Supplemental Materials: Examining the Effect of Genes on Depression as Mediated by Smoking and Modified by Sex

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Supplemental Table S1. Mediation, sex stratified mediation, and sex moderated mediation results for the indirect effect of the SNP on depression through log of pack-years of cigarette smoking in the UK Biobank adjusting for age, sex, genetic ancestry via PCs, income, education, and location (urban vs rural).

Chr	Marker	Gene/ nearest gene	Position	Allele Freq.	Prev. smok. assoc. **	Indirect Effect (All)			Indirect Effect (Female)			Indirect Effect (Male)			Sex Moderated Indirect Effect		
						Beta	95% CI	P	Beta	95% CI	P	Beta	95% CI	P	Beta	95% CI	P
1	rs10127497	SGIP1	66584461	0.14	30	-1.4E-5	(-3.8E-4, 3.6E-4)	0.95	-3.9E-5	(-6.8E-4, 6.2E-4)	0.91	-1.5E-5	(-4.4E-4, 4.0E-4)	0.94	-6.9E-8	(-7.7E-4, 6.8E-4)	0.98
1	rs6699744	LOC105378797	72359461	0.61	-	2.6E-4	(1.1E-5, 5.3E-4)	0.05	3.3E-4	(-1.4E-4, 7.9E-4)	0.16	2.1E-4	(-8.2E-5, 5.1E-4)	0.17	-9.5E-5	(-6.9E-4, 4.0E-4)	0.69
1	rs6424532	LOC105378800	73198339	0.49	-	4.7E-4	(2.2E-4, 7.3E-4)	8.0E-4	5.9E-4	(1.5E-4, 1.1E-3)	8.0E-3	3.6E-4	(6.7E-5, 6.5E-4)	0.02	-2.0E-4	(-6.9E-4, 3.9E-4)	0.45
1	rs7548151	ASTN1	177057847	0.08	30, 31	3.4E-4	(-1.4E-4, 8.0E-4)	0.16	1.1E-4	(-7.2E-4, 9.2E-4)	0.76	4.8E-4	(-5.6E-5, 1.0E-3)	0.08	3.9E-4	(-3.8E-4, 1.3E-3)	0.42
5	rs40465	LOC105379109	104646025	0.33	-	-1.1E-4	(-3.9E-4, 1.6E-4)	0.40	-1.2E-4	(-6.0E-4, 3.5E-4)	0.64	-1.2E-4	(-4.4E-4, 2.0E-4)	0.46	1.6E-5	(-4.2E-4, 5.9E-4)	0.94
6	rs3132685	HCG9	29978172	0.13	-	3.7E-4	(-2.5E-5, 7.6E-4)	0.06	5.0E-4	(-1.6E-4, 1.2E-3)	0.14	2.4E-4	(-1.8E-4, 6.7E-4)	0.26	-2.8E-4	(-1.1E-3, 4.8E-4)	0.43
6	rs112348907	KCNQ5	72878230	0.30	30	-3.3E-5	(-3.2E-4, 2.4E-4)	0.82	6.6E-5	(-4.5E-4, 5.6E-4)	0.81	-7.8E-5	(-4.1E-4, 2.4E-4)	0.64	-1.3E-4	(-6.4E-4, 4.2E-4)	0.74
7	rs3807865	TMEM106B	12210776	0.41	-	1.6E-4	(-1.0E-4, 4.2E-4)	0.22	3.3E-4	(-1.4E-4, 8.0E-4)	0.16	5.3E-5	(-2.4E-4, 3.5E-4)	0.73	-2.8E-4	(-7.6E-4, 2.1E-4)	0.31
7	rs2402273	LSM8 / CTTNBP2	117960370	0.41	30, 32-39	1.5E-4	(-1.1E-4, 4.2E-4)	0.26	-1.3E-4	(-5.9E-4, 3.2E-4)	0.57	3.3E-4	(4.5E-5, 6.4E-4)	0.02	5.0E-4	(-6.6E-5, 9.7E-4)	0.08
9	rs263575	BNC2 / CNTLN	17033842	0.46	30, 31	-1.6E-4	(-4.3E-4, 9.7E-5)	0.22	-4.2E-4	(-8.8E-4, 2.9E-5)	0.07	-3.2E-6	(-2.9E-4, 2.9E-4)	0.96	4.1E-4	(-3.9E-5, 9.4E-4)	0.11
10	rs1021363	SORCS3	104851081	0.64	30	-2.0E-4	(-4.6E-4, 6.5E-5)	0.13	-2.5E-4	(-7.3E-4, 2.1E-4)	0.29	-1.6E-4	(-4.6E-4, 1.6E-4)	0.29	1.3E-4	(-4.2E-4, 7.3E-4)	0.73
11	rs10501696	GRM5	89014994	0.50	30, 40, 41	-3.0E-4	(-5.6E-4, -3.4E-5)	0.03	-6.4E-4	(-1.1E-3, -1.8E-4)	3.8E-3	-8.7E-5	(-3.9E-4, 2.2E-4)	0.59	5.6E-4	(-3.1E-5, 1.2E-3)	0.05
13	rs9530139	B3GLCT	31273187	0.19	30	2.3E-5	(-3.0E-4, 3.4E-4)	0.89	-2.5E-4	(-8.4E-4, 2.9E-4)	0.39	1.9E-4	(-1.9E-4, 5.7E-4)	0.31	4.4E-4	(-1.3E-4, 1.0E-3)	0.15
15	rs28541419	MRPL46	88402647	0.23	30	3.4E-5	(-2.6E-4, 3.4E-4)	0.85	-1.2E-4	(-6.5E-4, 4.2E-4)	0.65	1.0E-4	(-2.1E-4, 4.8E-4)	0.47	2.4E-4	(-4.2E-4, 8.6E-4)	0.75

Note: cells are highlighted green when p < 0.05/14, and cells are highlighted yellow when 0.05/14 <= p < 0.05.

** Full citations listed in References section of the main manuscript.

Supplemental Table S2. Mediation, sex stratified mediation, and sex moderated mediation results for the indirect effect of the SNP on depression through log of pack-years of cigarette smoking in COPDGene adjusting for age, sex, genetic ancestry via PCs, income, education, and location (urban vs rural).

Chr	Marker	Gene/ nearest gene	Position	Allele Freq.	Prev. smok. assoc. **	Indirect Effect (All)			Indirect Effect (Female)			Indirect Effect (Male)			Sex Moderated Indirect Effect		
						Beta	95% CI	P	Beta	95% CI	P	Beta	95% CI	P	Beta	95% CI	P
1	rs10127497	SGIP1	66584461	0.14	30	-8.2E-6	(-1.3E-3, 1.3E-3)	0.99	-3.5E-4	(-3.6E-3, 2.7E-3)	0.81	8.4E-5	(-9.3E-4, 1.3E-3)	0.91	3.1E-04	(-2.2E-3, 2.9E-3)	0.87
1	rs6699744	LOC105378797	72360489*	0.20	-	1.5E-4	(-9.6E-4, 1.3E-3)	0.77	-9.1E-4	(-4.0E-3, 1.4E-3)	0.47	2.6E-4	(-8.3E-4, 2.0E-3)	0.64	1.5E-03	(-5.3E-3, 4.6E-3)	0.19
1	rs6424532	LOC105378800	73200931*	0.47	-	2.6E-4	(-7.5E-4, 1.3E-3)	0.53	-4.8E-4	(-2.9E-3, 1.4E-3)	0.60	2.7E-4	(-6.3E-4, 1.6E-3)	0.58	8.6E-04	(-7.0E-4, 3.0E-3)	0.31
1	rs7548151	ASTN1	177057847	0.09	30, 31	-3.6E-4	(-2.1E-3, 1.2E-3)	0.63	-9.0E-4	(-5.4E-3, 3.0E-3)	0.65	-8.7E-5	(-1.7E-3, 1.2E-3)	0.83	4.3E-04	(-3.4E-3, 3.8E-3)	0.91
5	rs40465	LOC105379109	104646025	0.33	-	7.5E-4	(-5.7E-5, 2.1E-3)	0.09	2.3E-3	(1.2E-4, 5.5E-3)	0.03	6.3E-5	(-6.9E-4, 1.1E-3)	0.90	-1.6E-03	(-4.4E-3, 6.1E-4)	0.18
6	rs112348907	KCNQ5	72878230	0.29	30	8.1E-4	(-1.3E-4, 2.2E-3)	0.11	5.9E-4	(-1.5E-3, 3.1E-3)	0.55	5.2E-4	(-8.7E-4, 2.8E-3)	0.47	6.9E-04	(-1.6E-3, 3.2E-3)	0.46
7	rs3807865	TMEM106B	12210776	0.41	-	-3.5E-4	(-1.5E-3, 4.5E-4)	0.43	4.0E-4	(-1.6E-3, 2.8E-3)	0.67	-3.3E-4	(-1.9E-3, 7.1E-4)	0.55	-1.1E-03	(-3.7E-3, 9.0E-4)	0.30
7	rs2402273	LSM8 / CTTNBP2	117960370	0.42	30, 32-39	6.4E-4	(-1.5E-4, 1.9E-3)	0.13	6.0E-4	(-1.6E-3, 2.9E-3)	0.54	2.9E-4	(-5.8E-4, 1.8E-3)	0.56	3.1E-04	(-2.5E-3, 3.1E-3)	0.81
9	rs263575	BNC2 / CNTLN	17033842	0.45	30, 31	-2.1E-4	(-1.2E-3, 6.5E-4)	0.64	1.4E-4	(-2.1E-3, 2.2E-3)	0.93	-1.7E-4	(-1.4E-3, 5.9E-4)	0.72	-5.0E-04	(-2.3E-3, 1.1E-3)	0.64
10	rs1021363	SORCS3	105109590*	0.03	30	-2.3E-3	(-5.7E-3, 1.8E-4)	0.07	-4.0E-3	(-0.01, 8.1E-4)	0.11	-7.9E-4	(-4.8E-3, 2.1E-3)	0.59	7.8E-04	(-5.3E-3, 6.9E-3)	0.77
11	rs10501696	GRM5	88584239*	0.01	30, 40, 41	-7.0E-3	(-1.6E-2, -4.0E-4)	0.03	-0.02	(-0.04, 1.0E-3)	0.08	-1.8E-3	(-0.01, 4.1E-3)	0.59	8.4E-03	(-7.4E-3, 0.03)	0.40
13	rs9530139	B3GLCT	31273187	0.19	30	-6.6E-4	(-2.1E-3, 4.2E-4)	0.24	-9.4E-4	(-3.8E-3, 1.7E-3)	0.45	-3.1E-4	(-2.3E-3, 7.7E-4)	0.59	-3.8E-06	(-2.8E-3, 3.3E-3)	0.92
15	rs28541419	MRPL46	88402647	0.24	30	-8.5E-4	(-2.3E-3, 2.0E-4)	0.12	-1.4E-3	(-4.5E-3, 7.9E-4)	0.22	-3.1E-4	(-2.0E-3, 6.7E-4)	0.60	3.4E-04	(-1.9E-3, 3.1E-3)	0.84

Note: cells are highlighted green when p < 0.05/14, and cells are highlighted yellow when 0.05/14 <= p < 0.05.

** Full citations listed in References section of the main manuscript.

Supplemental Figure S1. These plots depict the effects from the mediation analyses for the SNP rs6424532 [*LOC105378800*]. For the plots in the top row, we adjusted for age, sex (except when stratified by sex), smoking status, and the first 8 PCs. For the plots in the bottom row we also adjusted for college education, low income, and urban living. The plots in column 1 are for the full sample (females and males), the plots in column 2 are females only, and the plots in column 3 are males only.
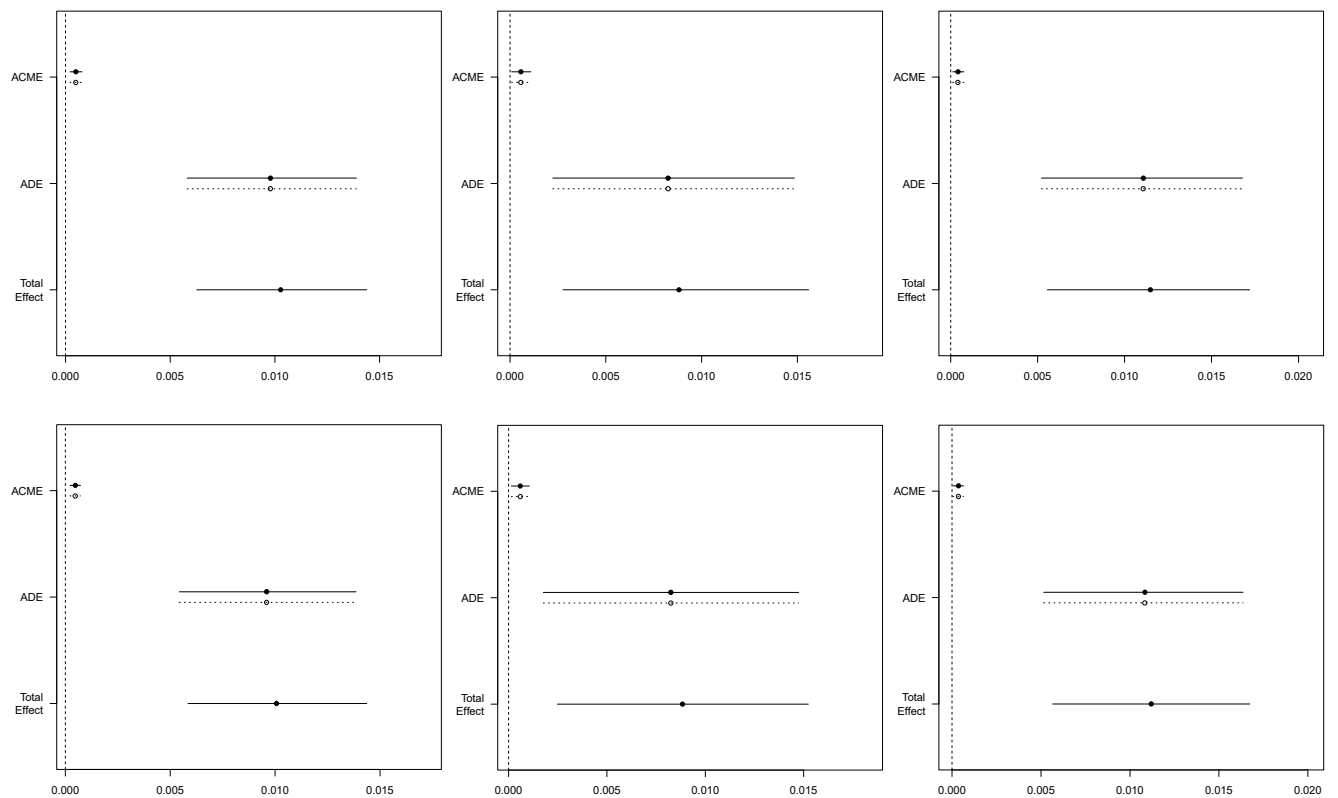
Supplemental Figure S2. These plots depict the effects from the mediation analyses for the SNP rs10501696 [*GRM5*]. For the plots in the top row, we adjusted for age, sex (except when stratified by sex), smoking status, and the first 8 PCs. For the plots in the bottom row we also adjusted for college education, low income, and urban living. The plots in column 1 are for the full sample (females and males), the plots in column 2 are females only, and the plots in column 3 are males only.
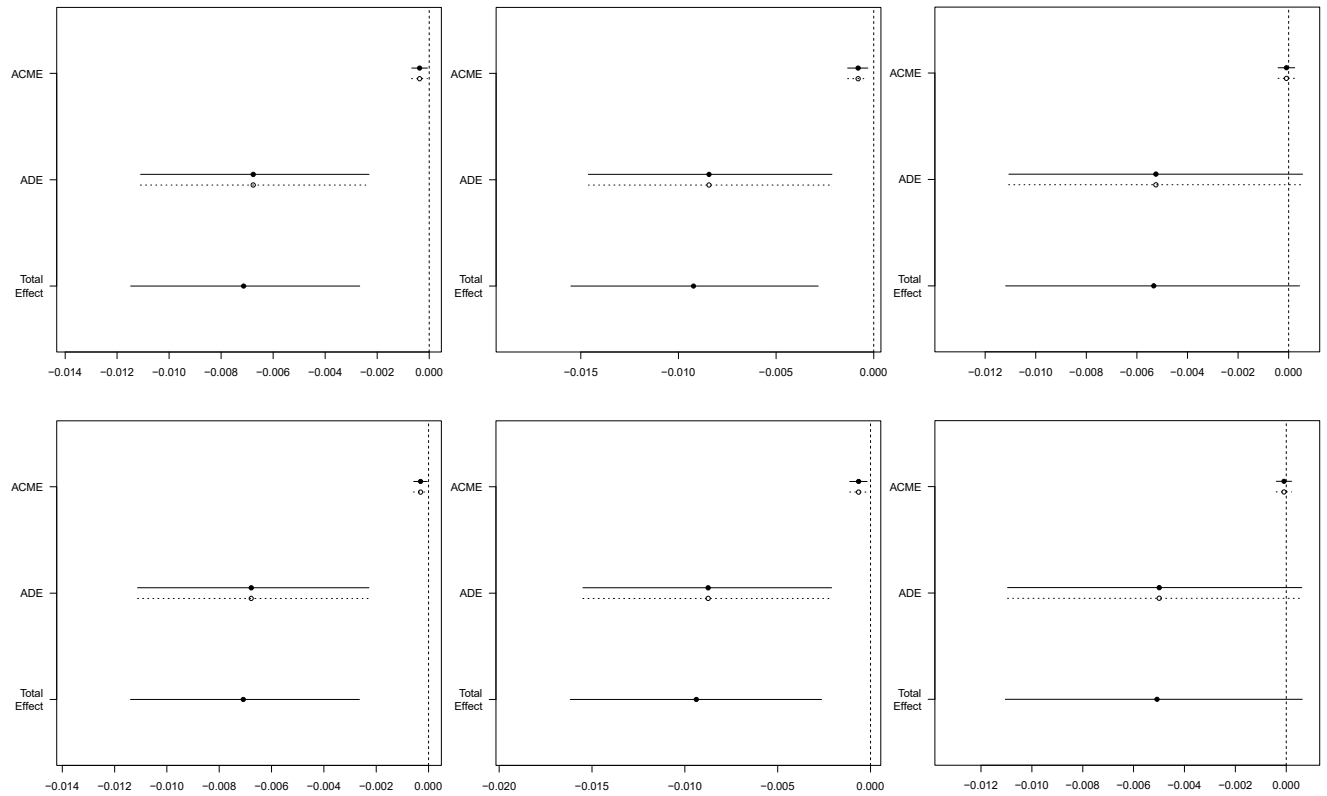
Supplemental Figure S3. The plot depicts the interaction of the SNP rs6424532 [*LOC105378800*] with sex and the log of pack-years on the probability of depression on the logit scale. For the legend, we define which colors correspond to female and which correspond to male with the corresponding number of risk alleles for the SNP rs6424532.
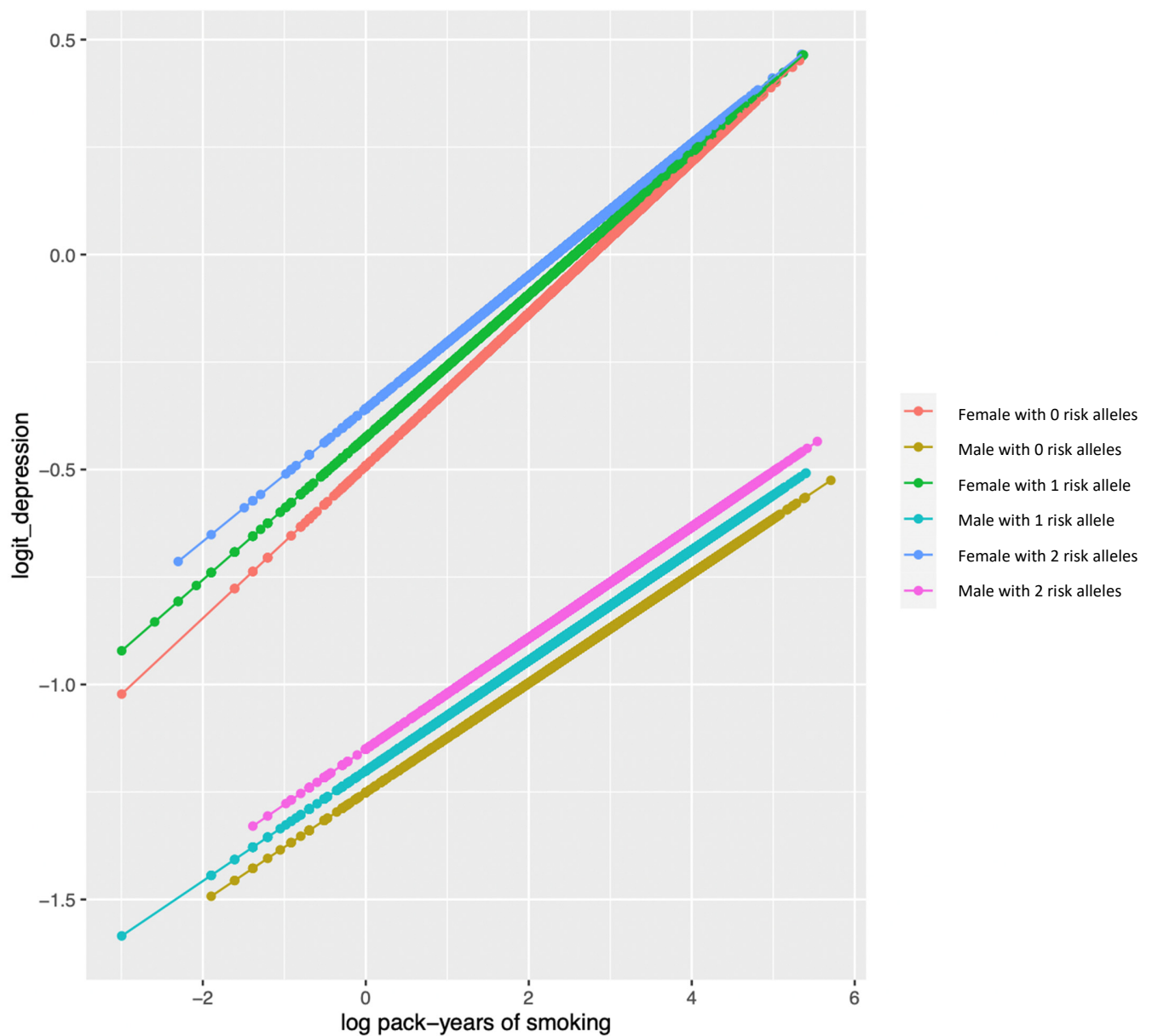
Supplemental Figure S4. The plot depicts the interaction of the SNP rs10501696 [*GRM5*] with sex and the log of pack-years on the probability of depression on the logit scale. For the legend, we define which colors correspond to female and which correspond to male with the corresponding number of risk alleles for the SNP rs10501696.
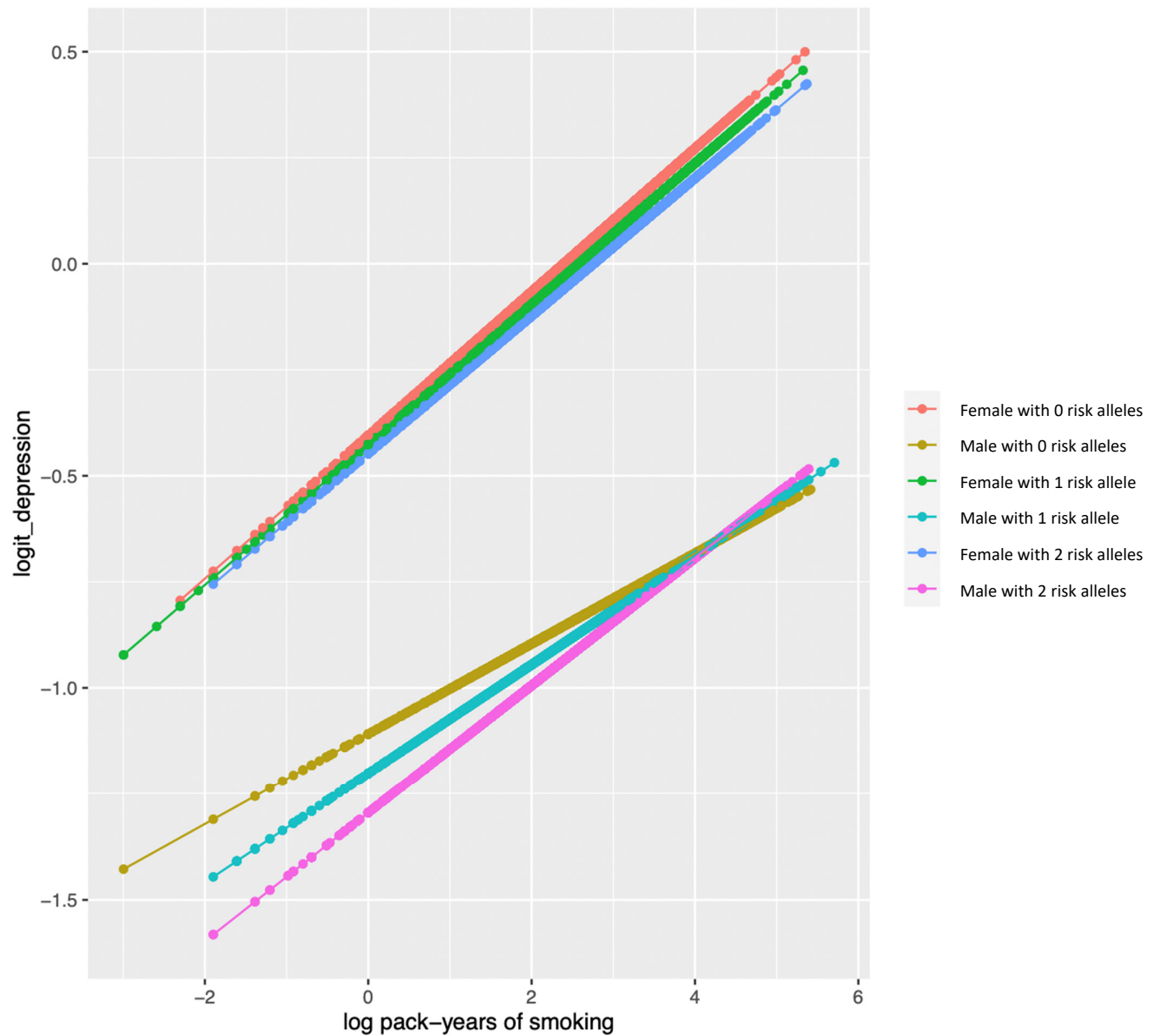
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