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Genetic and environmental risk factors in the non-medical use of over-the-counter or prescribed analgesics, and their relationship to major classes of licit and illicit substance use and misuse in a population-based sample of young adult twins

Nathan A. Gillespie[1,2], Timothy C. Bates[3], Ian B. Hickie[4], Sarah E. Medland[2], Brad Verhulst[6], Robert M. Kirkpatrick[1], Kenneth S. Kendler[1], Nicholas G. Martin[2] & Eric G. Benotsch[5]

Virginia Institute for Psychiatric and Behavior Genetics, Virginia Commonwealth University, VA, USA,[1] QIMR Berghofer Medical Research Institute, QLD, Australia,[2] Department of Psychology, University of Edinburgh, UK,[3] Brain and Mind Centre, University of Sydney, NSW, Australia,[4] Psychology Department, Virginia Commonwealth University, VA, USA[5] and Psychology Department, Michigan State University, MI, USA[6]

ABSTRACT

Background and Aims The non-medical use of over-the-counter or prescribed analgesics (NMUA) is a significant public health problem. Little is known about the genetic and environmental etiology of NMUA and how these risks relate to other classes of substance use and misuse. Our aims were to estimate the heritability NMUA and sources of genetic and environmental covariance with cannabis and nicotine use, cannabis and alcohol use disorders and nicotine dependence in Australian twins. **Design** Biometrical genetic analyses or twin methods using structural equation univariate and multivariate modeling. **Setting** Australia. **Participants** A total of 2007 young adult twins [66% female; μ_{age} = 25.9, standard deviation (SD) = 3.6, range = 18–38] from the Brisbane Longitudinal Twin Study retrospectively assessed between 2009 and 2016. **Measurements** Self-reported NMUA (non-opioid or opioid-based), life-time nicotine, cannabis and opioid use, DSM-V cannabis and alcohol use disorders and the Fagerström Test for Nicotine Dependence. **Findings** Life-time NMUA was reported by 19.4% of the sample. Univariate heritability explained 46% [95% confidence interval (CI) = 0.29–0.57] of the risks in NMUA. Multivariate analyses revealed that NMUA is moderately associated genetically with cannabis (r_g = 0.41) and nicotine (r_g = 0.45) use and nicotine dependence (r_g = 0.34). In contrast, the genetic correlations with cannabis (r_g = 0.15) and alcohol (r_g = 0.07) use disorders are weak. **Conclusions** In young male and female adults in Australia, the non-medical use of over-the-counter or prescribed analgesics appears to have moderate heritability. NMUA is moderately associated with cannabis and nicotine use and nicotine dependence. Its genetic etiology is largely distinct from that of cannabis and alcohol use disorders.

Keywords Comorbidity, gene, non-medical use, over-the-counter, prescribed analgesics, substance use, twin.

Correspondence to: Nathan A. Gillespie, 800 E Leigh St, Virginia Institute for Psychiatric and Behavior Genetics, Virginia Commonwealth University, VA 23219, USA. E-mail: nathan.gillespie@vcuhealth.org
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INTRODUCTION

The non-medical use of over-the-counter (OTC) or prescribed analgesics is one of the fastest-growing drug trends in the United States [1–3]. However, very little is known about the sources of individual differences in this emerging class of substance use or how these differences relate to the genetic and environmental risks that are known to predict other major classes of substance use and misuse.

The non-medical use of either prescribed or OTC analgesics (NMUA) is a clear public health threat. In the United States, deaths related to NMUA now exceed those for all other illicit substances including cocaine and heroin, and continue to increase [4]. Between 1993 and 2005 the prevalence of the non-medical use of prescribed opioids among US college students increased by 343% [5]. Among the 1.2 million emergency department visits in the United States in 2009 involving non-medical use of

pharmaceuticals or dietary supplements, approximately 50% involved the non-medical use of prescribed opioid-based analgesics [6]. In Australia in 2016, prescribed and OTC analgesics were the most commonly misused pharmaceuticals in the past 12 months, which made this class the second most illicitly used substance after cannabis [7]. The non-medical use of opiate or non-steroidal analgesics is associated with a variety of negative physical effects, including tachycardia, seizures, agitation, dependence and death [8,9]. In terms of comorbid substance use, the non-medical use of prescribed opioids has been linked to the risk of transitioning to other classes of illicit SU and SUDs [10–13].

Despite these trends and consequences, the genetic epidemiology of this class of substance use remains completely unknown. Specifically, the degree to which the genetic risk factors underpinning comorbid licit and illicit substance use and misuse are also responsible for individual differences in NMUA remains to be determined.

We hypothesize that familial aggregation in the NMUA will be largely explained by genetic risks and that these risks will be correlated with the genetic risks in other forms of licit and illicit substance use, including opioid use as well as common classes of substance use disorders involving cannabis, alcohol and nicotine. These predictions are based on widely accepted findings showing heritability estimates ranging from 40 to 70% across substances [14–17], along with evidence that genetic risks in licit and illicit substance abuse or dependence, at least in males, are largely common across substances [18,19] and indeed are shared more broadly with the spectrum of externalizing psychopathology [20,21]. Although evidence supports two distinct genetic risk factors underpinning individual differences in substance use disorders [22],l with one predisposing to illicit (cannabis and cocaine) and the other to licit (alcohol, caffeine and nicotine) drug dependence, both factors are highly correlated [22] and recent studies demonstrate moderate to high genetic correlations between licit and illicit abuse and dependence disorders in both males and females [23]. Because of the degree of shared genetic risks between licit and illicit substance use, despite their diverse pharmacology [18,19], we hypothesize that the genetic correlation between NMUA and common classes of substance use and misuse will be high.

The degree to which environmental risk factors related to NMUA are shared with other drug classes is unclear. Quantifying heritability and establishing if the genetic and environmental pathways leading to NMUA are linked to other major classes of substance use and misuse will provide valuable insight into the etiology of NMUA which may, in turn, inform future intervention and prevention programs.

Aims

This report has two aims. The first is to estimate the contribution of genes and environment to the NMUA. This includes determining if there are significant sex differences in the prevalence of use, including sex differences in the relative proportions of genetic and environmental risks. The second aim is to determine if the genetic and environmental risks in life-time cannabis and nicotine use are correlated with NMUA. This aim will also determine if the genetic and environmental risks in cannabis use disorder, nicotine dependence and alcohol use disorder are similarly correlated with NMUA.

METHODS

Participants

The sample consists of male and female adult twins from the ongoing and population-based Brisbane Longitudinal Twin Study (BLTS) [24–26]. Participants are of European ancestry, predominately Anglo Saxon, who were ascertained beginning 1992 to study melanocytic naevi, and have since been followed-up on multiple occasions. The BLTS is a longitudinal, phenotypically rich collection of psychiatric phenotypes, environmental and psychological risk factors, and neurobiological correlates of psychiatric disorders [24–26]. The sample comprises 2900 twins (including 700 siblings and 2100 parents) with assessments at 12, 14, 16 and 21 years. Typical response rates across the BLTS projects since 1992 range from 73 to 85% [24–26].

BLTS data for this report come from the 19UP Project [66% female; μ_{age} = 25.9, standard deviation (SD) = 3.6, range = 18–38] collected between 2009 and 2015 and which relied on a combination of telephone and on-line self-report surveys to assess SU and SUDs [25–27]. The 19UP was a US National Institute on Drug Abuse (NIDA) and Australian National Health and Medical Research Council (NHMRC)-funded project to study the pathways to cannabis use and misuse [25,26], comorbid substance use and misuse, internalizing and externalizing disorders along with a wide array of general health, behavioral and life-style measures [27].

Measures

The non-clinical data used to test our hypotheses included life-time nicotine, cannabis and opioid use (e.g. heroin morphine, methadone, codeine, etc.), as well as the non-medical use of OTC or prescribed analgesics (NMUA). NMUA included codeine-based and non-steroidal anti-inflammatory drugs (e.g. cough medicine, acetaminophen, codeine phosphate hemihydrate, doxylamine succinate, ibuprofen, acetaminophen, acetaminophen and codeine

phosphate hemihydrate, codeine, hydrocodone, etc.). Non-medical use was defined as substances not taken in quantities or in a manner prescribed by a medical practitioner. All four life-time use measures were assessed as dichotomous outcomes beginning with the phrase: 'In your life, have you ever used [substance]'. Alcohol use was not included because the life-time prevalence was 98% at the time of assessment.

Diagnostic data included criteria for the Fagerström Test for Nicotine Dependence (FTND) [28], DSM-V alcohol use disorder and DSM-V cannabis use disorder (CUD) [marijuana, hashish, tetrahydrocannabinol (THC) or ganja] [29]. All three diagnoses were based on the period(s) when subjects reported using each substance the most. Subjects answered the AUD psychiatric criteria only if they endorsed having consumed five (males)/four (females) or more drinks at least once a week for 1 month or more. Subjects answered the CUD psychiatric criteria if they endorsed having smoked cannabis six or more times life-time or 11 or more times in a month. Finally, subjects answered FTND psychiatric criteria if they reported having smoked 100 or more cigarettes life-time.

In order to avoid sparse data and improve computational efficiency when using raw ordinal data methods, we recoded the AUD, CUD and FTND criteria sum scores. The total AUD and CUD criteria were recoded onto three-point ordinal scales (0–1, 2–3, ≥ 4), which combined the DSM-V categories of 'moderate' and 'high'. The total FTND criteria were also recoded onto a three-point ordinal scale (0–1, 2–3, ≥ 4). Here, we combined (i) 'low' and 'low to moderate dependence' and (ii) 'moderate dependence' and 'high dependence'.

For the FTND and CUD diagnoses, nicotine and cannabis non-users were excluded and their diagnosis coded as missing. Our rationale was based on the possibility that non-users are potentially heterogeneous and comprise individuals with varying degrees of environmental risk (including exposure opportunities) and levels of genetic liability that cannot be accurately assessed here. Recoding non-users to 'zero', instead of missing, falsely assumes that knowledge of an individual's diagnosis status can be known in the absence of self-reported data on either the use or exposure to a substance. Assigning non-users to zero inflates the denominator in prevalence estimates, thereby altering not only the item threshold but all subsequent variance–covariance estimates. Although only 1.7% of the sample (n = 34) reported no life-time alcohol use, the same procedure was followed for AUD.

Among the 2773 twins eligible to participate in the 19UP Project, 2007 (72%) provided complete responses to the non-medical use of analgesics item for life-time use. This included 214 complete and 56 incomplete same-sex MZ female twin pairs, 132 complete and 86 incomplete same-sex monozygotic (MZ) male twin pairs, 157 complete and 37 incomplete same-sex DZ female twin pairs, 97 complete and 66 incomplete same-sex DZ male twin pairs and 216 complete and 130 incomplete opposite-sex MZ female twin pairs.

Statistical analyses

Prevalence and measures of association

The prevalence of the non-medical use of analgesics, along with pairwise polychoric correlations between all the above binary and ordinal measures of substance use and misuse, were calculated using the full information maximum likelihood (FIML) raw data method using the OpenMx software package (version 2.9.9.1) [30] in R (version 3.4.1) [31]. We did not use weighted least squares (WLS), as considerably larger samples are required to arrive at reliable weight matrix estimates [32]. Given the numbers of incomplete twin pairs (see Supporting information, Table S2), WLS would result in significant listwise deletion, thereby altering the accuracy of the threshold estimates. The raw ordinal data FIML option [30] has the advantage of not only being more robust to violations of non-normality. Critically, FIML enables the analysis of missing or incomplete data as well as the direct estimation of covariate effects, e.g. age and sex, on the item thresholds. More accurate thresholds improve the estimation of the polychoric correlations. Polychoric correlations were first proposed by Pearson [33,34]. They are based on the central limit theorem of theoretical statistics, which assumes that underlying an observed binary or ordinal variable there exists a continuous, normally distributed latent liability and that the joint distribution of each scale with the liability scales underlying other items is bivariate normal [35,36]. Polychoric (or tetrachoric for binary or dichotomous variables) represent correlations between the underlying liability distributions rather than observed dichotomous or ordinal distributions.

Burnham & Anderson have argued that choice between Akaike's information criterion (AIC) and alternatives such as the Bayesian Information Criterion (BIC) should be determined by the philosophical context of what is assumed about reality [37]. We have argued elsewhere that the advantage of AIC is its deep theoretical connections to cross-validation [38]. Specifically, in large samples, the AIC is expected to select that model in the candidate set which minimizes the error of prediction in new samples of the same size from the population (where the error is based on a log-likelihood function) [38]. In particular, the AIC is expected to minimize the Kullback–Leibler (KL) divergence from full reality at the given sample size. A sensible objective of model selection is to choose the model that has the smallest KL divergence from full reality. The full reality, of

course, is not known, and may not even be knowable. Indeed, a complete description of full reality would be infinitely long. If we accept the possibility that no statistical model can completely describe reality, then the premise of there being a 'true model' that generated the data becomes somewhat dubious. In summary, because full reality may be unknowable, we did not presume that the true model is knowable from our data and, consequently, chose our fit index based on this philosophy. Rather than proposing to identify the true model, the AIC selects the best-approximating model based on an optimal balance of parsimony and model fit.

Univariate twin modeling

To test the hypothesis that familial aggregation in the non-medical (life-time) use of analgesics is entirely explained by additive genetic risk factors, we fitted univariate biometrical genetic models [32] that exploit the expected genetic and environmental correlations between MZ and dizygotic (DZ) twins. Specifically, we fitted twin models using the FIML raw ordinal data methods in the OpenMx software package (version 2.9.9.1) [30] in R (version 3.4.1) [31]. This approach assumes that the categories in a binary or ordinal variable are imprecise indicators of a latent normal liability distribution. These categorical thresholds are conceived of as cut-points along a standard normal distribution that relate category frequencies to cumulative probabilities indicating increasing levels of risk. In $OpenMx_{2.0}$ [39], thresholds can be adjusted for covariates such as age and sex. Based on the Classical Twin Design [32,40], our method of univariate modeling also assumes that individuals differences in substance use or variance in an observed behavior can be decomposed into additive (A) genetic, shared environmental (C) and non-shared or unique (E) environmental variance components [32,40]. As MZ twin pairs are genetically identical and DZ twin pairs share, on average, half their genes, the expected twin-pair correlations for additive genetic effects are 1.0 and 0.5, respectively. An important assumption is that the common environments (C) are equal in MZ and DZ twin pairs, and because non-shared environments (E) are uncorrelated, E necessarily includes measurement error. All models include the covariates of age and sex.

The univariate A, C and E parameters were estimated using a 'variance components' or direct symmetric approach, which directly estimates a set of symmetrical variance components matrices [41]. This approach may return nonsensical values in some situations (e.g. heritability estimates larger than 1, or non-positive definite covariance matrices). However, the absence of boundaries on the estimates (as in the pathway coefficients approach) yields asymptotically unbiased parameter estimates and corrects for Type I and Type II errors [41].

Multivariate twin modeling

To test the hypotheses that genetic risk factors in the NMUA are shared with common forms of licit and illicit substance use and misuse we fitted common and independent pathway models (see Fig. 1) (Neale & Cardon [32]), again using the OpenMx software package (version 2.9.9.1) [30] in R (version 3.4.1) [31]. In Fig. 1, the reference model is the Cholesky decomposition (i) is a method of triangular decomposition where the first observed phenotypical measure is assumed to be caused by a latent factor (A1) that can explain the variance in the remaining variables. The second variable is assumed to be caused by a second latent factor (A2) that explains variation in the second as well as the remaining observed variables. This pattern continues until the final observed variable is explained by a latent variable which is constrained from explaining the variance in any of the previously observed variables. A 'Cholesky decomposition' is specified for each latent source of additive genetic (A), shared environmental (C) and individual-specific environmental variance (E).

The common pathway model (ii) predicts that a single, common latent liability to substance use or misuse, which can be decomposed into A, C and E components of variance. The common pathway is 'indicated' by the strength of the factor loadings to each of the observed phenotypical measures. Residual variance or risks unique to each measure of substance use or misuse can be further decomposed into variable specific 'as', 'cs' and 'es' components. In contrast, the independent pathway model (iii) predicts that latent genetic and environmental risk factors each independently account for any observed comorbidity between the substance use and misuse phenotypes. For each aim, the best-fitting model was determined based on an optimal balance of complexity and explanatory power using the AIC [27]. For each best-fitting model, the A and C parameters are successively fixed to zero and their significance determined using a likelihood ratio test.

RESULTS

Prevalence of life-time NMUA

Table 1 shows prevalence and age initiation for life-time NMUA, cannabis, nicotine and opioid use, along with the age of onset for AUD, ND and CUD. Psychiatric criteria for AUD, ND and CUD were based on the period of heaviest use. The prevalence of life-time NMUA was marginally higher among females (20.2 versus 18.4%). The prevalence of life-time NMUA was lower compared to life-time use of cannabis or nicotine, but higher than the life-time prevalence of opioids. For males and females alike, the average age of NMUA initiation occurred after nicotine but before cannabis and opioid use. Finally, the prevalence of NMUA was marginally lower among males.

Measures of association

Among males and females, NMUA was correlated with life-time opioid use (r = 0.60–0.67) (see Table 2a). In contrast, the phenotypical correlations between NMUA and life-time cannabis or nicotine use were smaller in males (r = 0.26–0.29) and much smaller in females (r = 0.10–0.15). As expected, the phenotypical correlations between cannabis and nicotine use were high. The correlations between opioid and cannabis (r = 0.42–0.60) or between opioid and nicotine (r = 0.39–0.43) use were higher than the correlations between NMUA and cannabis (r = 0.10–0.26) or between NMUA and nicotine (r = 0.15–0.29) use.

In terms of the associations between NMUA and substance misuse, NMUA did not correlate phenotypically very highly with AUD, ND or CUD (see Table 2b), with point estimates ranging from 0.15 to 0.32 among males and from 0.11 to 0.24 among females. In contrast, correlations between the three measures of substance misuse were moderate to high (r = 0.43–0.72).

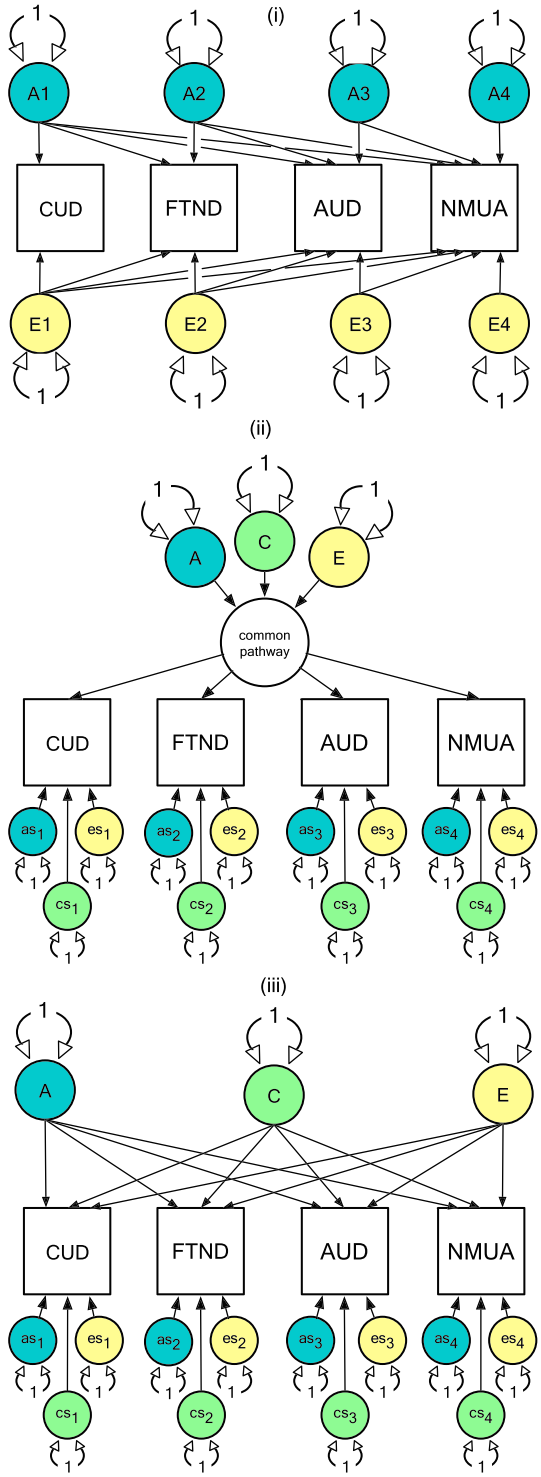

Figure 1 The Cholesky decomposition (i) common (ii) and independent (iii) pathway models to explain sources comorbid substance use (or misuse) in terms of genetic (a), shared environmental (c) and non-shared (e) environmental risks. For brevity, the shared environmental risk factors are omitted from the Cholesky. The common and independent pathway models include variable specific genetic (as_{1-4}) and environmental (cs_{1-4}, es_{1-4}) risks unique to each substance. All latent variables (circles) are standardized. All pathways with single-headed arrows are estimated. CUD = DSM-V cannabis use disorder; FTND = Fagerström Test for Nicotine Dependence; AUD = DSM-V alcohol use disorder (AUD); NMUA = life-time non-medical use of over-the-counter or prescription analgesics [Colour figure can be viewed at wileyonlinelibrary.com]

Sex differences

Before modeling the genetic etiology of NMUA, we first tested the significance of age and sex effects on the prevalence of each variable (see Supporting information, Table S1). Specifically, we tested age and sex effects on the mean latent liability. For NMUA, a model without any age and sex differences did not deteriorate significantly ($\Delta\chi^2$ = 1.97, Δ degree of freedom (d.f.) = 2, P = 0.37). Similarly, there were no sex differences in the prevalence of life-time opioid use. In contrast, males were significantly more likely to report life-time cannabis and nicotine use and be diagnosed with DSM-V alcohol use disorder, cannabis use disorder and nicotine dependence. Older subjects were also more likely to endorse life-time cannabis, nicotine and opioid use, as well as receive a diagnosis of nicotine dependence.

Twin pair correlations

MZ and DZ twin-pair polychoric correlations, including 95% confidence intervals based on combined male and female data with sex and age included as covariates, are shown in the Supporting information, Table S2. For NMUA, the DZ twin-pair correlation is approximately half of the MZ counterpart, which is consistent with the hypothesis that familial aggregation is entirely explained by additive genetic risk factors. For nicotine and opioid use and alcohol use disorder the DZ twin-pair correlations did not exceed half of the MZ correlations, suggesting familial

Table 1 Prevalence of life-time cannabis, nicotine, illicit opioid, alcohol use disorder, nicotine dependence, cannabis use disorder and life-time non-medical use of over-the-counter or prescription analgesics (NMUA).

	Sample size			*Prevalence*			*Age of initiation (SD)*	
	Total	*Male*	*Female*	*Total*	*Male*	*Female*	*Male*	*Female*
1. Cannabis use	2100	910	1190	56.0%	63.7%	50.0%	17.5 (2.73)	17.6 (2.81)
2. Nicotine use	2012	873	1139	45.2%	37.7%	51.0%	16.0 (3.07)	15.3 (2.28)
3. Opioid use	2005	870	1135	6.1%	6.4%	5.8%	20.4 (0.03)	19.8 (0.04)
4. Alcohol use disorder	1989	846	1126	45.5%	56.0%	37.5%	15.8 (1.80)	16.1 (1.77)
5. FTND	1162	557	605	36.9%	40.0%	34.2%	NA	NA
6. Cannabis use disorder	1024	512	512	24.2%	29.5%	18.9%	NA	NA
7. NMUA	2007	871	1136	19.4%	18.4%	20.2%	16.2 (0.05)	15.9 (0.06)

FTND = Fagerström Test for Nicotine Dependence; SD = standard deviation; NA = not applicable. Substance use disorders based on the period when subjects reported using the most. All non-users coded as missing.

Table 2 Pairwise polychoric phenotypical correlations (and standard errors) between life-time non-medical use of over-the-counter or prescription analgesics (NMUA) and measures of (a) substance use and (b) substance use disorders. Males are below the diagonal.

	(a) Correlations with life-time substance use				*(b) Correlations with substance use disorders*				
	1	*2*	*3*	*4*		*1*	*2*	*3*	*4*
1. Cannabis use	1	0.74 (0.04)	0.42 (0.07)	0.10 (0.05)	1. CUD	1	0.44 (0.04)	0.50 (0.05)	0.11 (0.00)
2. Nicotine use	0.78 (0.03)	1	0.43 (0.07)	0.15 (0.05)	2. FTND	0.43 (0.05)	1	0.72 (0.04)	0.22 (0.00)
3. Opioid use	0.60 (0.08)	0.39 (0.08)	1	0.60 (0.06)	3. AUD	0.46 (0.05)	0.70 (0.04)	1	0.24 (0.00)
4. NMUA	0.26 (0.06)	0.29 (0.06)	0.67 (0.06)	1	4. NMUA	0.15 (0.00)	0.24 (0.00)	0.32 (0.00)	1

CUD = DSM-V cannabis use disorder; FTND = Fagerström Test for Nicotine Dependence; AUD = DSM-V alcohol use disorder (AUD). Substance use disorders based on the period when subjects reported using the most. All non-users coded as missing.

aggregation attributable to additive genetic risks. In contrast, the DZ correlations for FTND and cannabis use disorder suggest familial aggregation attributable to a combination of shared environmental and additive genetic risks. Note, however, that the 95% confidence intervals for most of the twin-pair correlations are wide.

Univariate results

When fitting univariate models to estimate the proportions of genetic and environmental risks in each variable, we first determined if the genetic (A) and environmental (C and E) risk factors could be constrained equal across sex (see Supporting information, Table S3). For NMUA, constraining these variance components did not result in a significant deterioration in model fit ($\Delta\chi^2 = 6.13$, Δd.f. = 3, $P = 0.11$), which suggests that the relative contribution of these risk factors is unchanged with respect to sex. Similarly, for all remaining variables, there were no significant sex differences in the variance components. Henceforth, all male and female data were combined and modeled with age and sex effects on the variable means.

Table 3 includes the standardized variance components based on each of the best-fitting univariate models (see Supporting information, Table S4). With the exception of life-time opioid use, all shared environmental risk factors could be removed from each univariate model without any significant deterioration in model fit. For life-time NMUA, additive genetic risk factors explained 46% of the total variation. Relative to cannabis use, nicotine use, nicotine dependence and cannabis use disorder, the genetic risk factors for NMUA explained a much smaller proportion of the total variance. Instead, the remaining proportion of variance was entirely explained by non-shared or random environmental risk factors including measurement error.

For life-time opioid use, neither the AE nor CE models deteriorated significantly when compared to the full ACE model and all three AICs were in close proximity. Therefore, the ACE was retained in Table 3 despite the non-significant estimate for A and the nonsensical negative variance estimate for C. In samples where there is greater sampling distribution variability, the observed MZ twin-pair correlations can be underestimated and the DZ correlations overestimated by chance alone. When this occurs, variance component estimates will often be negative but not significant, implying that the parameter is not statistically distinguishable from zero [41]. Negative shared environmental variance components may be due to stochastic

Table 3 Standardized components of variance (and 95% confidence intervals) attributable to additive genetic (A), shared environmental (C), and non-share or random environmental (E) risks based on the best fitting univariate models for substance use and misuse.

	A	*C*	*E*
1. Cannabis use	0.77 (0.68–0.85)	–	0.23 (0.15–0.32)
2. Nicotine use	0.70 (0.60–0.79)	–	0.30 (0.21–0.40)
3. Opioid use	0.49 (−0.52–0.99)	−0.20 (−0.79–0.57)	0.71 (0.40–0.99)
4. AUD	0.49 (0.38–0.60)	–	0.51 (0.40–0.62)
5. FTND	0.72 (0.60–0.81)	–	0.28 (0.19–0.40)
6. CUD	0.65 (0.47–0.80)	–	0.34 (0.20–0.53)
7. NMUA	0.46 (0.29–0.57)	–	0.54 (0.43–0.71)

A = additive genetic; C = common environmental risks; E = non-shared environment risk factors; AUD = DSM-V Alcohol Use Disorder; FTND = Fagerström Test for Nicotine Dependence; CUD = DSM-V cannabis use disorder; NMUA = life-time non-medical use of over-the-counter or prescription analgesics. Substance use disorders based on the period when subjects reported using the most. All non-users coded as missing.

variation in the estimate or to a genuinely different source of variation such as genetic dominance [41]. *Post-hoc* power calculations using the R-based acePowOrd function [42] revealed insufficient power (19%) to detect an additive genetic variance of 25% based on the AE model in Supporting information, Table S4. Given the lack of statistical power to resolve the sources of familial aggregation, life-time opioid use was excluded from all subsequent analyses.

Multivariate results

Life-time cannabis, nicotine and opioid use and NMUA

To test the hypothesis that comorbid cannabis and nicotine use and NMUA can be explained by common genetic risks, we first fitted an ACE Cholesky as a reference for comparing the common independent pathway models (see Supporting information, Table S5). When compared to the full Cholesky, neither of the hypothesis-driven models provided a better fit when judged by the AIC.

We then determined if the additive genetic or the shared environmental risks could be removed from the Cholesky. As shown in Supporting information, Table S5, all shared environmental risks could be removed from the model. Table 4 shows the standardized proportions of variance attributed to the additive genetic and non-shared environmental variance for each variable based on the multivariate AE Cholesky. We then estimated the latent genetic and environmental factor correlations, which revealed that the additive genetic risks in NMUA were modestly correlated with those for cannabis and nicotine use. In contrast, aspects of the unique environment that comprise individual differences in NMUA were unrelated to those for life-time cannabis and nicotine use.

Life-time alcohol use disorder (AUD), nicotine dependence (ND), cannabis use disorder (CUD) and NMUA

To test the hypothesis that cannabis use disorder, nicotine dependence, alcohol use disorder and NMUA can be explained by common risks, we again fitted a Cholesky as a reference, followed by the common and independent pathway models (see Supporting information, Table S6). Neither the common nor independent pathway models provided a good fit to the data. Subsequent hypothesis testing revealed that shared environmental risk factors could be entirely removed from the Cholesky without any significant deterioration in fit. Standardized multivariate components of variance are shown in Table 5, along with the additive genetic and non-shared environmental correlations. The correlations between the additive genetic risks

Table 4 Standardized proportions of variance along with additive genetic and non-shared environmental risk factor correlations (95% confidence intervals) based on the best-fitting multivariate AE Cholesky decomposition of cannabis use, nicotine use and life-time non-medical use of over-the-counter or prescription analgesics (NMUA).

	Variance components		*Additive genetic (below diagonal) and non-shared environmental correlations*		
	A	*E*	*1*	*2*	*3*
1. Cannabis use	0.80 (0.71–0.87)	0.20 (0.13–0.29)	1	0.71 (0.50–0.88)	−0.28 (−0.54 to 0.00)
2. Nicotine use	0.72 (0.62–0.80)	0.28 (0.20–0.38)	0.78 (0.71–0.85)	1	−0.18 (−0.42 to 0.00)
3. NMUA	0.47 (0.41–0.61)	0.53 (0.39–0.59)	0.41 (0.24–0.56)	0.45 (0.27–0.60)	1

A = additive genetic; E = non-shared environment risk factors.

Table 5 Standardized proportions of variance along with additive genetic and non-shared environmental risk factor correlations (95% confidence intervals) based on the best fitting multivariate AE Cholesky decomposition of CUD, FTND, AUD and life-time non-medical use of over-the-counter or prescription analgesics (NMUA).

	Variance components		*Additive genetic (below diagonal) and non-shared environmental correlations*			
	A	*E*	*1*	*2*	*3*	*4*
1. CUD	0.68 (0.50–0.81)	0.32 (0.19–0.50)	1	0.71 (0.50–0.88)	−0.28 (−0.54 to 0.00)	−0.28 (−0.54 to 0.00)
2. FTND	0.76 (0.65–0.84)	0.24 (0.16–0.35)	0.67 (0.54–0.82)	1	−0.18 (−0.42 to 0.00)	−0.18 (−0.42 to 0.00)
3. AUD	0.51 (0.40–0.61)	0.49 (0.39–0.60)	0.40 (0.18–0.62)	0.25 (0.08–0.41)	1	−0.18 (−0.42 to 0.00)
4. NMUA	0.46 (0.30–0.61)	0.54 (0.39–0.70)	0.15 (0.06–0.41)	0.34 (0.14–0.54)	0.07 (−0.14 to 0.29)	1

A = additive genetic; E = non-shared environment risk factors; AUD = DSM-V alcohol use disorder; FTND = Fagerström Test for Nicotine Dependence; CUD = DSM-V cannabis use disorder. Substance use disorders based on the period when subjects reported using the most. All non-users coded as missing.

for NMUA and the three substance use disorders ranged from small to moderate (0.07–0.34). The highest genetic correlation was with FTND. The additive genetic correlation between NMUA and AUD was non-significant. Finally, the unique environments risks in NMUA were unrelated to those in substance use disorders.

DISCUSSION

Almost one-fifth of this Australian sample of young adults reported life-time non-medical use of OTC or prescribed analgesics (NMUA). There were no sex and age differences in the prevalence of this class of substance use. Regarding the etiology, life-time NMUA could be explained by a combination of genes and random aspects of the environment. Commensurate with other family studies on substance use and misuse [18,21,43], the shared familial environment played no significant role in the risk of NMUA. Contrary to our hypothesis, genes that increase the risk of NMUA were only moderately related to the genes for life-time cannabis and nicotine use. In terms of substance misuse, this class of substance use was genetically unrelated to alcohol use disorder and, while the genetic correlations with cannabis and nicotine use disorders were significant, they were small to very modest. Overall, the genetic risks in this newer class of substance use were mostly distinct from the more prevalent classes of licit and illicit substances and misuse.

Our finding of no significant sex differences in life-time NMUA is commensurate with the 2013 National Drug Strategy Household Survey (NDSHS) in Australia based on a nationally representative sample of 23 855 respondents, which found that the prevalence of past 12-month use was similar among males (3.3%) and females (3.2%) [44].

In the 2016 NDSHS [45], pain-killers and opioids were combined into one section while the use of non-opioid OTC substances such as paracetamol and aspirin were removed. This was because they were not known to be misused for cosmetic purposes, induce or enhance a drug experience or to enhance performance [45]. Despite the removal of all non-opioid OTCs from the 2016 survey, the past 12- month prevalence of NMUA increased slightly to 3.6% [45], suggesting that non-opioid OTCs were not being misused, nor were they being endorsed by respondents in the 2013 survey.

The finding of no significant shared environmental risks in the life-time NMUA contrasts with reports that have investigated cannabis [46–49] and nicotine [50,51] initiation, as well as individual differences in the frequency of nicotine, alcohol, cannabis and other classes of substance use [52–55], nearly all of which have revealed evidence of significant shared environmental risks. The decline in shared environmental risk factors over time is

characteristic of the progression to more frequent substance use and the variation in psychiatric criteria indicative of misuse [56]. Beyond the associations with other forms of substance use examined here, it is plausible that the liability to NMUA represents a more severe, emerging class of substance use. For instance, NMUA has been linked to psychiatric symptoms by us [57–60] and others [61]. In non-genetic information studies, we have documented numerous adverse associations between NMUA and stimulants with behaviors such as high-risk sexual behavior [62,63], driving under the influence [60] and sexual assault [64,65]. However, attempts to determine empirically the degree of impairment associated with this class of substance use *vis-à-vis* other substances are currently hampered by a lack of available abuse and dependence criteria and the appropriate application of item response theory analysis [66] beyond the scope of the present analyses.

Limitations

Our findings must be interpreted in the context of four potential limitations. First, our sample comprises a population-based sample of young adult Australians, predominately of Anglo Saxon ancestry. Although our findings may not generalize to other populations, given the higher rates of prescribed opioid use [67] and opioid-related mortality [68] in Anglo Saxon ancestral populations, this is an ideal sample for preliminary investigation and one of the few with genetically informative NMUA data. With respect to genetic relatedness, we have detected no significant genetic differences between our sample, large population-based samples from the United States, western and eastern Europe [69,70].

Secondly, opioids refer to the entire family of natural, synthetic and semi-synthetic forms. Our self-report assessment of life-time opioid use included heroin (semi-synthetic), morphine (opium alkaloid), methadone (fully synthetic) and codeine (opium alkaloid). At the time of assessment, many OTC analgesics in Australia contained codeine [71]. Codeine was also included among the list of NMUA examples. This may have inflated the phenotypical association with life-time self-reported illicit opioid use. However, if subjects were responding to life-time codeine use in both items, then the prevalence and components of genetic and environmental variance ought to have been identical. Future research would benefit from more fine-grained assessment of illicit opioids, non-medical use of opioid prescription medications and non-medical use of OTC medications. We also note that Australia has seen an increase in both codeine dependence and death-related to overdose from codeine-containing OTC products [9]. Consequently, as of February 2018 codeine-based drugs were rescheduled to be available only by prescription [71]. Changes in the rescheduling of codeine-based medications are likely to impact the prevalence and individual differences in use, and potentially the relative contribution of genes and environment to its use and misuse.

Thirdly, the NMUA assessment included non-steroidal or non-opioid analgesics. Their inclusion and any ensuing heterogeneity may have attenuated the association between life-time non-medical use of opioid-based analgesics and other classes of SU and SUD. We note that the prevalence of NMUA in the NDSHS surveys between 2013 and 2016 did not change, despite the removal of non-opioid OTC from the list of survey items [45]. This is consistent with non-opioid analgesics not being known to be misused for cosmetic purposes or to induce or to enhance a drug experience or to enhance performance [7].

Fourthly, non-medical use was defined as not taken in quantities or manner prescribed by a medical practitioner. This definition may have benefited with an expanded description that included 'exceeding the recommendations on the label' for the non-medical use of OTC medications.

Fifthly, the NMUA assessment was life-time. Psychiatric criteria for abuse and dependence were not assessed. The extent to which the genetic and environmental risks in this measure predict the risk of transitioning to chronic NMUA is unknown. Our work has previously shown that the genetic and environmental risks in licit and illicit substance use are partly, but not entirely, related to corresponding diagnoses of substance misuse [46,48,72]. Although very high genetic correlations between major classes of illicit and licit substance use disorders have been observed [55], it is unclear if the genetic risks in chronic non-medically prescribed or OTC analgesics use will be highly correlated with those for CUD, AUD and ND.

Conclusion

Life-time non-medical or OTC use of analgesics is moderately heritable, and there is no evidence that aspects of the familial or shared environmental risks are etiologically significant. Twin modeling suggests that the genetic risks in this emergent class of substance use are mostly etiologically distinct. There was no genetic overlap with alcohol use disorder and very little overlap with cannabis use disorder. There was, however, a moderate degree of genetic overlap between NMUA and life-time cannabis use, nicotine use and nicotine dependence.

Declaration of interests

None.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 The change in each univariate model fit when age and sex differences on the mean latent liability to substance use and misuse are removed. If significant, the standard effects (β) for age and sex are shown.
Table S2 Aggregated monozygotic (MZ) and dizygotic (DZ) twin pair polychoric correlations (including 95% confidence intervals) based on combined male and female data. Also shown are the complete same- and opposite-sex MZ and DZ twin pair correlations.
Table S3 Summary of the observed changes in model fit when comparing sex-specific (separate male and female genetic and environmental risks) versus no sex differences for each of the substance use and misuse variables.
Table S4 Univariate model fitting comparisons.
Table S5 Comparisons between the Cholesky, common and independent pathway models for lifetime cannabis, nicotine and lifetime non-medical use of over-the-counter or prescription analgesics.
Table S6 Comparisons of the Cholesky, common and independent pathway models for lifetime cannabis use disorder, Fagerström Test for Nicotine Dependence, alcohol use disorder and lifetime non-medical use of over-the-counter or prescription analgesics.