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# Differential Etiologic Associations of Heroin Use and Prescription Opioid Misuse With Psychopathology

Genevieve F. Dash[1], Ian R. Gizer[1], Nicholas G. Martin[2], and Wendy S. Slutske[3, 4]
[1] Department of Psychological Sciences, University of Missouri
[2] QIMR Berghofer, Brisbane, Queensland, Australia
[3] Department of Family Medicine and Community Health, University of Wisconsin
[4] Center for Tobacco Research and Intervention, University of Wisconsin

Patterns of association with externalizing and internalizing features differ across heroin use and prescription opioid misuse (POM). The present study examined whether heroin use and POM display differential etiologic overlap with symptoms of conduct disorder (CD), adult antisocial behavior (AAB), and major depressive episodes (MDEs), how aggregating heroin use and POM into a single phenotype may bias results, and explored potential sex differences. Seven thousand one hundred and sixty-four individual twins from the Australian Twin Registry (ATR; 59.81% female; $M_{age} = 30.58$ years) reported lifetime heroin use, POM, CD symptoms, AABs, and MDE symptoms within a semi-structured interview. Biometric models decomposed phenotypic variance and covariance into additive genetic, common environmental, and unique environmental effects. The proportion of variance in heroin use attributable to factors shared with CD, AAB, and MDE, respectively, was 41%, 41%, and 0% for men and 26%, 19%, and 42% for women; for POM, the proportions were 33%, 35%, and 20% for men and 15%, 9%, and 13% for women. CD and AAB were more strongly genetically correlated with heroin use among women and with POM among men. MDE was more strongly genetically correlated with POM than with heroin use among men, but more strongly genetically correlated with heroin use than with POM among women. Analyses using an aggregate opioid (mis)use variable were biased toward POM, which was the more prevalent phenotype. Magnitude and source of etiologic influence may differ across forms of opioid (mis)use and sex. Disaggregating heroin use and POM in future opioid research may be warranted.

***General Scientific Summary***

This study provides preliminary evidence of differences in the magnitude and source of etiologic associations of heroin use and prescription opioid misuse (POM) with psychopathology. Whereas conduct disorder showed differences in the source of shared etiology (genes vs. environment) across heroin use and POM, overlap with depression was solely attributable to genetic influences across both opioid types. However, depression showed differences in the magnitude of shared genetic etiology with heroin use versus POM that also differed across men and women.

*Keywords:* opioids, heroin, prescription misuse, conduct disorder, depression

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Genevieve F. Dash https://orcid.org/0000-0002-4394-0700
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Correspondence concerning this article should be addressed to Genevieve F. Dash, Department of Psychological Sciences, University of Missouri, 210 McAlester Hall, 320 South 6th Street, Columbia, MO 65211, United States. Email: genevievedash@mail.missouri.edu

High rates of opioid use and related mortality over the past two decades have prompted much research into epidemiologic patterns of opioid initiation, use and misuse, overdose, and related deaths (De Nadai et al., 2019; Schepis et al., 2019; Scholl et al., 2019; Spencer et al., 2019; Wilson, 2020). However, heroin use and prescription opioid misuse (POM) are not often compared directly as potentially distinct behaviors. It has been suggested that, although POM substantially increases the risk of heroin use and many people who currently use heroin-initiated opioid use via POM, POM is "neither necessary nor sufficient" to explain increases in heroin use and related deaths (Compton et al., 2016). It may be the case that, despite overlapping pharmacological characteristics (Compton et al., 2016; Inaba & Cohen, 2014), genetic and environmental risk factors underlying the (mis)use of these two substances may differ in potentially significant ways.

Twin data have been critical in understanding the role of common liability in drug use behaviors (Karkowski et al., 2000; Kendler et al., 2000, 2003, 2007). Twin studies leverage assumptions about the nature of twin relatedness to ascertain the relative influence of genes and environment on behaviors of interest, and can be extended to estimate the correlation between such genetic and environmental influences across pairs of traits. Our recent work in this area has suggested that heroin use and POM may be influenced by partially distinct sources of genetic and environmental risk. Namely, data from a large twin cohort indicated that heroin use was strongly influenced by common environmental influences, while POM had a more robust genetic component; there was a modest but nonsignificant genetic correlation between the two ($r_G = .39$) and environmental correlations were negligible and nonsignificant ($r_C = .08$; $r_E = .06$) (Dash et al., 2022). Extending into a multivariate framework, we found that most of the phenotypic variance in heroin use (78%–80%) was attributable to general liability shared across ten other drug types, while much of the variance in POM (45%–75%) was drug-specific. Similarly, all of the genetic influence on heroin use was attributable to a common genetic factor, while 69%–74% of the genetic variance in POM was drug-specific (Dash, Gizer, et al., 2023).

Externalizing and internalizing characteristics have well-established genetic influences (Arcos-Burgos et al., 2012; Cohen-Woods et al., 2013; Flint & Kendler, 2014; Gizer et al., 2016) and may underpin potentially unique genetic liability factors for heroin use versus POM. It is evident in both community-based and treatment-seeking samples that heroin use is robustly associated with externalizing spectrum behaviors and related psychopathology (Darke et al., 2017; Smith et al., 2017). For example, conduct disorder (CD) increased the odds of illegal polydrug use (including heroin) as compared to prescription drug misuse among community-based adults (Dash et al., 2021), and antisocial personality disorder was associated with significantly higher odds of heroin use, but not misuse of OxyContin, oxycodone, or methadone, among community-based adults who use drugs (Smith et al., 2017). Similarly, community-based youth who initiated heroin use between ninth and 12th grade had significantly higher average scores on indexes of impulsivity, such as positive and negative urgency, than those who did not initiate heroin use (Kelley-Quon et al., 2019). Treatment-seeking individuals who use heroin evidence higher delay discounting as compared to those who exclusively misuse prescription opioids (Karakula et al., 2016). Such findings suggest that there may be a uniquely strong association between externalizing features and heroin use that is not similarly shared with POM.

Seemingly somewhat less aligned with externalizing features than heroin use, POM often presents in the context of internalizing spectrum behaviors. Hopelessness is associated with the consumption of prescription opioids—medically sanctioned or not (Chinneck et al., 2018)—and one study found that nearly 56% of college students reporting POM in the past 6 months screened positively for major depressive disorder (Davis et al., 2020). Rosoff et al. (2021) identified potentially causal associations between dimensions of internalizing psychopathology and prescription opioid use, with genetic liability for depression significantly increasing prescription opioid use risk. Other studies have also found that exposure to prescription opioids increases the risk of depression, suggesting a likely bidirectional relationship between the two (Grattan et al., 2012; Scherrer et al., 2014).

In contrast to the apparent discrepancy in POM's and heroin's magnitudes of association with externalizing behavior, a similar discrepancy does not seem to characterize POM's and heroin's magnitudes of association with internalizing features. Youth who initiate heroin use during high school do not report more depression or anxiety symptoms than those who do not initiate heroin use despite significantly higher levels of impulsivity (Kelley-Quon et al., 2019). Rates of mood disorders, anxiety disorders, and suicidality are comparable among adults reporting heroin use and those reporting POM (Rigg & Monnat, 2015; Wu et al., 2011), though depression has been found to increase odds of prescription drug misuse as compared to illegal polydrug use (including heroin) (Dash et al., 2021).

## Present Study

These patterns of effect suggest that etiologic relationships between heroin use and POM with psychopathology may differ. With the goal of identifying who is vulnerable to various forms of hazardous opioid use and through what mechanisms this vulnerability may operate, the present study aimed to test and compare the degree to which genetic and environmental influences in heroin use and POM are shared with externalizing behaviors (CD symptoms, adult antisocial behavior [AAB]) and major depressive episode (MDE) symptoms. Further, we aimed to explore how the use of an aggregate opioid (mis)use variable that collapses heroin and POM into a single phenotype, a common approach in the behavior genetics literature (Gaddis et al., 2022; Hatoum et al., 2022; Karkowski et al., 2000; Kember et al., 2022; Kendler et al., 1999, 2003, 2006; Polimanti et al., 2020; Van den Bree et al., 1998; Zhou et al., 2020), might produce results biased toward the more frequently used opioid type. Given evidence of sex differences in the genetic etiology of heroin and other opioid (mis)use (Van den Bree et al., 1998), such that genetic influences on opioid use predominate among men and common environmental influences predominate among women, we also aimed to explore how patterns of genetic and environmental overlap of opioid phenotypes with CD, AAB, and MDE may differ across sex. We hypothesized that the genetic correlation between heroin use and CD/AAB would be stronger than that between POM and CD/AAB and that the genetic correlation between POM and MDE would be stronger than that between POM and CD/AAB. We anticipated results from the aggregate opioid (mis)use models would be biased toward the more prevalent opioid phenotype (in this case, POM). Given the limited extant literature upon which to build theory-driven hypotheses, the analyses examining sex differences were exploratory.

## Method

### Participants and Procedure

ATR Cohorts II and III (Hopper et al., 2013) include Australian twins of primarily European ancestry born between 1964 and 1979. ATR Cohort II data were collected between 1996 and 2000 via a telephone interview; ATR Cohort III data were collected between 2005 and 2009 via computer-assisted telephone interview. The combined sample was comprised of 7,164 individual twins ($M_{age} = 30.58$ years [$SD = 2.64$], range = 22–43) from both complete and incomplete same-sex pairs (monozygotic male [MZM] = 1,555; monozygotic female [MZF] = 2,405; dizygotic male [DZM] = 1,324; dizygotic female [DZF] = 1,880). Of the full sample, 6,026 individual twins (84.12%) were part of a complete twin pair (MZM = 1,264; MZF = 2,122; DZM = 1,030; DZF = 1,610). The original data collection was approved by the Institutional Review Boards at Washington University and Queensland Institute of Medical Research Berghofer, and secondary analysis of these data was determined to be exempt by the University of Missouri Institutional Review Board. Requests for data can be made through Twins Research Australia (https://www.twins.org.au/research).

### Measures

In both ATR cohorts, assessments were conducted within the Semi-Structured Assessment for the Genetics of Alcoholism, adapted for the Australian population (SSAGA-OZ; Bucholz et al., 1994).

#### *Drug Use*

Ahead of their interview, participants were provided with a respondent booklet containing nine lists of substances corresponding to a class of drug, including opioids. Individual opioid drugs were described by name and by common slang terms, where relevant. The list included heroin and prescription opioid drugs such as codeine, methadone, and morphine. For each list, participants were asked "Have you ever used any of the items in List [X]?" to query lifetime drug use. A positive response prompted a query as to which drug(s) on the list they had used, with instructions for reporting the use of medically indicated drugs ("when not prescribed or more than prescribed"). Responses were coded as binary (yes/no) variables. An aggregate opioid (mis)use variable was created such that respondents who endorsed heroin use, POM, or both were coded positively for aggregate opioid (mis)use.

#### *Psychopathology*

Participants were administered a *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) diagnostic assessment of CD symptoms. Items queried behaviors that occurred prior to age 18. Endorsed symptoms were summed to create a cumulative CD symptom score. Participants who met the criteria for CD were subsequently assessed for AAB. Participants were queried regarding the frequency of engagement in a series of 17 antisocial behaviors (e.g., taking advantage of others without remorse, stealing or destroying property, physically harming others on purpose) since age 18. Endorsed behaviors were summed to create a total AAB score. Participants were also administered a *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) assessment of lifetime MDEs, which queried their most severe period of depression. Endorsed symptoms were summed to create a total symptom count score.

### Analytic Plan

#### *The Classical Twin Design*

The classical twin design conceptualizes variance in a given phenotype as being comprised of three sources of variance: genes (additive [*A*] or dominant [*D*]), common (shared) environment (*C*), and unique (unshared/individual-specific) environment (*E*). Because monozygotic (MZ) twins share all of their genetic material, they are assumed to be genetically identical such that $r_G = 1.00$. Dizygotic (DZ) twins are assumed to share, on average, 50% of their segregating genes, such that $r_G = .50$. Common environment is assumed to be fully shared across twins and is correlated equivalently in MZ and DZ pairs, such that $r_C = 1.00$. The unique environment is assumed to be perfectly uncorrelated across twins of both zygosities, such that $r_E = .00$, and also includes measurement error. By imposing these correlations on observed twin data, variance in a given trait can be decomposed in *A*, *C* (or *D*), and *E* influences. This can be extended to two or more traits to estimate the contribution of genes and environment to the covariance between phenotypes.

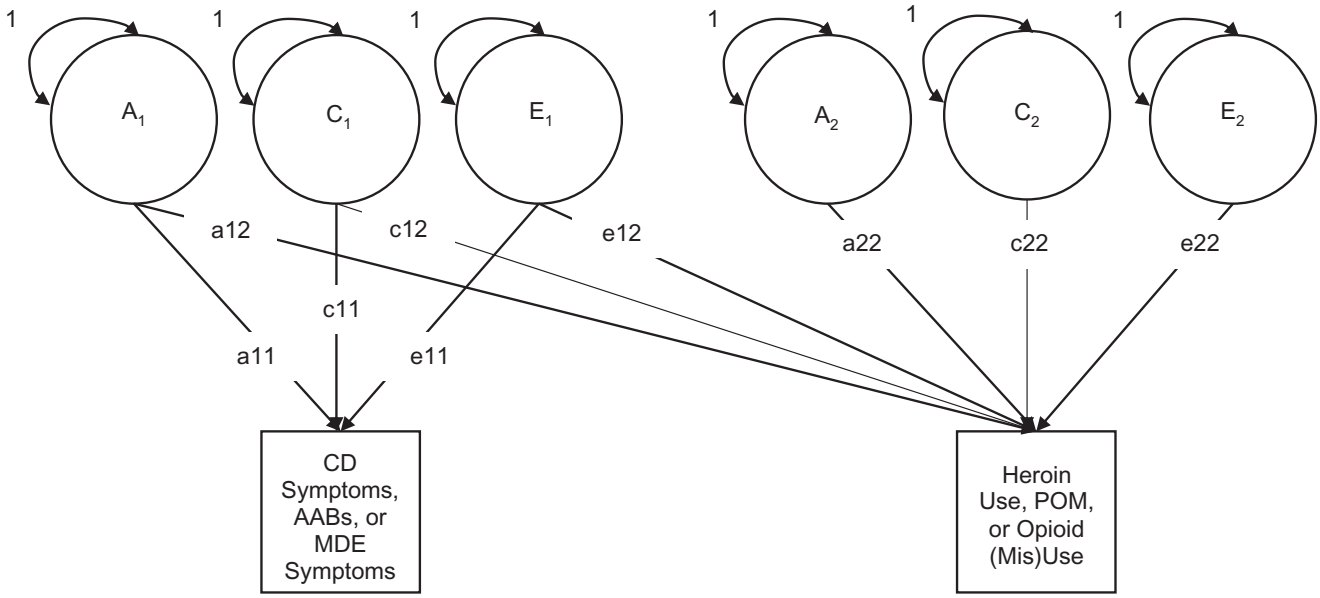
#### *Biometric Modeling*

Analyses were conducted in Mplus Version 8 (Muthén, 2017). First, four- and two-group univariate biometric models were run. These models estimated twin correlations for each phenotype within each zygosity group (four-group: MZM, MZF, DZM, DZF; two-group: MZ, DZ) and partitioned the variation in drug use liability into additive genetic (*A*), common environmental (*C*), and unique (individual-specific) environmental (*E*) influences; the latter also includes measurement error. In the four-group model, the thresholds (prevalences) for men and women were allowed to differ and the cohort was included as a covariate; in the two-group model, sex and cohort were included as covariates. Quantitative sex differences, or differences in the proportion of genetic, common environmental, and individual-specific environmental factors, were examined by constraining parameter estimates for men and women to equality within the four-group models; a significant decrement in model fit under these constraints would indicate the presence of quantitative sex differences. Model comparisons were conducted with Wald tests.

Next, a series of bivariate Cholesky models (see Figure 1) were run for each pair of phenotypes to decompose their covariance into *A*, *C*, and *E* components. The cohort was included as a covariate in all models and sex was included as a covariate in models that were not stratified by sex. Phenotypic (within-twin cross-trait) and cross-twin cross-trait correlations were derived from the full, freely estimated models. Model comparison was subsequently conducted by testing whether nonsignificant parameters could be constrained to zero via Wald tests to identify the best fit and most parsimonious model. Correlations between the genetic ($r_G$), common environmental ($r_C$), and unique environmental ($r_E$) influences on pairs of phenotypes were calculated within

**Figure 1**

*Simplified Depiction of Full Bivariate Cholesky Model*




*Note.* CD = conduct disorder; AAB = adult antisocial behavior; MDE = major depressive episode; POM = prescription opioid misuse; A = additive genetic factor; C = common environmental factor; E = unique environmental factor; 11 = paths from the first component factor to the psychopathology phenotype; 12 = the path from the first component factor to the opioid phenotype; 22 = the path from the second component factor to the opioid phenotype. The figure depicts model for one twin for ease of interpretation.

the best-fit models as follows:

$$r_G = \frac{a_{11} \times a_{12}}{\sqrt{a_{11}^2} \times \left(a_{12}^2 + a_{22}^2\right)} \quad r_C = \frac{c_{11} \times c_{12}}{\sqrt{c_{11}^2} \times \left(c_{12}^2 + c_{22}^2\right)}$$
$$r_E = \frac{e_{11} \times e_{12}}{\sqrt{e_{11}^2} \times \left(e_{12}^2 + e_{22}^2\right)}, \quad (1)$$

where "11" notation represents the path from the first component factor ($A_1/C_1/E_1$ in Figure 1) to the first phenotype (CD symptoms, AABs, or MDE symptoms), "12" notation represents the path from the first component factor to the second phenotype (heroin use, POM, or opioid (mis)use), and "22" notation represents the path from the second component factor ($A_2/C_2/E_2$ in Figure 1) to the second phenotype. Within the bivariate Cholesky model, the first component factor is the sole cause of the first phenotype and a partial cause of the second phenotype; the second component factor is a residual, representing the variance in the second phenotype independent of the first component factor and first phenotype (Loehlin, 1996). Variance component estimates were standardized and scaled to reflect the proportion of variance in each trait attributable to each factor.

Both univariate and bivariate models were fitted by the method of robust weighted least squares directly to the raw twin data, which uses data from incomplete as well as complete twin pairs and is robust to nonindependence of clustered data and distributional nonnormality. This approach uses a pairwise present method data to handle missing data, which were minimal (<1%). A liability-threshold model, which assumes that there is a latent liability continuum underlying the binary drug use variables, was employed (Neale & Cardon, 2013). Bias-corrected bootstrapped confidence intervals were estimated. Correlations were compared using Cumming's 50% overlap rule (Cumming, 2009). Model code is available upon request to the first author. Analyses were not preregistered and should be considered exploratory.

## Results

### Descriptive Statistics

The prevalence of heroin use, POM, and aggregate opioid (mis)use, as well as mean counts of CD symptoms, AABs, and MDE symptoms by zygosity group and in the full sample, are presented in Table 1. Of the full sample, 1.31% endorsed heroin use, 7.76% endorsed POM, and 8.33% endorsed any opioid (mis)use. Rates of POM and aggregate opioid (mis)use were comparable across men and women, $\chi^2(1) = 0.57$, $p = .45$; $\chi^2(1) = 0.04$, $p = .85$, whereas heroin use was more prevalent among men, $\chi^2(1) = 20.23$, $p < .001$. Mean symptom counts for CD, AAB, and MDE in the full sample were 0.84, 0.25, and 1.81, respectively. The mean numbers of CD symptoms, $t(7{,}160) = 20.33$, $p < .001$, and AABs, $t(7{,}159) = 20.21$, $p < .001$, were higher among men, while the mean number of MDE symptoms was higher among women, $t(7{,}118) = -10.58$, $p < .001$. These differences are consistent with well-established epidemiologic patterns of drug use and psychopathology (Marsh et al., 2018; Nolen-Hoeksema, 2001; Piccinelli & Wilkinson, 2000; Rosenfield, 2000).

### Univariate Models

Univariate (cross-twin within-trait) twin correlations for opioid phenotypes are presented in Table 2 (correlations from the two-group models are available in Table S1 of the online supplemental materials;

**Table 1**
*Descriptive Statistics for Each Phenotype by Zygosity*

| | Combined | | Men | | Women | |
|---|---|---|---|---|---|---|
| Phenotype | MZ *n* (%) | DZ *n* (%) | MZ *n* (%) | DZ *n* (%) | MZ *n* (%) | DZ *n* (%) |
| Heroin use | 48 (1.21) | 46 (1.44) | 28 (1.80) | 31 (2.34) | 20 (0.83) | 15 (0.80) |
| POM | 331 (8.36) | 225 (7.02) | 129 (8.30) | 86 (6.50) | 202 (8.40) | 139 (7.39) |
| Opioid (mis)use | 346 (8.74) | 251 (7.83) | 139 (8.94) | 103 (7.78) | 207 (8.61) | 148 (7.87) |
| Phenotype | *M* (*SD*) | *M* (*SD*) | *M* (*SD*) | *M* (*SD*) | *M* (*SD*) | *M* (*SD*) |
| CD symptoms | 0.78 (1.22) | 0.86 (1.26) | 1.12 (1.50) | 1.23 (1.52) | 0.57 (0.94) | 0.60 (0.96) |
| AAB | 0.23 (3.36) | 0.27 (2.92) | 0.40 (0.81) | 0.47 (0.84) | 0.12 (0.44) | 0.13 (0.44) |
| Depression symptoms | 1.79 (2.81) | 1.85 (2.87) | 1.24 (2.48) | 1.55 (2.69) | 2.14 (2.96) | 2.06 (2.97) |

*Note.* MZ = monozygotic; DZ = dizygotic; POM = prescription opioid misuse; CD = conduct disorder; AAB = adult antisocial behavior.



correlations reported in text were significant unless denoted by *ns*). Heroin use was more strongly correlated within twin pairs ($r_{MZ} = .59–.88$; $r_{DZ} = .36–.79$) than was POM ($r_{MZ} = .32–.47$; $r_{DZ} = .19–.24$), indicating more robust familial (genetic, common environmental) influences for heroin use. The magnitude of MZ compared to DZ correlations for heroin use indicated that genetic influences predominate among men, while common environmental influences predominate among women. For POM, the magnitude of MZ compared to DZ correlations indicated that genetic influences predominate for both men and women. As anticipated, correlations for aggregate opioid (mis)use ($r_{MZ} = .33–.49$; $r_{DZ} = .17–.25$) were more aligned with those for POM than with those for heroin use. Variance estimates from univariate models are depicted in Figure 2 (estimates from two-group models are depicted in Figure S1 of the online supplemental materials). Estimates for heroin use, POM, and MDE could be constrained to equality across sex, Wald $\chi^2(2) = 3.97$, $p = .14$; Wald $\chi^2(2) = 1.31$, $p = .52$; Wald $\chi^2(2) = 4.96$, $p = .08$. Estimates for CD, Wald $\chi^2(2) = 82.37$, $p < .001$, and AAB, Wald $\chi^2(2) = 192.51$, $p < .001$, could not. As such, variance estimates for all phenotypes are presented separately by sex to maintain consistency and interpretability.

## Bivariate Models

Bivariate twin correlations (within-twin cross-trait [phenotypic], cross-twin cross-trait) are presented in Table 2 (correlations from the two-group models are available in Table S1 of the online supplemental materials; correlations reported in text were significant unless denoted by *ns*). Heroin use and POM were comparably correlated with CD at the phenotypic level among men ($r = .29–.30$); among women, heroin use appeared to be more strongly correlated with CD ($r = .27$) as compared to POM ($r = .19$). Among both men and women, cross-twin cross-trait correlations appeared somewhat stronger for heroin use and CD ($r_{MZ} = .27–.29$; $r_{DZ} = .19–.19$) than for POM and CD ($r_{MZ} = .12–.19$; $r_{DZ} = .11–.15$). Such a pattern suggests a higher degree of overlapping familial influences for heroin use and CD than for POM and CD. Correlations of heroin use and POM with AAB were of comparable magnitude at the phenotypic level among men ($r = .23–.25$) and women ($r = .13–.18$). Cross-twin cross-trait correlations with AAB were also comparable across heroin use ($r_{MZ} = .26$; $r_{DZ} = .15$) and POM ($r_{MZ} = .22$; $r_{DZ} = .14$) among men, but not women ($r_{MZ} = .24$; $r_{DZ} = .12$ vs. $r_{MZ} = .12$; $r_{DZ} = .06$). Heroin use and POM were roughly comparably correlated with MDE at the phenotypic level ($r = .21–.32$ and $.22–.22$), respectively. Among men, cross-twin cross-trait correlations for heroin use and MDE ($r_{MZ} = .19$; $r_{DZ} = .07$, *ns*) were similar to those of POM and MDE ($r_{MZ} = .17$; $r_{DZ} = .11$); among women, associations were stronger for heroin use and MDE ($r_{MZ} = .37$; $r_{DZ} = .20$) than for POM and MDE ($r_{MZ} = .12$; $r_{DZ} = .06$, *ns*). As anticipated, the pattern of correlations for aggregate opioid (mis)use was notably more similar to that for POM than for heroin use.

Results from the best-fit bivariate Cholesky models in men and women are presented in Tables 3 (CD), 4 (AAB), and 5 (MDE); results from the two-group models (pooled across sex) are available in Tables S2 (CD), S3 (AAB), and S4 (MDE) of the online supplemental materials. The parameter labels in the tables may be cross-referenced with Figure 1 to facilitate interpretation. Parameters $a11$, $c11$, and $e11$ (i.e., paths from $A_1$, $C_1$, and $E_1$ to the first phenotype; see Figure 1) capture the total variance in the psychopathology trait (CD symptoms, AABs, or MDE symptoms) in each respective model. Parameters $a12$, $c12$, and $e12$ (i.e., paths from $A_1$, $C_1$, and $E_1$ to the second phenotype) and parameters $a22$, $c22$, and $e22$ (i.e., paths from $A_2$, $C_2$, and $E_2$ to the second phenotype) capture the total variance in the opioid trait (heroin use, POM, or aggregate opioid (mis)use; see Figure 1). Parameter values are directly interpretable as the proportion of variance in the trait attributable to that parameter.

### *CD Symptoms*

**Heroin Use Models.** In models for both men and women, parameters reflecting loadings of heroin use on common environmental ($c12$) and unique environmental ($e12$) factors shared with CD could be constrained to zero, Wald $\chi^2(2) = 0.66$, $p = .72$; Wald $\chi^2(2) = 1.56$, $p = .46$; for men, the residual common environmental parameter for heroin use ($c22$) could also be constrained to zero, Wald $\chi^2(3) = 0.66$, $p = .88$. Under the best-fit models, 41% and 26% of the total phenotypic variance in heroin use was attributable to factors shared with CD for men and women, respectively. All of this variance was captured by genetic influences ($A_1$), corresponding to 71% of the total genetic variance in heroin use for men ($r_G = .84$) and 67% of the total genetic variance in heroin use for women ($r_G = .80$). Under the best-fit two-group model, 15% of the variance in heroin use was shared with CD. This was attributable to genetic ($r_G = .36$, *ns*) and common environmental ($r_C = 1.00$, fixed) influences.

**Table 2**

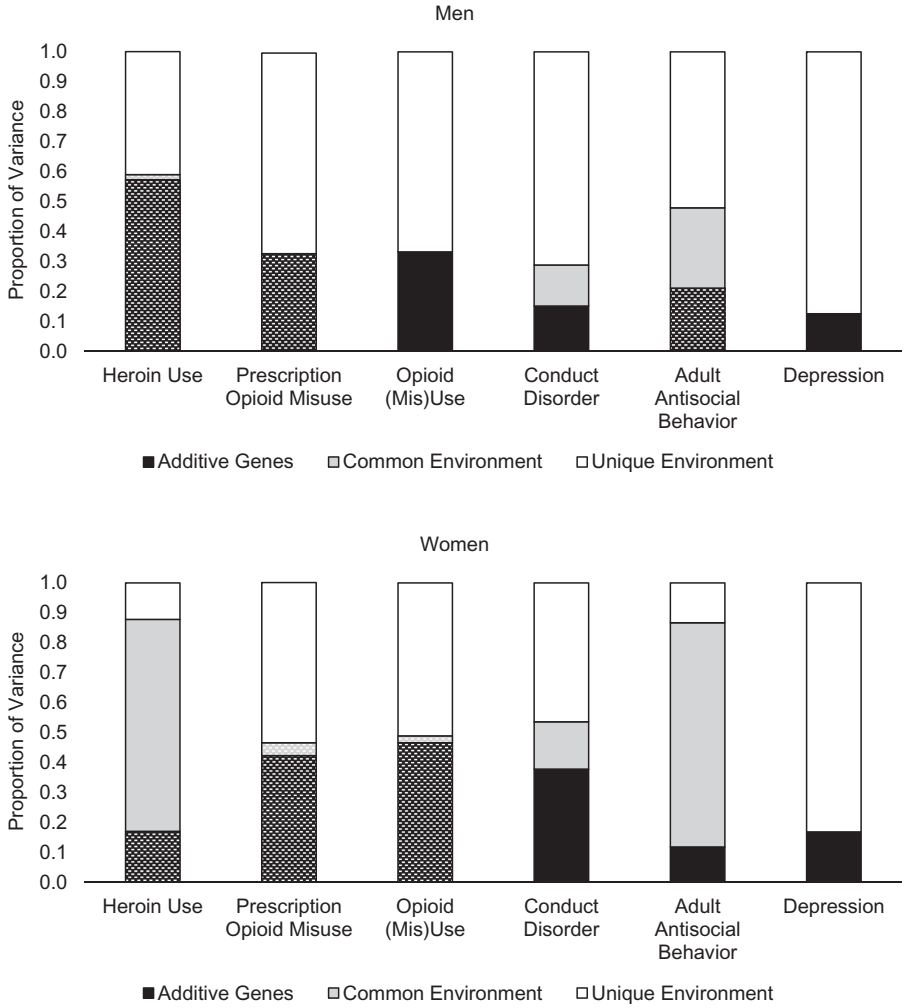
*Univariate and Bivariate Twin Correlations Derived From Freely Estimated Biometric Models*

| | Heroin use | POM | Opioid (mis)use | CD symptoms | | AAB | | Depression symptoms | |
|---|---|---|---|---|---|---|---|---|---|
| | Cross-twin within-trait | Cross-twin cross-trait | — | Within-twin cross-trait | Cross-twin cross-trait | Within-twin cross-trait | Cross-twin cross-trait | Within-twin cross-trait | Cross-twin cross-trait |
| Zygosity | *r* [95% CI] | *r* [95% CI] | — | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] |
| Heroin use | | | | | | | | | |
| MZM | **.59 [0.23–0.84]** | **.50 [0.25–0.67]** | — | **.30 [0.22–0.36]** | **.29 [0.19–0.40]** | **.25 [0.17–0.32]** | **.26 [0.12–0.36]** | **.21 [0.11–0.31]** | *.19 [0.01–0.29]* |
| MZF | **.88 [0.66–0.98]** | **.51 [0.30–0.67]** | — | **.27 [0.15–0.35]** | **.27 [0.12–0.36]** | .13 [–0.10–0.18] | **.24 [0.11–0.36]** | **.32 [0.21–0.52]** | **.37 [0.20–0.53]** |
| DZM | **.36 [0.20–0.50]** | **.25 [0.13–0.34]** | — | **.30 [0.22–0.36]** | *.19 [0.06–0.30]* | **.25 [0.17–0.32]** | *.15 [0.05–0.24]* | **.21 [0.11–0.31]** | .07 [0.00–0.16] |
| DZF | **.79 [0.51–0.93]** | **.36 [0.14–0.54]** | — | **.27 [0.15–0.35]** | *.19 [0.05–0.33]* | .13 [–0.10–0.18] | .12 [–0.04–0.18] | **.32 [0.21–0.52]** | *.20 [0.08–0.31]* |
| | Within-twin cross-trait | Cross-twin within-trait | — | Within-twin cross-trait | Cross-twin within-trait | Within-twin cross-trait | Cross-twin within-trait | Within-twin cross-trait | Cross-twin within-trait |
| Zygosity | *r* [95% CI] | *r* [95% CI] | — | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] |
| POM | | | | | | | | | |
| MZM | **.63 [0.47–0.74]** | *.32 [0.10–0.53]* | — | **.29 [0.23–0.34]** | **.19 [0.10–0.28]** | **.23 [0.17–0.29]** | **.22 [0.14–0.31]** | **.22 [0.16–0.29]** | **.17 [0.08–0.25]** |
| MZF | **.62 [0.47–0.75]** | **.47 [0.34–0.60]** | — | **.19 [0.13–0.23]** | **.12 [0.05–0.19]** | **.18 [0.13–0.24]** | *.12 [0.04–0.20]* | **.22 [0.16–0.28]** | *.12 [0.05–0.20]* |
| DZM | **.63 [0.47–0.74]** | *.19 [0.07–0.42]* | — | **.29 [0.23–0.34]** | *.11 [0.03–0.18]* | **.23 [0.17–0.29]** | **.14 [0.06–0.22]** | **.22 [0.16–0.29]** | *.11 [0.04–0.18]* |
| DZF | **.62 [0.47–0.75]** | **.24 [0.14–0.39]** | — | **.19 [0.13–0.23]** | **.15 [0.09–0.23]** | **.18 [0.13–0.24]** | .06 [–0.03–0.11] | **.22 [0.16–0.28]** | .06 [0.00–0.12] |
| | — | — | Cross-twin within-trait | Within-twin cross-trait | Cross-twin cross-trait | Within-twin cross-trait | Cross-twin cross-trait | Within-twin cross-trait | Cross-twin cross-trait |
| Zygosity | — | — | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] | *r* [95% CI] |
| Opioid (Mis)Use | | | | | | | | | |
| MZM | — | — | **.33 [0.12–0.52]** | **.29 [0.24–0.35]** | **.19 [0.10–0.27]** | **.23 [0.17–0.29]** | **.24 [0.16–0.32]** | **.21 [0.14–0.28]** | **.17 [0.08–0.25]** |
| MZF | — | — | **.49 [0.37–0.63]** | **.20 [0.15–0.24]** | **.13 [0.06–0.20]** | **.18 [0.13–0.23]** | *.12 [0.04–0.20]* | **.23 [0.17–0.28]** | **.13 [0.06–0.21]** |
| DZM | — | — | *.17 [0.05–0.28]* | **.29 [0.24–0.35]** | **.12 [0.05–0.20]** | **.23 [0.17–0.29]** | **.15 [0.09–0.22]** | **.21 [0.14–0.28]** | *.08 [0.01–0.13]* |
| DZF | — | — | **.25 [0.14–0.33]** | **.20 [0.15–0.24]** | **.17 [0.10–0.24]** | **.18 [0.13–0.23]** | .06 [–0.02–0.10] | **.23 [0.17–0.28]** | *.07 [0.01–0.13]* |

*Note.* Correlations between opioid (mis)use and heroin use or POM were not calculated as the latter variables are the component parts of the former. POM = prescription opioid misuse; CD = conduct disorder; AAB = adult antisocial behavior; CI = confidence interval; MZM = monozygotic male; MZF = monozygotic female; DZM = dizygotic male; DZF = dizygotic female. Bold font indicates significant correlation, $p < .001$; italic font indicates significant correlation, $p < .05$.

**Figure 2**

*Proportion of Variance in Opioid Use and Psychopathology Attributable to Additive Genes, Common Environment, and Unique Environment in Men and Women*




*Note*. Patterned fill represents a nonsignificant variance estimate ($p > .05$).

**POM Models.** For men, parameters reflecting loadings of POM on common environmental ($c12$) and unique environmental ($e12$) factors shared with CD, as well as the residual common environmental parameter for POM ($c22$), could be constrained to zero, Wald $\chi^2(3) = 5.97$, $p = .11$. Under the best-fit model, 33% of the total phenotypic variance in POM was attributable to factors shared with CD. All of this variance was captured by genetic influences ($A_1$), corresponding to 92% of the genetic variance in POM ($r_G = .96$). Contrary to hypotheses, this correlation was not significantly different than the genetic correlation between CD and heroin use ($r_G = .84$). For women, parameters reflecting loadings of POM on genetic ($a12$) and unique environmental ($e12$) factors shared with CD, as well as the residual common environmental parameter for POM ($c22$), could be constrained to zero, Wald $\chi^2(3) = 3.61$, $p = .31$. Under the best-fit model 15% of the total phenotypic variance in POM was attributable to factors shared with CD. All phenotypic variance in POM attributable to factors shared with CD was captured by common environmental influences ($C_1$), making the genetic correlation 0; in line with hypotheses, this was significantly smaller than the genetic correlation between CD and heroin use ($r_G = .80$). Because the residual common environmental parameter for POM ($c22$) was constrained to zero, the common environmental correlation was necessarily 1.00. Under the best-fit two-group model, 7% of the variance in POM was shared with CD. This was attributable to genetic ($r_G = .18$, *ns*), common environmental ($r_C = 1.00$, fixed), and unique environmental ($r_E = .16$) influences.

**Aggregate Opioid (Mis)Use Models.** As hypothesized, the results of the aggregate opioid (mis)use models were nearly identical to those for POM. The same set of parameter constraints could be imposed within the respective models for men and women, as well as in the two-group models (see Table S2 in the online supplemental materials), with nearly identical parameter estimates.

**Table 3**
*Proportion of Variance Attributable to Each Path and Genetic and Environmental Correlations Between Opioid Phenotypes and CD Symptoms in Best-Fit Bivariate Cholesky Models*

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Parameter | Heroin use $\chi^2(22) = 22.00, p = .46$ | POM $\chi^2(22) = 26.48, p = .23$ | Opioid (mis)use $\chi^2(22) = 26.52, p = .23$ | Heroin use $\chi^2(21) = 18.34, p = .63$ | POM $\chi^2(21) = 21.25, p = .51$ | Opioid (mis)use $\chi^2(22) = 22.41, p = .44$ |
| $a11^2$ (P) | *0.21 (0.09–0.50)* | *0.21 (0.11–0.48)* | *0.21 (0.11–0.47)* | *0.31 (0.11–0.55)* | *0.30 (0.04–0.48)* | *0.30 (0.04–0.48)* |
| $c11^2$ (P) | 0.22 (0.00–0.35) | *0.22 (0.01–0.34)* | *0.22 (0.01–0.34)* | *0.18 (0.00–0.35)* | *0.19 (0.07–0.39)* | *0.19 (0.07–0.39)* |
| $e11^2$ (P) | **0.57 (0.48–0.66)** | **0.57 (0.49–0.66)** | **0.57 (0.49–0.66)** | *0.51 (0.43–0.60)* | **0.51 (0.42–0.60)** | **0.51 (0.42–0.60)** |
| $a12^2$ (O) | *0.41 (0.14–0.93)* | *0.33 (0.13–0.64)* | *0.33 (0.14–0.62)* | *0.26 (0.07–0.72)* | 0.00 (fixed) | 0.00 (fixed) |
| $c12^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | *0.15 (0.06–0.39)* | *0.17 (0.07–0.41)* |
| $e12^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) |
| $a22^2$ (O) | 0.17 (0.00–0.68) | 0.03 (0.00–0.37) | 0.01 (0.00–0.32) | 0.15 (0.00–0.88) | *0.35 (0.02–0.60)* | *0.35 (0.04–0.61)* |
| $c22^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | **0.59 (0.20–0.87)** | 0.00 (fixed) | 0.00 (fixed) |
| $e22^2$ (O) | **0.42 (0.05–0.77)** | **0.65 (0.46–0.86)** | **0.66 (0.49–0.85)** | 0.00 (0.00–0.15) | **0.50 (0.28–0.68)** | **0.48 (0.26–0.65)** |
| Correlation | | | | | | |
| $r_G$ [95% CI] | **.84 [0.44–1.00]** | **.96 [0.51–1.00]** | **.98 [0.53–1.00]** | **.80 [0.28–1.00]** | .00 (fixed) | .00 (fixed) |
| $r_C$ [95% CI] | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | **1.00 (fixed)** | **1.00 (fixed)** |
| $r_E$ [95% CI] | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) |

*Note.* CD = conduct disorder; POM = prescription opioid misuse; a = additive genes; c = common environment e = unique environment; P = psychopathology variance component; O = opioid variance component; 11 = paths from the first component factor to the psychopathology phenotype; 12 = the path from the first component factor to the opioid phenotype; 22 = the path from the second component factor to the opioid phenotype; CI = confidence interval. Bold font indicates significant correlation, $p < .001$; italic font indicates significant correlation, $p < .05$.

### *AAB*

AAB models among women provided an extremely poor fit to the data and failed to meet recommended thresholds for indexes of model fit. Results are presented for transparency (see Table 4), but only results for men and the two-group model are described below.

**Heroin Use Models.** For men, parameters reflecting loadings of heroin use on common environmental (*c*12) and unique environmental (*e*12) factors shared with AAB, as well the residual common environmental parameter (*c*22), could be constrained to zero, Wald $\chi^2(3) = 0.07, p = .99$. Under this best-fit model, 41% of the variance in heroin use was attributable to factors shared with AAB. All of this variance was captured by genetic influences ($A_1$; $r_G = .84$). Under the best-fit two-group model, 16% of the variance in heroin use was shared with AAB. This was attributable to genetic ($r_G = .38$, *ns*) and common environmental ($r_C = 1.00$, fixed) influences.

**POM Models.** For men, parameters reflecting loadings of POM on common environmental (*c*12) and unique environmental (*e*12) factors shared with AAB, as well the residual genetic (*a*22) and common environmental (*c*22) parameters, could be constrained to zero, Wald $\chi^2(4) = 0.60$, $p = .96$. Under this best-fit model, 35% of the variance in POM was attributable to factors shared with AAB. All of this variance was captured by genetic influences ($A_1$); because the residual genetic parameter for heroin use (*a*22) could be constrained to zero, the genetic correlation was necessarily 1.00. Under the best-fit two-group model, 11% of the variance in POM was shared with AAB. This was attributable to genetic ($r_G = .44$, *ns*) and common environmental ($r_C = 1.00$, fixed) influences.

**Aggregate Opioid (Mis)Use Models.** For men, parameters reflecting loadings of opioid (mis)use on the unique environmental (*e*12) factor shared with AAB, as well the residual common environmental (*c*22) parameter, could be constrained to zero, Wald $\chi^2(2) = 0.01$, $p = .99$. Under this best-fit model, 22% of the variance in opioid (mis)use was attributable to factors shared with AAB. Most of this variance was captured by genetic influences ($A_1$). The results for the two-group model were nearly identical to those for POM.

### *MDE Symptoms*

**Heroin Use Models.** For men, parameters reflecting loadings of heroin use on genetic (*a*12) and unique environmental (*e*12) factors shared with MDE, as well as all common environmental parameters (*c*11, *c*12, *c*22), could be constrained to zero, Wald $\chi^2(5) = 2.64$, $p = .76$. Under this best-fit model, 0% of the variance in heroin use was attributable to factors shared with MDE; as such, $r_G$, $r_C$, and $r_E$ were necessarily 0. For women, parameters reflecting loadings of heroin use on common environmental (*c*12) and unique environmental (*e*12) factors shared with MDE, as well as the common environmental parameter for MDE (*c*11) and the residual genetic parameter for heroin use (*a*22), could be constrained to zero, Wald $\chi^2(4) = 0.79$, $p = .79$. Under the best-fit model, 42% of the total phenotypic variance in heroin use was attributable to factors shared with MDE. All of this variance was captured by genetic influences ($A_1$); because the residual genetic parameter for heroin use (*a*22) could be constrained to zero, the genetic correlation was necessarily 1.00. Under the best-fit two-group model, 22% of the variance in heroin use was shared with MDE. This was attributable solely to genetic influences ($r_G = .69$).

**POM Models.** In models for both men and women, parameters reflecting loadings of POM on unique environmental factors shared

**Table 4**
*Proportion of Variance Attributable to Each Path and Genetic and Environmental Correlations Between Opioid Phenotypes and AAB in Best-Fit Bivariate Cholesky Models*

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Parameter | Heroin use $\chi^2(22) = 14.36, p = .89$ | POM $\chi^2(23) = 20.22, p = .63$ | Opioid (mis)use $\chi^2(21) = 16.13, p = .76$ | Heroin use $\chi^2(22) = 17.79, p < .001$ | POM $\chi^2(24) = 144.94, p < .001$ | Opioid (mis)use $\chi^2(24) = 144.18, p < .001$ |
| $a11^2$ (P) | 0.16 (0.06–0.38) | *0.16 (0.08–0.37)* | 0.15 (0.00–0.37) | **0.32 (0.17–0.50)** | **0.32 (0.17–0.52)** | **0.32 (0.17–0.52)** |
| $c11^2$ (P) | 0.15 (0.00–0.30) | *0.15 (0.00–0.25)* | 0.15 (0.00–0.32) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) |
| $e11^2$ (P) | **0.70 (0.60–0.79)** | **0.70 (0.60–0.78)** | **0.70 (0.60–0.78)** | **0.68 (0.50–0.83)** | **0.68 (0.48–0.83)** | **0.68 (0.48–0.83)** |
| $a12^2$ (O) | *0.41 (0.14–0.96)* | *0.35 (0.15–0.61)* | 0.18 (0.00–0.44) | *0.19 (0.07–0.44)* | *0.09 (0.04–0.20)* | *0.09 (0.04–0.20)* |
| $c12^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.04 (0.00–0.20) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) |
| $e12^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.02 (0.00–0.16) | 0.00 (fixed) | 0.00 (fixed) |
| $a22^2$ (O) | 0.17 (0.00–0.65) | 0.00 (fixed) | 0.12 (0.00–0.37) | 0.00 (fixed) | **0.44 (0.27–0.66)** | **0.46 (0.29–0.69)** |
| $c22^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | **0.71 (0.53–0.93)** | 0.00 (fixed) | 0.00 (fixed) |
| $e22^2$ (O) | *0.42 (0.04–0.77)* | **0.65 (0.39–0.85)** | **0.67 (0.46–0.85)** | 0.08 (0.00–0.33) | **0.47 (0.25–0.66)** | **0.45 (0.22–0.62)** |
| Correlation | | | | | | |
| $r_G$ [95% CI] | **.84 [0.44–1.00]** | 1.00 (fixed) | .77 (nc) | 1.00 (fixed) | **.41 [0.27–0.60]** | **.41 [0.28–0.59]** |
| $r_C$ [95% CI] | .00 (fixed) | .00 (fixed) | 1.00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) |
| $r_E$ [95% CI] | .00 (fixed) | .00 (fixed) | .00 (fixed) | –.48 (nc) | .00 (fixed) | .00 (fixed) |

*Note.* AAB = adult antisocial behavior; POM = prescription opioid misuse; a = additive genes; c = common environment; e = unique environment; P = psychopathology variance component; O = opioid variance component; 11 = paths from the first component factor to the psychopathology phenotype; 12 = the path from the first component factor to the opioid phenotype; 22 = the path from the second component factor to the opioid phenotype; CI = confidence interval; nc = not calculatable, estimate approached boundary condition. Bold font indicates significant correlation, $p < .001$; italic font indicates significant correlation, $p < .05$.

with MDE ($e12$), as well as all common environmental parameters ($c11$, $c12$, and $c22$), could be constrained to zero, Wald $\chi^2(4) = 2.45, p = .65$; Wald $\chi^2(4) = 6.71, p = .08$. Under the best-fit models, 20% and 13% of the total phenotypic variance in POM was attributable to factors shared with MDE among men and women, respectively. All of this variance was captured by genetic influences ($A_1$), corresponding to 56% of the genetic variance in POM among men ($r_G = .75$) and 25% of the genetic variance in POM among women ($r_G = .49$). As hypothesized, the genetic correlation for men was significantly larger than the genetic correlation between MDE and heroin use ($r_G = .00$); contrary to hypotheses, the genetic correlation for women was significantly smaller than the genetic correlation between MDE and heroin use ($r_G = 1.00$). Under the best-fit two-group model, 15% of the variance in POM was shared with MDE. This was attributable solely to genetic influences ($r_G = .56$).

**Aggregate Opioid (Mis)Use Models.** The same set of parameter constraints as for POM could be imposed for men, women, and in the two-group model, (see Table S4 in the online supplemental materials), and with nearly identical parameter estimates.

## Discussion

The present study aimed to evaluate the genetic and environmental etiology of heroin use and POM in the context of their relative relationships with externalizing (CD and AAB) and internalizing (MDE) spectrum behaviors across men and women. We hypothesized that there would be differences in the etiologic overlap of heroin use and POM with CD, AAB, and MDE. First, we expected that heroin use would be more strongly genetically associated with CD and AAB than POM would be. Heroin use did indeed share slightly more variance with CD and AAB than did POM in both men and women, though differences in magnitude should be interpreted cautiously given the small proportion of the sample endorsing heroin use. Additionally, the genetic correlations of heroin use with both CD and AAB were larger than those for POM and both CD and AAB among women. Among men, the genetic correlations between heroin use and both CD and AAB were comparable to those between POM and both CD and AAB despite heroin use displaying a higher absolute magnitude of variance attributable to genetic factors shared with CD and AAB; this is because heroin use emerged with more residual genetic influence in addition to variance attributable to genetic factors shared with CD and AAB. Here, too, results should be interpreted with caution due to sample size and resultant limitations in power. Second, we expected that POM would be more strongly genetically associated with MDE than heroin use would. POM did indeed share more variance with MDE than did heroin use among men, but not among women; similarly, the genetic correlation between POM and MDE was stronger than that between POM and heroin use for men, but not for women. In sum, hypotheses were partially supported, insofar as differences in patterns of etiologic overlap, and sex differences in these patterns, did emerge. Extending these findings to samples with higher rates of heroin use may help to further clarify the nature of the relative relationships between heroin use and POM with various forms of psychopathology.

One way to interpret these findings is that the pattern of etiologic overlap differs in both source and magnitude. For CD, results indicated differences in the source of shared etiology across opioid types. Specifically, among women, the overlap between heroin use and CD was attributable to genetic influences, while the overlap

**Table 5**

*Proportion of Variance Attributable to Each Path and Genetic and Environmental Correlations Between Opioid Phenotypes and Depression Symptoms in Best-Fit Bivariate Cholesky Models*

| | Men | | | Women | | |
|---|---|---|---|---|---|---|
| Parameter | Heroin use $\chi^2(24) = 34.72$, $p = .07$ | POM $\chi^2(23) = 20.06$, $p = .64$ | Opioid (mis)use $\chi^2(23) = 18.12$, $p = .75$ | Heroin use $\chi^2(23) = 23.66$, $p = .42$ | POM $\chi^2(23) = 15.10$, $p = .89$ | Opioid (mis)use $\chi^2(23) = 14.84$, $p = .90$ |
| $a11^2$ (P) | **0.22 (0.14–0.31)** | **0.22 (0.14–0.31)** | **0.22 (0.14–0.31)** | **0.30 (0.24–0.37)** | **0.30 (0.24–0.36)** | **0.30 (0.24–0.36)** |
| $c11^2$ (P) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (0.00–0.00) |
| $e11^2$ (P) | **0.78 (0.69–0.86)** | **0.78 (0.69–0.86)** | **0.78 (0.69–0.86)** | **0.70 (0.64–0.76)** | **0.70 (0.64–0.76)** | **0.70 (0.64–0.76)** |
| $a12^2$ (O) | 0.00 (fixed) | *0.20 (0.10–0.38)* | *0.18 (0.09–0.35)* | *0.42 (0.17–0.84)* | **0.13 (0.06–0.22)** | **0.13 (0.07–0.23)** |
| $c12^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) |
| $e12^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) |
| $a22^2$ (O) | *0.56 (0.20–0.97)* | 0.16 (0.00–0.39) | 0.17 (0.00–0.37) | 0.00 (fixed) | **0.40 (0.23–0.63)** | **0.42 (0.24–0.63)** |
| $c22^2$ (O) | 0.00 (fixed) | 0.00 (fixed) | 0.00 (fixed) | **0.54 (0.28–0.79)** | 0.00 (fixed) | 0.00 (fixed) |
| $e22^2$ (O) | *0.44 (0.03–0.80)* | **0.64 (0.40–0.84)** | **0.66 (0.44–0.86)** | 0.04 (0.00–0.29) | **0.47 (0.25–0.65)** | **0.45 (0.23–0.63)** |
| Correlation | | | | | | |
| $r_G$ [95% CI] | .00 (fixed) | **.75 [0.49–1.00]** | **.72 [0.48–1.00]** | **1.00 (fixed)** | **.49 [0.34–0.66]** | **.49 [0.35–0.65]** |
| $r_C$ [95% CI] | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) |
| $r_E$ [95% CI] | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) | .00 (fixed) |

*Note.* POM = prescription opioid misuse; a = additive genes; c = common environment; e = unique environment; P = psychopathology variance component; O = opioid variance component; 11 = paths from the first component factor to the psychopathology phenotype; 12 = the path from the first component factor to the opioid phenotype; 22 = the path from the second component factor to the opioid phenotype; CI = confidence interval. Bold font indicates significant correlation, $p < .001$; italic font indicates significant correlation, $p < .05$.

between POM and CD was underpinned by common environmental influences. Interestingly, the patterns of association of CD with heroin use and POM were quite similar among men, suggesting that the mechanisms of cooccurrence of these phenotypes may vary across sex. A shift toward shared genetic influences in both men and women for AAB also suggests a potential developmental change in the cooccurrence of these behaviors with opioid use. With respect to MDE, results indicated differences in the magnitude of shared etiology across opioid types. Among men, one-fifth of the variance in POM was attributable to factors shared with MDE while none of the variance in heroin use was attributable to factors shared with MDE; similarly, the genetic correlation between POM and MDE was substantial while genetic and environmental overlap between heroin use and MDE could be constrained to zero. Differences in the magnitude of association with MDE across heroin use and POM were also evident among women, but differed in direction: the proportion of variance in heroin use attributable to a factor shared with MDE was over three times the magnitude of that for POM. Similarly, the genetic correlation of MDE with heroin use was nearly twice the magnitude of that for POM among women. Again, further research in larger samples will be needed to replicate and elucidate the pattern of findings presented here.

Understanding the relative overlap between heroin use and POM with psychopathology is important in leveraging mental health interventions to mitigate the risk for heroin use and POM, and therefore related morbidity and mortality (Volkow et al., 2019). One benefit to this is that risk for future opioid (mis)use may be mitigated even prior to opioid exposure or opportunity to use (Dasgupta et al., 2018; Volkow et al., 2019), as behaviors such as those stemming from CD tend to emerge before drug use within the typical developmental trajectory (Darke et al., 2017; Fairchild et al., 2019). Overlapping environmental etiology, such as that identified among women, may be a particularly fruitful starting point, given the modifiable nature of the environment. In other words, the etiologic overlap between CD and POM suggests that early family- and/or school-based interventions for some youth displaying such externalizing characteristics may serve to mitigate the risk for future opioid involvement. Though further research is certainly needed to evaluate these practical implications, this is synchronous with calls to address social determinants of opioid (mis)use (Dasgupta et al., 2018) in part through early intervention in adverse environments. Evidence suggests that environmental/social adversity may moderate genetic influences on both internalizing and externalizing behavior (Belsky & Domingue, 2023; Dash, Karalunas, et al., 2023); if genetic influences on psychopathology overlap with opioid use behaviors, such environmental interventions may also serve to attenuate liability to opioid use at the population level over time. As such, an important next step will be to examine how environmental influences such as social adversity and drug availability may moderate genetic risk for heroin use and POM.

The overlap between POM and psychopathology was smaller than expected, particularly among women (13%–15%). However, this is consistent with some literature demonstrating that POM is only associated with adverse outcomes under particular conditions. Most POM occurs in an "on-label" manner: via an oral route of administration (Green et al., 2017; Kirsh et al., 2012; McCabe et al., 2007) with pills obtained from a personal prescription, family member, or friend (Han et al., 2017; Lipari & Hughes, 2017; McCabe et al., 2007; Park & Wu, 2020) for the purpose of managing pain (Han et al., 2017, 2018; McCabe et al., 2007; McCabe, Boyd, Cranford, &

Teter, 2009; Schuler et al., 2020). POM under these conditions is not associated with an elevated risk of use-related problems (Carlson et al., 2016; McCabe et al., 2007, 2013; McCabe, Boyd, Cranford, & Teter, 2009; McCabe, Boyd, & Teter, 2009). However, POM behaviors that are more aligned with other forms of illegal drug use (e.g., acquisition via diversion/black market, nonoral route of administration) are more strongly associated with heroin and other legal drug use (Carlson et al., 2016; Guarino et al., 2018; McCabe et al., 2007; Monico & Mitchell, 2018). The presence of counterfeit pills that can be purchased on the black market adds a layer of nuance, and there is evidence to suggest that factors such as the source of prescription opioids may be indicative of a propensity for risky drug use behavior (e.g., using personal prescription vs. purchasing on the black market; Ford & Lacerenza, 2011; McCabe et al., 2007). These factors highlight that POM cannot be easily operationalized as "on-label" or "illegal" use and emphasize the need for a more nuanced conceptualization of POM and its multiple dimensions. Disentangling POM when not prescribed versus more than prescribed, integrating the route of POM administration, and considering POM motives in future research will be important components of elucidating the nature of these relationships. Unfortunately, we were unable to disentangle such conditions in the present study, though this issue highlights the need to implement finer-grained measurement of opioid (mis)use behaviors, and particularly POM, in future research.

Relatedly, results of the aggregate opioid (mis)use models supported the notion that a broader operationalization of opioid (mis)use can lead to results biased toward the more commonly endorsed opioid (mis)use behavior. Twin correlations, univariate models, and bivariate models of aggregate opioid (mis)use mirrored those for POM quite closely, failing to capture the distinct results emerging for heroin use. This is unsurprising given the relative prevalence of the opioid (mis)use phenotypes, but nonetheless illustrates the importance of disaggregating opioid use phenotypes rather than lumping them together as a unitary behavior. The feasibility of such an approach can certainly be limited by low endorsement rates (Reuter et al., 2021), in which case simply reporting the relative proportion of heroin use versus POM in a given sample is a straightforward and viable alternative.

## Limitations

Results should be interpreted in light of limitations. Most notably, the phenotypes of interest were endorsed with relative infrequency, compromising the power of analyses to detect meaningful effects, particularly within sex-stratified models. To address this, we conducted power analyses using Verhulst's power calculator for twin studies (Verhulst, 2017), the results of which are detailed in Tables S5–S8 and Figures S2–S17 of the online supplemental materials. In univariate models for POM, the sample size was sufficient to detect an additive genetic variance component of .50 or larger and .70 or larger with 80% power in the full sample and sex-stratified models, respectively. In the univariate models for heroin use, the sample size was sufficient to detect an additive genetic parameter of .90 or larger with 80% power in the full and male samples; the female sample was less sufficient, powered to detect an additive genetic parameter of .80 with 20% power. The full sample was sufficient to detect a genetic correlation of .70 with 80% power in bivariate POM models. For the POM–CD model, the sex-stratified samples were sufficient to detect a genetic correlation of .90 with 80% power; for the POM–MDE model, the female sample was sufficient to detect a genetic correlation of .80 with 80% power, but the male sample was insufficient to detect any effect with 80% power. Power for the bivariate models involving heroin use could not be estimated with adequate precision. It was difficult to determine whether inconsistencies in results across sex-stratified and full-sample models were attributable to enhanced power in the latter models or to true sex differences in patterns of effect that were masked when men and women were collapsed into a single group.

Beyond considerations of power, it is unclear how this Australian sample of predominantly European ancestry will generalize to other groups. More severe forms of psychopathology and drug use were underrepresented in this community-based sample, which may have impacted the degree of variability within the sample as well as heritability estimates, as higher-acuity phenotypes (e.g., use disorder vs. use only) tend to display stronger genetic influence. Further research in clinical samples may help to shed further light on the relationships examined here. Additionally, CD as operationalized here reflected retrospective reports of behaviors occurring before age 18 and AAB reflected behaviors occurring after 18, while the MDE measure included symptoms experienced throughout the lifetime; as such, the psychopathology constructs were not temporally aligned. We were also unable to account for how drug access and psychopathology may be confounded; for example, individuals with internalizing disorders are more likely to receive prescription opioids, in part due to the strong link between depression and chronic pain (Scaini et al., 2022; Sheng et al., 2017). Relatedly, we were unable to account for salient factors such as chronic pain that are relevant to prescription opioid exposure. Finally, we were restricted to binary metrics of drug use. Despite these limitations, the present study provides novel insight into the relative etiology of heroin use and POM, their relative relationships with psychopathology, and the ways in which the operationalization of opioid (mis)use as a single behavior may be introducing bias and noise into studies of opioid-related phenotypes.

## Conclusions

Much of the literature on opioid use and misuse, particularly behavior genetic studies, has historically aggregated heroin use and POM into a single "opioid use" behavior. However, emerging evidence suggests that they may be influenced by partially distinct genetic and environmental influences (Dash et al., 2022; Dash, Gizer, et al., 2023). Though such patterns should not be overinterpreted given the limitation of endorsement rates in the present sample, heroin use and POM also appear to be distinct in regard to the magnitude and source of their etiologic associations with externalizing and internalizing spectrum behaviors. Taken together, this emerging literature underscores the importance of disaggregating heroin use and POM both in conducting replicable research and in addressing the US opioid crisis. POM is often seen as a causal driver of heroin use (Compton et al., 2016; Dasgupta et al., 2018; Siegal et al., 2003), leading public health policy to focus on prescribing practices rather than more deeply rooted socioeconomic causes of opioid-related morbidity and mortality (Dasgupta et al., 2018). Pursuing the notion that heroin use and POM may be partially unique behaviors is requisite to both a more nuanced scientific understanding of these behaviors and a more nuanced approach to public health policy.

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