Substance abuse in parents and subsequent risk of offspring psychiatric morbidity in late adolescence and early adulthood: a longitudinal analysis of siblings and their parents

ABSTRACT

The effects of substance abuse on other family members are not fully established. We estimate the contribution of parental substance abuse on offspring psychiatric morbidity in late adolescence and early adulthood, with emphasis on the timing and persistency of exposure. We used a nationally representative 20% sample of Finnish families with children born in 1986-1996 (n=136,604) followed up in 1986–2011. We identified parental substance abuse and offspring psychiatric morbidity from hospital discharge records, death records and medication registers. The effects of parental substance abuse at ages 0–4, 5–9 and 10–14 on psychiatric morbidity after age 15 were estimated using population averaged and sibling fixed effects models; the latter controlling for unobserved factors shared by siblings. Parental substance abuse at ages 0-14 was associated with about 2-fold increase in offspring psychiatric morbidity. Adjustment for childhood parental education, income, social class and family type reduced these effects by about 50%, with some further attenuation after adjustment for time-varying offspring characteristics. In the fixed effects models those exposed at 0-4 or 5-9 years had about 20-30% excess morbidity. Furthermore, siblings with early exposure at ages 0-4 combined with repeated exposure in later childhood had about 80-90% higher psychiatric morbidity as compared to never exposed siblings. Childhood exposure to parental substance abuse is strongly associated with subsequent psychiatric morbidity. Although these effects are to a large extent due to other characteristics shared within the parental home, repeated exposure to parental substance abuse is independently associated with later psychiatric morbidity.

Keywords: Substance abuse, parents, offspring, siblings, mental health

Introduction

It is well established that excessive alcohol consumption and other substance abuse are associated with social disadvantage, poor health and higher mortality for the user [1]. However, these studies do not adequately acknowledge that substance abuse may also pose harm to others – sometimes referred to as collateral damage or spill-over effects of substance abuse [2,3]. This study assesses the impact of substance abuse on others by studying its effects on the psychiatric morbidity of a particularly vulnerable group, the children of substance users [4].

Heavy maternal drinking and other substance abuse are known to be associated with poorer birth outcomes and early life health conditions including preterm birth, low birth weight and foetal alcohol syndrome [5,1,6,7]. Prenatal exposure to alcohol and other drugs has also been shown to associate with childhood behavioural problems and cognitive development [6], and children of substance-abusing mothers are more likely to be hospitalized for injuries and infectious diseases [8]. A less healthy start in life may entail consequences for offspring also in the long run. Prior evidence indicates that parental substance use disorders associate with offspring psychopathology in adolescence and early adulthood, with a particularly strong intergenerational link in alcohol and other substance use disorders [9–12]. However, many of the previous studies assessing health consequences of parental substance abuse focus either on short-term effects or more general measures of lifetime exposures, and much less is known about longer-term effects, particularly with regard to time-specific or cumulative effects across the life course [13,14]. Furthermore, studies using population-based family data are still few, and the existing evidence is largely based on student, clinical, and high-risk community samples of limited generalizability [15,12].

Life-course theory posits that the effect of childhood experiences on later health may depend on the timing of events [16]. During sensitive periods adverse exposures have stronger effects on later disease risk than exposures at other times. Sensitive period ‘denotes the time in which the developing

child is particularly responsive to certain forms of experience or particularly hindered by their absence' [17]. In addition to sensitive periods, life course models also stress the importance of duration and accumulation of exposures for later health outcomes. However, few studies have assessed the timing and persistency of exposure to parental substance abuse on offspring health, although cross-sectional studies have reported older children of alcoholic parents to be more resilient [15]. Two longitudinal US studies based on community samples of children of alcoholics and their controls found a strong effect of having ever experienced parental alcohol abuse, as well as time-varying effects of exposures to parental alcohol abuse on offspring externalizing behaviour [18], and maternal alcohol abuse on internalizing behaviour [19]. In a Swedish register study, parental substance abuse in childhood was consistently associated with psychiatric disorder in late adolescence and early adulthood with no evidence of particularly sensitive periods, but excess risk among those with repeated exposure [14]. Similar results were found in another Swedish study on young adult alcohol use disorders [20].

Disentangling causal pathways has also remained difficult. Families with parental substance abuse are typically also characterised by poor parental mental health and social disadvantage [13,11]. Some of the children of substance abusing parents are thus likely to face additional concurrent risk factors for poorer health outcomes. In addition to other parental health problems besides substance use, these include adverse socioeconomic characteristics, strain on family relationships, unstable home environment, disrupted parenting and child maltreatment [21,22]. Although many studies have been able to control for some of these factors, such as parental socioeconomic status, the cross-sectional and observational nature of most studies hampers the identification of confounding factors and mediating mechanisms. Many studies are also based on retrospective self-reports of childhood adversity. Significant residual confounding may thus bias the results.

This study adds to the literature in three ways. First, we focus on the timing of exposure to parental substance abuse in three different stages of childhood (ages 0–4, 5–9 and 10–14 years) in order to establish sensitive periods of exposure. Second, we estimate the effects of repeated exposure to

parental substance abuse. Third, to obtain a more accurate understanding of the mechanisms and causal effects of parental substance abuse on offspring mental health we estimate both population averaged models controlling for observed parental characteristics and time-varying offspring characteristics, as well as sibling fixed effects models that control for all unobserved characteristics shared by siblings. Finally, the analyses are based on high quality register data on a large population-representative sample of Finnish families with children followed for exposures to parental substance abuse from birth to age 14, and for psychiatric morbidity from age 15 over the years 2001–2011. These administrative data are unique as they do not suffer from reporting bias, selective loss to follow-up or small sample size.

Data and methods

Data and variables

This study was based on annually updated individual-level register data maintained by Statistics Finland. We used data that consist of a 20% random sample of Finnish households with at least one child aged 0–14 at the end of 2000, a 20% sample of 0–14-year-olds not living in private households at the end of 2000, and non-coresident biological parents of all 0–14-year-olds in the two samples. The data were linked with individual-level sociodemographic information for both offspring and their parents for years 1987–2011, hospital discharge records (maintained by the National Institute for Health and Welfare) for 1986–2011, and the national prescription register on all purchases of prescription medication (maintained by the Social Insurance Institution of Finland) for 2001–2011.

In the current study, we included individuals born in years 1986–1996 (n=136,604) and followed them from the beginning of the year of their 15th birthday until first incidence of psychiatric morbidity, the end of the year of their 25th birthday, emigration, death, or the end of year 2011, whichever came first. Offspring psychiatric morbidity was defined on the basis of indicators available in administrative register data: psychotropic medication purchases (including the Anatomical

Therapeutic Chemical (ATC) codes N05 and N06 but not N06D) or admission to inpatient hospital care with a psychiatric diagnosis (International Classification of Diseases (ICD-10) codes F10–69, F80–98) (for more detail see Supplementary Table 1). Defined in this way about 20% of all offspring psychiatric cases were based on hospital data.

Exposure to parental substance abuse in each calendar year at ages 0–14 was assessed using information of hospital diagnoses and cause of death of the biological parents in years 1986–2010. We used the tenth revision of ICD for years 1996–2010 to identify mental and behavioural disorders due to alcohol (F10) and substance use (F11–16, F18–19), alcohol-related diseases (E24.4, E52, G31.2, G40.51, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86, Y90–91), toxic effects and poisoning by alcohol (T51, X45) and other substances (T40, T42.3–42.4, T42.6–42.7, T43.0–43.5, T43.8–43.9, T50.7, T36, X44) and other contact with health services due to alcohol (R78.0, Z50.2, Z71.4, Z72.0) or substance use (R78.1–78.5, Z50.3, Z71.5, Z72.2). Corresponding ICD-8 codes were used for 1986 and ICD-9 codes for 1987–1995 (for more detail see Supplementary Table 1). Substance abuse was identified if any of the codes were reported as primary or additional hospital diagnosis, or as the underlying or contributory cause of death. Deaths accounted for 6% of all annual substance abuse cases. 80% of all cases were related to alcohol, of which most common were mental and behavioural disorders due to use of alcohol. We classified exposure to parental substance abuse according to the age of the child at exposure and frequency of exposures.

Covariates

We used parental education, household income, occupational social class and family type, measured at ages 0-14, to adjust for the socioeconomic characteristics of the childhood family. Parental education at ages 0-14 was based on the highest achieved educational level of either parent in the household, and categorized as tertiary, secondary and basic education or no qualifications. The average household income across ages 0-14 was measured in terms of the household's total income subject to state taxation, the information of which is collected by the Finnish Tax Administration and

the Social Insurance Institution. Total income was divided by the number of consumption units in the household according to the OECD-modified scale to adjust for household structure. The longest held parental occupational social class was classified as upper-white-collar, lower-white-collar, manual, farmer, self-employed, and other or unknown. The variable refers to the household's reference person, which usually is the parent with higher income. Family type of the parental home was classified as intact two-parent family, ever single-parent family, reconstituted two-parent family and ever living with others, in institution or family type unknown (usually referring to institutional residence).

Offspring social characteristics at age 15+ included family type, education and economic activity, and were measured annually as time-variant during the follow-up. Family type combined information on marital status and living arrangements, and was categorized as child, married, cohabiting, single parent, living alone, living with others and family status unknown. Education refers to both achieved qualifications and enrolment in education, classified as tertiary qualifications, secondary qualifications and enrolment in further education, secondary qualifications and not in education, basic education and enrolment in further education, basic education and not in further education. Economic activity was classified as employed, student, unemployed and other or unknown.

We used gender, region of residence based on hospital districts (N=20), language (Finnish, Swedish, other), indicator for psychiatric morbidity before the age of 15 and calendar year as control variables in all models.

Statistical methods

We used Cox proportional hazards regression to estimate the relative effects of exposure to parental substance abuse at different age periods on incident psychiatric morbidity in the offspring. We estimated both standard population averaged models and sibling fixed effects models. We first estimated separate models for exposure to parental substance abuse at each 5-year period of childhood (e.g. exposed at age 0–4 vs. no exposure at this age) and exposure at any stage at ages 0–14 (ever exposed vs. never exposed). Model 1 was adjusted for gender, region of residence, language and

psychiatric morbidity below age 15, and the baseline hazard was allowed to vary by calendar year (strata-option in Stata) to account for the increasing prevalence in psychotropic medication use. In the population averaged models, we further adjusted for the characteristics of the childhood family in model 2, and for time-varying offspring characteristics during the follow-up in model 3. Finally, we fitted fixedeffects models based on 91,428 children in sibships. The number of siblings discordant for the outcome and exposure to parental substance abuse (ever/never; age at exposure) and thus contributing to the estimates in regression models varied between 779 and 1956 depending on the definition of exposure. These models controlled for all unobserved time-invariant characteristics shared by siblings, such as shared genetic makeup, parental resources and parenting styles.

We next estimated the effects of repeated exposure during ages 0-14. Hazard ratios were calculated for the eight combinations of exposures at different age periods, the never-exposed establishing the reference group. A set of sensitivity analyses was performed to assess the robustness of these models. Stata 14.2 was used for all analyses [23].

Results

Main results

In the first 15-years of life 6.3% of children had been exposed to parental substance abuse at least once (Table 1). The prevalence of exposure at the three age periods 0–4, 5–9 and 10–14 years was 1.9, 3.0 and 3.7% respectively. Altogether about 9% of men and 15% of women experienced subsequent psychiatric morbidity between the ages 15 and 25. Among those exposed to parental substance abuse at different stages of childhood this proportion was 19–23% among men and 25–29% among women with indication of somewhat higher psychiatric morbidity if exposed early in life.

These differences translate into an adjusted hazard ratio of psychiatric morbidity of about two for the exposed men and women combined (Table 2). Adjusting for social characteristics in the parental home – parental education, household income, occupational social class and family type – attenuated

these associations by about half. Adjustment for offspring time-varying education, economic activity and family type during the follow-up reduced these associations further. In the sibling fixed effects model the risk of psychiatric morbidity among children ever exposed to parental substance abuse (HR=1.09; 95% CI 0.84–1.42) was not statistically different from that of the never-exposed siblings. However, our results indicate an excess risk of 20-30% for psychiatric morbidity for children exposed at ages 0–4 and 5–9 compared to siblings exposed at other ages or never.

The effects of repeated exposure to parental substance abuse at different age periods were clearly amplified if children were exposed at all three age periods (Figure 1, Supplementary Table 2); those exposed throughout childhood had 2.64 (95% CI 2.29–3.04) higher risk of psychiatric morbidity in early adulthood compared to the never-exposed. For other combinations of repeated exposure at different age periods, the excess risk was typically about two-fold. In the fully adjusted models, children exposed to parental substance abuse had 20–60% higher risk of later psychiatric morbidity with largest effect among those exposed at all three periods. The sibling fixed effects models broadly confirm these results by showing a high excess risk of psychiatric morbidity among children with repeated exposure to parental substance abuse as compared to never-exposed siblings.

Sensitivity analyses

We carried out sensitivity analyses on our main results (Supplementary Table 3). First, because biological parents do not necessarily reside with their children, parental substance abuse also does not in all cases occur while children and parents live together. To estimate the possible effects that this may have, we ignored any exposure episodes of substance abuse that occurred without co-residence. Our analyses indicate that about 2/3rd of parental substance abuse took place while children were residing with biological parents. With this more restricted exposure variable the patterns of excess risk of psychiatric morbidity in early adulthood were similar to, or somewhat stronger than those observed with the broader definition of exposure.

Second, our main analyses combined exposures to maternal or paternal substance abuse. Separate analyses on maternal and paternal substance abuse indicate relatively small differences, although with some tendency for maternal substance abuse having stronger effects. Third, the effects of exposure to parental alcohol abuse – 80% of all parental substance abuse exposure – were somewhat smaller than those for all substance abuse combined.

Fourth, siblings were identified through the mother, and may thus have different biological fathers. Confirmatory analyses that restricted our sibling analyses to sibships that shared both biological parents showed – in concordance with our main results – that exposure early in life combined with later exposure had large effects on subsequent psychiatric morbidity, although the number of siblings were reduced in these analyses by about a $1/4^{th}$, and the confidence intervals around our estimates increased further.

Finally, in order to evaluate whether our findings were sensitive to model specification, we experimented with a different parametrisation of the timing of first exposure and number of years of exposure to parental substance abuse. These analyses broadly support our main analyses in indicating that early age at first exposure and repeated exposures are risk factors for later life psychiatric incidence (Supplementary Table 4).

Discussion

Main results and their interpretation

Parental substance abuse remains a significant social problem. Based on parental medical records, over 10% of Finns born in 1991 had experienced serious parental substance abuse before age 18 [24]. Also, about one in five Finnish adults report excessive alcohol use in their childhood family [25]. Using family-based data we estimated the effects of parental substance abuse on offspring psychiatric morbidity, focusing particularly on the timing and persistency of exposure. We showed that exposure to parental substance abuse at age 0–14 was associated with about a two-fold increase in psychiatric

morbidity in late adolescence and early adulthood. Adjustment for parental education, income, social class and family type reduced these effects by about 50%, with some further attenuation after adjustment for offspring personal time-varying education, economic activity and family type. In the fixed effects specification those with exposure to parental substance abuse at age 0-4 and 5–9 had about 20–30% higher risk to experience psychiatric morbidity compared to siblings not exposed at that particular age. Those with repeated exposures over the three stages of childhood had highest morbidity. In particular, in the fixed effect specification those with early repeated exposure at ages 0–9 or 0–14 had about 80–90% higher psychiatric morbidity as compared to never exposed siblings.

Adjusted for demographic factors and childhood psychiatric morbidity, our estimates of the association between parental substance abuse and later offspring psychiatric morbidity – hazard ratios of about two – fall within the mid-range of estimates from previous studies [10,14,20,26]. Exact comparisons are difficult because study designs and measurements vary, but independent effects of parental problem drinking on offspring mental health in adulthood have also been observed in propensity score matching based analyses controlling for an extensive range of demographic, household, economic and geographic factors [27]. In our study, adjustment for observed childhood factors attenuated the effects of parental substance use by about 50%. This attenuation is more than has typically been observed in prior observational studies and we believe this is because of the lack of adjustment for family type and family change in many prior studies. However, another Finnish study showed that exposure to parental substance abuse below age seven was a significant predictor of mental disorders in adolescence and that this association was strongly attenuated after controlling for parental mental disorders, education, poverty, and family structure [26]. Overall, causal directions between parental substance abuse and other family risk factors are of course difficult to establish as it is feasible to hypothesize effects running both ways.

A unique aspect of our data and study design is that we were able to estimate sibling fixed effects models. These models allow for stronger causal inference as they control for all observed family

characteristics as well as characteristics shared by siblings that are not directly observed in the data. Factors that were not accounted for in the population averaged models may include stable parental characteristics related to genetic endowments, temperament or parenting styles. The effects in the fixed effects models were somewhat smaller than those in the population averaged models. However, the results from the fixed effects models demonstrate a 20–30% increase in psychiatric morbidity if exposed to parental substance abuse at ages 0–9, and thus provide more persuasive evidence for a causal effect of parental substance abuse at various stages of childhood on subsequent offspring morbidity.

According to the life-course theory exposure to childhood adversities during sensitive periods may have stronger effects on later disease risk than exposure at other times [16]. Furthermore, longer duration and accumulation of exposures may amplify effects. Overall, prior longitudinal evidence on sensitive periods to parental substance abuse is weak and inconclusive [14,18–20]. Our results provide modest evidence – both in the descriptive findings and fixed-effects models – that exposure in early childhood, particularly when combined with repeated exposure to parental substance abuse, has somewhat more harmful effects on subsequent psychiatric morbidity than exposure in later childhood. Overall, however, differences in the age at exposure appear to be relatively small. In the fixed-effect specification, those with early exposure at ages 0–4 combined with exposure also at later stages had about 80–90% higher psychiatric morbidity as compared to non-exposed siblings. Together with previous evidence on long-term and repeated exposures to parental substance use [14,19,20], these findings demonstrate significant cumulative effects. In our study we did not assess accumulation of exposures in terms of the number of substance abusing parents, but existing evidence on families with multiple members with substance use disorders also point to the importance of cumulative risk exposures in childhood [10,12,28].

Methodological considerations

An advantage of our data is that it allows longitudinal sibling comparisons in the association between parental substance abuse and offspring psychiatric morbidity. Specifically, the Cause-of-Death Register, the Hospital Discharge Register and the National Prescription Register used for identifying parental substance abuse and offspring psychiatric morbidity, have been shown to have good quality and practically complete national coverage [29–32]. Several Finnish studies have also shown high concordance between registered purchases and self-reported use of psychotropic medication [33–35].

However, in the interpretation of our results some particularities of the data need to be considered. As both our exposure and outcome are based on registers they are likely to reflect more serious end of the spectrum of substance abuse and psychiatric morbidity, which may lead to a lower prevalence of the exposure and outcome on the one hand and a stronger association between the two on the other. Furthermore, it is possible that the parent had been suffering from problems related to substance use already long before being admitted to the hospital. Such under-detection of pre-clinical health problems is possible with all data types. However, our analyses are unlikely to be hampered by false positive parental substance abuse cases. Thus, our identification of children exposed to parental substance use at all stages of childhood is likely to be very accurate, while identification of not exposed children an underestimate. Hence, any detection biases are likely to lead to our estimates of repeated exposure being biased downward. Ultimately, our results only provide evidence of the effects of more serious manifestations of substance abuse on offspring psychiatric morbidity.

With regard to the study outcome, some misclassification may rise from non-psychiatric use of psychotropic medication for indications such as incontinence and pain [36,37], but these biases are likely to be more severe at ages older than late adolescence and early adulthood. Unfortunately, the indications of psychotropic medication prescriptions were unavailable in the data. About 20% of all offspring psychiatric cases were based on hospital data. Again, hospital-based ascertainment is likely to identify more severe cases, but additional analyses indicate that although these were more strongly

affected by parental substance use than medication-based cases, the patterns were similar to our main findings. For example, being exposed to parental substance use at age 0-4 was associated with a HR of 2.45 (95% CI 2.14-2.80) for hospital-based cases and a HR of 2.03 (95% CI 1.88-2.21) for medication-based cases (results not shown).

We carried out several sensitivity analyses that corroborated our findings. First, we showed that a more restricted definition of exposure that only included episodes of substance abuse that occurred with co-residence were similar to or somewhat stronger than those observed in the total sample. The tendency for stronger effects highlights the more severe nature of actually living with a parent having substance abuse problems. Furthermore, redefinitions of exposure also demonstrated the robustness of the results. Our main results were also broadly replicated in models with different parameterisation of the timing and chronicity of exposure.

Finally, although sibling comparison is an attractive tool to control for unmeasured confounding shared in sibships, estimates from sibling models are not without limitations. Taken together potential misclassification of concordant sibling pairs as discordant pairs, unadjusted confounders not shared by siblings or contamination effects between exposure and outcome between siblings can bias the estimates away from or towards zero. The sibling comparison estimates that we provide must thus be seen as part of a broader attempt at methodological triangulation; together with the results of our population averaged models with measured covariates as well as prior evidence based on, for example, propensity score matching techniques [27], the analyses provide reasonably strong evidence for causal effects.

Conclusions

Overall, we show that exposure to parental substance abuse is associated with subsequent psychiatric morbidity in offspring. In accordance with the life-course theory, repeated exposure amplified these effects, but we did not obtain strong evidence for the existence of sensitive periods of exposure. The results are based on objective measurement of exposure and outcome in health care registers that most likely reflect a more severe manifestation of problems. The analyses thus reflect the top of the iceberg, but also clearly identify the potential for intervention, as both parents and their children have been in contact with the health care system. The results highlight the need to tackle the consequences of substance abuse to others in a family context, in particular the emergence of psychiatric morbidity in offspring.

Table 1 Children exposed to parental substance abuse by age of exposure and subsequent psychiatric morbidity at the age of 15–25; number of observations (N), distribution (%) and prevalence (%) with 95 % confidence intervals (CI) of psychiatric morbidity

				Psychiatric morbidity			
				Men		Women	
Age	Exposure	N	%	%	95% CI	%	95% CI
0—4	No	133993		9.5	(9.3—9.7)	15.1	(14.8—15.3)
	Yes	2611	1.9	22.5	(20.3—25.0)	28.0	(25.6—30.5)
5—9	No	132462		9.4	(9.2—9.7)	14.9	(14.6—15.2)
	Yes	4142	3.0	20.5	(18.8—22.3)	28.6	(26.6—30.6)
10—14	No	131569		9.4	(9.2—9.6)	15.0	(14.7—15.2)
	Yes	5035	3.7	19.2	(17.7—20.8)	25.5	(23.7—27.2)
	Never exposed	127979	93.7	9.2	(8.9—9.4)	14.6	(14.3—14.9)
	Ever exposed	8625	6.3	19.0	(17.8—20.2)	25.9	(24.5—27.2)

Table 2 Children exposed to parental substance use by age at exposure and subsequent psychiatric morbidity at the age of 15–25; hazard ratios (HR) and 95 % confidence intervals (CI) from different regression models

				Model 1		Model 2		Model 3		Sibling fixed-effects[a]	
Age	Exposure	N	%	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
0-4	No	133993		1.00		1.00		1.00		1.00	
	Yes	2611	1.9	2.04	(1.88-2.20)	1.44	(1.33-1.56)	1.36	(1.25-1.47)	1.20	(0.90-1.60)
5-9	No	132462		1.00		1.00		1.00		1.00	
	Yes	4142	2.9	1.99	(1.87-2.12)	1.45	(1.36-1.55)	1.37	(1.28-1.46)	1.33	(1.01-1.74)
10-14	No	131569		1.00		1.00		1.00		1.00	
	Yes	5035	3.4	1.79	(1.69-1.90)	1.33	(1.25-1.41)	1.25	(1.18-1.34)	0.97	(0.77-1.23)
	Total never	127979	93.7	1.00		1.00		1.00		1.00	
	Total ever	8625	6.3	1.86	(1.78-1.95)	1.40	(1.33-1.47)	1.33	(1.26-1.40)	1.09	(0.84-1.42)

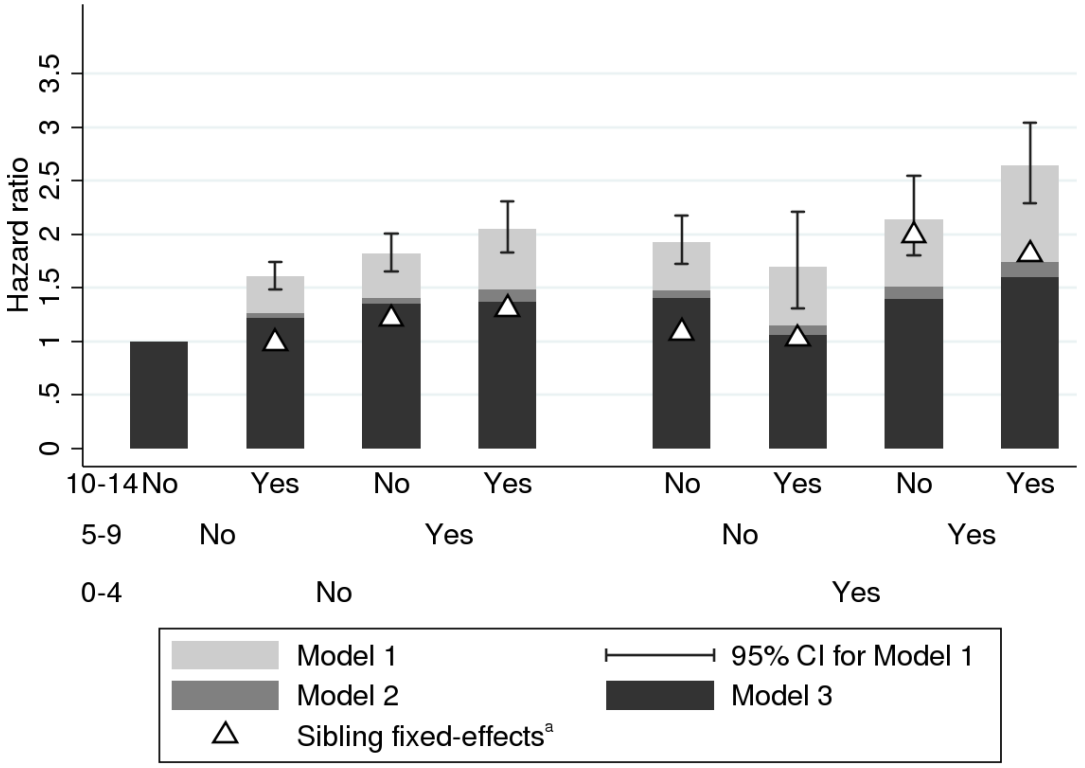
Model 1: Gender, region of residence, language, calendar year and psychiatric morbidity before the age of 15

Model 2: Model 1 + parental education, household income, occupational social class and family type at the age of 0-14

Model 3: Model 2 + time-varying family type, education and economic activity of offspring at the age of 15+

[a] Model 1; based on 91,428 children in sibships

Figure 1 Cumulative exposure to parental substance abuse and subsequent psychiatric morbidity at the age of 15–25; hazard ratios (HR) from different regression models



Model 1: Gender, region of residence, language, calendar year and psychiatric morbidity before the age of 15

Model 2: Model 1 + parental education, household income, occupational social class and family type at the age of 0–14

Model 3: Model 2 + time varying family type, education and economic activity of offspring at the age of 15+

[a] Sibling fixed-effects based on 91,428 children in sibships; model 1

Supplementary Table 1 The Anatomical Therapeutic Chemical (ATC) and the International Classification of Diseases 9th (ICD-9 for 1987–1995[a]) and 10th (ICD-10 for post-1996) Revision codes for identifying offspring psychiatric morbidity and parental substance abuse

Offspring psychiatric morbidity	**ATC**	**ICD-10**
Psycholeptics	N05	
Psychoanaleptics (excl. anti-dementia drugs)	N06 (excl. N06D)	
Mental and behavioural disorders (excl. organic mental disorders and mental retardation)		F10–69, F80–98
Parental substance abuse	**ICD-9**	**ICD-10**
Alcohol		
Mental and behavioural disorders due to use of alcohol	291, 303, 3050	F10
Alcoholic polyneuropathy	3575	G62.1
Alcoholic cardiomyopathy	4255	I42.6
Alcoholic gastritis	5353	K29.2
Alcoholic liver disease	5710–5713	K70
Alcohol-induced pancreatitis	5770D–5770F, 5771C–5771D	K85.2, K86.0
Toxic effects of alcohol	980	T51
Accidental poisoning by alcohol	E851	X45
Other alcohol-related diseases	2650A, 5307A	E24.4, E52, G31.2, G40.51, G72.1, Y90–91
Contact with health services due to use of alcohol		R78.0, Z50.2, Z71.4, Z72.1
Other substances		
Mental and behavioural disorders due to psychoactive substance use (excl. alcohol and tobacco)	292, 3040–3045, 3049, 3052-3057, 3059	F11–16, F18–19
Poisoning	965, 967, 9685, 9690–9699, 9701	T40, T42.3–42.4, T42.6–42.7, T43.0–43.5, T43.8–43.9, T50.7, T36[b], X44[b]
Abuse of non-dependence-producing substances		F55[b]
Other diseases related to substance use		B17.1, B18.2
Contact with health services due to substance use		R78.1–78.5, Z50.3, Z71.5, Z72.2

[a] Corresponding ICD-8 codes were used for 1986

[b] From 1998 onwards, ICD-10 codes F55, T36 and X44 have been used together with ATC codes to indicate the poisoning-causing substance (N02A, opioids; N02B/N05A/N06, non-dependence-producing substances; N03AE/N05BA–BB/N05C, hypnotics and sedatives)

Supplementary Table 2 Cumulative exposure to parental substance use and subsequent psychiatric morbidity at the age of 15–25; hazard ratios (HR) and 95 % confidence intervals (CI) from different regression models

Age at exposure									
0-4	No				Yes				
5-9	No		Yes		No		Yes		
10-14	No	Yes	No	Yes	No	Yes	No	Yes	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	Total N
				Cox regression					
Model 1	1.00	1.60 (1.48-1.74)	1.82 (1.65-2.01)	2.05 (1.83-2.31)	1.93 (1.72-2.17)	1.70 (1.31-2.21)	2.14 (1.80-2.55)	2.64 (2.29-3.04)	
Model 2	1.00	1.27 (1.16-1.38)	1.41 (1.27-1.55)	1.49 (1.32-1.67)	1.48 (1.31-1.66)	1.15 (0.88-1.49)	1.51 (1.27-1.80)	1.74 (1.51-2.02)	
Model 3	1.00	1.22 (1.12-1.32)	1.35 (1.22-1.50)	1.37 (1.21-1.54)	1.41 (1.25-1.58)	1.06 (0.81-1.38)	1.39 (1.17-1.66)	1.60 (1.38-1.85)	
N	127979	2985	1867	1162	1219	279	504	609	136604
				Sibling fixed-effects					
Model 1	1.00	0.98 (0.73-1.33)	1.21 (0.81-1.82)	1.30 (0.85-2.00)	1.08 (0.69-1.70)	1.03 (0.51-2.08)	1.99 (1.07-3.68)	1.81 (1.01-3.25)	
N[a]	86518	1826	1087	667	654	131	241	304	91428

Model 1: Gender, region of residence, language, calendar year and psychiatric morbidity before the age of 15

Model 2: Model 1 + parental education, household income, occupational social class and family type at the age of 0-14

Model 3: Model 2 + time-varying family type, education and economic activity of offspring at the age of 15+

[a] Number of children in sibships out of whom 1956 are discordant for outcome and exposure to parental substance abuse

Supplementary Table 3 Cumulative exposure to parental substance abuse and subsequent psychiatric morbidity at the age of 15–25; hazard ratios (HR) and 95 % confidence intervals (CI) from different regression models

Age at exposure									
0-4	No				Yes				
5-9	No		Yes		No		Yes		
10-14	No	Yes	No	Yes	No	Yes	No	Yes	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	Total N
				Cox regression					
Only coresident parent's substance abuse[a]	1.00	1.27 (1.14-1.42)	1.40 (1.25-1.56)	1.41 (1.13-1.75)	1.36 (1.22-1.52)	0.84 (0.49-1.41)	1.26 (1.00-1.59)	1.93 (1.42-2.64)	
N	131229	1670	1477	343	1386	87	287	125	136604
Only father's substance abuse[a]	1.00	1.10 (1.00-1.22)	1.26 (1.12-1.42)	1.37 (1.20-1.58)	1.33 (1.17-1.52)	1.16 (0.86-1.58)	1.24 (1.01-1.53)	1.56 (1.32-1.85)	
N	130198	2154	1374	852	1016	194	392	424	136604
Only mother's substance abuse[a]	1.00	1.33 (1.17-1.51)	1.47 (1.26-1.71)	1.34 (1.09-1.65)	1.41 (1.15-1.72)	1.02 (0.62-1.66)	1.96 (1.47-2.60)	1.55 (1.15-2.10)	
N	133868	1056	654	321	361	75	134	135	136604
Only parental alcohol abuse[a]	1.00	1.19 (1.09-1.31)	1.27 (1.13-1.42)	1.25 (1.09-1.43)	1.24 (1.08-1.42)	1.16 (0.87-1.56)	1.30 (1.07-1.59)	1.40 (1.17-1.68)	
N	129715	2483	1489	931	968	211	398	409	136604
				Sibling fixed effects					
Fixed effects: shared biological mother and father[b]	1.00	0.89 (0.62-1.29)	1.26 (0.73-2.17)	1.13 (0.63-2.03)	0.95 (0.52-1.72)	0.82 (0.31-2.21)	1.96 (0.88-4.39)	1.48 (0.65-3.40)	
N[c]	83318	1696	947	592	551	97	202	243	87646

[a] Model 3; see Model 3 terms in Supplementary Table 2; [b] Model 1; see Model 1 terms in Supplementary Table 2; [c] Number of children in sibships out of whom 1394 are discordant for outcome and exposure to parental substance abuse

Supplementary Table 4 Age at first exposure to parental substance abuse and subsequent psychiatric morbidity at the age of 15–25; hazard ratios (HR) and 95 % confidence intervals (CI), children ever exposed to parental substance abuse at the age of 0–14 (n=8,625)

	One		Two		Three		Four or more	
	HR	95 % CI	HR	95 % CI	HR	95 % CI	HR	95 % CI
Age at first exposure								
0-4	1.00		0.77	(0.61-0.98)	0.97	(0.75-1.25)	1.14	(0.95-1.37)
5-9	0.95	(0.80-1.12)	0.99	(0.80-1.22)	0.95	(0.75-1.21)	1.00	(0.80-1.23)
10-14	0.86	(0.74-1.01)	0.80	(0.63-1.02)	0.91	(0.65-1.28)	0.86	(0.45-1.62)
N	4845		1593		836		1351	

Model 3; see Model 3 terms in Supplementary Table 2

References

1. Rehm J, Baliunas D, Borges GLG, Graham K, Irving H, Kehoe T, et al. The relation between different dimensions of alcohol consumption and burden of disease: an overview. Addiction. 2010;105:817–43.

2. Rogers RG, Lawrence EM, Montez JK. Alcohol's Collateral Damage: Childhood Exposure to Problem Drinkers and Subsequent Adult Mortality Risk. Soc Forces. 2016;95:809–36.

3. Gell L, Ally A, Buykx P, Hope A, Meier P. Alcohol's harm to others. Inst Alcohol Stud Lond UK [Internet]. 2015 [cited 2017 Aug 28]; Available from: http://cdn.basw.co.uk/upload/basw_13716-2.pdf

4. Solis JM, Shadur JM, Burns AR, Hussong AM. Understanding the Diverse Needs of Children whose Parents Abuse Substances. Curr Drug Abuse Rev. 2012;5:135–47.

5. Henderson J, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. J Epidemiol Community Health. 2007;61:1069–73.

6. Behnke M, Smith VC, Abuse C on S, Newborn C on FA. Prenatal Substance Abuse: Short- and Long-term Effects on the Exposed Fetus. Pediatrics. 2013;131:e1009–24.

7. Huizink AC. Prenatal Maternal Substance Use and Offspring Outcomes. Eur Psychol. 2015;20:90–101.

8. Raitasalo K, Holmila M, Autti-Rämö I, Notkola I-L, Tapanainen H. Hospitalisations and out-of-home placements of children of substance-abusing mothers: A register-based cohort study. Drug Alcohol Rev. 2015;34:38–45.

9. Marmorstein NR, Iacono WG, McGue M. Alcohol and illicit drug dependence among parents: associations with offspring externalizing disorders. Psychol Med. 2009;39:149–55.

10. Hill SY, Tessner KD, McDermott MD. Psychopathology in offspring from families of alcohol dependent female probands: a prospective study. J Psychiatr Res. 2011;45:285–94.

11. Sørensen HJ, Manzardo AM, Knop J, Penick EC, Madarasz W, Nickel EJ, et al. The Contribution of Parental Alcohol Use Disorders and Other Psychiatric Illness to the Risk of Alcohol Use Disorders in the Offspring. Alcohol Clin Exp Res. 2011;35:1315–20.

12. Mellentin AI, Brink M, Andersen L, Erlangsen A, Stenager E, Bjerregaard LB, et al. The risk of offspring developing substance use disorders when exposed to one versus two parent(s) with alcohol use disorder: A nationwide, register-based cohort study. J Psychiatr Res. 2016;80:52–8.

13. Christoffersen MN, Soothill K. The long-term consequences of parental alcohol abuse: a cohort study of children in Denmark. J Subst Abuse Treat. 2003;25:107–16.

14. Björkenstam E, Burström B, Vinnerljung B, Kosidou K. Childhood adversity and psychiatric disorder in young adulthood: An analysis of 107,704 Swedes. J Psychiatr Res. 2016;77:67–75.

15. Park S, Schepp KG. A Systematic Review of Research on Children of Alcoholics: Their Inherent Resilience and Vulnerability. J Child Fam Stud. 2015;24:1222–31.

16. Ben-Shlomo Y, Kuh D. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. Int J Epidemiol. 2002;31:285–93.

17. Sylva K. Critical periods in childhood learning. Br Med Bull. 1997;53:185–97.

18. Hussong AM, Huang W, Curran PJ, Chassin L, Zucker RA. Parent alcoholism impacts the severity and timing of children's externalizing symptoms. J Abnorm Child Psychol. 2010;38:367–80.

19. Hussong AM, Cai L, Curran PJ, Flora DB, Chassin LA, Zucker RA. Disaggregating the distal, proximal, and time-varying effects of parent alcoholism on children's internalizing symptoms. J Abnorm Child Psychol. 2008;36:335–46.

20. Edwards AC, Lönn SL, Karriker-Jaffe KJ, Sundquist J, Kendler KS, Sundquist K. Time-specific and cumulative effects of exposure to parental externalizing behavior on risk for young adult alcohol use disorder. Addict Behav. 2017;72:8–13.

21. Harter SL. Psychosocial adjustment of adult children of alcoholics: A review of the recent empirical literature. Clin Psychol Rev. 2000;20:311–37.

22. Staton-Tindall M, Sprang G, Clark J, Walker R, Craig CD. Caregiver Substance Use and Child Outcomes: A Systematic Review. J Soc Work Pract Addict. 2013;13:6–31.

23. StataCorp. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP; 2015.

24. Jääskeläinen M, Holmila M, Notkola I-L, Raitasalo K. A typology of families with parental alcohol or drug abuse. Addict Res Theory. 2016;24:288–99.

25. Raitasalo K, Holmila M, Mäkelä P. Drinking in the presence of underage children: Attitudes and behaviour. Addict Res Theory. 2011;19:394–401.

26. Jääskeläinen M, Holmila M, Notkola I-L, Raitasalo K. Mental disorders and harmful substance use in children of substance abusing parents: A longitudinal register-based study on a complete birth cohort born in 1991. Drug Alcohol Rev. 2016;35:728–40.

27. Balsa AI, Homer JF, French MT. The health effects of parental problem drinking on adult children. J Ment Health Policy Econ. 2009;12:55–66.

28. Hill SY, Shen S, Lowers L, Locke-Wellman J, Matthews AG, McDermott M. Psychopathology in offspring from multiplex alcohol dependence families with and without parental alcohol dependence: A prospective study during childhood and adolescence. Psychiatry Res. 2008;160:155–66.

29. National Agency for Medicines and Social Insurance Institution. Finnish Statistics on Medicines 2011 [Internet]. Helsinki, Finland: National Agency for Medicines and Social Insurance Institution; 2012. Available from: http://www.fimea.fi/documents/160140/753095/22707_SLT_2011_net.pdf

30. Sund R. Quality of the Finnish Hospital Discharge Register: A systematic review. Scand J Public Health. 2012;40:505–15.

31. Lahti RA, Penttilä A. The validity of death certificates: routine validation of death certification and its effects on mortality statistics. Forensic Sci Int. 2001;115:15–32.

32. Mathers CD, Ma Fat D, Inoue M, Rao C, Lopez AD. Counting the dead and what they died from : an assessment of the global status of cause of death data. Recensement des décès et des causes de décès : une évaluation de l' état des données relatives aux causes de décès dans le monde : résumé [Internet]. 2005 [cited 2017 Jul 10]; Available from: http://www.who.int/iris/handle/10665/72966

33. Haukka J, Suvisaari J, Tuulio-Henriksson A, Lönnqvist J. High concordance between self-reported medication and official prescription database information. Eur J Clin Pharmacol. 2007;63:1069–74.

34. Rikala M, Hartikainen S, Saastamoinen LK, Korhonen MJ. Measuring psychotropic drug exposures in register-based studies--validity of a dosage assumption of one unit per day in older Finns. Int J Methods Psychiatr Res. 2013;22:155–65.

35. Rikala M, Hartikainen S, Sulkava R, Korhonen MJ. Validity of the Finnish Prescription Register for measuring psychotropic drug exposures among elderly finns: a population-based intervention study. Drugs Aging. 2010;27:337–49.

36. Gardarsdottir H, Heerdink ER, van Dijk L, Egberts ACG. Indications for antidepressant drug prescribing in general practice in the Netherlands. J Affect Disord. 2007;98:109–15.

37. Sihvo S, Isometsä E, Kiviruusu O, Hämäläinen J, Suvisaari J, Perälä J, et al. Antidepressant utilisation patterns and determinants of short-term and non-psychiatric use in the Finnish general adult population. J Affect Disord. 2008;110:94–105.