k \leq \beta_E + \delta(1-p)$. From Cauchy-Schwarz inequality, we have $\sum_k \varrho_k(\mu_k - \mu)\sigma_{Ek} \leq (bss \times wss)^{\frac{1}{2}}$, and then $\{\sum_k \varrho_k (\mu_k - \mu)\sigma_{Ek}\} / \{\sum_k \varrho_k (\mu_k - \mu)^2\} \leq (wss/bss)^{\frac{1}{2}}$. When N is large, the limiting value of $E(\hat{\delta}^{\text{MR}}) - \delta$ is bounded from above by $\{\beta_E + \delta(1-p)\}\{p(1-p)\}^{-\frac{1}{2}}(wss/bss)^{\frac{1}{2}}$. Given p, β_E and δ, the upper bound increases as wss/bss increases, or equivalently, as bss/tss decreases. So $\hat{\delta}^{\text{AWE}}$ can control for the bias by putting less weight on $\hat{\delta}^{\text{MR}}$ when the bias of $\hat{\delta}^{\text{MR}}$ increases.

In terms of simulation studies, we consider the situation where the ecological bias of $\hat{\delta}^{\text{MR}}$ is large and assess the performance of $\hat{\delta}^{\text{AWE}}$ (Appendix Figure 9 and Table 6). It shows that bias of $\hat{\delta}^{\text{AWE}}$ is well-controlled and is not to a level of practical concern even when the ecological bias is substantial.

Appendix B.3: Derivation of $\hat{\mathbf{v}}(\hat{\delta})$ and $\mathbf{v}(\hat{\delta})$ under G-E independence assumption

Under the dominant model, for the k-th study, denote n_{1k} (n_{0k}) as the number of carriers (non-carrier), for $k = 1, ..., K$; denote the sample mean of E for the carrier (non-carrier) group as m_{1k} (m_{0k}), and denote the sample variance of E for carrier (non-carrier) group as s_{E1k}^2 (s_{E0k}^2), where $\frac{1}{n_{1k}} \sum_{i:\, G_{ki}=1} (E_{ki} - m_{1k})^2$. Approximately, $m_{1k} = m_{0k} = m_k$, $s_{E1k}^2 = s_{E0k}^2 = s_{Ek}^2$ under assumption 1. $\hat{\mathbf{v}}(\hat{\delta})$ can be derived as follows:

(1) IPD analysis: Let $\boldsymbol{X}$ be the design matrix and $\boldsymbol{Y}$ be the response in model (1). $\hat{\delta}^{\text{IPD}}$ can be obtained as the corresponding element in $(\boldsymbol{X}^\top \boldsymbol{X})^{-1} \boldsymbol{X}^\top \boldsymbol{Y}$, and its estimated variance $\hat{\mathbf{v}}(\hat{\delta}^{\text{IPD}})$ is the sub 3×3

matrix of $(\boldsymbol{X}^\top\boldsymbol{X})^{-1}\hat{\sigma}^2$, where

$$
\begin{aligned}
(\boldsymbol{X}^\top\boldsymbol{X})^{-1} &= \left(\begin{array}{cccc|ccc}
n_1 & 0 & \cdots & 0 & n_{11} & n_1 m_1 & n_{11} m_1 \\
 & n_2 & & \vdots & n_{12} & n_2 m_2 & n_{12} m_2 \\
 & & \ddots & 0 & \vdots & \vdots & \vdots \\
 & & & n_K & n_{1K} & n_K m_K & n_{1K} m_K \\
\hline
 & & & & \sum_k n_{1k} & \sum_k n_{1k} m_k & \sum_k n_{1k} m_k \\
 & & & & & \sum_{k,\,i} E_{ki}^2 & \sum_{k,\,i:G_{ki}=1} E_{ki}^2 \\
 & & & & & & \sum_{k,\,i:G_{ki}=1} E_{ki}^2
\end{array}\right)^{-1}_{(K+3)(K+3)} \\
&= \left(\begin{array}{cc}
\ddots & \cdots \\
\vdots & \left(\begin{array}{ccc}
\sum_k n_k^{-1} n_{0k} n_{1k} & 0 & \sum_k n_k^{-1} n_{1k} n_{0k} m_k \\
 & \sum_k n_k s_{Ek}^2 & \sum_k n_{1k} s_{E1k}^2 \\
 & & \sum_k (n_{1k} s_{E1k}^2 + n_k^{-1} n_{1k} n_{0k} m_k^2)
\end{array}\right)^{-1}_{3\times 3}
\end{array}\right)_{(K+3)(K+3)}.
\end{aligned}
$$

$$
\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{IPD}}) = \hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}^{\mathrm{IPD}})_{(3,3)} = \big\{(\sum_k n_{1k} s_{E1k}^2)(\sum_k n_{0k} s_{E0k}^2)/(\sum_k n_k s_{Ek}^2) + \sum_k n_k^{-1} n_{1k} n_{0k} (m_k - \overline{m})^2\big\}^{-1}\hat{\sigma}^2.
$$

(2) Inverse-variance weighted estimator: Let $\boldsymbol{X}_k$ be the design matrix and $\boldsymbol{Y}_k$ be the response of study k. $\hat{\delta}_k$ and $\hat{\mathbf{v}}(\hat{\delta}_k)$ can be obtained through the corresponding element of $(\boldsymbol{X}_k^\top \boldsymbol{X}_k)^{-1}\boldsymbol{X}_k^\top \boldsymbol{Y}_k$ and $(\boldsymbol{X}_k^\top \boldsymbol{X}_k)^{-1}\hat{\sigma}_k^2$ respectively. $\hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}_k)$ is the sub 3×3 matrix of $(X_k^\top X_k)^{-1}\hat{\sigma}_k^2$, where $(X_k^\top X_k)^{-1} =$

$$
\left(\begin{array}{c|ccc}
n_k & n_{1k} & n_k m_k & n_{1k} m_k \\
\hline
 & n_{1k} & n_{1k} m_k & n_{1k} m_k \\
 & & \sum_i E_{ki}^2 & \sum_{i:G_{ki}=1} E_{ki}^2 \\
 & & & \sum_{i:G_{ki}=1} E_{ki}^2
\end{array}\right)^{-1}
= \left(\begin{array}{cc}
\cdot & \cdots \\
\vdots & \left(\begin{array}{ccc}
n_k^{-1} n_{0k} n_{1k} & 0 & n_k^{-1} n_{1k} n_{0k} m_k \\
 & n_k s_{Ek}^2 & n_{1k} s_{E1k}^2 \\
 & & n_{1k} s_{E1k}^2 + n_k^{-1} n_{1k} n_{0k} m_k^2
\end{array}\right)^{-1}
\end{array}\right).
$$

Compare $\hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}_k)^{-1}$ with $\hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}^{\mathrm{IPD}})^{-1}$, we have $\hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}^{\mathrm{MIVW}}) = \big\{\sum_k \hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}_k)^{-1}\big\}^{-1} = \hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}^{\mathrm{IPD}})$, which implies $\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{MIVW}}) = \hat{\mathbf{v}}(\hat{\delta}^{\mathrm{IPD}}) = \big\{\sum_k \hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}_k)^{-1}\big\}^{-1}_{(3,3)}$. For $\hat{\delta}_k$, we have $\hat{\mathbf{v}}(\hat{\delta}_k) = \hat{\mathbf{v}}(\hat{\boldsymbol{\beta}}_k)_{(3,3)} = n_k s_{Ek}^2 \hat{\sigma}_k^2/(n_{1k} s_{E1k}^2 n_{0k} s_{E0k}^2)$. Then

$$
\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{UIVW}}) = \big\{\sum_k \hat{\mathbf{v}}(\hat{\delta}_k)^{-1}\big\}^{-1} = \big\{\sum_k (n_{1k} s_{E1k}^2 n_{0k} s_{E0k}^2)/(n_k s_{Ek}^2 \hat{\sigma}_k^2)\big\}^{-1}.
$$

(3) Meta-regression: From model (2), $\hat{\lambda}_{Gk} = \sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)Y_{ki}/\sum_{i=1}^{n_k}(G_{ki} - \overline{G}_k)G_{ki}$ and $\hat{\mathbf{v}}(\hat{\lambda}_{Gk}) = n_{1k}^{-1} n_{0k}^{-1} n_k \hat{\sigma}_{\eta k}^2$. Let $w_k = \hat{\mathbf{v}}(\hat{\lambda}_{Gk})^{-1}$, and let $\overline{m} = (\sum_k w_k m_k)/(\sum_k w_k)$ that can be simplified as $(\sum_k n_k^{-1} n_{1k} n_{0k} \hat{\sigma}_{\eta k}^{-2} m_k)/(\sum_k n_k^{-1} n_{1k} n_{0k} \hat{\sigma}_{\eta k}^{-2})$. Then $\hat{\delta}^{\mathrm{MR}}$ and $\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{MR}})$ can be derived as

$$
\begin{aligned}
\hat{\delta}^{\mathrm{MR}} &= \{\sum_k w_k (m_k - \overline{m})^2\}^{-1}\{\sum_k w_k (m_k - \overline{m})\hat{\lambda}_{Gk}\}, \\
\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{MR}}) &= \{\sum_k w_k (m_k - \overline{m})^2\}^{-1} = \{\sum_k n_k^{-1} n_{1k} n_{0k} \hat{\sigma}_{\eta k}^{-2} (m_k - \overline{m})^2\}^{-1}.
\end{aligned}
$$

(4) Asymptotic model based variance $\mathbf{v}(\hat{\delta})$: Suppose $n_k/N \to \varrho_k \in (0,1)$ as $N \to \infty$. If we assume $\sigma_k^2 = \sigma^2$ for $k = 1, ..., K$, we have $\hat{\sigma}^2 \xrightarrow{p} \sigma^2$, $\hat{\sigma}_k^2 \xrightarrow{p} \sigma^2$, as $N \to \infty$. Under the IPD model

(1), where the homoscedasticity assumption has been implicitly made for the regression model, we have $\mathbf{v}(Y_{ki}|\boldsymbol{X}_{ki}) = \sigma^2$ that does not depend on $\boldsymbol{X}_{ki}$. Therefore, $\mathbf{v}(\hat{\lambda}_{Gk}) = n_{1k}^{-1}n_{0k}^{-1}n_k\mathbf{v}(Y_{ki}) = n_{1k}^{-1}n_{0k}^{-1}n_k\,\sigma^2$. Moreover, under assumption 1, we have the facts that: (i) $m_{1k} \xrightarrow{p} \mu_k$, $m_{0k} \xrightarrow{p} \mu_k$, $m_k \xrightarrow{p} \mu_k$, as $n_k \to \infty$; (ii) $s_{E1k}^2 \xrightarrow{p} \sigma_{Ek}^2$, $s_{E0k}^2 \xrightarrow{p} \sigma_{Ek}^2$, $s_{Ek}^2 \xrightarrow{p} \sigma_{Ek}^2$, as $n_k \to \infty$. For dominant model, $n_{1k}/n_k \to p_k$, as $n_k \to \infty$. Let $\overline{\mu} = \{\sum_k n_kp_k(1-p_k)\mu_k\}/\{\sum_k n_kp_k(1-p_k)\}$. $\overline{m} \xrightarrow{p} \overline{\mu}$ as $N \to \infty$. The asymptotic model based variance can be derived as follows

$$\begin{aligned}
\mathbf{v}(\hat{\delta}^{\mathrm{IPD}}) &= \mathbf{v}(\hat{\delta}^{\mathrm{MIVW}}) = \{(\sum_k n_kp_k\sigma_{Ek}^2)(\sum_k n_k(1-p_k)\sigma_{Ek}^2)/(\sum_k n_k\sigma_{Ek}^2) + \sum_k n_kp_k(1-p_k)(\mu_k-\overline{\mu})^2\}^{-1}\sigma^2,\\
\mathbf{v}(\hat{\delta}^{\mathrm{UIVW}}) &= \{\sum_k n_kp_k(1-p_k)\sigma_{Ek}^2\}^{-1}\sigma^2,\\
\mathbf{v}(\hat{\delta}^{\mathrm{MR}}) &= \{\sum_k n_kp_k(1-p_k)(\mu_k-\overline{\mu})^2\}^{-1}\,\sigma^2.
\end{aligned}$$

By Slutsky's theorem, for large N, $\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{IPD}})$, $\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{MIVW}})$, $\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{UIVW}})$, $\hat{\mathbf{v}}(\hat{\delta}^{\mathrm{MR}})$ are consistent estimators of $\mathbf{v}(\hat{\delta}^{\mathrm{IPD}})$, $\mathbf{v}(\hat{\delta}^{\mathrm{MIVW}})$, $\mathbf{v}(\hat{\delta}^{\mathrm{UIVW}})$, $\mathbf{v}(\hat{\delta}^{\mathrm{MR}})$ respectively.

Appendix B.4: Proof of Remark 4 and Theorem 2

Proof of Remark 4: We first show the results for centered covariate E in Remark 4 and prove the following four propositions P1 - P4. If each study k has E centered at their respective study specific means m_k, consider the model $Y_{ki} = \beta'_{0k} + \beta'_G G_{ki} + \beta'_E E'_{ki} + \delta' G_{ki}E'_{ki} + \epsilon_{ki}, i = 1, ..., n_k$, where $E'_{ki} = E_{ki} - m_k$. If E is centered at the overall mean m for the IPD analysis (an IPD analysis using data centered at study mean m_k for each study lacks interpretability of the main effect parameters), consider model $Y_{ki} = \beta^\star_{0k} + \beta^\star_G G_{ki} + \beta^\star_E E^\star_{ki} + \delta^\star G_{ki}E^\star_{ki} + \epsilon_{ki}, i = 1, ..., n_k, k = 1, ..., K$, where $E^\star_{ki} = E_{ki} - m$. In this new parametrization, we have $(\beta'_E, \delta') = (\beta_E, \delta)$ and $\beta'_G = \beta_G + m_k\delta$ depending on k, denoted as β'_{Gk}; $(\beta^\star_E, \delta^\star) = (\beta_E, \delta)$ and $\beta^\star_G = \beta_G + m\delta^\star$. $\hat{\delta}^{\mathrm{IPD}}$, $\hat{\delta}^{\mathrm{UIVW}}$, $\hat{\delta}^{\mathrm{REM}}$, $\hat{\delta}^{\mathrm{MR}}$ and $\hat{\delta}^{\mathrm{AWE}}$ remain invariant with centered E since $\delta' = \delta^\star = \delta$. Thus, results in Theorems 1-3 (involving $\hat{\delta}^{\mathrm{IPD}}$, $\hat{\delta}^{\mathrm{UIVW}}$, $\hat{\delta}^{\mathrm{MR}}$ and $\hat{\delta}^{\mathrm{AWE}}$) also hold for these centered models. However, results corresponding to $\hat{\delta}^{\mathrm{MIVW}}$ need to be modified. Denote $\hat{\delta}^{\mathrm{MIVW}'}$ as the MIVW estimator obtained by pooling $(\beta'_{Gk}, \beta'_E, \delta')$ with 3×3 covariance matrix and denote $\hat{\delta}^{\mathrm{MIVW2}'}$ as the MIVW estimator obtained by pooling only the two common effects (β'_E, δ') with 2×2 covariance matrix from the centered model. The following four propositions P1 - P4 hold.

Propositions. Under assumption 1, we have

P1. $\mathbf{v}(\hat{\delta}^{\mathrm{MIVW}'}) = \mathbf{v}(\hat{\delta}^{\mathrm{MIVW2}'})$.

P2. $\mathbf{v}(\hat{\delta}^{\mathrm{IPD}})^{-1} = \mathbf{v}(\hat{\delta}^{\mathrm{MIVW2}'})^{-1} + \mathbf{v}(\hat{\delta}^{\mathrm{MR}})^{-1}$.

P3. $\mathbf{v}(\hat{\delta}^{\mathrm{UIVW}}) \geq \mathbf{v}(\hat{\delta}^{\mathrm{MIVW2}'})$. The equality holds if and only if $p_k = p$, for $k = 1, 2, ..., K$.

P4. For $\hat{\delta}^{\mathrm{AWE2}'} = w\hat{\delta}^{\mathrm{MIVW2}'} + (1-w)\hat{\delta}^{\mathrm{MR}}$, $0 \leq w \leq 1$, we have that $\mathbf{v}(\hat{\delta}^{\mathrm{AWE2}'})^{-1}$ attains its maximum at $\mathbf{v}(\hat{\delta}^{\mathrm{MIVW2'}})^{-1} + \mathbf{v}(\hat{\delta}^{\mathrm{MR}})^{-1}$ if and only if $w = \mathbf{v}(\hat{\delta}^{\mathrm{MR}})/\{\mathbf{v}(\hat{\delta}^{\mathrm{MIVW2'}}) + \mathbf{v}(\hat{\delta}^{\mathrm{MR}})\}$.

Proof of P1: For the centered model, we have

$$
\begin{aligned}
(\boldsymbol{X}_k'^{\top}\boldsymbol{X}_k')^{-1} &\approx \begin{pmatrix} n_k & n_{1k} & 0 & 0 \\ & n_{1k} & 0 & 0 \\ & & \sum_i E_{ki}'^{\,2} & \sum_{i:G_{ki}=1} E_{ki}'^{\,2} \\ & & & \sum_{i:G_{ki}=1} E_{ki}'^{\,2} \end{pmatrix}^{-1}, \quad \text{then} \\
\mathbf{v}(\hat{\boldsymbol{\beta}}^{\mathrm{MIVW2'}}) &= \big(\sum_k \mathbf{v}(\hat{\beta}_{Ek}', \hat{\delta}_k')^{-1}\big)^{-1} = \begin{pmatrix} \sum_k n_k\sigma_{Ek}^2 & \sum_k n_k p_k \sigma_{E1k}^2 \\ & \sum_k n_k p_k \sigma_{E1k}^2 \end{pmatrix}^{-1} \sigma^2 \quad \text{and} \\
\mathbf{v}(\hat{\boldsymbol{\beta}}^{\mathrm{MIVW'}}) &= \big(\sum_k \mathbf{v}(\hat{\boldsymbol{\beta}}_k')^{-1}\big)^{-1} = \begin{pmatrix} \sum_k n_k p_k(1-p_k) & 0 & 0 \\ & \sum_k n_k\sigma_{Ek}^2 & \sum_k n_k p_k \sigma_{E1k}^2 \\ & & \sum_k n_k p_k \sigma_{E1k}^2 \end{pmatrix}^{-1} \sigma^2, \text{ so} \\
\mathbf{v}(\hat{\delta}^{\mathrm{MIVW'}}) &= \mathbf{v}(\hat{\delta}^{\mathrm{MIVW2'}}) = \frac{\sum_k n_k \sigma_{Ek}^2}{\{\sum_k n_k p_k \sigma_{Ek}^2\}\{\sum_k n_k(1-p_k)\sigma_{Ek}^2\}}\,\sigma^2.
\end{aligned}
$$

There is no efficiency gain by pooling all three parameters $(\beta_{Gk}', \beta_E', \delta')$ over polling the two common parameters (β_E', δ') under a centered model.

Proof of P2: From Appendix B.3,

$$
\mathbf{v}(\hat{\delta}^{\mathrm{IPD}})^{-1} = \Big[\underbrace{(\sum_k n_k p_k \sigma_{Ek}^2)(\sum_k n_k(1-p_k)\sigma_{Ek}^2)/(\sum_k n_k\sigma_{Ek}^2)}_{\mathbf{v}(\hat{\delta}^{\mathrm{MIVW2'}})^{-1}\sigma^2} + \underbrace{\sum_k n_k p_k(1-p_k)(\mu_k - \overline{\mu})^2}_{\mathbf{v}(\hat{\delta}^{\mathrm{MR}})^{-1}\sigma^2}\Big]\sigma^{-2}.
$$

Proof of P3: To show $\mathbf{v}(\hat{\delta}^{\mathrm{UIVW}}) \geq \mathbf{v}(\hat{\delta}^{\mathrm{MIVW2'}})$, it is sufficient to show $\big(\sum_k n_k p_k(1-p_k)\sigma_{Ek}^2\big)(\sum_k n_k \sigma_{Ek}^2) \leq (\sum_k n_k p_k \sigma_{Ek}^2)(\sum_k n_k(1-p_k)\sigma_{Ek}^2)$, or equivalently, $\sum_k n_k^2 p_k(1-p_k)\sigma_{Ek}^4 + \sum_{i\neq j} n_i n_j p_i(1-p_i)\sigma_{Ei}^2\sigma_{Ej}^2 \leq \sum_k n_k^2 p_k(1-p_k)\sigma_{Ek}^4 + \sum_{i\neq j} n_i n_j p_i(1-p_j)\sigma_{Ei}^2\sigma_{Ej}^2$. Then it is sufficient to show for $\forall\, i,j,\ n_i n_j p_i(1-p_i)\sigma_{Ei}^2\sigma_{Ej}^2 + n_j n_i p_j(1-p_j)\sigma_{Ej}^2\sigma_{Ei}^2 \leq n_i n_j p_i(1-p_j)\sigma_{Ei}^2\sigma_{Ej}^2 + n_j n_i p_j(1-p_i)\sigma_{Ej}^2\sigma_{Ei}^2$ $\Leftrightarrow \forall\, i,j,\ n_i n_j(p_i - p_j)^2\sigma_{Ei}^2\sigma_{Ej}^2 \geq 0$, which is apparently true. All the above equalities hold if and only if $p_i = p_j$, $\forall\, i,j$, i.e., $p_k = p$, for $k = 1, 2, ..., K$.

Proof of P4: Following Lemma 1, $cov(\hat{\delta}_k, \hat{\lambda}_{Gk}) = 0$ and $cov(\hat{\beta}_{Ek}, \hat{\lambda}_{Gk}) = 0$. Because $\hat{\delta}^{\mathrm{MR}}$ is a linear combination of $\hat{\lambda}_{Gk}$ and $\hat{\beta}^{\mathrm{MIVW2'}}$ is a linear combination of $\hat{\beta}_{Ek}$ and $\hat{\delta}_k$, we have $cov(\hat{\delta}^{\mathrm{MIVW2'}}, \hat{\delta}^{\mathrm{MR}}) = 0$. The rest of the proof is similar as Theorem 1.

Proof of the results in Remark 4 (continued): According to P1 - P3, we can show that $\mathbf{v}(\hat{\delta}^{\mathrm{UIVW}}) \geq \mathbf{v}(\hat{\delta}^{\mathrm{MIVW2'}}) = \mathbf{v}(\hat{\delta}^{\mathrm{MIVW'}}) \geq \mathbf{v}(\hat{\delta}^{\mathrm{IPD}})$. These results are consistent with Lin and Zeng (2010), because that the true model has three common fixed-effects and that pooling a subset of the common parameters in constructing MIVW would lead to efficiency loss. For the centered model, the MIVW estimator is not fully efficient. A solution is to consider an alternative AWE, $\hat{\delta}^{\mathrm{AWE2'}} = \{\mathbf{v}(\hat{\delta}^{\mathrm{MR}})\hat{\delta}^{\mathrm{MIVW2'}} +$

$\mathbf{v}(\hat{\delta}^{\text{MIVW2}'})\hat{\delta}^{\text{MR}}\}/\{\mathbf{v}(\hat{\delta}^{\text{MIVW2}'}) + \mathbf{v}(\hat{\delta}^{\text{MR}})\}$. According to propositions P1 and P3, under assumption 1, we have $\mathbf{v}(\hat{\delta}^{\text{IPD}})^{-1} = \mathbf{v}(\hat{\delta}^{\text{AWE2}'})^{-1} = \mathbf{v}(\hat{\delta}^{\text{MIVW2}'})^{-1} + \mathbf{v}(\hat{\delta}^{\text{MR}})^{-1} \geq \mathbf{v}(\hat{\delta}^{\text{UIVW}})^{-1} + \mathbf{v}(\hat{\delta}^{\text{MR}})^{-1} = \mathbf{v}(\hat{\delta}^{\text{AWE}})^{-1}$. The equality holds if and only if $p_k = p$, for $k = 1, 2, ..., K$. So $\hat{\delta}^{\text{AWE2}'}$ is fully efficient under only assumption 1.

Denote $\hat{\delta}^{\text{MIVW2}}$ as the MIVW pooling (β_E, δ) from the un-centered model. We have $\hat{\delta}^{\text{MIVW2}} = \hat{\delta}^{\text{MIVW2}'}$ since $(\beta_E, \delta) = (\beta'_E, \delta')$. The above results still hold if $\hat{\delta}^{\text{MIVW2}'}$ is substituted by $\hat{\delta}^{\text{MIVW2}}$.

Proof of Theorem 2: Following propositions P1 and P2, $\mathbf{v}(\hat{\delta}^{\text{IPD}})^{-1} \geq \mathbf{v}(\hat{\delta}^{\text{UIVW}})^{-1} + \mathbf{v}(\hat{\delta}^{\text{MR}})^{-1}$ under assumption 1. The equality holds if and only if $p_k = p$, for $k = 1, 2, ..., K$.

Appendix B.5: Proof of Theorem 3

Proof of Theorem 3: Under both assumptions 1 and 2, the variance of $\hat{\delta}^{\text{IPD}}$, $\hat{\delta}^{\text{UIVW}}$ and $\hat{\delta}^{\text{MR}}$ can be further simplified from the calculation in Appendix B.3 as $\mathbf{v}(\hat{\delta}^{\text{IPD}}) = [p(1-p)\sum_k n_k\{\sigma^2_{Ek} + (\mu_k - \mu)^2\}]^{-1}\sigma^2$, $\mathbf{v}(\hat{\delta}^{\text{UIVW}}) = \{p(1-p)\sum_k n_k\sigma^2_{Ek}\}^{-1}\sigma^2$ and $\mathbf{v}(\hat{\delta}^{\text{MR}}) = \{p(1-p)\sum_k n_k(\mu_k - \mu)^2\}^{-1}\sigma^2$. Now we have $\mathbf{v}(\hat{\delta}^{\text{IPD}})^{-1} = \mathbf{v}(\hat{\delta}^{\text{UIVW}})^{-1} + \mathbf{v}(\hat{\delta}^{\text{MR}})^{-1}$. From Theorem 1, $\mathbf{v}(\hat{\delta}^{\text{AWE}})^{-1} = \mathbf{v}(\hat{\delta}^{\text{UIVW}})^{-1} + \mathbf{v}(\hat{\delta}^{\text{MR}})^{-1}$, then $\mathbf{v}(\hat{\delta}^{\text{IPD}})^{-1} = \mathbf{v}(\hat{\delta}^{\text{AWE}})^{-1}$.

Suppose $n_k/N \to \varrho_k \in (0,1)$ as $N \to \infty$. We have $m_k \xrightarrow{p} \mu_k$, $s^2_{Ek} \xrightarrow{p} \sigma^2_{Ek}$, $m \xrightarrow{p} \mu$, $s^2_E \xrightarrow{p} \sigma^2_E$, as $N \to \infty$. Then $TSS/N = s^2_E \xrightarrow{p} \sigma^2_E$, $WSS/N = \sum_k n_k s^2_{Ek}/N \xrightarrow{p} \sum_k \varrho_k\sigma^2_{Ek}$, $BSS/N = \sum_k n_k(m_k - m)^2/N \xrightarrow{p} \sum_k \varrho_k(\mu_k - \mu)^2$, as $N \to \infty$. Because $TSS = WSS + BSS$, TSS/N is both consistent estimator of σ^2_E and $\sum_k \varrho_k\sigma^2_{Ek} + \sum_k \varrho_k(\mu_k - \mu)^2$. So we have $\sigma^2_E = \sum_k \varrho_k\{\sigma^2_{Ek} + (\mu_k - \mu)^2\}$, i.e., $tss = wss + bss$. Therefore, $\mathbf{v}(\hat{\delta}^{\text{UIVW}}) = \{Np(1-p)wss\}^{-1}\sigma^2$, $\mathbf{v}(\hat{\delta}^{\text{MR}}) = \{Np(1-p)bss\}^{-1}\sigma^2$ and $\mathbf{v}(\hat{\delta}^{\text{IPD}}) = \mathbf{v}(\hat{\delta}^{\text{AWE}}) = \{Np(1-p)tss\}^{-1}\sigma^2$.

Appendix B.6: Distribution of (G, E) in the simulation study

For G, without assumption 2, the MAF q_k is independently generated from $U(0.15, 0.35)$ for each study k, and then G_{ki} is generated as (AA, Aa, aa) with probability $\left(q_k^2, 2q_k(1-q_k), (1-q_k)^2\right)$ that follows HWE. With assumption 2, the MAF q is generated from $U(0.15, 0.35)$, and then G_{ki} is generated as (AA, Aa, aa) with probability $\left(q^2, 2q(1-q), (1-q)^2\right)$. Susceptibility models including dominant, additive and co-dominant models are considered under each simulation.

For E, the k-th study mean of E was sampled from $\mu_k \sim N(\mu, \sigma^2_\mu)$ with known μ and between study variance σ^2_μ. The k-th study variance $\sigma^2_{E_k}$ was sampled from $\sigma^2_{E_k} \sim \sigma^2_\mu \times U(c_1, c_2)$ with choices of constant (c_1, c_2) satisfy the two cases that $wss/bss = 2$ and $bss/wss = 2$ respectively. With assumption 1, the values of E of the k-th study were sampled from $E_{ki}|\mu_k, \sigma^2_{E_k} \sim N(\mu_k, \sigma^2_{E_k})$ that is independent of G. Without assumption 1, potential $G - E$ dependence was considered through the group mean μ_{gk} as follows. $(\mu_{0k}, \mu_{1k}, \mu_{2k})$ was calculated from the following equations $\mu_k n_k = \sum_{g=0,1,2} n_{gk}\mu_{gk}$ and $\mu_{2k} = \mu_{1k} + d_1\sigma_{E_k} = \mu_{0k} + d_2\sigma_{E_k}$, where $d_1 \sim U(0, 0.5)$ and $d_2 \sim U(d_1, 1)$. In general, $\sigma_{E_k} > \sigma_{E_k,\mathrm{w}} \gg \sigma_{E_k,\mathrm{w}}/\sqrt{n_{gk}}$, where the common within group variance $\sigma^2_{E_k,\mathrm{w}}$ is calculated from $n_k\sigma^2_{E_k} = n_k\sigma^2_{E_k,\mathrm{w}} + \sum_{g=0,1,2} n_{gk}(\mu_{gk} - \mu_k)^2$. Thus, the k-th study mean is μ_k, and the group means μ_{gk} are potentially dependent on G. Then E_{ki} were sampled from $E_{ki}|G_{ki} = g, \mu_{gk}, \sigma^2_{E_k,\mathrm{w}} \sim N(\mu_{gk}, \sigma^2_{E_k,\mathrm{w}})$ in order to guarantee that the k-th study variance of E is $\sigma^2_{E_k}$. Then the first and second moments of E are the same with or without assumption 1. Numerically, E has identical marginal distributions with or without assumption 1, as it has symmetric distributions under this setting.