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Mental health in youth prenatally exposed to opioids and poly-drugs and raised in permanent foster/adoptive homes: A prospective longitudinal study

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ABSTRACT

Background: Little is known about the mental health of prenatally opioid- and polydrug-exposed youth raised in foster/adoptive families.
Aim: To compare mental health problems among two groups of youth, one prenatally drug-exposed group with participants who were mainly placed in permanent foster or adoptive homes in early infancy and a group without known prenatal risk factors who were raised by their birth parents.
Methods: The sample consisted of 45 drug-exposed and 48 nonexposed youth between 17 and 22 years old from an original sample of 136 followed since birth. An extended version of the Mini International Neuropsychiatric Interview was used to assess lifetime psychiatric disorder, and participants completed the Achenbach Adult Self-Report form and Cantril's Ladder of Life Satisfaction Scale.
Results: A higher proportion of the youth in the drug-exposed group had lifetime experiences with major depressive episodes, alcohol abuse and attention deficit, hyperactivity disorder ($OR > 3$, $p \leq .030$). They scored higher on the aggressive behavior scale, had more sexual partners and were younger at their sexual debut ($p \leq .030$). There were no group differences in current self-reported satisfaction with life.
Conclusion: Youth exposed to drugs prenatally continue to represent a risk group despite early placement in permanent foster and adoptive homes. The factors contributing to this elevated risk may be multifaceted and involve adverse prenatal conditions including but not limited to drug exposure, genetics, and postnatal environmental conditions. The results highlight the need for longitudinal follow-up in the transition to adulthood as well as qualified service provision for these youth and their families.

1. Introduction

Maternal opioid and polydrug use, including opioid maintenance treatment in pregnancy, has been reported to be related to a range of adverse outcomes, such as an increased risk of preterm birth, low birth weight, neonatal withdrawal symptoms, visual impairments, reduced fine motor skills, poor school performance, lower cognitive abilities, smaller neuroanatomical volumes and altered white matter maturation [1–3], as well as impairments in attention, executive function, impulse control and behavior regulation [4–10]. An increased risk of attentional and behavioral dysregulation may be a precursor of mental health problems and risk behavior later in life [11]. There are few reports regarding internalizing problems, and the results are divergent [5,10]. Most studies to date concern infants and young children, and knowledge regarding how they fare in the transition to adulthood is scarce [12]. We identified only three studies reporting on mental health diagnoses and behavioral problems among prenatally polydrug- or opioid-exposed children above the age of 10 years [4–6]. Thus, the present study investigates the mental health and behavior problems of youth with a history of opioid and polydrug exposure in utero.

There is no reason to believe that the effects of prenatal conditions are confined to early development. There is an indication of increasing difficulties during childhood, for example, in emotional regulation, for drug-exposed children [10]. Generally, dysregulation in childhood has

Abbreviations: ADHD, attention deficit, hyperactivity disorder; ASR, adult self-report form; *b*, unstandardized regression coefficient; MINI, Mini International Neuropsychiatric Interview; OR, odds ratios

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been found to be a common precursor of adolescent behavioral and emotional dysregulation symptoms, such as substance use and crime [11]. However, we have not found any studies of the relationship between prenatal opioid or polysubstance exposure and later substance abuse or dependence.

It is difficult to distinguish among the possible causal factors for these children's developmental problems, e.g., genetic vs pre- and postnatal environmental risk. Consequently, drug-exposed children raised by foster or adoptive parents from an early age under stable caregiving conditions are of particular interest, as postnatal conditions are assumed to be normalized [13]. However, research on foster children in general (i.e., with no information on drug exposure) has presented divergent results regarding the development of these children, and a meta-analysis of longitudinal studies did not find positive changes over time in mental health [14].

In summary, there is a lack of knowledge on long-term mental health outcomes for youth with a history of opioid and polydrug exposure in utero. Thus, the objectives of the present study were to investigate current and lifetime psychiatric disorders, behavioral problems, drug abuse, sexual behavior and current subjective quality of life in youth born to mothers with opioid and polysubstance use during pregnancy where the majority were placed in permanent foster or adoptive homes in early infancy (labeled risk group). We hypothesized that the risk group would have significantly more mental health problems than a comparison group of youth with no known biomedical risk at birth who were raised by their birth parents. We also investigated other variables of significance; the children's age at placement and number of placements [13], differences between children from foster vs adoptive homes (e.g., [4]), birthweight [15,16], and prenatal opioid exposure [3].

2. Methods

2.1. Participants

The current study utilizes a sample of 93 youth who have been followed prospectively since early infancy. It compares a group of children mainly raised in foster or adoptive homes who were born to mothers who used illegal opiates and polysubstances during pregnancy (risk group, $n = 45$) with children who did not face such risk and were raised by their biological parents (comparison group, $n = 48$). Recruitment of the cohort took place from 1991 to 1996. Of the 136 original participants, 98 participated in the present study (see flow chart, Fig. 1). However, one participant did not complete the mental health assessment, and four other participants were excluded because they were evaluated in their first year to have fetal alcohol syndrome or fetal alcohol spectrum disorder.

The risk group was recruited in a naturalistic setting from an inpatient clinic (Aline Infant and Family Center) for high-risk infants and families in Oslo, Norway (for more details, see [17]). Most (84%) of the youth in the risk group were moved to permanent foster or adoptive homes before the age of one year ($n = 38$); six moved after one year of age, and one grew up with one birth parent. As of the last assessment, one had moved back in with a birth parent.

Information concerning prenatal exposure was gathered through interviews with the birth mothers during pregnancy and from their medical and social records [17]. A limitation of many studies on prenatal substance exposure, including this one, is that detailed and valid information about drug use during the entire pregnancy is not available. The birth mothers of the risk cohort were heavy heroin and polydrug users and often had trouble accounting for the amount, timing and frequency of drug use during pregnancy. For these reasons, we have included only what is presumed to be the most reliable information: the women's main drug of choice and information about what other substances they used. The most common main drug of choice, beside tobacco (100%), was illegal opiates (heroin; $n = 20$, 44%), followed by benzodiazepines ($n = 6$, 13%), alcohol ($n = 5$, 11%) and antipsychotic medications ($n = 5$, 11%). The drug-dependent mothers had, on average, used 3.4 different drugs, including tobacco, during pregnancy (range 2 to 6). For more information about their drug use, see Supplementary Table A.1. Most of the infants in the risk group ($n = 35$, 78%) had postnatal withdrawal symptoms, as extracted from the children's medical records, and 20 (44%) received medical assistance for neonatal abstinence syndrome.

The comparison group was recruited from local well-baby clinics in Oslo (for more details, see [17]). All youth in the comparison group lived with their birth parents. None of the mothers in the comparison group reported alcohol or illicit drug use, but 6 (13%) reported sporadic cigarette smoking.

2.2. Descriptive information

As illustrated in Table 1, the risk group had lower gestational age, birth weight, birth length and head circumference than the comparison group. In the risk group, nine (20%) had a birth weight below 2500 g, and seven (16%) had a gestational age below 37 weeks, compared to none in the comparison group. When the lower gestational age in the risk group was taken into account, the group difference in birth weight was reduced to a trend ($b = 206.8$ g; $F = 3.63$; $p = .060$). The comparison group was younger ($M = 18.4$ years) than the risk group ($M = 19.4$ years) at the current assessment (Table 1). The gender distribution was not significantly different between the two groups (Table 1). The caregivers of the youth in the risk group had less education than the caregivers of the youth in the comparison group (Table 1). As age, gender, and low socioeconomic status are well-established predictors of mental health problems in adolescents in general, the present study controlled for these factors in all analyses. Seven (15%) participants in the risk group had not been in an educational or paid work position the past six months, compared to two (5%) in the comparison group ($OR = 4.08$, 95% CI 0.80 to 20.91, $p = .089$).

2.3. Attrition

The youth who participated in the current analyses ($N = 93$) were significantly better off than nonparticipants ($N = 43$) on many measures (Supplementary Table A.2). Participants were less often from the risk group. In the risk group, participating youth had more often moved to stable foster/adoptive homes before one year of age, had higher birth weights and were more often girls than the non-participants, whereas there was an opposite gender difference in the comparison group. There were no other significant participation*group interactions. Participants and nonparticipants did not differ in maternal use of heroin as the main drug of choice, neonatal abstinence, gestational age, birth length, head circumference at birth or parental socioeconomic status at one year of age.

2.4. Measures

The Norwegian translation of the Mini International Neuropsychiatric Interview (MINI) version 6.0.0 [18] was used as a clinical diagnostic interview. The interview was extended with part W, the diagnostic interview for ADHD, from the Norwegian translation of MINI Plus version 5.0.0 [19]. The interview is widely used in clinical practice and research and has been extensively validated [20]. The original interview specifies only current mental health for some diagnoses. We extended the interview to include questions about lifetime suicidality, anxiety disorders, substance disorders and eating disorders. Thus, the questions were asked twice: as presented in the original interview, regarding current mental health, and in terms of whether such problems had existed at any time during the participant's life. The present article focuses on lifetime mental health problems due to the low expected frequency of current mental disorders relative to the sample size.

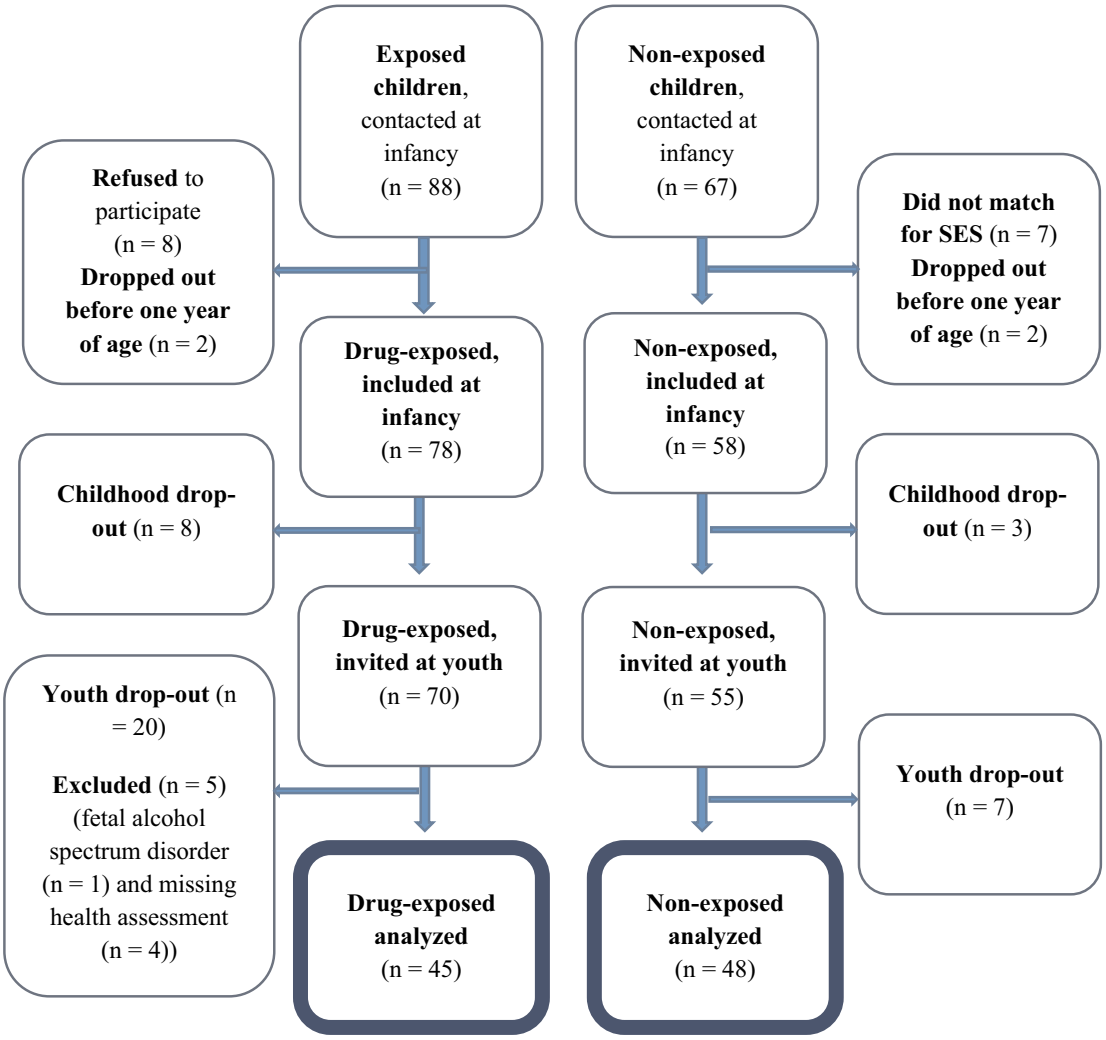

Fig. 1. Flow of inclusion and drop-out of participants.

Table 1
Descriptive information for the risk and comparison groups.

	Risk group (n = 45)			Comparison group (n = 48)			Significance test of difference		
	Mean/n	SD/%	Range	Mean/n	SD/%	Range	Mean diff./OR	95% CI	p
Gestational age (weeks)	38.5	2.2	31.0–42.0	40.6	1.2	38.0–42.5	2.0	1.3–2.8	< .001
Birth weight (grams)	3142.6	676.7	1160–4380	3761.7	461.2	2620–4615	619.1	381.9–856.4	< .001
Head circumference (cm)	34.2	1.8	28.0–37.0	35.7	1.2	32.0–38.0	1.5	0.9–2.1	< .001
Caregivers' education level[a]	1.6	0.7	0.0–3.0	2.1	0.7	0.5–3.0	0.5	0.2–0.8	< .001
Gender (female)	22	48.9%		16	33.3%		0.52	0.23–1.21	.144
Age at interview (years)	19.4	1.3	17.6–21.9	18.4	0.4	17.3–18.9	−1.0	−1.4 to −0.6	< .001
In paid labor past 6 months[b]	26	60.5%		31	70.5%		0.64	0.26–1.56	.372
In school past 6 months[b]	28	65.1%		32	72.7%		0.70	0.28–1.74	.493

Note. The significance of the mean group differences was tested with general linear regression models. The significance of the differences in dichotomous variables (paid labor or education) was tested with Pearson's exact test.

[a] n = 44 in the risk group and n = 48 in the comparison group. Caregivers' education level was the mean current education level, with 0 indicating that none of the caregivers had any secondary education and 3 indicating that both caregivers had four years or more of tertiary education.

[b] n = 43 in the risk group and n = 44 in the comparison group. Seven (16%) of the participants in the risk group were neither working nor in school in the past 6 months compared to two (5%) in the comparison group (OR = 4.08, 95% CI 0.80 to 20.91, p = .089).

Adult self-report (*18–59*) (ASR) [21] questionnaires were completed by the participants to assess externalization, internalization and attention problems experienced currently or in the past 6 months. The questionnaire includes 126 statements rated on a 3-point scale: 0 (Not true), 1 (Somewhat or sometimes true) and 2 (Very true or often true). Externalization problems are characterized by statements in the dimensions of aggressive behavior, rule-breaking behavior and intrusive behavior, whereas internalization problems are characterized by the dimensions of anxiety/depression, withdrawal and somatic complaints. In addition, the ASR includes statements concerning thought problems and attention problems. Similar to the other questionnaires from the Achenbach system of empirically based assessments (http://

www.aseba.org/), the ASR is one of the most commonly used and validated questionnaires to measure behavioral and mental health problems and is acknowledged to be both reliable and valid.

Cantril's Ladder of Life Satisfaction, a vertical visual-analog scale, was used to measure quality of life [22]. Participants were asked to indicate which step on a 10-step ladder currently represented their life. The bottom step represented the worst (1) and the top step the best (10) life imaginable. As a measure of global quality of life, visual-analog scales have good validity and reliability [23].

A questionnaire made for the present study included questions concerning sexual behavior, alcohol consumption and smoking (see Supplementary information). These questions were similar to questions previously used in another longitudinal Norwegian study [24].

In addition to age and gender, sociodemographic information included caregivers' education. Caregivers' education level was measured as the mean education level of the current caregiving parents with a possible range of 0–3, where 0 indicated that none of the caregivers had any secondary education, and 3 indicated that both caregivers had four years or more of tertiary education.

2.5. Procedure

All interviews were conducted by one of the authors (EN), who is a specialist in clinical child and adolescent psychology and has extensive clinical and research practice. After the diagnostic interview, the participants were asked whether they had unmet needs for professional support. When needed, EN referred the participants to appropriate mental health services. The project was approved by the Regional Committees for Medical and Health Research Ethics, reference number 2012/1630. All participants signed consent forms. All participants were above 16 years of age and were thus above the judicial age limit for consenting to participate in health-related research [25]. The project was funded by the Norwegian Research Council (project number 213762).

2.6. Statistics

Exact Pearson chi-square tests were used to analyze bivariate group differences in grouped variables. Logistic regressions were used to analyze group differences in dichotomous health factors while controlling for age, gender and caregivers' education level. Linear regression models were used to analyze group differences in continuous variables, both bivariate and controlled for gender, age and caregivers' education levels. The participants' reports of their mental health on the ASR were standardized (z-values) based on raw scores before being entered into the models. Thus, the reported b-values are standard deviations between groups and are comparable to Cohen's *d*. All analyses were performed with IBM SPSS Statistics version 22 using a 5% significance level and two-tailed tests.

3. Results

3.1. Diagnosis

The diagnostic interview showed that compared to the comparison group, a significantly higher proportion of the risk group had experienced a major depressive episode, alcohol abuse and ADHD *during their lives* after taking into account differences in gender, age and caregivers' education (Table 2 and Fig. 2). A significantly higher proportion of the youth in the risk group had ever had any of the diagnoses in the category “other mental health problems” (Table 2). These mainly included suicidality ($n = 13$), psychotic experiences ($n = 8$) or antisocial personality disorder ($n = 7$) (see Supplementary Table A.3 for information on each separate diagnosis). The proportion of risk group members who reported having previously been diagnosed with ADHD (36%) or prescribed medication for ADHD (32%) was quite similar to the proportion that reported having had ADHD in the diagnostic interview (42%). The risk group also had a tendency to report more *current* mental health problems in the diagnostic interview; however, with the exception of the combination of other diagnoses, these group differences were not significant after covariates were taken into account (Supplementary Table A.4).

3.2. Self-reported mental health and behavior

The ASR responses resembled the information shared during the diagnostic interviews that focused on lifetime mental disorders. Thus, all group differences were in the direction that participants in the risk group were more often above cut-off for clinical level of problems and had more problems on average than the comparison group, both before and after demographic control variables were considered (Table 3). When gender, age and caregivers' education were controlled for, only the level of aggressive behavior differed significantly between the groups ($b = 0.74$, $p = .006$). When we organized the responses according to DSM-oriented scales, there were no significant between-groups differences when all demographic covariates were taken into account, despite significant bivariate differences in depression, somatic problems, ADHD and antisocial behavior (all $p < .05$).

There was no significant group difference in how the youth evaluated their current quality of life (Table 4). When controlling for gender, age and caregivers' education, the risk group was significantly younger at the time of their first sexual intercourse and had a higher number of sexual partners than the comparison group (Table 4). Seven members of the risk group had been or had made someone else pregnant, compared with two in the comparison group. There were no significant differences in alcohol consumption. Seven members of the risk group vs one member of the comparison group smoked daily. The group differences in pregnancy and smoking were not significant when covariates were taken into account.

3.3. Sensitivity analyses

We found results similar to those presented in Tables 2–4 when we excluded the one participant in the risk group brought up by a biological mother. The effect sizes were, with few exceptions, similar when we excluded youth in the risk group born to mothers whose main drug of choice was not opioids. However, the group differences in attention deficit (according to the clinical interview) and self-reported aggression were negligible in this subsample after controlling for covariates ($OR = 0.99$, $p = .994$ and $b = 0.29$, $p = .398$, respectively).

3.4. Birth weight and care situation

Birth weight did not significantly mediate any of the group differences in mental health problems reported on the ASR (Supplementary Table A.5). Neither the number of caregivers nor the age at which the youth in the risk group had moved to their permanent caregiver were significantly related to self-reported mental health problems (Supplementary Table A.6). There was a tendency for youth who lived with foster families to report fewer problems on the ASR than youth who lived with adoptive parents, but none of these differences were statistically significant (Supplementary Table A.7).

4. Discussion

To our knowledge, this is the first study to present the prevalence of psychiatric diagnoses in youth born to mothers with opioid or polysubstance abuse during pregnancy. With the exception of alcohol dependence, the risk group faced a two- to eight-fold higher lifetime risk of mental disorders than the comparison group. These group differences were statistically significant for major depressive episodes, alcohol abuse and ADHD. The risk group also reported higher levels of

Table 2
Lifetime diagnoses according to MINI interview among the youth in the risk and comparison groups.

	Risk group (n = 45)		Comparison (n = 48)		Bivariate group difference			Controlling for gender, age and caregivers' education[a]		
	n	%	n	%	*OR*	95 CI	p	*OR*	95 CI	p
Major depressive episode	24	53.3	10	20.8	4.34	1.75–10.79	.001	3.43	1.14–10.32	.028
Any manic or bipolar disorder[b,c]	16	35.6	9	18.8	2.39	0.93–6.17	.101	2.26	0.65–7.85	.201
Any anxiety disorder[b,d]	28	62.2	17	35.4	3.00	1.29–6.99	.008	2.48	0.86–7.16	.094
Any drug dependence or abuse disorder	19	42.2	12	25.0	2.19	0.91–5.29	.123	2.12	0.66–6.81	.209
Alcohol dependence	13	28.9	11	22.9	1.37	0.54–3.47	.636	0.95	0.27–3.40	.935
Alcohol abuse	10	22.2	2	4.2	6.57	1.35–31.92	.012	7.50	1.28–44.08	.026
Substance dependence	8	17.8	1	2.1	10.16	1.22–84.92	.013	6.87	0.58–81.30	.126
Substance abuse	6	13.3	1	2.1	7.23	0.84–62.65	.054	3.57	0.27–46.80	.333
Attention deficit, hyperactivity disorder	19	42.2	4	8.3	8.04	2.47–26.22	< .001	5.09	1.24–20.95	.024
Other[b,e]	17	37.8	6	12.5	4.25	1.49–12.10	.007	4.54	1.23–16.81	.023

Note. Pearson's exact 2-tailed chi-square test was used for bivariate analyses. Logistic regression analyses were used to analyze differences between groups, controlling for gender, age and caregivers' education.

[a] Information about caregivers' education is missing for one participant in the risk group; thus, n is one less than for the bivariate analyses.

[b] See Supplementary Table A.3 for details of each specific diagnosis.

[c] Any hypomanic episode, bipolar I disorder, bipolar II disorder, or bipolar disorder NOS.

[d] Any of agoraphobia, social phobia (generalized and nongeneralized), obsessive-compulsive disorder, posttraumatic stress disorder, or general anxiety disorder.

[e] Any of psychotic disorder, eating disorder (anorexia, bulimia or anorexia nervosa), antisocial personality disorder, or moderate or high suicidality.

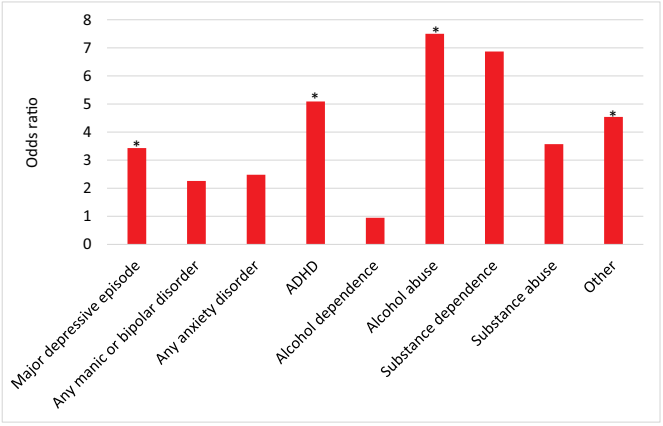

Fig. 2. Odds ratio for lifetime diagnoses in the risk group relative to the comparison group.
Odds ratios according to logistic regression analyses when controlling for gender, age and caregivers' education. "Other" diagnoses include any of the following: psychotic disorder, eating disorder (anorexia, bulimia or anorexia nervosa), antisocial personality disorder, or moderate or high suicidality.
ADHD = attention deficit, hyperactivity disorder.
*$p \leq .05$.

behavioral problems, such as aggressive behavior. Furthermore, participants in the risk group reported a sexual debut at a younger age and a higher number of sexual partners. However, there was no significant group difference in self-reported quality of life.

The prevalence of mental disorders found in the present study seems to be in accordance with that found in the few prevalence studies of similarly prenatally exposed risk groups. We found a somewhat higher lifetime prevalence of mental disorders in general than was found in a study of younger children [5]. However, the prevalence of drug dependence or abuse disorder found in our study is somewhat lower than reported previously in a study of young adults (mean age 23 years) with parents with opioid addiction who had no known prenatal exposure (42% vs 66%) [26].

Our findings of more ADHD, an earlier sexual debut, more sexual partners and more aggressive behavior in the risk group than in the comparison group support previous findings of problems with executive functioning, attention abilities, impulse control and behavior regulation among children born to women who were on opioid maintenance treatment [5,7] or used illicit opioids [8–10] during pregnancy relative to comparison groups or population norms. However, to our knowledge, this is the first clinical study to investigate whether youth with established prenatal opioid and polydrug exposure are at increased risk of drug dependence or abuse. Our findings indicate that the youth in the risk group did not drink more often than those in the comparison group. However, if and when the youth in the risk group drank alcohol, their drinking had a higher risk of meeting the definition of alcohol abuse. The group differences in dependence or abuse of other substances were not significant. The odds ratios were, however, substantial, and if the estimates are replicated in larger samples, the risk of substance abuse and dependency disorders will be an important target for prevention.

In contrast to the only known published study of depression among opiate-exposed adolescents [5], we found a higher prevalence of depressive episodes in the risk group. The results of the few studies that have examined internalizing problems using nondiagnostic questionnaires differ, with some finding more problems [27], others not finding more internalizing problems [5], and still others finding many different behavior and emotional problems [28]. The group differences in internalizing problems based on self-report in the present study were small ($d < 0.3$) and not statistically significant. Thus, our findings regarding internalizing problems were discrepant; there was a substantial difference in prevalence of diagnosed problems but insignificant differences in self-reported problems. This discrepancy may be related to the differences in time as we investigated the lifetime prevalence of diagnosis, whereas the questionnaires were related to behaviors in the present or in the past 6 months.

All but one youth in the present sample were raised in foster or adoptive families, often defined as a risk factor in itself. The prevalence of mental health problems in our "double risk group" was similar to or somewhat higher than that found in studies of youth in foster care in general. Most studies reporting on the prevalence of mental health problems in foster or adoptive children have either investigated younger children or used questionnaires rather than standardized diagnostic interviews. However, one comparable study in Missouri of 373 youth (17-year-olds) in foster care found that 37% had a psychiatric diagnosis in the past year and reported a lifetime prevalence of 61% [29]. The study found lifetime prevalence rates of 27%, 14% and 20% for major depression, PTSD and ADHD, respectively, which are lower than our findings. Another study investigated 732 adolescents aged 17–18 years in three Midwestern US states who had been in out-of-

Table 3
Mental health over the past 6 months according to the adult self-report form questionnaire among youth in the risk and comparison groups.

	Risk group (n = 42)		Comparison (n = 44)		Bivariate group difference		Controlling for gender, age and caregivers' education		Risk group above clinical level (n = 42)		Comparison above clinical level (n = 44)	
	Mean	*SD*	Mean	*SD*	*b*	*p*	*b*	*p*	*n*	%	*n*	%
Total scales												
Total problems	0.29	1.15	−0.27	0.74	0.56	.009	0.41	.139	6	14.3	1	2.3
Internalized	0.24	1.08	−0.23	0.87	0.46	.031	0.25	.361	8	19.0	3	6.8
Externalized	0.33	1.24	−0.31	0.55	0.64	.002	0.52	.058	6	14.3	0	0
Dimensions												
Anxious or depressed	0.20	1.10	−0.19	0.86	0.39	.068	0.17	.542	5	11.9	1	2.3
Withdrawn	0.06	1.15	−0.06	0.84	0.13	.563	0.18	.524	2	4.8	0	0
Somatic complaints	0.31	1.14	−0.30	0.75	0.61	.004	0.34	.206	1	2.4	0	0
Thought problems	0.28	1.11	−0.27	0.80	0.55	.010	0.47	.082	7	16.7	2	4.5
Attention problems	0.17	1.04	−0.16	0.95	0.32	.134	0.32	.256	3	7.1	1	2.3
Aggressive behavior	0.42	1.17	−0.40	0.58	0.81	< .001	0.74	.006	2	4.8	0	0
Rule-breaking behavior	0.30	1.26	−0.29	0.54	0.59	.006	0.36	.168	4	9.5	0	0
Intrusive	0.00	1.02	−0.00	0.99	0.00	.988	0.01	.974	2	4.8	1	2.3

Note. Mean z-values and number of participants scoring above the clinical level on the adult self-report (ASR) form. Group differences in means were analyzed by general linear regression analyses. Information about caregivers' education is missing for one participant in the risk group; thus, there is one fewer participant when controlling for covariates than for the bivariate analyses.
b = unstandardized regression coefficients.

home care for at least one year [30]. The results revealed a lower lifetime prevalence of PTSD (15%), major depression (8%), alcohol abuse or dependency (14%), any other substance abuse or dependency (6%), social phobia (1%) and generalized anxiety disorder (1%) compared to our findings. Studies of children and youth in foster care seldom have access to information about their prenatal drug exposure. However, one would expect that children in foster care are exposed to drugs in utero more often than the general population but probably not as extensively as the youth in our sample. Most studies of youth in foster care include participants who were older at the first change of care than the participants in our sample, e.g., the youth investigated by Keller et al. [30] had a mean age of 11 years upon entering the child welfare system. As a higher age at entry into foster or adoption care is commonly related to more mental health problems [13,31], one would have expected a lower prevalence of mental health problems in our sample.

It is probable that factors in addition to prenatal drug exposure and the home environment contribute to enhanced risk, e.g., genetic and epigenetic factors and other prenatal and postnatal risk factors. However, in clinical studies such as ours, it is impossible to separate the different causal mechanisms. Thus, it is important to take into account the results from experimental studies on animals. Experimental studies

Table 4
Other measures of health among youth in the risk and comparison groups.

	Risk group (n = 42)		Comparison (n = 44)		Bivariate group difference			Controlling for gender, age and caregivers' education[a]		
	Mean/*n*	*SD*/%	Mean/*n*	*SD*/%	*b*/*OR*	95% CI	*p*	*b*/*OR*	95% CI	*p*
Current quality of life[b]	7.2	1.9	7.4	1.5	−0.28	−1.01–0.46	.454	−0.05	−1.00–0.89	.910
Sexual behavior										
Ever had sexual intercourse	40	93.0%	29	65.9%	6.90	1.83–26.04	.003	3.70	0.80–17.18	.096
Age at sexual debut (years)[c]	15.3	1.8	15.9	1.2	−0.56	−1.33–0.21	.185	−1.07	−2.01 to −0.12	.028
Number of sexual partners[d]	9.4	11.5	4.0	2.8	5.39	1.03–9.73	.016	5.37	0.68–10.06	.026
Been or made anybody pregnant	7	16.7%	2	4.5%	4.08	0.80–20.91	.089	2.38	0.30–19.07	.413
Alcohol consumption										
Twice per month or more[e,f]	22	52.4%	26	60.5%	0.72	0.30–1.70	.515	0.54	0.18–1.67	.282
Typically five or more alcohol units[e,f]	29	69%	27	62.8%	1.32	0.54–3.25	.649	2.35	0.69–8.07	.174
Smoking daily[f]	7	16.7%	1	2.3%	8.60	1.01–73.26	.028	8.27	0.77–89.30	.082

Note. General linear regression models were used to analyze group differences in the continuous variables: quality of life, age at sexual debut, and number of partners. Pearson's exact 2-tailed chi-square test was used for bivariate analyses of dichotomous variables: ever had sexual intercourse, ever been pregnant and smoking daily. Logistic regression analyses were used to analyze differences between groups in dichotomous variables when controlling for gender, age and caregivers' education.
b = unstandardized regression coefficients; *OR* = odds ratios.
[a] Information about caregivers' education is missing for one participant in the risk group; thus, n is one fewer than for the bivariate analyses.
[b] Current quality of life was measured by a the vertical visual-analog Ladder of Life Satisfaction [22], with the bottom step (1) indicating the worst life the participant can imagine and the top step (10) representing the best life imaginable.
[c] n = 40 in the risk group and 29 in the comparison group.
[d] n = 37 in the risk group and 29 in the comparison group.
[e] n = 42 in the risk group and 43 in the comparison group.
[f] Frequency of alcohol consumption was measured by the question "How often have you consumed alcohol past 12 months?" with five reply alternatives: never, monthly or less, 2–4 times a month, 2–3 times a week, or 4 times a week or more. Quantity of alcohol consumption was measured by the question "How many glasses (alcohol units) do you typically drink when you drink alcohol?" with 6 reply alternatives: less than one, 1–2, 3–4, 5–6, 7–9, and 10 or more. Smoking was measured by a question with five reply alternatives: have never smoked, have tried smoking, previously smoked but stopped, smoke sometimes and smoke daily with the specification of the number of cigarettes smoked per day. The replies were dichotomized before analysis.

suggest that prenatal exposure to opioids, e.g., methadone and buprenorphine, influence tolerance of morphine and perception of pain, increase the reward effect from later use of opioids or methamphetamine and are related to postnatal symptoms of anxiety or depression [3]. There are concerns that opioid consumption may have epigenetic consequences for future generations as possible epigenetic changes due to long use of opioids have been found in humans and transgenerational effects after methadone exposure have been found in experimental studies [3,32].

4.1. Strengths/limitations

A major strength of the present study is its prospective method, which followed the same risk and comparison groups from birth with a high retention rate (68%) across a 20-year period. This reduces the risk of selection bias and ensures vital information about the drop-out group. Although exact information about drug doses and the amount of exposure was limited, this design also provides certainty that the children were prenatally exposed to opioids and other drugs, and the early adoption/foster care to some extent disentangles pre- and postnatal effects. This is a strength relative to studies of children growing up with addicted parents, where postnatal risk factors are numerous, and studies of children in foster care, where prenatal exposure is often uncertain.

As is common for prospective studies, we had skewed drop-out as the risk group included participants with fewer risk factors (e.g., higher birth weight and a higher likelihood of early placement with an alternative caregiver) than the original sample. This skewness, combined with the exclusion of participants with fetal alcohol spectrum disorder, may have contributed to an underestimation of the differences between the groups.

Almost all effect sizes went in the direction in which the risk group was worse off than the comparison group after demographic covariates were considered. However, most of these group differences were not statistically significant. This may partly be due to the combination of a small sample size and the investigation of problems with low expected prevalence, e.g., mental health diagnosis. Thus, substantial group differences in the prevalence of mental health diagnoses (i.e., odds ratios between 2 and 8 for all but one of the diagnostic groups) were estimated to be statistically nonsignificant.

The comparison group was a convenience sample and may not be representative of the Norwegian population. Although the foster and adoptive parents had a high socioeconomic status relative to the Norwegian population [17,33], the comparison group had an even higher socioeconomic status (Table 1). We controlled for socioeconomic status in all analyses, but it may nonetheless hamper the generalizability of the study.

The lifetime prevalence of mental health problems in the comparison group was high, but it was not outside the range reported in previous population-based studies. We report, for example, prevalence rates of depression and anxiety similar to those of a large population-based study in the US [34]. However, other studies have found much lower levels; e.g., Sund, Larsson [35] reported a 6% lifetime prevalence of major depression among junior high school students in central Norway. There are substantial differences in the reported prevalence of mental disorders across different studies of adolescents, e.g., a 4–25% lifetime prevalence of major depression [36]. Three main reasons are as follows: 1) differences in age, with younger samples reporting a lower prevalence [36]; 2) differences in cohorts, with the prevalence increasing over time, especially for internalizing problems such as depression [36]; 3) and differences in tools, with some studies investigating aggregated problems or using questionnaires or expert opinions that do not tap into each diagnosis. As is common when using the MINI on young adults, we may have overestimated alcohol dependency in both groups [37].

The interviewer's knowledge of group membership may have influenced the results. However, lifetime diagnoses of ADHD according to the MINI greatly overlapped with the participants' responses to a yes/no question regarding prior ADHD diagnosis, with a sensitivity of 83% and a specificity of 88% for the total sample. A small proportion of the participants not previously diagnosed (6 in the risk group and 3 in the comparison group) was found to have had ADHD during their lives according to the MINI interview (12% possible false positive). This indicates a high degree of validity of the diagnostic interview. We unfortunately did not gather information about other prior diagnoses.

5. Conclusion

This study indicates that youth prenatally exposed to opioids and polydrugs have a high prevalence of lifetime mental health disorders and risk behaviors despite early placement in permanent foster or adoptive homes. The factors contributing to this elevated risk may be multifaceted and involve adverse prenatal conditions including but not limited to drug exposure, genetics, and factors related to postnatal environmental conditions. It is probable that these factors contribute over time through transactional processes [38], as was found in large prospective birth cohort studies [39]. It is impossible for clinical studies to separate the different causal mechanisms. We should therefore take into account results from animal and cell culture studies, which indicate that prenatal drug exposure in itself is a probable contributing causal factor [3]. Future work should investigate treatment alternatives for pregnant women with opioid and polysubstance abuse. Our results highlight the need for a longitudinal follow-up that includes preventive interventions promoting good mental health and the careful use of alcohol and other drugs as well as regular mental health and drug use check-ups during upbringing and the transition to adulthood.

Declaration of competing interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.earlhumdev.2019.104910.

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