**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.

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| 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. |

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| 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 |  | Cross-Twin Cross-Trait |  | Within-Twin Cross-Trait |  | Cross-Twin Cross-Trait |
|  |  | *r* [95% CI] |  | *r* [95% CI] |  | *r* [95% CI] |  | *r* [95% CI] |
| Prescription Misuse | MZ | M | **.87 [.78, .92]\*\*** | Prescription Misuse | **.69 [.53, .81]\*\*** | Prescription Misuse | **.86 [.79, .91]\*\*** | Prescription Misuse | **.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 |  | Within-Twin Cross-Trait |  | Cross-Twin Within-Trait |  | Cross-Twin Cross-Trait |
|  |  | *r* [95% CI] |  | *r* [95% CI] |  | *r* [95% CI] |  | *r* [95% CI] |
| Ecstasy Use | MZ | M | **.82 [.66, .91]\*\*** | Meth Use | **.83 [.75, .89]\*\*** | Meth Use | **.64 [.27, .86]\*\*** | Ecstasy Use | **.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. |

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| Table S3*Variation in opioid use propensity attributable to attributable to additive genetic (a2), shared environmental (c2), and unique environmental (e2) factors in men and women* |
|  |  |  | Men | Women | Model Fit |
|  | *rg* | *a2* | *c2* | *e2* | *a2* | *c2* | *e2* | χ2 | df | *p* |
| Model | Prescription Misuse |
| 1a. ACE free, *rg* 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, *rg* 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, *rg* 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, *rg* 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, *rg* 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, *rg* 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, *rg* 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, *rg* 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; *rg=*correlation between genetic influences in opposite sex twin pairs; values may not add to 1 due to rounding error. |

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| Table S4*Variation in stimulant use propensity attributable to additive genetic (a2), shared environmental (c2), and unique environmental (e2) factors in men and women* |
|  |  |  | Men | Women | Model Fit |
|  | *rg* | *a2* | *c2* | *e2* | *a2* | *c2* | *e2* | χ2 | df | *p* |
| Model | Prescription Misuse |
| 1a. ACE free, rg 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, rg 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, rg 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, rg 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, rg 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, rg 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, rg 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, rg 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; *rg=*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 (a2), shared environmental (c2), and unique environmental (e2) factors in men (a) and women (b)*