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Association of parental substance misuse with offspring substance misuse and criminality: a genetically informed register-based study

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Abstract

Background. Genetically informed studies have provided mixed findings as to what extent parental substance misuse is associated with offspring substance misuse and antisocial behavior due to shared environmental and genetic factors.

Methods. We linked data from nationwide registries for a cohort of 2 476 198 offspring born in Sweden 1958–1995 and their parents. Substance misuse was defined as International Classification of Diseases diagnoses of alcohol/drug use disorders or alcohol/drug-related criminal convictions. Quantitative genetic offspring-of-siblings analyses in offspring of monozygotic and dizygotic twin, full-sibling, and half-sibling parents were conducted.

Results. Both maternal and paternal substance misuse were robustly associated with offspring substance misuse [maternal adjusted hazard ratio (aHR) = 1.83 (95% confidence interval (CI) 1.80–1.87); paternal aHR = 1.96 (1.94–1.98)] and criminal convictions [maternal aHR = 1.56 (1.54–1.58); paternal aHR = 1.66 (1.64–1.67)]. Additive genetic effects explained 42% (95% CI 25–56%) and 46% (36–55%) of the variance in maternal and paternal substance misuse, respectively, and between 36 and 44% of the variance in substance misuse and criminality in offspring. The associations between parental substance misuse and offspring outcomes were mostly due to additive genetic effects, which explained 54–85% of the parent-offspring covariance. However, both nuclear and extended family environmental factors also contributed to the associations, especially with offspring substance misuse.

Conclusions. Our findings from a large offspring-of-siblings study indicate that shared genetic influences mostly explain the associations between parental substance misuse and both offspring substance misuse and criminality, but we also found evidence for the contribution of environmental factors shared by members of nuclear and extended families.

Introduction

Alcohol and drug use disorders tend to run in families (Mellentin *et al.* 2016; Merikangas *et al.* 1998). Offspring of parents with substance use disorders (SUDs) have an elevated risk of problematic substance use as compared to offspring of parents without SUDs (Lieb *et al.* 2002; Walden, Iacono, & McGue, 2007). In addition, offspring of parents with SUDs are at increased risk for antisocial behavior (Hussong *et al.* 2007).

Several mechanisms have been proposed to mediate these risks. For example, individuals with a family history of SUDs have been found to differ from those without a family history in amygdalar, hippocampal, basal ganglia, and cerebellar volumes, as well as in brain responses related to inhibitory control (Cservenka, 2016). Parental SUDs are also associated with offspring's lower general cognitive ability (Khemiri *et al.* 2020), poorer performance in specific cognitive domains such as working memory and executive functioning, higher impulsivity and risk-taking, and altered emotional reactivity (Cservenka, 2016; Weinberg, 1997). Further, a family history of alcohol use disorders is associated with a reduced subjective response to alcohol, leading to higher levels of consumption (Quinn & Fromme, 2011).

Social learning effects of parental modeling could also contribute to the parent-offspring resemblance in substance use (Petraitis, Flay, & Miller, 1995). Alcohol-related cognitions (i.e. alcohol-related knowledge, norms, and expectancies) are thought to be important for the development of alcohol use, but associations with parental alcohol use have been inconsistent (Voogt *et al.* 2017). Environmental effects could also be indirect: children of parents with SUDs are at risk for various adverse exposures such as parental divorce early on in life, and substance use problems are likely to interfere with parenting and increase the

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likelihood of maltreatment or neglect (Hafekost *et al.* 2017; Smith, Wilson, & Comm Subst Use, 2016; Windle & Windle, 2018). These factors might, in turn, increase the risk for substance use problems and antisocial behavior in the offspring (Sheridan, 1995). Finally, affiliation with substance-using and antisocial peers could mediate the associations between parental SUDs and offspring substance use and antisocial behaviors (Bountress, Chassin, & Lemery-Chalfant, 2017; Henry, Fulco, Agbeke, & Ratcliff, 2018; Mahedy *et al.* 2018).

Importantly, besides the question of the specific mediating mechanisms, the broader question remains as to what extent the intergenerational associations are due to genetic and environmental influences. While genetic differences explain 40–50% of individual differences in the risk of SUDs within generations (Dick, Prescott, & McGue, 2010; Polderman *et al.* 2015; Verhulst, Neale, & Kendler, 2015), the relative importance of genetic and environmental factors for intergenerational transmission of substance misuse is less clear. Specifically, while non-genetic factors shared by siblings typically explain 10–20% of the variance in SUD risk (Dick *et al.* 2010; Polderman *et al.* 2015; Verhulst *et al.* 2015), it is not well known whether exposure to parental SUDs increases the risk for offspring SUDs beyond the contribution of genetic risk transmitted from parents to offspring. Besides a direct effect of the exposure, intergenerational associations may reflect shared genetic effects on the exposure and the outcome, formed by the parental and offspring phenotypes (Plomin, Defries, & Loehlin, 1977). This has been stressed in the context of parental SUDs, calling for genetically informed research designs (McGue, 1997).

Effects of the rearing environment can be separated from genetic factors in adoption studies, which compare the resemblance of offspring with their biological and adoptive parents. Early adoption studies highlighted genetic effects on alcohol and drug abuse as well as antisocial behavior (Cadoret, Cain, & Grove, 1980; Cadoret, Yates, Troughton, Woodworth, & Stewart, 1995; Crowe, 1974; Goodwin *et al.* 1974; Moffitt, 1987). More recent analyses of families with biological and adoptive relatives as well as families with stepparents and biological parents who did not live with their offspring have suggested that both genetic and environmental factors contribute to the parent-offspring transmission of alcohol and drug misuse as well as antisocial behavior (Kendler, Ohlsson, Sundquist, & Sundquist, 2015c; Kendler *et al.* 2014, 2015a).

Adoption studies may, however, suffer from selection biases and other methodological limitations, which makes it necessary to utilize other designs to replicate findings. The Children-of-Twins (CoT) design compares offspring of monozygotic (MZ) and dizygotic (DZ) twin parents who are discordant for the exposure (D'Onofrio, Lahey, Turkheimer, & Lichtenstein, 2013; McAdams *et al.* 2014, 2018). Based on this contrast, genetic and environmental associations between parent and offspring phenotypes can be distinguished. A review of CoT studies found that previous studies of parental substance misuse have been conducted in relatively small samples derived from only two cohorts of twin parents (McAdams *et al.* 2014). Findings have been mixed, with some studies reporting no support for an environmental effect of parental substance misuse (Slutske *et al.* 2008) while others have been unable to reliably separate genetic *v.* environmental effects (Duncan *et al.* 2006, 2008). Similarly, CoT studies of parental substance misuse and offspring antisocial behavior have been inconclusive (Haber *et al.* 2010; Waldron, Martin, & Heath, 2009).

The CoT design has recently been expanded into a more general offspring-of-siblings design where offspring of parents who are full or half-siblings are studied (Chang *et al.* 2014; Kuja-Halkola, D'Onofrio, Larsson, & Lichtenstein, 2014; Latvala, Kuja-Halkola, Langstrom, & Lichtenstein, 2015; McAdams *et al.* 2018). Importantly, this design can utilize much larger sample sizes compared to CoT studies and is expected to result in improved statistical power and representativeness.

The focus of the present study was to investigate genetic and environmental contributions to the associations between parental substance misuse and offspring outcomes. Specifically, we aimed first to describe individual-level associations of maternal and paternal substance misuse with substance misuse and criminality in the offspring, and then to estimate the relative contributions of genetic and environmental factors on the parent-offspring associations. We conducted quantitative genetic offspring-of-siblings analyses in a large Swedish nationwide register-based dataset and included criminality as an outcome in addition to substance misuse to also study the intergenerational association between parental substance misuse and offspring antisocial behavior.

Methods

Study population

We conducted a population-based cohort study by linking several Swedish longitudinal registers, using the unique personal identity number given to all Swedish citizens at birth and to immigrants upon arrival to Sweden as key. Data on substance misuse and criminality were available for the period 1973–2013. To maximize the sample size but minimize missing information due to left and right censoring, we included in the study population offspring born in Sweden to parents who were born between 1943 and 1983. We identified the sample from the Total Population Register (Ludvigsson *et al.* 2016), which provides links to biological parents for each individual born since 1932. Requiring the offspring to have a register-based follow-up at least until age 18 and non-missing information on both parents resulted in data for 2 476 198 individuals (51% men) in the offspring generation, who were born between 1958 and 1995.

The parent generation was further linked to their parents (i.e. grandparents of the offspring generation) in order to identify full siblings and maternal/paternal half-siblings in the parental generation. The Swedish Twin Registry was used to identify MZ and DZ twin parents. Thus, we could identify cousins in the offspring generation with different types of relationships. From these cousins, we extracted information for two different types of analyses: *within-family* and *quantitative genetic* analyses (see below). For the *within-family* analyses, we used 337 672 paternal and 341 680 maternal full cousins randomly selecting one offspring per nuclear family. We used two different samples also for the *quantitative genetic* analyses. We identified 744 679 extended families related through the father and then we randomly selected up to two full or half-siblings per nuclear family, resulting in 938 347 parents and 1 619 271 offspring included in the analysis (online Supplementary Tables S1 and S2). Similarly, 759 067 maternally related extended families including 958 773 parents and 1 662 574 offspring were studied (online Supplementary Tables S3 and S4). The samples used in the different analyses are summarized in Fig. 1.

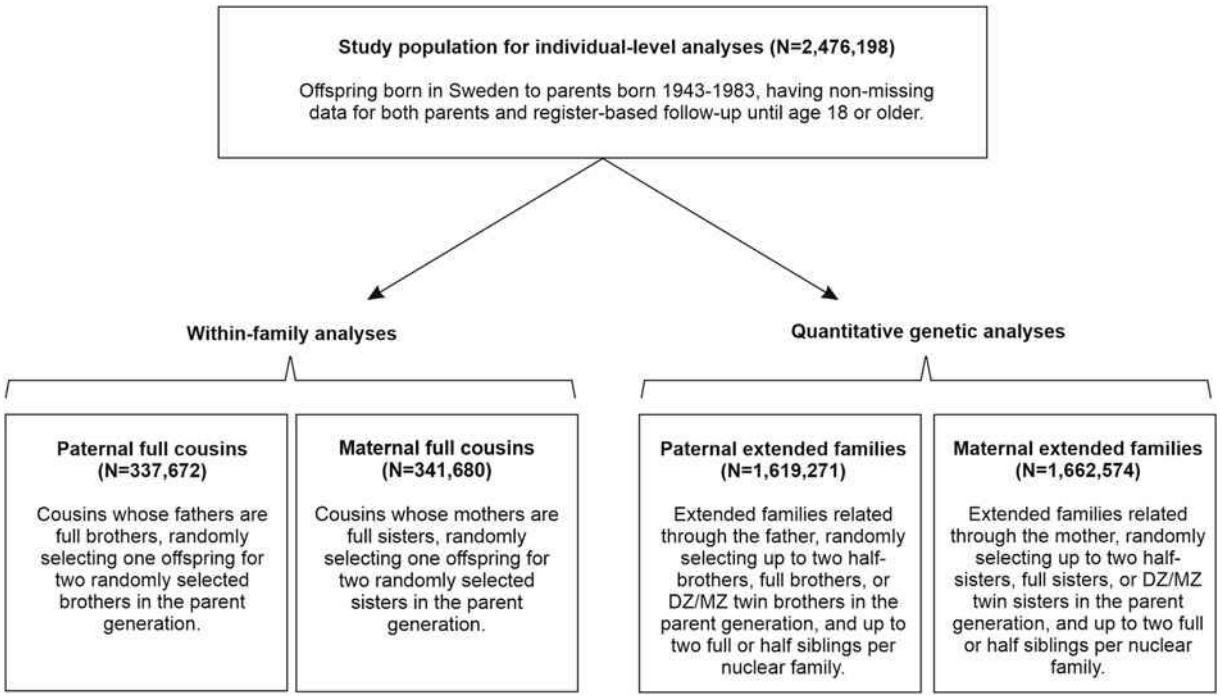

Fig. 1. Samples used for individual-level, within-family, and quantitative genetic analyses. All Ns refer to the offspring generation. The samples used in within-family analyses are subsamples of those used in the quantitative genetic analyses.

Measures

Substance misuse

We used an omnibus measure of substance misuse combining alcohol and drug-related medical diagnoses and criminal convictions. Diagnoses came from the National Patient Register (NPR) which contains details of all individual episodes of hospitalization in Sweden since 1973 and of outpatient treatments since 2001, and convictions were available from the National Crime Register for individuals aged 15 (age of criminal responsibility) and older since 1973. This measure captures a wide range of alcohol and drug-related events but does not include all individuals with substance misuse, as many of them are not registered in any medical or governmental registry. Similar measures have been used in earlier register-based studies of alcohol and drug misuse (Kendler *et al.* 2015c; Latvala, Kuja-Halkola, D'Onofrio, Larsson, & Lichtenstein, 2016). Substance misuse events were defined as having an International Classification of Diseases (ICD) diagnosis of mental and behavioral disorders due to alcohol or drugs (excluding tobacco) in the NPR (ICD-8 codes 291, 303, 304; ICD-9 codes 291, 303–305; ICD-10 codes F10-F16, F18, F19) or a court conviction of alcohol- or drug-related crime defined as (1) violations of the Narcotic Drugs Act which include possession of substances for personal use, supply, manufacture, and consumption, and (2) convictions of driving under the influence of alcohol and/or illicit substances. Substance misuse was defined identically for parents and offspring.

Criminality

Criminality in the offspring was defined as any conviction of violent crimes (i.e. murder, manslaughter, assault, kidnapping, illegal restraint, illegal coercion or threats, robbery, threats or violence against an officer, arson, gross violation of a person's integrity, and harassment), sexual crimes (i.e. rape, sexual coercion, child molestation, sexual intercourse with a child, child pornography offenses, pimping, and sexual harassment), property crimes (e.g. theft, larceny, burglary, embezzlement), and traffic crimes (e.g. crimes against road safety, and unlawful driving of a vehicle), but excluded substance-related convictions which were included in the definition of substance misuse.

Covariates

As parental covariates, we included both parents' birth year (as continuous variables), immigrant status, educational level, and lifetime history of any psychiatric disorders other than alcohol and drug use disorders in the NPR [ICD-8 codes 290–315 (excluding 291, 303, 304); ICD-9 codes 290–319 (excluding 291, 303–305); ICD-10 codes F00-F09, F20-F99]. Immigrant status was a dichotomous variable denoting whether the parent was born outside of Sweden. Educational level was defined as the highest attained education, available for the years 1990–2013 in the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). As offspring covariates, we included birth year (continuous variable) and sex. Finally, we used dates of emigration from Sweden and death, available from the Migration Register and the Cause of Death Register, respectively, to correctly define follow-up time for offspring outcomes.

Statistical methods

Individual-level analysis

Following descriptive analyses, we fitted Cox proportional hazard regression models to estimate the relative hazard of substance misuse and criminality registrations during the follow-up among individuals with parental substance misuse as compared to those without parental substance misuse. We conducted separate analyses for maternal and paternal substance misuse as

exposure and for the two outcomes, following the participants from birth until the occurrence of the first substance misuse registration or criminal conviction, respectively. Those who had no registrations during the study period contributed person-time at risk until the end of follow-up (31 December 2013), emigration, or death, whichever occurred first. In the first model, we adjusted for parent's birth year, and offspring birth year and sex. The second model added the co-parent's birth year and substance misuse as well as immigrant status, educational level, and psychiatric disorders for both parents. Graphical inspection of the Schoenfeld residuals did not reveal violations of the proportional hazards assumption. The models were fitted with adjustment of standard errors for the non-independence of siblings in the offspring generation using a cluster-robust sandwich estimator.

Within-family analysis

We conducted stratified Cox regression analyses within clusters of paternal and maternal full cousins. These models use information from cousins who are discordant for parental substance misuse and by design rule out all factors that are constant within clusters, including unmeasured genetic and shared environmental factors (Allison, 2009). Full cousin offspring of fathers who were brothers and mothers who were sisters were included, and the estimates were compared with results from the individual-level models, taking reduced hazard ratios (HRs) as evidence for familial (i.e. genetic and environmental factors shared between full cousins) influences contributing to the parent-offspring associations.

Quantitative genetic modeling

To estimate the contributions of genetic and environmental factors to the intergenerational associations, we conducted quantitative genetic structural equation models in extended family pedigree data. We used an extension of the classical twin model, which decomposes variance into additive genetic influences (A), shared environmental (C) and non-shared environmental (E) influences. In contrast to the standard twin model, our model estimates intergenerational bivariate associations between parental substance misuse and the offspring outcomes. The model decomposes the shared environmental variance into environmental influences shared by all members of an extended family (i.e. fathers/mothers who are full siblings, MZ twins, or maternal half-siblings, and their offspring) (T) and into environmental influences only shared by members of a nuclear family (i.e. father/mother and his/her offspring) (N) (Kuja-Halkola *et al.* 2014). The model partitions the association between parental substance misuse and offspring outcomes into the A, T and N components and estimates the proportion of the correlation explained by each factor (Fig. 2).

The model has been described in detail elsewhere (Kuja-Halkola *et al.* 2014; Latvala *et al.* 2015), but a comparison with the classical twin design is illustrative. The parent generation part of the model includes the variance components A, T, and N, which are analogous to the A, C, and E components of the twin design. The nuclear family component N is non-shared between sibling parents, and thus contains all individual-specific influences, including measurement error, in the parent generation. In the offspring generation, the variance is decomposed into the A, T, N, and E components. Here the A and E components correspond perfectly with the same components of the classical twin design. The difference is in the shared environmental variance, which is captured in the C component in twin studies but divided into the nuclear family environmental component N and the extended family environmental component T in the current model.

We estimated a liability-threshold model with binary outcome variables indicating substance misuse and criminal convictions during follow-up. The liability-threshold model assumes each individual to have an unobserved normally distributed liability for the outcome, and those with observed events are assumed to have a liability exceeding the threshold (Posthuma *et al.* 2003). The quantitative genetic models were adjusted for parental and offspring birth year and for offspring sex. The OpenMx package (Neale *et al.* 2016) in the software R (R Core Team, 2013) was used for modeling.

Sensitivity analyses

To test the robustness of our findings, we conducted the following sensitivity analyses. First, while the main individual-level and within-family analyses included lifetime measures of exposures and outcomes, to rule out reverse associations between exposures and outcomes we repeated the Cox regression models defining parental substance misuse as a time-varying covariate and studied associations with offspring outcomes (i) during the lifetime, and (ii) by age 18. Second, to rule out the potential effect of left censoring in the exposure (i.e. unknown parental substance misuse status before the start of the registers in 1973), we repeated the Cox models including only offspring whose parents were born 1958 or later and thus had information about substance misuse since age 15. Third, we investigated the evidence for differential associations by offspring sex by conducting the individual-level analyses separately for sons and daughters. Finally, we sought to test possible carry-over effects in within-family analyses stratified by whether the earlier-born or the later-born sibling parent had substance misuse.

Results

Descriptive data of the study population are presented in Table 1. There were 366 641 (14.8%) individuals with paternal and 113 190 (5.6%) individuals with maternal substance misuse in the offspring generation, while 188 352 (7.6%) individuals had substance misuse and 309 221 (12.5%) had criminal convictions. Person-years at risk and incidence rates for substance misuse and criminal convictions are given in online Supplementary Table S5. The median length of follow-up was 27.3 (interquartile range: 21.7–35.2) years for substance misuse and 26.2 (20.8–34.1) years for criminal convictions.

Individual-level and within-family analyses

Table 2 shows HRs for substance misuse and criminal convictions associated with paternal and maternal substance misuse. In minimally adjusted models, both paternal and maternal substance misuse more than doubled the risk for offspring substance misuse [paternal: HR = 2.51 (95% confidence interval (CI) 2.49–2.54), maternal: HR = 2.81 (2.77–2.86)] and criminality [paternal: HR = 2.07 (2.05–2.09), maternal: HR = 2.20 (2.17–2.23)]. In fully adjusted models, the associations were reduced but both paternal and maternal substance misuse were still robustly associated with the offspring outcomes (HRs between 1.56 and 1.96).

Associations were further reduced in stratified Cox regression models within pairs of full cousins (Table 2), suggesting the contribution of familial factors. In fully adjusted models, HRs for the

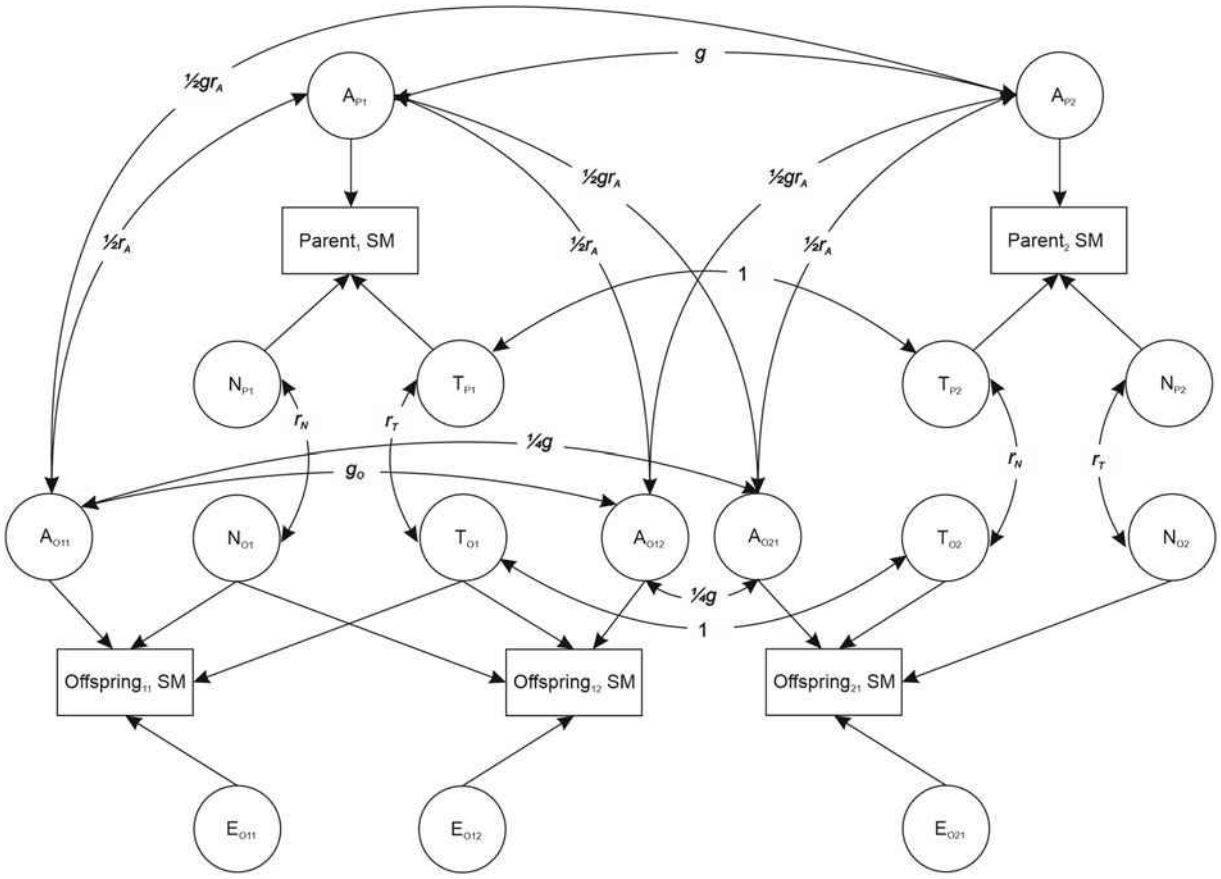

Fig. 2. Quantitative genetic model for the association between parental and offspring substance misuse (SM), showing additive genetic (A), extended family environmental (T), nuclear family environmental (N), and individual-specific environmental (E) variance components and their correlations (*r*) in the parent (P) and offspring (O) generations. The figure shows a pair of sibling parents ($Parent_1$, $Parent_2$), two siblings in the offspring generation in nuclear family 1 ($Offspring_{11}$, $Offspring_{12}$), and, for simplicity, one sibling in the offspring generation in nuclear family 2 ($Offspring_{21}$). *g* denotes the genetic relatedness between the sibling parents and gets the value 1, 0.5, and 0.25 in parents who are MZ twins, DZ twins or full siblings, and half-siblings, respectively. g_o denotes the genetic relatedness between offspring within nuclear families, either 0.5 or 0.25 for full siblings and half-siblings, respectively. Please note that the T and N components in the parent generation correspond to the shared and non-shared environmental components, respectively, in the classical twin model. While, in the offspring generation, the N and E components correspond to the shared and non-shared environmental components, respectively, and the T component corresponds to an environmental effect shared between cousins.

associations between parental substance misuse and offspring outcomes within extended families ranged from 1.41 to 1.57.

Quantitative genetic models

Online Supplementary Tables S6–S9 provide unadjusted and adjusted correlations between family members. We report estimates from the full offspring-of-siblings models in Table 3. Additive genetic influences explained 46% of the variance in paternal and 42% in maternal substance misuse and between 36 and 44% of the variance in offspring substance misuse and criminality. Environmental factors shared between parent and offspring members of extended families (T) and offspring members of nuclear families (N) made only small contributions within generations, explaining 2–5% of the variance. Additive genetic factors (A) explained most of the parent-offspring covariance between parental substance misuse and the offspring outcomes. The proportion of covariance explained by A effects ranged from 54% (95% CI 25–84%), between maternal substance misuse and offspring substance misuse, to 85% (72–97%), between paternal substance misuse and offspring criminality, and the corresponding genetic correlations were between 0.70 and 0.98. With the exception of the association between maternal substance misuse and offspring criminality, also extended and nuclear family environmental components significantly contributed to the association between parental substance misuse and offspring outcomes. These contributions were most notable for the association between maternal and offspring substance misuse [$T = 17\%$ (2–31%), $N = 29\%$ (12–45%)].

Sensitivity analyses

Analyses with parental substance misuse as a time-varying covariate found similar associations with offspring substance misuse and criminality as the main analysis with lifetime exposure variables when adjusted for covariates (online Supplementary Table S10). Estimates were also similar in analyses restricted to the offspring of parents born since 1958 (online Supplementary Table S11). Further, individual-level associations between paternal substance misuse and offspring outcomes were similar for sons and daughters, whereas the associations between maternal substance misuse and offspring outcomes were larger in daughters than in sons (online Supplementary Table S12). Finally, we found no systematic

Table 1. Characteristics of offspring ($N = 2\,476\,198$) by parental substance misuse

	Parental substance misuse ($N = 436\,222$)	No parental substance misuse ($N = 2\,039\,976$)
[redacted]		

Table 2. Cox proportional hazard ratios (95% confidence intervals) for substance misuse and criminal convictions associated with paternal and maternal substance misuse

	Individual-level analysis		Within-family analysis[a]	
	Minimally adjusted model[b]	Fully adjusted model[c]	Minimally adjusted model[b]	Fully adjusted model[c]
[redacted]				

[a]Stratified Cox regression in pairs of paternal/maternal full cousins.
[b]Adjusted for parental and offspring birth years and offspring sex.
[c]Further adjusted for birth year and substance misuse of the co-parent, and immigrant status, educational level and psychiatric disorders of both parents.

differences between the associations of earlier-born *v.* later-born sibling parent's substance misuse with the offspring outcomes (online Supplementary Table S13).

Discussion

Using nationwide register data from 2.5 million individuals with follow-up time up to over 35 years, we found parental substance misuse to be robustly associated with substance misuse and

Table 3. Offspring-of-siblings model estimates (95% confidence intervals) for the proportions of variance and covariance of parental substance misuse and offspring outcomes due to additive genetic (A), extended family environmental (T), nuclear family environmental (N), and individual-specific environmental (E) factors

	Paternal substance misuse		Maternal substance misuse	
Parental A variance	0.46 (0.36–0.56)		0.42 (0.25–0.56)	
Parental T variance	0.07 (0.02–0.12)		0.06 (0.00–0.12)	
Parental N variance[a]	0.47 (0.42–0.52)		0.52 (0.45–0.60)	
	Offspring substance misuse	Offspring criminality	Offspring substance misuse	Offspring criminality
Offspring A variance	0.44 (0.34–0.53)	0.36 (0.23–0.48)	0.39 (0.32–0.47)	0.37 (0.31–0.44)
Offspring T variance	0.02 (0.00–0.03)	0.04 (0.02–0.06)	0.04 (0.02–0.05)	0.04 (0.03–0.05)
Offspring N variance[a]	0.04 (0.00–0.08)	0.05 (0.01–0.09)	0.05 (0.02–0.07)	0.04 (0.01–0.06)
Offspring E variance	0.51 (0.46–0.55)	0.56 (0.50–0.62)	0.52 (0.48–0.56)	0.55 (0.51–0.58)
Parent-offspring phenotypic correlation	0.26 (0.26–0.27)	0.23 (0.23–0.24)	0.26 (0.26–0.27)	0.23 (0.22–0.23)
Parent-offspring A explained covariance	0.67 (0.50–0.84)	0.85 (0.72–0.97)	0.54 (0.25–0.84)	0.84 (0.50–1.18)
Parent-offspring T explained covariance	0.13 (0.06–0.21)	0.07 (0.01–0.13)	0.17 (0.02–0.31)	0.05 (−0.12–0.21)
Parent-offspring N explained covariance	0.19 (0.09–0.30)	0.08 (0.00–0.15)	0.29 (0.12–0.45)	0.11 (−0.07–0.30)
Parent-offspring A correlation (genetic correlation)	0.79 (0.61–0.97)	0.98 (0.84–1.00)	0.70 (0.32–1.00)	0.97 (0.56–1.00)
Parent-offspring T correlation	1.00 (0.56–1.00)	0.34 (0.18–0.50)	0.95 (0.06–1.00)	0.21 (−0.48–0.90)
Parent-offspring N correlation	0.38 (0.06–0.69)	0.12 (0.02–0.22)	0.48 (0.18–0.78)	0.18 (−0.12–0.49)

All models were adjusted for parental and offspring birth years and offspring sex. Confidence intervals are Wald-type hence boundaries can span outside parameter space (e.g. correlation upper boundary above 1); we have truncated such boundaries in the table.

[a]Please note that the T and N components in the parent generation correspond to the shared (C) and non-shared environmental (E) components, respectively, in the classical twin model. While, in the offspring generation, the N and E components correspond to the shared and non-shared environmental components, respectively, and the T component corresponds to an environmental effect shared between cousins.

criminal convictions in offspring. The associations were similar for paternal and maternal substance misuse, and they were not fully explained by childhood socioeconomic status or parental psychiatric comorbidity. Within-family analyses in full cousins suggested the associations were not independent of familial factors shared between sibling parents. To better understand the sources of this familial resemblance, we conducted quantitative genetic models in more than 700 000 maternal and paternal extended families and found genetic factors to explain most of the covariance of parental substance misuse with offspring substance misuse and criminality.

Genetic factors explained 54–67% of the association between parental and offspring substance misuse. This finding concurs with previous evidence from adoption studies highlighting the genetic contribution to the parent-offspring resemblance in alcohol and drug use problems (Cadoret *et al.* 1980, 1995; Goodwin *et al.* 1974; Kendler *et al.* 2015a, 2015c). Interestingly, our results suggested a possibly stronger genetic contribution to the association between parental substance misuse and offspring criminality, with genetic factors explaining approximately 85% of the intergenerational association. This genetic contribution is consistent with evidence from twin studies of shared genetic influences on substance misuse and antisocial behavior (Kendler, Prescott, Myers, & Neale, 2003; Kendler *et al.* 2016; Krueger *et al.* 2002) and from adoption studies of parental and offspring externalizing behavior (Hicks, Foster, Iacono, & McGue, 2013).

Besides genetic influences, we found evidence for the contribution of both nuclear and extended family environmental factors to the associations of parental substance misuse with offspring substance misuse and criminality. The nuclear family environmental factor explained 19–29% of the intergenerational resemblance in substance misuse. In other words, our findings suggest that parents and offspring, as well as siblings living together, resemble each other in their risk for substance misuse even when the contribution of genetic influences is accounted for. While our study cannot establish causality, a causal effect of parental substance misuse on the offspring would be detected as a contribution of the nuclear family environmental component in the model. Such an effect might be mediated through factors such as social learning, problems in parenting, exposure to adverse rearing environment, or effects on offspring psychological development (Cservenka, 2016; Hafekost *et al.* 2017; Smith *et al.* 2016; Weinberg, 1997; Windle & Windle, 2018). Importantly, our findings from an offspring-of-siblings design replicate earlier adoption studies, which have also found support for parent-offspring associations independent of genetic factors (Kendler *et al.* 2014, 2015a, 2015c). However, the contribution of nuclear environmental factors for the association between parental substance misuse and offspring criminal behavior was somewhat less clear. It should also be noted that the nuclear environmental component also includes possible confounding factors shared by parents and offspring.

The extended family environmental component also contributed, although to a lesser degree, to the intergenerational associations, suggesting that the risks in parents and offspring within extended families correlate even when shared genetic effects and environmental influences within nuclear families are accounted for. While more difficult to interpret, this could reflect broader

socioeconomic or cultural factors operating within extended families. Taken together, our findings on the nuclear and extended family environmental contributions are compatible with twin studies finding that environmental factors shared between co-twins partly explain the risk for SUDs and criminal behavior (Dick *et al.* 2010; Kendler *et al.* 2015b, 2016; Verhulst *et al.* 2015).

Our results extend the earlier findings from a CoT study reporting shared genetic factors influencing the parent-offspring resemblance in alcohol use disorder (Slutske *et al.* 2008), as well as other CoT studies which have had limited success in differentiating genetic influences from direct effects of parental substance misuse (Duncan *et al.* 2006, 2008; Haber *et al.* 2010; Waldron *et al.* 2009). Taken together, our results and findings from other designs clearly indicate passive gene-environment correlation (Plomin *et al.* 1977) as a key mechanism giving rise to the intergenerational transmission of substance use problems and antisocial behavior whereas evidence for an environmental effect of exposure to parental substance misuse on offspring outcomes is less consistent and may depend on the outcome. Passive gene-environment correlation refers to the situation where parents provide their children with both the genetic risk and the environmental exposures associated with the risk of substance misuse and antisocial behavior. Our findings regarding the environmental contributions to the parent-offspring resemblance in substance misuse are similar to those from recent genetically informative studies of parental depressive and anxiety disorders, which have found evidence for both genetic and environmental effects of parental, especially maternal, internalizing disorders on offspring internalizing disorders (Eley *et al.* 2015; Hannigan *et al.* 2018; Tully, Iacono, & McGue, 2008). Taken together, existing evidence indicates that genetic effects should feature centrally in theoretical models of intergenerational transmission of psychopathology and that they should not be disregarded when developing and evaluating intervention efforts to reduce the intergenerational burden of mental health problems. On the other hand, these findings also further underline the importance of accounting for genetic risks in studies of environmental effects on child development and demonstrate that such environmental factors can indeed be separated from genetic effects.

Our findings should be considered in the context of several limitations. First, register-based data only include a subset of all parents and offspring with substance misuse. In addition to diagnosed disorders, we included alcohol and drug-related criminal convictions to widen the definition of substance misuse, but our results are best interpreted as pertaining to more severe substance use problems in parents and offspring. Complementing this perspective, evidence from an adoption study suggests genetic influences also contribute to the parent-offspring similarity in patterns of non-disordered alcohol use (McGue, Malone, Keyes, & Iacono, 2014). Second, our main analyses included lifetime registrations of parental exposure and offspring outcomes, raising the issue of timing of the possible environmental effects as well as reverse causality. Lifetime data were used because register-based dates of diagnoses or criminal convictions related to alcohol or drug use disorders do not correspond well with the true onset of substance use problems (McGorry, Purcell, Goldstone, & Amminger, 2011). However, when using parental substance misuse registrations as time-varying covariates predating offspring outcomes we found similar associations as the main analyses both in the individual-level and within-family analyses. This suggests that our findings with lifetime measures are unlikely to be significantly biased. Relatedly, we also found similar estimates when using data from parental birth cohorts with register-based coverage of substance misuse starting no later than at age 15, suggesting that the inclusion of earlier cohorts with left-censored data did not distort our findings. Fourth, the main Cox regression analyses and quantitative genetic models were conducted pooling data from sons and daughters, which might have concealed sex-specific effects. However, sensitivity analyses did not suggest notable sex-specificity of the associations between parental substance misuse and the offspring outcomes; thus, we aimed to maximize statistical power in the intergenerational models. Fifth, cohort effects could have affected our results. We adjusted all analyses for parental and offspring birth years, which had an effect on the intergenerational associations and reduced the possible bias due to cohort differences. Finally, the offspring-of-siblings design makes several assumptions, the validity of which needs to be critically assessed (D'Onofrio *et al.* 2013). For example, they assume that there are no carry-over effects from uncles/aunts to their nephews/nieces. We aimed to test this by comparing the within-family associations in extended families where the older *v.* the younger sibling parent had substance misuse but found no systematic differences in the associations. Further, we conducted both fixed effects within-family analyses and quantitative genetic modeling which are based on partly different assumptions, supporting the validity of our findings.

In conclusion, in a large population-based family study we found consistent support for genetic influences contributing to the associations of parental substance misuse with offspring substance misuse and criminality. Independent of genetic influences, environmental factors shared within nuclear and extended families also partly explained the intergenerational associations.

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