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A longitudinal analysis of siblings and their parents

Martikainen, Pekka

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1 Substance abuse in parents and subsequent risk of offspring
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3 a longitudinal analysis of siblings and their parents

4 ABSTRACT

5 The effects of substance abuse on other family members are not fully established. We estimate the
6 contribution of parental substance abuse on offspring psychiatric morbidity in late adolescence and
7 early adulthood, with emphasis on the timing and persistency of exposure. We used a nationally
8 representative 20% sample of Finnish families with children born in 1986-1996 (n=136,604) followed
9 up in 1986–2011. We identified parental substance abuse and offspring psychiatric morbidity from
10 hospital discharge records, death records and medication registers. The effects of parental substance
11 abuse at ages 0–4, 5–9 and 10–14 on psychiatric morbidity after age 15 were estimated using
12 population averaged and sibling fixed effects models; the latter controlling for unobserved factors
13 shared by siblings. Parental substance abuse at ages 0-14 was associated with almost 2-fold increase
14 in offspring psychiatric morbidity (HR=1.86, 95% CI 1.78-1.95). Adjustment for childhood parental
15 education, income, social class and family type reduced these effects by about 50%, with some further
16 attenuation after adjustment for time-varying offspring characteristics. In the sibling fixed effects
17 models those exposed at 0-4 or 5-9 years had 20% (HR=1.20, 95% CI 0.90-1.60) and 33% (HR=1.33,
18 95% CI 1.01-1.74) excess morbidity respectively. Also in sibling models those with early exposure
19 at ages 0-4 combined with repeated exposure in later childhood had about 80-90% higher psychiatric
20 morbidity as compared to never exposed siblings (e.g. for those exposed throughout childhood
21 HR=1.81, 95% CI 1.01-3.25). Childhood exposure to parental substance abuse is strongly associated
22 with subsequent psychiatric morbidity. Although these effects are to a large extent due to other

23 characteristics shared within the parental home, repeated exposure to parental substance abuse is
24 independently associated with later psychiatric morbidity.

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

26 **Introduction**

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

33 Heavy maternal drinking and other substance abuse are known to be associated with poorer birth
34 outcomes and early life health conditions including preterm birth, low birth weight and foetal alcohol
35 syndrome [5,1,6,7]. Prenatal exposure to alcohol and other drugs has also been shown to associate
36 with childhood behavioural problems and cognitive development [6], and children of substance-
37 abusing mothers are more likely to be hospitalized for injuries and infectious diseases [8]. A less
38 healthy start in life may entail consequences for offspring also in the long run. Prior evidence indicates
39 that parental substance use disorders associate with offspring psychopathology in adolescence and
40 early adulthood, with a particularly strong intergenerational link in alcohol and other substance use
41 disorders [9–12]. Studies using linked population registration data from Denmark and Sweden show
42 that parental substance use has an impact on a broad range of mental health outcomes in adolescence
43 and early adulthood including psychiatric disorders, self-harm, and substance misuse [13,14].
44 However, several commentators have stressed the need for more studies using population-based
45 family data, as most of the existing evidence is based on student, clinical, and high-risk community
46 samples of lesser generalizability [15,12,13]. It has also been pointed out that many of the previous
47 studies assessing health consequences of parental substance abuse still focus either on short-term
48 effects or more general measures of lifetime exposures, and much less is known about timing or
49 accumulation of exposure to parental substance abuse at different stages of childhood [14,15,12].

50

51 Life-course theory posits that the effect of childhood experiences on later health may depend on the
52 timing of events [16]. During sensitive periods adverse exposures have stronger effects on later
53 disease risk than exposures at other times. Sensitive period ‘denotes the time in which the developing
54 child is particularly responsive to certain forms of experience or particularly hindered by their absence’
55 [17]. In addition to sensitive periods, life course models also stress the importance of duration and
56 accumulation of exposures for later health outcomes. However, few studies have assessed the timing
57 and persistency of exposure to parental substance abuse on offspring health, although cross-sectional
58 studies have reported older children of alcoholic parents to be more resilient [15]. Two longitudinal
59 US studies based on community samples of children of alcoholics and their controls found a strong
60 effect of having ever experienced parental alcohol abuse, as well as time-varying effects of exposures
61 to parental alcohol abuse on offspring externalizing behaviour [18], and maternal alcohol abuse on
62 internalizing behaviour [19]. In a Swedish register study, parental substance abuse in childhood was
63 consistently associated with psychiatric disorder in late adolescence and early adulthood with no
64 evidence of particularly sensitive periods, but excess risk among those with repeated exposure [14].
65 Similar results were found in another Swedish study on young adult alcohol use disorders [20].

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

74 mediating mechanisms. Many studies are also based on retrospective self-reports of childhood
75 adversity. Significant residual confounding may thus bias the results.

76 This study adds to the literature in three ways. First, we focus on the timing of exposure to parental
77 substance abuse in three different stages of childhood (ages 0–4, 5–9 and 10–14 years) in order to
78 establish sensitive periods of exposure. Second, we estimate the effects of repeated exposure to
79 parental substance abuse. Third, to obtain a more accurate understanding of the mechanisms and
80 causal effects of parental substance abuse on offspring mental health we estimate both population
81 averaged models controlling for observed parental characteristics and time-varying offspring
82 characteristics, as well as sibling fixed effects models that control for all unobserved characteristics
83 shared by siblings. Finally, the analyses are based on high quality register data on a large population-
84 representative sample of Finnish families with children followed for exposures to parental substance
85 abuse from birth to age 14, and for psychiatric morbidity from age 15 over the years 2001–2011.
86 These administrative data are unique as they do not suffer from reporting bias, selective loss to follow-
87 up or small sample size.

88 **Data and methods**

89 *Data and variables*

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

98 In the current study, we included individuals born in years 1986–1996 (n=136,604) and followed
 99 them from the beginning of the year of their 15th birthday until first incidence of psychiatric morbidity,
 100 the end of the year of their 25th birthday, emigration, death, or the end of year 2011, whichever came
 101 first. Offspring psychiatric morbidity was defined on the basis of indicators available in
 102 administrative register data: psychotropic medication purchases (including the Anatomical
 103 Therapeutic Chemical (ATC) codes N05 and N06 but not N06D) or admission to inpatient hospital
 104 care with a psychiatric diagnosis (International Classification of Diseases (ICD-10) codes F10–69,
 105 F80–98) (for more detail see Supplementary Table 1). Defined in this way about 20% of all offspring
 106 psychiatric cases were based on hospital data.

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

121 *Covariates*

122 We used parental education, household income, occupational social class and family type, measured
 123 at ages 0-14, to adjust for the socioeconomic characteristics of the childhood family. Parental
 124 education at ages 0-14 was based on the highest achieved educational level of either parent in the
 125 household, and categorized as tertiary, secondary and basic education or no qualifications. The
 126 average household income across ages 0-14 was measured in terms of the household's total income
 127 subject to state taxation, the information of which is collected by the Finnish Tax Administration and
 128 the Social Insurance Institution. To adjust for household structure, total income was divided by the
 129 number of consumption units in the household according to the modified scale of the Organisation
 130 for Economic Co-operation and Development (OECD). The scale assigns a value of 1 to the head of
 131 household, 0.5 to all other adult household members and 0.3 to all children [23]. The longest held
 132 parental occupational social class was classified as upper-white-collar, lower-white-collar, manual,
 133 farmer, self-employed, and other or unknown. The variable refers to the household's reference person,
 134 which usually is the parent with higher income. Family type of the parental home was classified as
 135 intact two-parent family, ever single-parent family, reconstituted two-parent family and ever living
 136 with others, in institution or family type unknown (usually referring to institutional residence).

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

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

148 *Statistical methods*

149 We used Cox proportional hazards regression to estimate the relative effects of exposure to parental
 150 substance abuse at different age periods on incident psychiatric morbidity in the offspring. We
 151 estimated both standard population averaged models and sibling fixed effects models. We first
 152 estimated separate models for exposure to parental substance abuse at each 5-year period of childhood
 153 (e.g. exposed at age 0–4 vs. no exposure at this age) and exposure at any stage at ages 0–14 (ever
 154 exposed vs. never exposed). Model 1 was adjusted for gender, region of residence, language and
 155 psychiatric morbidity below age 15, and the baseline hazard was allowed to vary by calendar year
 156 (strata-option in Stata) to account for the increasing prevalence in psychotropic medication use. In
 157 the population averaged models, we further adjusted for the characteristics of the childhood family in
 158 model 2, and for time-varying offspring characteristics during the follow-up in model 3. Finally, we
 159 fitted fixed effects models based on 91,428 children in sibships. The number of siblings discordant
 160 for the outcome and exposure to parental substance abuse (ever/never; age at exposure) and thus
 161 contributing to the estimates in regression models varied between 779 and 1956 depending on the
 162 definition of exposure. These models controlled for all unobserved time-invariant characteristics
 163 shared by siblings, such as shared genetic makeup, parental resources and parenting styles.

164 We next estimated the effects of repeated exposure during ages 0-14. Hazard ratios were calculated
 165 for the eight combinations of exposures at different age periods, the never-exposed establishing the
 166 reference group. A set of sensitivity analyses was performed to assess the robustness of these models.
 167 Stata 14.2 was used for all analyses [24].

168 **Results**

169 *Main results*

170 In the first 15-years of life 6.3% of children had been exposed to parental substance abuse at least
 171 once (Table 1). The prevalence of exposure at the three age periods 0–4, 5–9 and 10–14 years was
 172 1.9, 3.0 and 3.7% respectively. Altogether about 9% of men and 15% of women experienced
 173 subsequent psychiatric morbidity between the ages 15 and 25. Among those exposed to parental
 174 substance abuse at different stages of childhood this proportion was 19–23% among men and 25–29%
 175 among women with indication of somewhat higher psychiatric morbidity if exposed early in life.

176 These differences translate into an adjusted hazard ratio of psychiatric morbidity of about two for the
 177 exposed men and women combined (Table 2). Adjusting for social characteristics in the parental
 178 home – parental education, household income, occupational social class and family type – attenuated
 179 these associations by about half. Adjustment for offspring time-varying education, economic activity
 180 and family type during the follow-up reduced these associations further. In the sibling fixed effects
 181 model the risk of psychiatric morbidity among children ever exposed to parental substance abuse
 182 (HR=1.09; 95% CI 0.84–1.42) was not statistically different from that of the never-exposed siblings.
 183 However, our results indicate an excess risk of 20-30% for psychiatric morbidity for children exposed
 184 at ages 0–4 and 5–9 compared to siblings exposed at other ages or never.

185 The effects of repeated exposure to parental substance abuse at different age periods were clearly
 186 amplified if children were exposed at all three age periods (Figure 1, Supplementary Table 2); those
 187 exposed throughout childhood had 2.64 (95% CI 2.29–3.04) higher risk of psychiatric morbidity in
 188 early adulthood compared to the never-exposed. For other combinations of repeated exposure at
 189 different age periods, the excess risk was typically about two-fold. In the fully adjusted models,
 190 children exposed to parental substance abuse had 20–60% higher risk of later psychiatric morbidity
 191 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 1/4th, 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

216 exposure to parental substance abuse. These analyses broadly support our main analyses in indicating
 217 that early age at first exposure and repeated exposures are risk factors for later life psychiatric
 218 incidence (Supplementary Table 4).

219 **Discussion**

220 *Main results and their interpretation*

221 Parental substance abuse remains a significant social problem. Based on parental medical records,
 222 over 10% of Finns born in 1991 had experienced serious parental substance abuse before age 18 [25].
 223 Also, about one in five Finnish adults report excessive alcohol use in their childhood family [26].
 224 Using family-based data we estimated the effects of parental substance abuse on offspring psychiatric
 225 morbidity, focusing particularly on the timing and persistency of exposure. We showed that exposure
 226 to parental substance abuse at age 0–14 was significantly associated with an almost two-fold
 227 (HR=1.86, 95% CI 1.78-1.95) increase in psychiatric morbidity in late adolescence and early
 228 adulthood. Adjustment for parental education, income, social class and family type reduced these
 229 effects by about 50%, with some further attenuation after adjustment for offspring personal time-
 230 varying education, economic activity and family type. In the sibling fixed effects specification those
 231 with exposure to parental substance abuse at age 0-4 and 5–9 had 20% (HR=1.20, 95% CI 0.90-1.69)
 232 and 33% (HR=1.33, 95% CI 1.01-1.74) higher risk to experience psychiatric morbidity respectively
 233 compared to siblings not exposed at that particular age. Those with repeated exposures over the three
 234 stages of childhood had highest morbidity. In particular, in the fixed effect specification those with
 235 early exposure at ages 0-4 combined with repeated exposure had about 80-90% higher psychiatric
 236 morbidity as compared to never exposed siblings (e.g. for those exposed throughout childhood
 237 HR=1.81, 95% CI 1.01-3.25).

238 Adjusted for demographic factors and childhood psychiatric morbidity, our estimates of the
 239 association between parental substance abuse and later offspring psychiatric morbidity – hazard ratios

240 of about two – fall within the mid-range of estimates from previous studies [10,14,20,27]. Exact
241 comparisons are difficult because study designs and measurements vary, but independent effects of
242 parental problem drinking on offspring mental health in adulthood have also been observed in
243 propensity score matching based analyses controlling for an extensive range of demographic,
244 household, economic and geographic factors [28]. In our study, adjustment for observed childhood
245 factors attenuated the effects of parental substance use by about 50%. This attenuation is more than
246 has typically been observed in prior observational studies and we believe this is because of the lack
247 of adjustment for family type and family change in many prior studies. However, another Finnish
248 study showed that exposure to parental substance abuse below age seven was a significant predictor
249 of mental disorders in adolescence and that this association was strongly attenuated after controlling
250 for parental mental disorders, education, poverty, and family structure [27]. Overall, causal directions
251 between parental substance abuse and other family risk factors are of course difficult to establish as
252 it is feasible to hypothesize effects running both ways.

253 A unique aspect of our data and study design is that we were able to estimate sibling fixed effects
254 models. These models allow for stronger causal inference as they control for all observed family
255 characteristics as well as characteristics shared by siblings that are not directly observed in the data.
256 Factors that were not accounted for in the population averaged models may include stable parental
257 characteristics related to genetic endowments, temperament or parenting styles. The effects in the
258 fixed effects models were somewhat smaller than those in the population averaged models. However,
259 the results from the fixed effects models demonstrate a 20–30% increase in psychiatric morbidity if
260 exposed to parental substance abuse at ages 0–9, and thus provide more persuasive evidence for a
261 causal effect of parental substance abuse at various stages of childhood on subsequent offspring
262 morbidity.

263 According to the life-course theory exposure to childhood adversities during sensitive periods may
264 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 [10,12,29].

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 [30–33]. Several Finnish studies have also shown high concordance between registered purchases and self-reported use of psychotropic medication [34–36].

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

290 of the exposure and outcome on the one hand and a stronger association between the two on the other.
291 Furthermore, it is possible that the parent had been suffering from problems related to substance use
292 already long before being admitted to the hospital. Such under-detection of pre-clinical health
293 problems is possible with all data types. However, our analyses are unlikely to be hampered by false
294 positive parental substance abuse cases. Thus, our identification of children exposed to parental
295 substance use at all stages of childhood is likely to be very accurate, while identification of not
296 exposed children an underestimate. Hence, any detection biases are likely to lead to our estimates of
297 repeated exposure being biased downward. Ultimately, our results only provide evidence of the
298 effects of more serious manifestations of substance abuse on offspring psychiatric morbidity.

299 With regard to the study outcome, some misclassification may rise from non-psychiatric use of
300 psychotropic medication for indications such as incontinence and pain [37,38], but these biases are
301 likely to be more severe at ages older than late adolescence and early adulthood. Unfortunately, the
302 indications of psychotropic medication prescriptions were unavailable in the data. About 20% of all
303 offspring psychiatric cases were based on hospital data. Again, hospital-based ascertainment is likely
304 to identify more severe cases, but additional analyses indicate that although these were more strongly
305 affected by parental substance use than medication-based cases, the patterns were similar to our main
306 findings. For example, being exposed to parental substance use at age 0-4 was associated with a HR
307 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
308 medication-based cases (results not shown).

309

310 We carried out several sensitivity analyses that corroborated our findings. First, we showed that a
311 more restricted definition of exposure that only included episodes of substance abuse that occurred
312 with co-residence were similar to or somewhat stronger than those observed in the total sample. The
313 tendency for stronger effects highlights the more severe nature of actually living with a parent having
314 substance abuse problems. Furthermore, redefinitions of exposure also demonstrated the robustness

315 of the results. Our main results were also broadly replicated in models with different parameterisation
316 of the timing and chronicity of exposure.

317

318 Finally, although sibling comparison is an attractive tool to control for unmeasured confounding
319 shared in sibships, estimates from sibling models are not without limitations. Taken together potential
320 misclassification of concordant sibling pairs as discordant pairs, unadjusted confounders not shared
321 by siblings or contamination effects between exposure and outcome between siblings can bias the
322 estimates away from or towards zero. The sibling comparison estimates that we provide must thus be
323 seen as part of a broader attempt at methodological triangulation; together with the results of our
324 population averaged models with measured covariates as well as prior evidence based on, for example,
325 propensity score matching techniques [28], the analyses provide reasonably strong evidence for
326 causal effects.

327

328 *Conclusions*

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

338

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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

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

Age	Exposure	N	%	Psychiatric morbidity			
				Men		Women	
				%	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

Age	Exposure	N	%	Model 1		Model 2		Model 3		Sibling fixed-effects ^a	
				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

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	HR	HR	HR	HR	HR	HR	HR	Total N
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	
Cox regression									
Model 1	1.00	1.60	1.82	2.05	1.93	1.70	2.14	2.64	
		(1.48-1.74)	(1.65-2.01)	(1.83-2.31)	(1.72-2.17)	(1.31-2.21)	(1.80-2.55)	(2.29-3.04)	
Model 2	1.00	1.27	1.41	1.49	1.48	1.15	1.51	1.74	
		(1.16-1.38)	(1.27-1.55)	(1.32-1.67)	(1.31-1.66)	(0.88-1.49)	(1.27-1.80)	(1.51-2.02)	
Model 3	1.00	1.22	1.35	1.37	1.41	1.06	1.39	1.60	
		(1.12-1.32)	(1.22-1.50)	(1.21-1.54)	(1.25-1.58)	(0.81-1.38)	(1.17-1.66)	(1.38-1.85)	
N	127979	2985	1867	1162	1219	279	504	609	136604
Sibling fixed-effects									
Model 1	1.00	0.98	1.21	1.30	1.08	1.03	1.99	1.81	
		(0.73-1.33)	(0.81-1.82)	(0.85-2.00)	(0.69-1.70)	(0.51-2.08)	(1.07-3.68)	(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								Total N	
	0-4	No				Yes				
	5-9	No		Yes		No		Yes		
	10-14	No	Yes	No	Yes	No	Yes	No		Yes
	HR	HR	HR	HR	HR	HR	HR	HR		
	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)	(95% CI)		
Cox regression										
Only coresident parent's substance abuse ^a	1.00	1.27	1.40	1.41	1.36	0.84	1.26	1.93		
		(1.14-1.42)	(1.25-1.56)	(1.13-1.75)	(1.22-1.52)	(0.49-1.41)	(1.00-1.59)	(1.42-2.64)		
N	131229	1670	1477	343	1386	87	287	125	136604	
Only father's substance abuse ^a	1.00	1.10	1.26	1.37	1.33	1.16	1.24	1.56		
		(1.00-1.22)	(1.12-1.42)	(1.20-1.58)	(1.17-1.52)	(0.86-1.58)	(1.01-1.53)	(1.32-1.85)		
N	130198	2154	1374	852	1016	194	392	424	136604	
Only mother's substance abuse ^a	1.00	1.33	1.47	1.34	1.41	1.02	1.96	1.55		
		(1.17-1.51)	(1.26-1.71)	(1.09-1.65)	(1.15-1.72)	(0.62-1.66)	(1.47-2.60)	(1.15-2.10)		
N	133868	1056	654	321	361	75	134	135	136604	
Only parental alcohol abuse ^a	1.00	1.19	1.27	1.25	1.24	1.16	1.30	1.40		
		(1.09-1.31)	(1.13-1.42)	(1.09-1.43)	(1.08-1.42)	(0.87-1.56)	(1.07-1.59)	(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	1.26	1.13	0.95	0.82	1.96	1.48		
		(0.62-1.29)	(0.73-2.17)	(0.63-2.03)	(0.52-1.72)	(0.31-2.21)	(0.88-4.39)	(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