Supplementary Materials

Are Prescription Misuse and Illicit Drug Use Etiologically Distinct? A Genetically-Informed Analysis of Opioids and Stimulants

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Biometric Models in Men and Women

Analyses were conducted in Mplus Version 8 (Muthén & Muthén, 2017). Univariate biometric models were fit for 1) prescription opioid misuse, 2) illicit opioid use, 3) prescription stimulant misuse, and 4) illicit stimulant use. Models estimated twin correlations and partitioned the variation in drug (mis)use liability into additive genetic (A; i.e., aggregate effects of genes), shared environmental (C; i.e., influence that makes twins similar), and unique (nonshared) environmental (E; i.e., influence that makes twins different) variance components. Thresholds (prevalences) were allowed to differ across sex. Sex differences were examined within biometric models. Quantitative sex differences (i.e., differences in the proportion of A, C, and E) were examined by constraining parameter estimates for men and women to be equal; qualitative sex differences (i.e., different genetic or environmental source of liability), were tested by constraining the genetic correlation or the shared environmental correlation for opposite-sex twin pairs to 0.5 (i.e., the genetic correlation for same-sex twin pairs) and 1 (i.e., the shared environmental correlation assumed across zygosity), respectively. Significant deterioration in model fit compared to an unconstrained model would indicate the presence of sex differences.

Table S1

Twin correlations of prescription misuse and illicit use in men and women

		Opioids		Stimulants	
		Univariate Correlations		Univariate Correlations	
Zygosity	Sex	Prescription Misuse	Illicit Use	Prescription Misuse	Illicit Use
		r [95% CI]	*r* [95% CI]	*r* [95% CI]	*r* [95% CI]
MZ	M	.22 [.01, .48]	**.31 [.12, .48]***	**.73 [.55, .84]****	**.82 [. 69, .92]****
	F	**.47 [.30, .66]****	**.86 [.55, .97]****	**.80 [.67, .88]****	**.73 [.58, .83]****
DZ	M	.19 [.01, .48]	**.30 [.16, .47]****	**.51 [.28, .73]***	**.49 [.39, .67]****
	F	**.25 [.14, .43]****	**.85 [.62, .96]****	**.41 [.33, .48]****	**.57 [.42, .72]****
OS		.16 [.00, .35]	**.50 [.36, .71]****	.14 [.00, .30]	.27 [.00, .47]
		Bivariate Correlations		Bivariate Correlations	
		Prescription and Illicit Opioid (Mis)Use		Prescription and Illicit Stimulant (Mis)Use	
Zygosity	Sex	Within-Twin	Cross-Twin	Within-Twin	Cross-Twin
		r [95% CI]	*r* [95% CI]	*r* [95% CI]	*r* [95% CI]
MZ	M	**.53 [.18, .73]****	**.51 [.32, .69]****	**.87 [.78, .92]****	**.69 [.51, .80]****
	F	.52 [.00, .75]	.43 [-.07, .70]	**.88 [.82, .93]****	**.66 [.55, .76]****
DZ	M	**.74 [.28, .91]****	**.38 [.07, .60]***	**.92 [.83, .96]****	**.48 [.06, .63]****
	F	**.57 [.21, .77]****	.18 [-.09, .42]	**.85 [.76, .90]****	**.42 [.19, .54]****
OS	(M)	.51 [-.06, .81]*	**.19 [.01, .31]***[a]	**.90 [.77, .94]****	.15 [-21, .37][a]
	(F)	**.36 [.19, .52]****	-.11 [-.28, .06][b]	**.91 [.78, .96]****	.24 [-.05, .44][b]
		Prescription Opioid and Stimulant Misuse		Illicit Opioid and Stimulant Use	
Zygosity	Sex	Within-Twin	Cross-Twin	Within-Twin	Cross-Twin
		r [95% CI]	*r* [95% CI]	*r* [95% CI]	*r* [95% CI]
MZ	M	**.41 [.17, .55]****	**.32 [.10, .45]****	**.67 [.53, .76]****	**.61 [.45, .76]****
	F	**.33 [.16, .47]****	**.29 [.11, .45]****	**.74 [.62, .84]****	**.61 [.38, .76]****
DZ	M	**.57 [.29, .71]****	.21[-.06, .52]	**.61 [.28, .88]****	.22 [-.17, .47]
	F	**.31 [.15, .49]****	.06 [-.12, .24]	**.80 [.66, .85]****	**.67 [.40, 80]****
OS	(M)	**.42 [.22, .60]****	.24 [-.14, .50][a]	**.71 [.57, .79]****	**.21 [.13, .33]***[a]
	(F)	.50 [-.08, .69]	-.23 [-.50, .10][b]	.18 [.00, .34]	.26 [-.23, .61][b]

Note. OS=dizygotic opposite sex pairs; [a] male twin prescription misuse correlated with female twin illicit use, [b] male twin illicit use correlated with female twin prescription misuse; **p<.001, *p<.01.

Table S2

Twin correlations between three forms of stimulant drug use in men and women

			Ecstasy Use		Methamphetamine Use	
	Zyg	Sex	Within-Twin Cross-Trait *r* [95% CI]	Cross-Twin Cross-Trait *r* [95% CI]	Within-Twin Cross-Trait *r* [95% CI]	Cross-Twin Cross-Trait *r* [95% CI]
Prescription Misuse	MZ	M	**.87 [.78, .92]****	**.69 [.53, .81]****	**.86 [.79, .91]****	**.65 [.42, .79]****
		F	**.87 [.81, .92]****	**.66 [.53, .76]****	**.84 [.76, .89]****	**.65 [.40, .78]****
	DZ	M	**.91 [.83, .96]****	**.49 [.24, .68]****	**.82 [.71, .90]****	.18 [-.18, .47]
		F	**.85 [.77, .91]****	**.42 [.22, .56]****	**.76 [.61, .85]****	.00 [-.23, .24]
	OS	(M)	**.90 [.81.95]****	.15 [-.11, .37]	**.73 [.49, 85]****	.36 [.01, .66]
		(F)	**.91 [.79, .96]****	**.25 [.01, .46]***	**.59 [.22, .83]****	.07 [-.32, .37]
	Zyg	Sex	Cross-Twin Within-Trait *r* [95% CI]	Within-Twin Cross-Trait *r* [95% CI]	Cross-Twin Within-Trait *r* [95% CI]	Cross-Twin Cross-Trait *r* [95% CI]
Ecstasy Use	MZ	M	**.82 [.66, .91]****	**.83 [.75, .89]****	**.64 [.27, .86]****	**.72 [.54, .84]****
		F	**.73 [.62, .83]****	**.83 [.75, .88]****	**.71 [.31, .88]****	**.67 [.44, .80]****
	DZ	M	**.50 [.38, .72]****	**.80 [.68, .88]****	**.32 [.10, .47]****	.30 [-.02, .60]
		F	**.57 [.40, .71]****	**.74 [.61, .83]****	**.36 [.16, .45]****	.17 [-.11. .47]
	OS	(M)	**.28 [.04, .47]***	**.77 [.59., 86]****	.14 [.00, .36]	.31 [-.06, .61]
		(F)		**.58 [.22, 97]****		.04 [-.32, 39]

Note. CI=confidence interval, zyg=zygosity; MZ=monozygotic, DZ=dizygotic; OS=dizygotic opposite sex, M=male twin, F=female twin; **p≤.001, *p≤.05.

Table S3

Variation in opioid use propensity attributable to attributable to additive genetic (a^2), shared environmental (c^2), and unique environmental (e^2) factors in men and women

			Men			Women			Model Fit		
		r_g	a^2	c^2	e^2	a^2	c^2	e^2	χ^2	df	*p*
Model					Prescription Misuse						
1a. ACE free, r_g DZO free	Estimate	.48	.06	.16	**.78**	**.43**	.04	**.54**	25.15	27	.57
	95% CI	.00, .50	.00, .53	.00, .49	**.51, 1.00**	**.02, .65**	.00, .46	**.34, .70**			
2a. ACE free, r_g DZO fixed	Estimate	.50	.08	.14	**.78**	**.44**	.03	**.53**	25.98	28	.57
	95% CI	fixed	.00, .44	.00, .39	**.56, .99**	**.07, .61**	.00, .45	**.38, .70**			
3a. ACE fixed, r_g DZO free	Estimate	.41	**.37**	.04	**.59**	**.37**	.04	**.59**	27.68	29	.54
	95% CI	.00, .50	**.06, .50**	.00, .36	**.48, .73**	**.06, .50**	.00, .36	**.48, .73**			
4a. ACE fixed, r_g DZO fixed	Estimate	0.50	**.40**	.01	**.59**	**.40**	.01	**.59**	27.92	30	.57
	95% CI	fixed	**.12, .51**	.00, .36	**.50, .73**	**.12, .51**	.00, .36	**.50, .73**			
Model					Illicit Use						
1b. ACE free, r_g DZO free	Estimate	**.29**	.02	**.29**	**.69**	.04	**.83**	**.14**	26.17	27	.51
	95% CI	**.10, .48**	.00, .36	**.16, .54**	**.46, .82**	.00, .39	**.56, .96**	**.01, .37**			
2b. ACE free, r_g DZO fixed	Estimate	.50	.03	**.28**	**.69**	.00	**.86**	**.14**	25.90	28	.58
	95% CI	fixed	.00, .69	**.15, .54**	**.35, .84**	.00, .52	**.56, .96**	**.02, .40**			
3b. ACE fixed, r_g DZO free	Estimate	**.16**	.00	**.71**	**.29**	.00	**.71**	**.29**	35.38	29	.19
	95% CI	**.16, .21**	.00, .00	**.53, .81**	**.19, .46**	.00, .00	**.53, .81**	**.19, .46**			
4b. ACE fixed, r_g DZO fixed	Estimate	0.50	.00	**.71**	**.29**	.00	**.71**	**.29**	37.19	30	.17
	95% CI	fixed	.00, .04	**.53, .81**	**.16, .45**	.00, .04	**.53, .81**	**.16, .45**			

Note. All models include age as a covariate; bold indicates significant parameter estimate; bolded model=preferred solution; DZO=opposite-sex dizygotic twins; CI=confidence interval; r_g=correlation between genetic influences in opposite sex twin pairs; values may not add to 1 due to rounding error.

Table S4

Variation in stimulant use propensity attributable to additive genetic (a^2), shared environmental (c^2), and unique environmental (e^2) factors in men and women

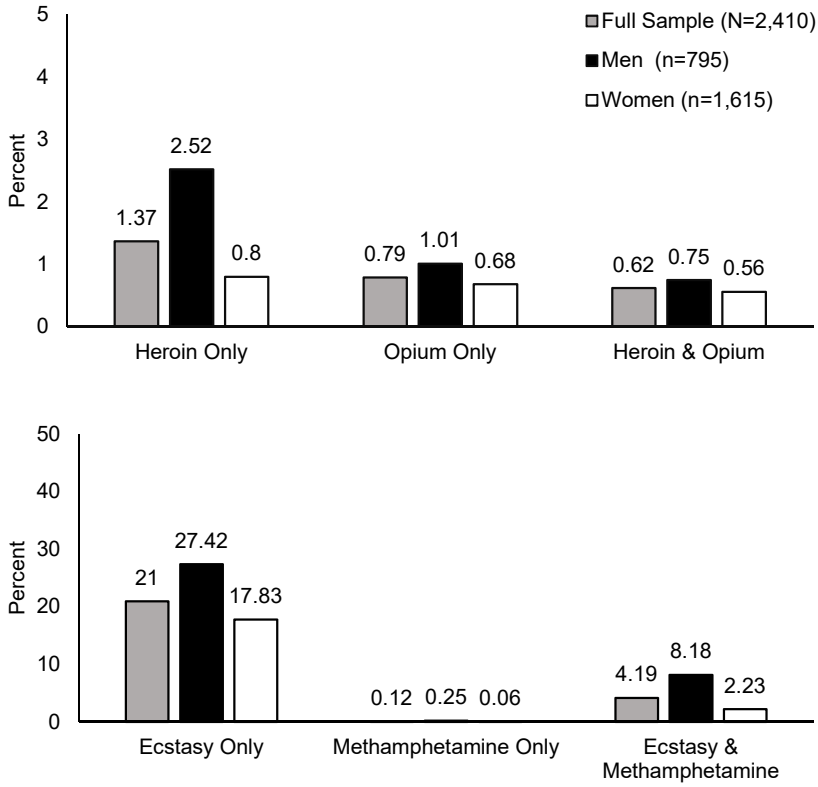
		Men				Women			Model Fit		
		r_g	a^2	c^2	e^2	a^2	c^2	e^2	χ^2	df	*p*
Model		Prescription Misuse									
1a. ACE free, r_g DZO free	Estimate	.15	**.46**	.28	**.27**	**.80**	.01	**.20**	20.75	27	.80
	95% CI	.00, .50	**.02, .82**	.00, .72	**.16, .45**	**.66, .89**	.00, .23	**.12, .31**			
2a. ACE free, r_g DZO fixed	Estimate	.50	.24	**.46**	**.30**	**.80**	.00	**.20**	20.95	28	.82
	95% CI	fixed	.00, .76	**.00, .75**	**.17, .52**	**.67, .89**	.00, .00	**.10, .31**			
3a. ACE fixed, r_g DZO free	Estimate	.18	**.78**	.01	**.21**	**.78**	.01	**.21**	22.12	29	.82
	95% CI	.00, .50	**.57, .87**	.00, .26	**.14, .30**	**.57, .87**	.00, .26	**.14, .30**			
4a. ACE fixed, r_g DZO fixed	Estimate	0.50	**.78**	.00	**.22**	**.78**	.00	**.22**	24.80	30	.73
	95% CI	fixed	**.68, .84**	.00, .00	**.16, .32**	**.68, .84**	.00, .00	**.16, .32**			
Model		Illicit Use									
1b. ACE free, r_g DZO free	Estimate	.00	**.65**	.17	**.18**	.31	**.42**	**.27**	26.73	27	.48
	95% CI	nc	**.17, .89**	.00, .62	**.08, .33**	.00, .67	**.08, .69**	**.18, .39**			
2b. ACE free, r_g DZO fixed	Estimate	.50	**.83**	.00	**.18**	.29	**.44**	**.28**	27.62	28	.48
	95% CI	fixed	**.62, .94**	.00, .75	**.08, .31**	.00, .69	**.03, .67**	**.17, .39**			
3b. ACE fixed, r_g DZO free	Estimate	.00	**.48**	**.29**	**.23**	**.48**	**.29**	**.23**	28.30	29	.50
	95% CI	nc	**.29, .69**	**.10, .45**	**.15, .31**	**.29, .69**	**.10, .45**	**.15, .31**			
4b. ACE fixed, r_g DZO fixed	Estimate	0.50	**.58**	.19	**.24**	**.58**	.19	**.24**	33.20	30	.31
	95% CI	fixed	**.29, .80**	.00, .42	**.16, .32**	**.29, .80**	.00, .42	**.16, .32**			

Note. Bold indicates significant parameter estimate; bolded model=preferred solution; DZO=opposite-sex dizygotic twins; CI=confidence interval; r_g=correlation between genetic influences in opposite sex twin pairs; nc=not calculable (estimate reached boundary condition); values may not add to 1 due to rounding error.

Figures

Figure S1

Prevalence of disaggregated illicit opioid and stimulant use in the full sample, men, and women



Note. Groups are mutually exclusive.

Figure S2

Variation in opioid and stimulant use propensity attributable to additive genetic (a^2), shared environmental (c^2), and unique environmental (e^2) factors in men (a) and women (b)