Pleiotropy Exercise Answers
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1) Which of the SNPs have genome-wide significant ($p<5\times10^{-8}$) associations for both phenotypes within a dataset?

		Phenotype 1		Phenotype 2	
Dataset	SNP	OR	P-value	OR	P-value
1	rs1008723	1.25	1.74E-61	1.26	1.02E-66
2	rs4135320	1.23	1.38E-53	1.24	1.12E-51
2	rs1441027	1.23	2.70E-52	1.09	3.24E-09

2) Did the multivariate analyses result in additional SNPs that had genome-wide significant cross phenotype associations? Which SNP(s)?

Yes, the multivariate analysis increased the significance of two SNPs

			Univariate Results			
			Phenotype 1		Phenotype 2	
Dataset	SNP	Multivariate P	OR	P-value	OR	P-value
1	rs1342326	3.12E-10	1.07	1.42E-06	1.07	5.14E-06
2	rs343927	3.39E-11	1.08	9.59E-09	1.08	3.06E-07

3) For each SNP analyzed in the mediation analysis, determine if there is evidence of biological or mediated pleiotropy. If mediated, is the mediation complete or incomplete?

Dataset1 : rs1342326				
	Estimate	95%_CI_Lo	95%_CI_Up	p-value
ACME(control)	5.28E-05	-5.03E-06	0	0.098
ACME(treated)	5.48E-05	-6.05E-06	0	0.098
ADE(control)	1.00E-02	5.58E-03	0.01	<2e-16***
ADE(treated)	1.00E-02	5.59E-03	0.01	<2e-16***
Total_Effect	1.01E-02	5.63E-03	0.01	<2e-16***
Prop_Mediated(control)	5.25E-03	-2.27E-04	0.02	0.098
Prop_Mediated(treated)	5.45E-03	-2.33E-04	0.02	0.098
ACME(average)	5.38E-05	-5.71E-06	0	0.098
ADE(average)	1.00E-02	5.59E-03	0.01	<2e-16***
Prop_Mediated(average)	5.35E-03	-2.30E-04	0.02	0.098

Dataset1 : rs1008723				
	Estimate	95%_CI_Lo	95%_CI_Up	p-value
ACME(control)	9.17E-05	-1.27E-04	0	0.4
ACME(treated)	1.05E-04	-1.45E-04	0	0.4
ADE(control)	3.74E-02	3.32E-02	0.04	<2e-16***
ADE(treated)	3.74E-02	3.32E-02	0.04	<2e-16***
Total_Effect	3.75E-02	3.33E-02	0.04	<2e-16***
Prop_Mediated(control)	2.45E-03	-3.37E-03	0.01	0.4
Prop_Mediated(treated)	2.81E-03	-3.85E-03	0.01	0.4
ACME(average)	9.84E-05	-1.37E-04	0	0.4
ADE(average)	3.74E-02	3.32E-02	0.04	<2e-16***
Prop_Mediated(average)	2.63E-03	-3.61E-03	0.01	0.4

Both rs1342326 and rs1008723 shows evidence of biological pleiotropy since neither the mediated effect estimate or the proportion mediated are significant.

Dataset2: rs4135320				
Estimate 95%	Estimate	95%_CI_Lo	95%_CI_Up	p-value
ACME(control)	0.00715	0.00584	0.01	<2e-16***
ACME(treated)	0.0078	0.00636	0.01	<2e-16***
ADE(control)	0.02416	0.02035	0.03	<2e-16***
ADE(treated)	0.0248	0.02085	0.03	<2e-16***
Total_Effect	0.03195	0.0276	0.04	<2e-16***
Prop_Mediated(control)	0.2238	0.18149	0.26	<2e-16***
Prop_Mediated(treated)	0.24398	0.20011	0.29	<2e-16***
ACME(average)	0.00747	0.00611	0.01	<2e-16***
ADE(average)	0.02448	0.02062	0.03	<2e-16***
Prop_Mediated(average)	0.23389	0.19108	0.28	<2e-16***

Dataset2: rs1441027				
Estimate 95% CI L	Estimate	95%_CI_Lo	95%_CI_Up	p-value
ACME(control)	0.00717	0.0059	0.01	<2e-16***
ACME(treated)	0.00731	0.00599	0.01	<2e-16***
ADE(control)	0.00529	0.00128	0.01	0.006**
ADE(treated)	0.00542	0.00131	0.01	0.006**
Total_Effect	0.0126	0.00839	0.02	<2e-16***
Prop_Mediated(control)	0.56946	0.43422	0.89	<2e-16***
Prop_Mediated(treated)	0.58044	0.4491	0.89	<2e-16***
ACME(average)	0.00724	0.00594	0.01	<2e-16***
ADE(average)	0.00536	0.0013	0.01	0.006**
Prop_Mediated(average)	0.57495	0.44109	0.89	<2e-16***

Dataset2: rs343927				
	Estimate	95%_CI_Lo	95%_CI_Up	p-value
ACME(control)	0.00298	0.00145	0	<2e-16***
ACME(treated)	0.00307	0.00149	0	<2e-16***
ADE(control)	0.00812	0.00423	0.01	<2e-16***
ADE(treated)	0.0082	0.00427	0.01	<2e-16***
Total_Effect	0.01118	0.00662	0.02	<2e-16***
Prop_Mediated(control)	0.26627	0.14569	0.42	<2e-16***
Prop_Mediated(treated)	0.27411	0.15102	0.42	<2e-16***
ACME(average)	0.00302	0.00147	0	<2e-16***
ADE(average)	0.00816	0.00425	0.01	<2e-16***
Prop_Mediated(average)	0.27019	0.14878	0.42	<2e-16***

All three SNPs (rs4135320, rs1441027 and rs343927) show evidence of mediation since the mediated effect and proportion mediated estimates are significant. Since in all three situations the estimated proportions are less than 1 and the 95% CI do not include 1 there is evidence that the mediation is incomplete. This means that there is some independent effect of the SNP on both phenotypes by some of the effect of the SNP on X2 acts through X1.