Mental Health and care situation in school-aged children prenatally exposed to alcohol and other substances: a hospital based study

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Scientific environment

This research work was conducted as part of a PhD programme at the Department of Clinical Medicine, University of Bergen. The main research environment was located at the Department of Child and Adolescent Psychiatry, Division of Psychiatry, and the Department of Pediatrics at Haukeland University Hospital. The research was carried out as collaborative work with the following: (1) the research group for paediatric follow-up studies, with Prof. Dr. Med. Trond Markestad, and later Prof. Dr. Med. Gottfried Greve, as group coordinator; (2) Alcohol and Drug Research Western Norway, Stavanger University Hospital, Norway (KORFOR); and (3) the Bergen Child Study at the Regional Centre for Child and Youth Mental Health and Child Welfare (RKBU), Uni Research Health, Norway, which provided the reference group.

This PhD research is part of the main project "Children exposed to substances during pregnancy", coordinated by paediatrician and child psychiatrist Prof. Dr. Med. Irene B. Elgen who also was the main supervisor for this PhD project. This study was co-supervised by Dr. Med. GP Siren Haugland.

Part of the work was carried out in collaboration with senior researcher Rolf Gjestad, Haukeland University Hospital; paediatrician and researcher Eivind Sirnes, Haukeland University Hospital; professor and researcher Mari Hysing, RKBU; psychologist and researcher Tormod Bøe, RKBU; psychologist and researcher Sondre Aasen Nilsen, RKBU; and Cand. Med. and researcher Silje Katrine Elgen Fevang, Haukeland University Hospital.

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Abstract

Background: Prenatal exposure to substances, including alcohol, opiates and illicit drugs, may influence a child's neurodevelopment and possibly impact on their subsequent mental health. Maternal use of substances is an increasing public health problem, and it is difficult to obtain a true estimate of the prevalence of prenatally substance-exposed children, partly due to stigmatization and the illegal nature of substance use. Alcohol has well-known teratogenic effects, and its prenatal exposure is associated with fetal alcohol spectrum disorders (FASD), with the development of neurodevelopmental impairments across the lifespan, including an increased risk of various mental health problems. In contrast, less is known about the long-term consequences of prenatal exposure to substances other than alcohol, and previous studies examining its possible effects on neurodevelopment and mental health have shown mixed results, although some studies have reported neurodevelopmental impairments persisting into school age and later into adolescence. It is difficult, however, to distinguish between the possible effects of prenatal substance exposure and those of other factors associated with a child's neurodevelopment and mental health such as genetic and environmental factors, including the caregiving environment.

Objective: The objective of this study was to assess mental health and investigate the care situation and use of supportive measures in a hospital-based population of school-aged children prenatally exposed to alcohol and other substances, compared to a reference group.

Methods: This study included children, aged between 6 and 14 years, with prenatal substance exposure who were referred to the Department of Pediatrics at Haukeland University Hospital in Bergen, Norway, from January 1997 to December 2012. Referral criteria included symptoms of developmental impairment, in the presence of a medical

history of prenatal exposure to substances. Children with confirmed prenatal exposure to substances, including alcohol, illicit drugs, illegal use of prescription drugs, and opioids used in opioid management treatment programmes (OMT), were included in the study. Of a total number of 128 children referred, 87% ($n = 111$) gave informed written consent and were included in the study. Based on the mother's main substance of use during pregnancy, children were systematically categorized into two groups: (1) prenatal exposure to alcohol (FASD group); and (2) prenatal exposure to other substances. Information on the care situation and use of supportive measures was obtained from the children's medical records, and relevant questionnaires were completed by their caregivers. Mental health was assessed using three different standardized questionnaires: (1) the Strength and Difficulties Questionnaire (SDQ); (2) the Swanson, Nolan and Pelham Questionnaire, revision IV (SNAP-IV); and (3) the Autism Spectrum Screening Questionnaire (ASSQ), which were completed by children's current caregivers. For mental health assessment, outcomes were compared to a reference group derived from the population-based Bergen Child Study (BCS).

Results: Of 111 children prenatally exposed to substances, 50 (45%) children were prenatally exposed to alcohol and 61 (55%) to other substances. More than half (59%) were boys, and 86% were living in foster care, of whom 30% were placed into foster care during their first year of life. In addition, 92% of the children in foster care had additional supportive measures, including reinforced foster care, school and/or social support. In the assessment of mental health using the SDQ, 105 children completed the questionnaire and were included in this part of the study. SDQ subscale mean scores, total difficulties scores and total impact scores were statistically significantly higher in the group of exposed children, compared to the reference group, indicating a higher rate of mental health problems in the exposed group, as well as problems in more than one domain of mental health. There was no statistically significant difference in scores between the group of

children mainly exposed to alcohol and the group mainly exposed to other substances. Further evaluation of mental health problems associated with social skills challenges, hyperactivity and inattention was performed for the group of children exposed to substances other than alcohol, using the SNAP-IV and ASSQ. The children's caregivers reported an increased number of symptoms associated with attention-deficit/hyperactivity disorder (ADHD) in the areas of both inattention and hyperactivity/impulsivity, as well as a higher number of symptoms associated with autism spectrum disorders (ASD), compared to the reference group.

Conclusion: In this hospital-based population of children prenatally exposed to alcohol and other substances, the children were found to have an increased risk of mental health problems affecting their daily life functioning, when compared to a reference group. The mental health problems present were not restricted to one specific area, but rather represented problems in more than one domain of mental health. Children mainly exposed to substances other than alcohol were found to have an increased level of symptoms associated with ASD and ADHD in the areas of inattention and hyperactivity/impulsivity. A high proportion of the prenatally exposed children lived in adoptive homes or in foster care. Children in foster care often had supportive measures, in addition to their placement outside their biological home. The high level of use of care and supportive measures could be a reflection of the children's increased care and support needs, which, in turn, may be associated with an increased risk of mental health problems in the group of substance-exposed children. Further research is needed both on diagnostic investigation of mental health problems and on determining the care and support needs in children prenatally exposed to substances.

Clinical implications: Because of the increased risk of mental health problems associated with prenatal substance exposure, early mental health assessment in children prenatally

exposed to substances should prove beneficial. In addition, children's caregivers should be aware of the range of mental health problems that exposed children are at risk of, and increased levels of supportive measures should be put in place accordingly.

List of publications

Paper I: Sandtorv, L., Haugland, S., & Elgen, I. (2017): "Care and Supportive Measures in School-Aged Children With Prenatal Substance Exposure", Scandinavian Journal of Public Health, Vol. 45: 782–8.

Paper II: Sandtorv, L., Hysing, M., Rognlid, M., Nilsen, S., & Elgen, I. (2017): "Mental Health in School-Aged Children Prenatally Exposed to Alcohol and Other Substances", Substance Abuse: Research and Treatment, Vol. 11: 1–8.

Paper III: Sandtorv, L., Fevang, S., Nilsen, S., Bøe, T., Gjestad, R., Haugland, S., & Elgen, I. (2018): "Symptoms Associated With Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorders in School-Aged Children Prenatally Exposed to Substances", Substance Abuse: Research and Treatment, Vol. 12: 1–8.

List of abbreviations

ADHD   Attention-deficit hyperactive disorder

ASD   Autism spectrum disorders

ASSQ   Autism Spectrum Screening Questionnaire

BCS   Bergen Child Study

CD   Conduct disorder

CDC   Centers for Disease Control and Prevention

CI   Confidence interval

CNS   Central nervous system

DSM-IV   Diagnostic and Statistical Manual of Mental Disorders, fourth edition

EPS   Educational Psychological Service

FAS   Fetal alcohol syndrome

FASD   Fetal alcohol spectrum disorders

GA   Gestational age

ICD-10   International Classification of Diseases, tenth revision

IQ   Intelligence quotient

NAS   Neonatal abstinence syndrome

ODD   Oppositional defiant disorder

OMT   Opioid management treatment programmes

OR   Odds ratio

RAD   Reactive attachment disorder

SD   Standard deviation

SDQ   Strengths and Difficulties Questionnaire

SES   Socio-economic status

SIDS   Sudden infant death syndrome

SNAP-IV   Swanson, Nolan and Pelham Questionnaire, revision IV

SPSS   Statistical Package for the Social Sciences

TDS	Total difficulties score
WHO	World Health Organization
WISC-R	Wechsler Intelligence Scale for Children-Revised
WPPSI	Wechsler Preschool and Primary Scale of Intelligence

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1. Introduction

1.1 Fetal development and prenatal substance exposure

Prenatal exposure to substances may influence neurodevelopment, and subsequent mental health, in children (1-6). Through their pharmacological properties, many substances are able to cross the placental barrier which serves as the interface regulating the transfer of materials between maternal and fetal circulations (6, 7). Placental passage of substances depends on various substance-related factors, including the molecular size and charge, protein-binding properties and lipid solubility (7, 8). In addition, any effects on the fetus as a consequence of substances crossing the placental barrier also depend on maternal factors, including metabolic and genetic factors, which may cause individual differences in both maternal and fetal substance uptake and elimination (7, 8).

Any exogenous substance that crosses the placental barrier has the potential to disrupt the normal and tightly regulated fetal neurodevelopment (9, 10). Substances can act either directly on molecular targets in the fetus or indirectly on the fetus through effects on the placenta or uterus (11). Alcohol, opiates and illicit drugs, including amphetamine, cocaine, cannabis and benzodiazepines, all have the pharmacological potential to rapidly enter the fetal circulation, and fetal exposure to these substances can adversely impact on fetal development (3, 5, 6, 12-14).

During the first 8 weeks of gestation, termed the embryonic period (10), the basic features of organs and body systems of the human embryo are established, along with significant embryonic growth and maturation during this period to reach the fetal stage of development (10). It has been postulated that fetal development is marked by critical time points that correspond to normal organ formation and development (10, 15). Thus, the risk of malformations and developmental impairments due to prenatal substance exposure may differ at different time points during pregnancy. Development of the central nervous system (CNS), including the brain, begins early during the embryonic period and continue into the fetal stage of development, through neuronal proliferation, migration,

differentiation and apoptosis (10, 15). However, full maturation of the brain is not completed until after birth (10), with further brain development and modulation continuing throughout childhood and adolescence (15). The postnatal growth of the brain involves not only an increase in size, but also neuronal proliferation and myelination. Importantly, the process of neuronal organization and interconnections is highly complex and under strict control via different mechanisms (10). It is known that both pre- and post-environmental factors can influence neurodevelopment (15), as brain plasticity is related to its responses to different experiences. Thus, several studies showed an association between brain development and function and various environmental factors such as drug exposure, early stressors, hormonal influences, sensory stimuli and parent–child relationships (16).

Previous research found an increased risk of neurodevelopmental impairments and mental health problems in association with prenatal substance exposure (2, 3, 6, 12, 17, 18). Moreover, established risk factors for mental health problems include genetic and environmental factors such as the caregiving environment (19). However, it is difficult to distinguish between the possible effects of prenatal substance exposure and those of established or unknown factors on a child's neurodevelopment and mental health. The aims of the present study were to assess mental health and investigate the care situation and use of supportive measures in a population of school-aged children prenatally exposed to alcohol and other substances, compared to a reference group.

1.2 Prenatal exposure to alcohol and other substances

Maternal substance use is defined as use of alcohol, prescribed or illicit use of opiates, use of illicit drugs and use of illegal prescribed psychoactive substances. Use of these substances is associated with a risk of abuse and dependence (20).

Alcohol comprises a large group of organic compounds containing a hydroxyl group, of which ethanol found in liquor, wine and beer is one example (21). In this context, and for the purpose of this thesis, the term alcohol is used to refer to ethanol.

Alcohol exerts well-known teratogenic effects, with the potential to cause congenital malformations and/or abnormal neurobehavioural manifestations later in life (22). Possible long-term effects of prenatal exposure to substances other than alcohol are less well established (2, 6). In view of this, it was considered appropriate, in this study, to distinguish between exposure to alcohol and exposure to substances other than alcohol when examining the effects of prenatal substance exposure.

Maternal substance use is a common public health problem worldwide. In the United States and Western European countries, the incidence of prenatal substance exposure has been rising over the past decade (23, 24). However, given the stigmatization associated with, and the illegal nature of illicit drug use, it is difficult to obtain a true estimate of the prevalence of substance-exposed children (6, 21, 25). These, together with underreporting of maternal substance use, have hampered efforts in setting up population-based studies to investigate the prevalence of prenatal substance exposure.

1.2.1 Prevalence of prenatal alcohol exposure

According to an American national survey on drug abuse and health in 2014, 10.8% of pregnant women consumed alcohol during pregnancy (6, 25, 26). In a European cross-country study, almost 16% of pregnant women consumed alcohol during pregnancy, with Norway presenting with one of the lowest estimates at 4.1% (27). The study demonstrated large variations between the participating countries, which could be explained by differences among countries in terms of sociocultural and socio-economic factors, legislation and public health advice and awareness campaigns from national health authorities (27). A recent systematic review and meta-analysis found a prevalence of 0.8% of fetal alcohol spectrum disorders (FASD) in the general population, with large

differences between populations, while other studies on the prevalence of FASD also reported large differences in prevalence across geographical and cultural populations (28, 29).

1.2.2 Prevalence of prenatal exposure to substances other than alcohol

Similarly to the prevalence of alcohol use, estimating the prevalence of opiate use and the illicit use of substances is challenging. According to an American national survey on drug abuse and health in 2014 (26), approximately 4% of pregnant women reported the use of illicit drugs during pregnancy. It was also shown that the incidence of neonatal abstinence syndrome (NAS) is increasing in the United States (5.8 per 1000 hospital births), as well as in other Western countries, suggesting an increased rate of prenatal opiate exposure (30, 31).

The World Health Organization (WHO) recommends opioid management treatment programs (OMT) for opioid-addicted pregnant women. Increasingly more women of childbearing age are enrolled in OMT, and this can possibly affect the increasing rate of NAS. According to the Norwegian health authorities, it is expected that about 30–60 children are born to mothers participating in OMT in Norway every year (32).

1.2.3 Children with prenatal alcohol exposure

The deleterious consequences of prenatal alcohol exposure were described in as early as the 1970s, and it is well established that alcohol exposure during pregnancy can adversely affect the fetal CNS and neurodevelopment in different ways (33). In animal studies, alcohol has been found to exert a direct toxic effect on neurons, by inhibiting neuronal cell division and proliferation and disrupting the process of neuronal migration and neuronal network formation in the developing brain (34). These toxic effects at a cellular level are reflected in the observed outcomes of prenatal alcohol exposure, including small

head circumference and craniofacial structural malformations, as well as cognitive impairment and learning disabilities.

Different terms have been used to describe the effects of prenatal alcohol exposure. FASD is one of the most recent terms in use (33) and therefore will be applied throughout the remaining course of this thesis. It has been shown that prenatal alcohol exposure may result in FASD (6, 17, 33). FASD comprises a spectrum of conditions presenting with mild to severe neurodevelopmental consequences, such as cognitive impairment and an increased risk of specific learning disabilities and mental health problems including attention-deficit/hyperactivity disorder (ADHD), anxiety, mood disorders and autism spectrum disorders (ASD), as well as growth restriction and dysmorphic features, with fetal alcohol syndrome (FAS) as the most severe consequence (6, 17, 33, 35). The diagnostic criteria of FAS, based on the Centers for Disease Control and Prevention (CDC) criteria, include: (1) the presence of facial dysmorphic features (smooth philtrum, thin vermilion border, small palpebral fissures); (2) growth restriction (pre- or postnatal height or weight ≤10th percentile); and (3) CNS impairment (structural, neurologic or functional abnormalities) (33). Differential diagnoses need to be considered in cases of suspected FAS, because the dysmorphic features present in FAS can also be observed in other syndromes (e.g. Williams syndrome and Dubowitz syndrome) (33). FASD is not a diagnostic term, but rather an umbrella term encompassing several diagnostic terms used to describe the full range of all possible effects of prenatal alcohol exposure (36).

Other important sequelae associated with prenatal alcohol exposure include an increased risk of miscarriage, preterm birth, pre- and postnatal growth restriction and sudden infant death syndrome (SIDS), as well as effects on various organ systems such as the cardiovascular, musculoskeletal, renal, ocular and auditory systems (6, 35).

The degree of impact of maternal alcohol use on fetal development depends on a variety of factors, including the timing and level of alcohol exposure and genetic background (37). Recent research exploring the epigenetic mechanisms involved in fetal

exposure to alcohol has suggested a link between the genetic background, environmental factors and neurodevelopmental outcomes (36, 37).

1.2.4 Children with prenatal exposure to substances other than alcohol

Substances other than alcohol include illicit drugs (e.g. heroin, amphetamine, cocaine and cannabis), prescription drugs such as benzodiazepines and opiates used illegally and opioids used in OMT. Prenatal exposure to these substances has been associated with preterm birth, low birthweight, small head circumference and withdrawal symptoms after birth (6, 38, 39). Of note, children prenatally exposed to opiates, in particular, are at risk of developing NAS (23, 30, 38), which has been found in 55–94% of children prenatally exposed to opioids (23, 30, 38, 40).

NAS is a complex disorder involving the CNS and gastrointestinal system, as well as metabolic and respiratory disturbances. Clinical manifestations range from mild symptoms, such as sneezing, irritability, hypertonia, mild tremors, sweating and poor feeding, to severe symptoms such as seizures, excessive weight loss, hyperthermia and respiratory disturbances (23, 30, 38). In addition, a recent follow-up study of children with NAS reported an increased risk of rehospitalization for maltreatment, trauma and mental health problems, compared to controls (4).

Systematic reviews of children prenatally exposed to substances other than alcohol found an increased risk of cognitive and behavioural impairments at preschool age (2, 5). Furthermore, several longitudinal studies found that cognitive difficulties as a result of prenatal substance exposure in preschool-aged children persisted into school age and adolescence. A recent study described increasing effects over time of prenatal substance exposure, compared to non-exposure, on cognition (2, 18, 41, 42), as well as an increased risk of mental health problems (2, 18). The latter will be described in more detail in Section 1.3.

Moreover, a review of neuroimaging studies of children prenatally exposed to substances highlighted findings from studies that showed smaller brain volumes and altered brain metabolic activity following prenatal substance exposure (43). A previous *in vitro* study of human neuronal cells showed that opiates promoted apoptotic cell death, suggesting a possible impact on fetal brain development (44). In addition, a recent animal study described an association between prenatal exposure to opiates and long-term behavioural changes related to cognitive function (45). However, results are conflicting, and further research on long-term consequences, including mental health outcomes, of prenatal exposure to substances other than alcohol is needed (5).

1.3 Mental health

Mental health is defined by the WHO as: "a state of well-being in which every individual realizes his or her own potential, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to her or his the community" (46).

In contrast, the term "mental health problems" is difficult to define as a distinct entity. Rather the term includes a continuum of symptoms, some of which will meet the diagnostic criteria for a psychiatric disorder (47). The diagnosis of a psychiatric disorder implies the presence of symptoms over a certain time period, and having an impact on daily functioning (20, 48). Approximately 8–10% of the general child population is diagnosed with a psychiatric disorder. In addition an increasing proportion of children are presenting with mental health problems without fulfilling the diagnostic criteria for any particular psychiatric disorder (20, 49-51). For the general child and adolescent populations, the prevalence of different mental health problems normally varies with age and gender (52).

Previous studies found an association between prenatal substance exposure and an increased risk of mental health problems, including ADHD, internalizing problems, such

as emotional problems like anxiety and mood disorders, and externalizing problems related to harmful and disruptive behaviour (2, 6, 53, 54). Of particular relevance to this present study is an increased risk of mental health problems among children in foster care (50, 55). In a Norwegian sample, Lehmann *et al*. found that one in two children in foster care had a psychiatric disorder (55), with the most common mental health problems being emotional disorders, behavioural disorders and ADHD. In addition, nearly one in five children were diagnosed with reactive attachment disorder (RAD), with a high comorbidity rate for emotional disorders, behavioural disorders and ADHD (55). The authors also found an increased risk of mental health problems associated with exposure to violence, serious neglect and the number of prior placements into foster care (55).

1.3.1 Emotional problems

Emotional problems include symptoms of anxiety and depressive disorders (20, 48). It is found that girls experienced more emotional problems than boys, especially during adolescence (56). A review of studies of psychiatric conditions associated with prenatal alcohol exposure described an increased risk of emotional problems and mood disorders, such as depression and anxiety, across the lifespan (14). Moreover, other studies reported an increased risk of emotional problems in children exposed to substances other than alcohol (2, 57), with a higher rate of emotional problems among girls with such exposure reported by Irner *et al*. (2014) (18).

1.3.2 Conduct problems

Conduct problems include oppositional defiant disorder (ODD), conduct disorder (CD) and disruptive behaviour disorder. An increased risk of behavioural disorders in children prenatally exposed to alcohol and to substances other than alcohol has been reported previously (6, 18, 58-60). In addition, a recent American review found that children with

FASD had approximately five times higher risk of ODD and three times higher risk of CD, compared to the general population (54).

1.3.3 Inattention, impulsivity and hyperactivity

The three core symptoms of ADHD are inattention, hyperactivity and impulsivity (20). In Norway, approximately 3% of children are diagnosed with ADHD, predominantly among older children and boys (61). ADHD is a complex disorder and may result from processes including both genetic and non-genetic factors, with possible involvement of neurobiological factors such as structural brain factors and neurotransmitters in the brain (15, 62, 63). Several studies have found an increased risk of ADHD in children prenatally exposed to alcohol and other substances (2, 6).

1.3.4 Social skills challenges

Social skills challenges, including peer problems, are related to problems with social interaction and communication, as well as restricted behaviour (20), all of which may relate to symptoms of Autism Spectrum Disorders (ASD). ASD comprise a range of symptoms, of which social impairments are the core symptom (64). The prevalence of ASD has been estimated to be just under 1%, with a predominance among boys (61). In recent years, there has been a rise in the prevalence, although any reasonable explanation has proven elusive (64).

A recent study found that prenatally alcohol-exposed children have a twofold higher risk of ASD, compared to the general population (54). However, there seems to be a lack of studies on the relationship between prenatal exposure to substances other than alcohol and the risk of ASD.

1.3.5 Reactive attachment disorder

Reactive attachment disorder (RAD) is characterized by social impairments (20, 48, 65). Whereas ASD is considered as a neurodevelopmental disorder, RAD is a disorder which may result from inadequate caregiving and can develop when a child's caregiving environment fails to establish and meet the child's care needs (20, 48, 65). Parental substance use is associated with an increased risk of child maltreatment and placement into foster care. Therefore, prenatally substance-exposed children may be at risk of inadequate caregiving conditions and foster care placement, which, in turn, would increase their risk of RAD.

1.4 Mental health problems and risk factors

Mental health problems are associated with several risk factors other than prenatal substance exposure, including genetic and epigenetic factors (15, 66), gender (52, 56), cognitive functioning (67, 68), socio-economic factors and environmental conditions, including caregiving environment (50, 53, 55, 60, 69-71). These risk factors will be discussed in more detail in the following sections.

1.4.1 Genetic and epigenetic factors

Genetic factors seem to play a significant role in a child's development and in the risk of acquiring certain mental health disorders. Children whose parents have ADHD are more likely to develop ADHD, probably due to a combination of both genetic and non-genetic factors (15, 62, 63).

The field of epigenetics attempts to explain how different environmental factors and experiences can impact on genetic expression. One proposed definition of epigenetics is: "An epigenetic trait is a stable heritable phenotype resulting from changes in a chromosome without alterations in the DNA sequence" (72). Based on this definition, it follows that exposure to substances and toxins, stress and maltreatment could alter a

child's genetic expression, either through effects of individual factors or through an interaction between the various factors (36, 73, 74). There is growing evidence of an association between life stressors in early childhood and subsequent emotional mental health problems (75, 76). This may be related to stress hormones, e.g. in the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis, acting as epigenetic factors (36, 75, 76). This illustrates the complexity in understanding risk factors in relation to others.

1.4.2 Cognitive functioning

Cognitive impairment is another risk factor for mental health problems (67, 68). It has been shown previously that lower cognitive functioning is related to an increased risk of mental health problems (67, 68). In addition, Sameroff *et al*. found that an increasing number of environmental risk factors was associated with a decrease in intelligence quotient (IQ) scores (77).

Concerning the risk of cognitive impairment in prenatal alcohol exposure, previous studies reported an association between prenatal alcohol exposure and cognitive impairments, including lower IQ (33). In contrast, other studies in children exposed to substances other than alcohol found the IQ to be within the normal range for this group (2, 78).

1.4.3 Socio-economic status

Low socio-economic status (SES) is a well-established risk factor for mental health problems (79), including both internalizing and externalizing problems (80, 81). The presence of a substance use disorder is associated with a low SES, which may increase the risk of mental health problems in children prenatally exposed to substances who are living with their biological parents (82).

1.4.4 Caregiving environment

Parents' ability to function as caregivers can be severely impaired by their use of substances, which is a risk factor for their children's placement into foster care (21, 55). As mentioned in Section 1.4.3, parental substance use increases the risk of low SES, which exposes families to an increased risk of poverty, family stress, low level of parental education, poor prenatal care and family instability (55, 83, 84). Use of substances during pregnancy is associated with a higher risk of poor maternal nutritional status and infections, along with possible impact on fetal development. For opioid-dependent pregnant women attending OMT, these risks have been found to decrease, indicating that OMT contributes to improved prenatal care in opioid-dependent pregnant women (85, 86).

Exposure to inadequate caregiving conditions early in life may affect mental health later in life. The prevalence of mental disorders in youth placed into foster care in Western countries has been estimated to be almost threefold higher than that in the general population (55, 87). Moreover, some studies in prenatally exposed children found that optimizing care conditions is likely to have a positive effect on cognitive and mental health outcomes (55, 69, 88).

Children born with NAS have special care needs related to their health issues. Neonates with NAS have greater care needs, compared with newborns without NAS, particularly in terms of feeding problems, extensive crying and sleep disturbances. Therefore, there could be a potential mismatch between a child's care needs and the biological parents' abilities as caregivers for the child, as illustrated in Figure 1.

Parental caregiving abilities

Prenatally substance-exposed
child's care needs
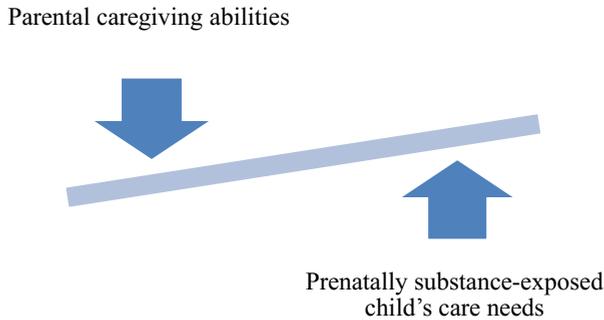
Figure 1. Potential mismatch between biological parents' caregiving abilities and the prenatally substance-exposed child's care needs.

Norwegian Child Welfare Services and the provision of supportive measures
Under Norwegian law, a child's biological parents are responsible for the provision of all necessary care and protection to meet the child's daily needs. If, for some reason, the biological parents are not able to provide the care required, the Child Welfare Services, which are responsible for child welfare protection in Norway, are legally obligated to intervene in order to ensure adequate care for the child, including supportive measures within or outside the biological home, temporary or permanent foster care placement or adoption (89). The Child Welfare Services are obliged to act in the best interests of the child at all times, even in cases where the parents and child's interests are in conflict (89, 90). Furthermore, the Child Welfare Services have to consider voluntary interventions before making any decision on initiating measures without parental consent (90).

According to official Norwegian statistics (2016) nearly 4% of all children and adolescents aged 0–22 years receive some kind of supportive measures from the Child Welfare Services, including foster care (90, 91). Of those children receiving supportive care, 40% live outside their biological home, the majority of whom are in foster care (90,

91). In Western societies, including Norway, about five in 1000 children are placed into care outside their biological home (89, 90, 92).

1.5 Prenatal substance exposure and risk of mental health problems

In summary, earlier research suggest that children prenatally exposed to alcohol and other substances are likely to be more vulnerable to developing mental health problems, with several associated risk factors which can be either cumulative and/or interacting (83, 93) (see Figure 2). For substances other than alcohol, results are more conflicting. It is possible that risk factors in the caregiving environment may have a greater impact on a child's development than prenatal substance exposure itself (83, 93). However, it is also possible that prenatal substance exposure affects neurodevelopment, and consequently the child's vulnerability to environmental factors. A possible cumulative effect of biological and environmental factors has been postulated (83, 94).
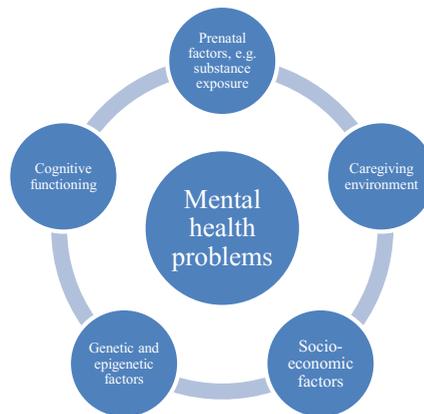
Figure 2. Possible associated and interacting risk factors related to mental health problems.

Regardless of the risk factors influencing mental health outcomes in prenatally substance-exposed children, there remains a need for in-depth knowledge and understanding of the types, especially the specific areas, of mental health problems that can affect these children, in order to define and facilitate the provision of appropriate and adequate support for the children, as well as their caregivers.

2. Aims

The overall aim of the work presented in this thesis was to investigate the long-term outcomes related to the care situation and mental health status in a hospital-based population of school-aged children prenatally exposed to alcohol and other substances. The study objectives were as follows:

- Paper I: to investigate the care situation of prenatally substance-exposed children and the level of use of supportive measures in their home and school settings;

- Paper II: to evaluate the overall mental health status of prenatally substance-exposed children, compared to a reference group, using the Strength and Difficulties Questionnaire (SDQ), which is a standardized mental health screening instrument;

- Paper III: to determine the mental health symptoms associated with particular domains of ADHD and ASD in children exposed to substances other than alcohol, compared to a reference group.

2.1 Study hypothesis

The work presented in this thesis was based on the following proposed hypotheses:

- The hospital-based population of children prenatally exposed to substances have an increased risk of foster care placement or of provision of school support or other supportive measures;

- The hospital-based population of children prenatally exposed to substances have an increased risk of mental health problems in one or more domains of mental health, compared to a reference group;

- Based on the known teratogenic effects of alcohol, children prenatally exposed to alcohol have increased mental health problems and care and supportive measures, compared to children exposed to substances other than alcohol.

3. Methods

The work presented in this thesis was part of the project "Children prenatally exposed to substances: growth, health and development", initiated and led by Dr. Med. Liv Marie Lægreid and Prof. Dr. Med. Irene B. Elgen, Department of Pediatrics and Department of Child and Adolescent Psychiatry at Haukeland University Hospital, which was conducted from 1997 to 2012.

The study described in this thesis was divided into three parts, with each part presented in its respective published research article denoted in this thesis as "Paper I", "Paper II" and "Paper III" (see List of publications).

3.1 Study participants

The project was based on a follow-up study including a hospital-based population of children who were referred to the Department of Pediatrics at Haukeland University Hospital in Bergen, Norway between January 1997 and December 2012. Study participants were aged ≥14 years at the point of data collection, with the oldest child aged 14.5 years/174 months.

Referral criteria included the presence of developmental impairments and a concomitant past medical history of prenatal alcohol or other substance exposure. Children transferred to Department of Pediatrics with symptoms of NAS after birth were also included in the study. Referrals were from health-care providers, social workers and physicians in primary community care units and paediatric and child psychiatric units.

During the recruitment period, the children's caregivers were invited to participate in the study by a letter of invitation containing information about the study. In addition, for those children in foster care, a letter detailing information about the study was sent to the social services agency responsible for the child. It was possible to accept participating in the entire study, or in parts of the study such as assessment of the care situation, complete mental health assessment or parts of the mental health assessment.

In Norway, children normally start at school in August in the year of their sixth birthday, although in some cases, children can be under 6 years old. A total of 128 children aged between 6 and 14 years were invited to participate in the study, including one child aged under 6 years. Of the 128 eligible children, 111 (87%) gave informed written consent and participated in the study, as follows (see Table 1):

- Paper I: all 111 children completed the relevant questionnaire for the work presented in this paper;
- Paper II: of the 111 participating children, 105 (95%) had their caregivers complete the SDQ;
- Paper III: of the 111 participating children, 61 were mainly exposed to substances other than alcohol, and of those 61 children, 57 (93%) completed the Swanson, Nolan and Pelham Questionnaire, revision IV (SNAP-IV) and Autism Spectrum Screening Questionnaire (ASSQ).

Table 1. Number of participants in the paper I, II and III.

Total number of eligible children prenatally exposed to substances, $N = 128$ *(age 6–14 years: defined as 6–14.5 years, i.e. 72–174 months)* Number of children who gave informed written consent, $n = 111$ (87%)		
Paper I **Care and Supportive measures** ($n = 111$)	**Paper II** **SDQ** ($n = 105$)	**Paper III** **ASSQ + SNAP-IV** ($n = 57$)
Children prenatally exposed to substances ($n = 111$)[1] 111 completed the questionnaire and were included	Children prenatally exposed to substances ($n = 111$)[1] 105 (95%) completed the SDQ and were included[2]	Children mainly exposed to substances other than alcohol ($n = 61/111$)[3] 57 (93%) completed the SNAP-IV and ASSQ and were included

[1]Including 50 children with FASD and 61 exposed to other substances,

[2]Excluding six children with missing SDQ,

[3]Excluding 50 children with FASD

3.2 Participant categorization according to prenatal substance exposure

Children with confirmed prenatal exposure to substances, including alcohol, illicit drugs, illegal use of prescription drugs, and opioids used in OMT, were included in the study. History of exposure was confirmed by information obtained from the mothers and obstetric or paediatric records, including data from referring units and medical reports of neonatal withdrawal symptoms after birth. Data were systematically recorded based on the mother's main drug of use during pregnancy, and the children were categorized into two groups: (1) prenatal exposure to alcohol (FASD group); and (2) prenatal exposure to other substances (other substances group). No valid information was available on doses of

substance used in pregnancy, including the number of units of alcohol consumed, or the exact timing of exposure during pregnancy.

If there was evidence of exposure to both alcohol and other substances, the child was placed in the FASD group, provided alcohol was the main substance of use by the mother, clinical evidence of FASD, and reports of regular, or more often than occasional, episodes of alcohol use during pregnancy. Also, if a child met the clinical criteria of FAS, the child was placed in the FASD group. Therefore, no children in the other substances group met the FAS criteria.

3.2.1 Fetal alcohol spectrum disorders (FASD)

The FASD group included cases of both FAS and FASD. The diagnosis of FAS or FASD was given after evaluation of the medical history and clinical examination by a paediatrician with relevant specialized training and neuropsychological testing. Differential diagnoses were considered in all cases, and paediatricians specially trained in the field, including paediatric endocrinologists and geneticists, were consulted in cases of uncertain diagnosis. FAS was diagnosed if a child with confirmed prenatal alcohol exposure met all of the following CDC criteria (33): (1) presence of facial dysmorphic features; (2) growth restriction; and (3) CNS impairment. Children with confirmed alcohol exposure who only fulfilled some, but not all, of the three FAS criteria were categorized into the FASD group.

CNS impairment was defined as the presence of learning disabilities (defined as an IQ score below 85) or a diagnosis of ADHD. Intellectual level was determined using either the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) test (95) or the Wechsler Intelligence Scale for Children-Revised (WISC-R) test (96). An IQ score below 70 was defined as intellectual disability, and an IQ score of 70–84 as low IQ. ADHD was diagnosed by a paediatrician and a child psychiatrist according to the International Classification of Diseases, tenth revision (ICD-10) criteria.

3.2.2 Prenatal exposure to substances other than alcohol

This group included children exposed to street drugs and polydrug use, as well as those exposed to opioids as part of the national OMT. The most common "other substances" reported in this group were opiates and polydrug use. Children in this group either had a medical history of prenatal exposure to one or more other substances or were diagnosed with NAS after birth. None of the children in this group met the criteria for FAS. Although non-documented (i.e. unknown) use of alcohol could not be totally excluded, the mother's main drug of use included substances other than alcohol.

3.2.3 The reference group

The reference group consisted of children participating in the Bergen Child Study (BCS), which is a longitudinal population-based study. There were no exclusion criteria, and all children attending grades 2–4 at 79 schools in a geographically delineated area in the academic years of 2002 and 2003 were invited to participate in the study ($n = 9430$) (51). Parent SDQs were completed for about two-thirds of the participating children ($n = 6297$) (51). Of the participating children in the BCS, about two out of three lived in a family categorized as having good or very good family economy, and about 50% of the mothers and fathers had higher education (80). More details about the reference group are presented in the papers by Heiervang *et al*. (2007) (51, 80, 97), Boe *et al*. (2012) (51, 80, 97) and Stormark *et al*. (2008) (51, 80, 97). In the present study, participants from the first two waves were included. The first wave of the BCS, was conducted in autumn 2002, and informed consent to participate was received from 7007 (74%) parents prior to study inclusion. The second wave was conducted 4 years later during spring 2006, comprising 5683 children aged 11–13 years (60% of the original target population). For every participating child in the hospital-based group of children prenatally exposed to substances, three children from the BCS population, who were gender- and age-matched

(± 0.9 years), were randomly selected into the reference group. Three controls were included for each case to improve the robustness of the analyses (98). As age was considered to be an important matching factor in the present study, a relatively narrow matching criterion of ± 0.9 years was used, which hence allowed three eligible controls from the BCS. A 3:1 ratio was considered to work best with the available data, since to achieve a 4:1 ratio between the controls and cases would require the age matching criterion to be extended to about ± 2 years.

3.3 Ethics

The study was approved by the Regional Committee for Medical Research Ethics in Norway (REK-West 2010/3301). For children prenatally exposed to substances, informed written consent was obtained from all participating caregivers, including the biological parents for children living in their biological home or, alternatively, the foster parents for children living in foster care. For children in foster care, the social welfare office legally responsible for the participating child also gave written content. In addition to the caregivers and social welfare office, children above 12 years of age also gave their independent consent to participate in the study. For the reference group, the caregivers gave informed written consent.

3.4 Measures and assessment

3.4.1 Withdrawal symptoms and neonatal abstinence syndrome

Children's symptoms compatible with withdrawal were recorded, and the abstinence symptoms were scored using a modified version of the Finnegan abstinence score (38). If a child had a Finnegan abstinence score of 8 or above, they were classified as having NAS.

3.4.2 Care situation

Based on medical records and the questionnaires completed by the children's respective caregivers, the following data were obtained:

(a) Current care status—biological or adopted family, or foster care (including foster homes and foster care institutions);

(b) For children living outside their biological home: age at their first placement and the total number of placements.

With regard to foster care, in the Norwegian foster care system, a temporary foster home is normally provided until a permanent home is found. More than two foster care placements can be related to disruptions in foster homes and unintentional placements between foster care situations (99).

If a child had moved out of their biological home before 1 year of age, placement outside the biological home was categorized as early placement.

3.4.3 Supportive measures and reinforced foster care

Supportive measures

In addition to the caregiving status, information on other supportive measures was also obtained. "School support" was defined as services from the Educational Psychological Service (EPS), as well as other academic support. "Social support" was defined as weekly counselling and support given by a social worker or paid personal support contact for recreational activities. "Additional home" (i.e. outside the foster home) at leisure time was recorded, e.g. weekend/visiting homes, in addition to the foster home. A combined variable "Any support" was also assessed, based on all the measures mentioned above, comprising at least one or more supportive measures, including reinforced foster home.

Reinforced foster care

Data on placement into reinforced foster homes or institutions were collected. In a reinforced foster home, one foster parent is compensated financially for caregiving in the home during daytime. For further reinforcement, children can be placed in a child welfare institution. Only two children were placed in an institution, and they were therefore categorized as being placed in a reinforced foster home for the purpose of the study analyses.

3.4.4 Cognitive functioning

Cognitive functioning in the exposed children was evaluated using either the WPPSI (95) or the WISC-R (96).

3.4.5 Mental health

Mental health assessment was based on three different standardized questionnaires: SDQ, SNAP-IV and ASSQ. All questionnaires contained items scored on a 3-point scale (i.e. 0, 1, 2). The questionnaires were completed by the child's current caregiver.

3.4.5.1 The Strengths and Difficulties Questionnaire (SDQ)

The SDQ is a general behavioural screening questionnaire for 4- to 17-year-olds and consists of 25 items describing positive and negative attributes of the children (100-102). In this study, the SDQ was completed by the children's caregivers. The SDQ is widely used in groups at-risk, such as children with chronic illness, those with intellectual disabilities and those prenatally exposed to substances (18, 103-105). The use of the SDQ as a screening instrument for mental health disorders in foster children has been previously validated (106).

The SDQ is divided into five subscales: (1) emotional problems; (2) hyperactivity problems; (3) conduct problems; (4) peer problems; and (5) prosocial behaviour. For subscales other than the prosocial behaviour subscale, a higher score represents increased

mental health problems (102). In this study, the emotional problems subscale, including questions on anxiety and depressive symptoms, was used to assess emotional symptoms. Furthermore, a total difficulties score (TDS) was computed by adding the first four subscale scores. Each item was scored on a 3-point scale, i.e. "not true", "somewhat true" and "certainly true", with total subscale scores ranging from 0 to 10 and TDS from 0 to 40 (102).

The impact supplement of the SDQ is activated by a positive response to one screening item, indicating difficulties in areas of emotions, concentration, behaviour or social skills. The impact supplement of the SDQ examines overall distress and social impairment at home, with friends, at school and in leisure activities. Each item is rated on a 4-point scale, rating difficulties as "not at all", "only a little", "quite a lot" and "a great deal". This is summed to a total impact score, with a maximum score of 10. If the child is not considered to have any impairments, the impact score is 0 (102). The SDQ has been demonstrated to have good psychometric properties (101, 105).

3.4.5.2 The Swanson, Nolan and Pelham Questionnaire, revision IV (SNAP-IV)

The SNAP-IV is a screening tool for ADHD (107). It contains nine items on inattention and nine items on hyperactivity/impulsivity, which correspond to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition (DSM-IV) criteria for ADHD (20). The reliability of SNAP-IV has been reported as good (108). Scores range from 0 to 18 for each scale. The SNAP Combined is calculated after summing the two scales, with the combined scores ranging from 0 to 36.

3.4.5.3 The Autism Spectrum Screening Questionnaire (ASSQ)

The ASSQ consists of 27 items reflecting the symptoms of ASD, i.e. social interaction, communication, restricted and repetitive behaviour, motor clumsiness and tics (109-111). One of the items (item 9) was inadvertently omitted for the reference group, and therefore

not included (110). Scores range from 0 to 52. In cases where the questionnaire was completed by parents, it was recommended to proceed with a diagnostic workup of ASD if the total ASSQ score was 17 or higher (111). Based on this, the ASSQ scores were dichotomized into high (≥17) and low scores (<17).

For 21 of the children in the exposed group, one or more answers on the ASSQ were missing. For missing data, the variables were replaced with imputed data based on the expectation–maximization method, and the ASSQ sum scores computed.

3.5 Statistical analysis

The questionnaire for obtaining data on the children's care situation and supportive measures was developed specifically for the study, and standardized assessment tools for mental health (i.e. SDQ, SNAP-IV and ASSQ) were included as part of the questionnaire. All questionnaires were optically read and checked for errors, and questionnaire data were recorded manually.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 22 for Papers I and II, and version 24 for Paper III (112). The statistical significance level was set at $p \leq 0.05$.

Where possible, missing data on the questionnaires were completed or corrected using information from the child's medical records. For missing items on the mental health assessment forms, the variables were replaced with imputed data based on the expectation–maximization method, and sum scores were computed after missing data had been imputed (113). This was only applicable to missing items on the ASSQ (in which case other assessment tools were completed).

For descriptive analyses, frequencies, means and standard deviations (SD) were used to describe the sample. Group differences were analysed using independent *t*-test and chi-square test [*p*-value, odds ratio (OR) and 95% confidence interval (CI)]. Levene's test was used to test homogeneity of variances. If variances were found to be statistically

unequal, the *t*-test not assuming equal variances was used (114). Effect sizes were estimated by Cohen's *d*, and standard interpretation was used (0.20 = small, 0.50 = moderate and 0.80 = large) (115).

3.5.1 Regression analyses

For the work presented in Paper I, binary logistic regression analyses, including covariate variables, were performed to adjust for the age at first placement into foster care.

For Paper II, a stepwise regression analysis for the substance-exposed group was performed, with the SDQ TDS as the dependent variable and gender, age, IQ, drug group and care situation as independent variables. Information about care situation and IQ was not available for the reference group. The Mann–Whitney *U* test was also used to assess the statistical significance when comparing the groups. This test is suitable for small-sized samples and where the distribution is not normal.

For Paper III, it is recommended to proceed with a diagnostic workup of ASD if the total ASSQ score is 17 or higher (111). Based on this, the ASSQ scores were dichotomized into high (≥17) or low (<17) scores, and a cut-off value of ≥17 was used to compare child placement outside the biological home before or after 1 year of age. Due to skewness in outcome variables in the reference group, the maximum likelihood robust (MLR) estimator, together with the program Mplus version 7.4 (116), was used for sensitivity analyses in order to compute corrected standard errors when testing group differences (117, 118). This analysis strategy does not assume equal variances when comparing the groups. When analysing the correlation between SNAP-IV and ASSQ scores, Spearman correlation was used.

In the sample of children prenatally exposed to substances, multiple regression analysis was used to predict the level of outcome variables SNAP Combined, SNAP Inattention and SNAP Hyperactivity/Impulsivity, and ASSQ Total score, Social difficulties, Motor/tics/OCD and Autistic style. Predictors were age, gender, IQ, NAS and

child placement outside the biological home before or after 1 year of age. The predictors for mental health outcome were based on earlier studies of prenatal substance exposure and mental health in children.

3.5.2 Power analyses

Power analyses were not performed prior to the study. All eligible children were invited to participate in the study. It is possible that some results could have been reported incorrectly as insignificant due to the low power of the study.

4. Summary of results

4.1 Paper I: *Care and supportive measures in school-aged children with prenatal substance exposure*

Of the 111 participating children, 50 were categorized in the alcohol-exposed group and 61 in the group of other substances.

The majority of children (86%) were living in foster care, including eight of the nine children born to mothers who participated in OMT; 11% were adopted, and 3% lived with their biological parents. Of the children in foster care, 66% had three or four foster care situations, and 15% had five or more foster care situations. The majority of children in foster care (70%) were placed after 1 year of age, with an increased risk of more than three foster care situations, compared to the group of children placed before 1 year of age (OR 3.7, 95% CI 1.2–11.9; $p = 0.001$).

Of the children in foster care, the vast majority (92%) received one or more supportive measures in their foster home and/or at school. Three out of four children received one or two supportive measures, and one out of four received three supportive measures. The most common supportive measure was school support, received by the majority of children in foster care. Seven children in foster care had no additional supportive measures, of whom five were placed into foster care during their first year of life. More than one in four of the participating children were in reinforced foster care. Substance exposure (alcohol or other substances), gender, number of placements and age at placement outside the biological home did not predict the need for reinforced foster care.

4.2 Paper II: *Mental health in school-aged children prenatally exposed to alcohol and other substances*

Of 105 children exposed to substances, 48 were exposed to alcohol (i.e. had FASD) and 57 were exposed to substances other than alcohol. The majority of the children (86%) lived in foster care or in adopted homes (12%). In the FASD group, 42% of the children were assigned a diagnosis of FAS. The mean IQ score was significantly higher ($p = 0.001$) in the group exposed to substances other than alcohol, compared to the FASD group.

SDQs for all the 105 children were completed by their caregivers, mean scores for all five SDQ subscales, TDS and total impact scores were statistically significantly higher for both the alcohol- and other substances-exposed groups, compared to the reference group. A large effect size was obtained for all subscales and TDS ($d \geq 0.80$), with the greatest difference noted for the hyperactivity subscale ($d = 2.29$).

When comparing the FASD group and the other substances group, no statistically significant differences were found in any of the five SDQ subscale scores, TDS or total impact scores. There were no differences in mean scores for any of the SDQ subscales between the nine children born to mothers participating in OMT and the other 48 children in the group exposed to substances other than alcohol.

Among the children living in foster care, there were no statistically significant differences in the mean TDS between those taken in foster care at birth, those placed before 1 year of age and those placed after 1 year of age (mean TDS 17, 18 and 20, respectively; $p = 0.30$). Only the IQ could explain some of the variances in TDS, among the variables of age, gender, IQ, substance group and care situation (adjusted $R^2 = 0.06$, 95% CI = 16–32; $p = 0.01$).

4.3 Paper III: *Symptoms associated with ADHD and ASD in school-aged children prenatally exposed to substances*

Of the children mainly exposed to substances other than alcohol, 57 children completed the relevant questionnaires. All, except one child, lived in foster care ($n = 54$) or with adopted parents ($n = 2$), and of the children adopted or in foster care ($n = 56$), more than one in three were placed outside their biological home before the age of 1 year. Symptoms compatible with neonatal abstinence were reported in 41 of the exposed children, of whom 18 were diagnosed with NAS.

Regarding mental health status, caregivers of children in the exposed group reported significantly more symptoms associated with ADHD in areas of both inattention and hyperactivity/impulsivity. Furthermore, caregivers reported more symptoms associated with ASD, compared to the reference group, using the ASSQ. Of the exposed children, 37% had high scores (≥ 17), compared to 3% in the reference group (OR 17.44, 95% CI 6.1–49.6; $p < 0.05$). There was no significant difference in high ASSQ scores between the exposed group of children taken into foster care before and those after 1 year of age ($p = 0.083$).

Of the available predictors for mental health outcomes in the exposed group, the IQ was a significant predictor for some of the mental health outcomes, and NAS for inattention as part of ADHD. Child placement outside the biological home before or after the age of 1 year did not affect the results.

When exploring a possible correlation between ASSQ Total score and SNAP, a moderate to strong relationship was found between high scores on ASSQ and high scores on SNAP, with the strongest correlation between ASSQ Social difficulties and both SNAP Inattention ($r = 0.702$; $p \leq 0.01$) and SNAP Hyperactivity/impulsivity ($r = 0.714$; $p \leq 0.01$).

5. Discussion

Results from this study conducted in a hospital-based population of school-aged children prenatally exposed to alcohol and other substances, suggest that exposed children are at an increased risk of mental health problems in different domains. These children have an increased risk of placement either in adopted homes or into foster care and, in addition to their out-of-biological home placement, are often provided with supportive measures, including school and social support.

5.1 Generalizability

In this hospital-based study, the study population included children referred to the hospital with neonatal abstinence symptoms, or developmental impairments later in childhood, and a concomitant past medical history of prenatal substance exposure. It is expected that the hospital-based study design and selection of study participants would most likely have a great impact on the generalizability of the study findings. Generalizability is related to the validity of findings from a particular study in a setting, and for a population different from the setting and population in that study (119). It is possible that the children represented in this present study were the most severely affected in the group of exposed children, and that any exposed children with normal functioning were not represented. Moreover, children with severe developmental impairments referred to the hospital could have had unknown prenatal substance exposure and not have been included in the study. In general, recruitment of representative population groups for studies of children prenatally exposed to substances can prove challenging, due to the stigmatizing and illegal nature of substance use, which makes it difficult to identify the whole group of exposed children in a population.

Therefore caution should be taken when interpreting the present findings, the concerns about the generalizability of the results are presented before the actual

discussion of the results on mental health problems and care situation below. The more general strengths and limitations are described in more detail in Section 5.3.

5.2 Prenatal substance exposure

Information about substance exposure was based solely on medical records and history, with no toxicology testing of the mothers during pregnancy or of the children after birth. This meant that the exact nature of substance exposure during pregnancy was difficult to establish. Moreover, it was not possible to ascertain that mothers to children categorized in the group of prenatal exposure to substances other than alcohol had not consumed any alcohol, in addition to other substances, during their pregnancy, and vice versa. Data collection relied on obstetric and paediatric records, as well as reports from mothers. In cases showing confirmation or evidence of a greater number of single episodes of alcohol exposure, the children were categorized in the FASD group. Because it was not possible to verify the accuracy of the types of substances to which the fetus was exposed from the information reported by the mothers, there is a potential risk of underestimating the actual prenatal exposure to specific substances (120, 121).

Alcohol is a well-known teratogenic substance. Earlier studies found an increased risk of mental health problems, including ADHD, specific learning disabilities, anxiety, mood disorders and ASD in children prenatally exposed to alcohol (3, 17, 33, 35, 54) (3, 17, 33, 35, 54), and findings presented in this thesis are in line with previous research (2, 6, 17, 54).

In contrast, previous studies have produced conflicting results on the effects of prenatal exposure to substances other than alcohol on mental health (6, 12, 122). However, an increased risk of ADHD among children prenatally exposed to substances has been reported, and some studies have found an increased risk of mental health problems when evaluating emotional and behavioural problems (2, 6, 12, 18), in agreement with findings presented in this thesis. In addition, the present study found an

increased risk of problems related to ADHD in areas of both inattention and hyperactivity/impulsivity, as well as social skills challenges, in the substance-exposed group. A recent study also found an increased risk of ASD in children with FASD (54). The results of the present study showed an increased risk of symptoms associated with ASD, especially with respect to social difficulties, in the group of children prenatally exposed to substances other than alcohol.

Both ADHD and ASD are complex disorders with neurobiological components likely to play an essential role in the underlying mechanisms (123). It is possible that prenatal exposure to substances other than alcohol leads to neurobiological vulnerability, thus increasing the risk of neurodevelopmental disorders. However, genetic predisposition has also been proposed as a risk factor for ADHD, which could explain the increased number of ADHD symptoms in children with prenatal exposure to substances other than alcohol (63). It has been reported that adults with a substance use disorder have a higher rate of ADHD symptoms, and ADHD itself is found to be an independent risk factor for substance abuse (62). Thus, prenatally substance-exposed children may be genetically predisposed to ADHD, which could possibly explain the increased level of ADHD symptoms in this group of children. In the present study, information about parents' mental health was not available.

5.3 Mental health problems

Symptoms of mental health problems presented in the exposed group of children compared to a reference group, were overall increased and not restricted to one category of mental health problems, suggesting an increased risk of developing problems in several domains or areas.

Mental health was assessed using the standardized questionnaires SDQ, SNAP-IV and ASSQ, thus increasing the robustness of data obtained, as well as study reproducibility. However, the mental health assessment tools used here (i.e. SDQ, SNAP-

IV and ASSQ) are not diagnostic tools, but rather screening tools of mental health and diagnostic assessment was not performed.

Furthermore, the increased risk of symptoms associated with ASD in children exposed to substances other than alcohol does not necessarily reflect a high prevalence rate of the diagnosis. ASD is characterized by symptoms of social impairment. However, other mental health disorders, such as RAD, have overlapping symptoms (20, 48). The present study used the ASSQ as a screening tool for symptoms associated with ASD and did not include a diagnostic assessment in the study population. Thus, the high ASSQ symptom scores could be related to ASD, RAD or other disorders or conditions associated with one or more of the risk factors in the exposed group. Therefore, diagnostic assessment is necessary to distinguish between these disorders and confirm a potential diagnosis.

5.4 Care situation

The fact that RAD could be associated with increased ASSQ scores is an important point to consider, since RAD could be related to foster care placement (55, 124) and a high proportion of the children included in the present study lived in foster care. Earlier studies found an increased risk of RAD among children in foster care (55, 124). RAD can result from inadequate caregiving and develop when a child's caregiving environment fails to address the child's care needs (20, 48, 65). Thus, one can expect that a high rate of foster care placements is associated with inadequate caregiving in the biological home, or several placements in itself to be associated with RAD. In this study, no association was found between early placement into foster care (i.e. before 1 year of age) and symptoms of ASD.

The majority of children included were placed outside their biological home and, in addition, were provided with supportive measures. The high rate of placement into foster care of children prenatally exposed to substances may be associated with factors related to the biological parents' decreased caregiving abilities or to the child's possible

increased care and support needs, or more likely to an interplay between both factors (see Figure 4).
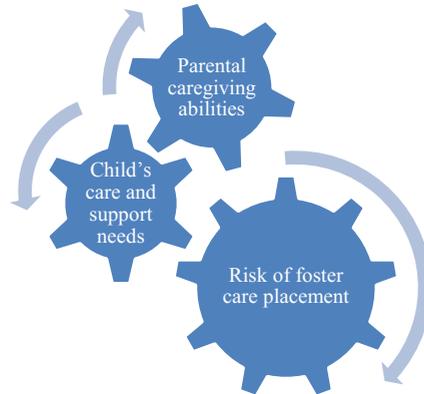
Figure 4. The high rate of foster care placement may be associated with decreased parental caregiving abilities or the child's possible increased care needs, or an interplay between these factors.

Parental substance use is associated with multiple risk factors which can affect adequate child care (84). Inadequate caregiving in the biological home may lead to foster care placement of the child. Thus, a high rate of foster care placement could be independent of factors related to a child's increased care needs. However, in addition, children may have increased care needs due to neurodevelopmental impairments, as well as withdrawal symptoms during the postnatal period. Neonates suffering from NAS have increased demands for appropriate support due to dysregulation, which can prove challenging to parents, irrespective of the parents' caregiving abilities. Moreover, an increased risk of cognitive impairments and mental health problems may also affect the care demands during childhood and adolescence to be above what would be expected according to age and developmental stage. Thus, this challenging scenario involving

increased care demands and decreased parental caregiving abilities can create a potential mismatch.

5.5 Strengths and limitations

5.5.1 Strengths

An important strength of this study is the relatively large population of school-aged children prenatally exposed to substances. The participation rate of eligible children was high, with full completion of the comprehensive questionnaires in the vast majority of cases.

Another strength is the use of standardized and validated screening tools to assess mental health, thus ensuring study reproducibility. The reference group included was taken from the large population of the Bergen Child Study and comprised children mainly from the same geographical area who were gender- and age-matched, thus enhancing the robustness of result comparability between the exposed and reference groups. Three controls were added for each case to improve the quality of the analyses (98). As age was considered to be an important matching factor in the present study, a relatively narrow matching criterion of ± 0.9 years was used, which allowed three eligible controls (3:1 ratio). To achieve a 4:1 ratio between the controls and cases, the age-matching criterion would have had to be extended considerably to about ± 2 years.

Moreover, the present study evaluated the long-term consequences of prenatal substance exposure on mental health and care situation in children aged from 6 to 14 years. Most previous research which was conducted in children at preschool age, including studies examining the effects of NAS in the postnatal period (2, 6). Less is known, however, regarding the long-term consequences of prenatal substance exposure in older age-groups, which warrants further studies focusing on this area (2, 18, 41, 60).

5.5.2 Limitations

Selection bias.

The hospital-based design of this study meant that the study population likely included predominantly the most severely affected children, which thus represented only the "tip of the iceberg" of the population of children prenatally exposed to substances. Therefore, this selection bias has a major impact on the generalizability of the study findings (see also Section 5.3.2.2 below).

Information bias

Errors may be introduced both from the observer and the participants of the study. The following biases are relevant to this study.

Observer bias: Children referred to the Department of Pediatrics all underwent clinical examination and psychological testing. However, the paediatricians and psychologists performing the examination and testing were not blinded to the children's medical and history background. Hence, results from the clinical evaluation and neuropsychological testing could be biased.

Recall bias: The present study was retrospective, and therefore subject to a risk of recall bias. In most cases, questionnaires were completed by foster parents, who, in some cases, provided second-hand information.

Confounding factors

The confounding factors presented below could explain the correlation or interaction between the outcome measures assessed in this study.

Nicotine exposure: Nicotine exposure is a known risk factor affecting a child's neurodevelopment (2, 6). However, data on maternal use of tobacco and nicotine during pregnancy were not available in this study.

Birthweight and gestational age: Information about birthweight and gestational age (GA) was missing for 34% (n= 111) of the children in the exposed group. Therefore, these two parameters were not included as matching criteria for the reference group. Prematurity has been associated with an increased risk of mental health problems in childhood and adolescence (125). Of note, both low birthweight and prematurity are associated with, and could be a consequence of, prenatal substance exposure, in which case low birthweight and prematurity do not act as confounders (126). Other risk factors associated with prenatal substance exposure, such as poor maternal nutrition and increased risk of infection, may also influence a child's birthweight and prematurity status (127).

Socio-economic status: In the present study, no valid data on the SES were available. In some cases, foster parents provided information about their own SES, whereas in other cases, foster parents reported on what they knew about the SES of the biological parents. Therefore, it was not possible to control for the SES as a potential confounder in this study even though low SES has been associated with an increased risk of mental health problems (80).

Parental mental health: The mental health of biological parents represents a potential confounding factor, given the link between genetic predisposition and several mental health disorders. However, information about parental mental health was not available and therefore not controlled for in this study.

5.6 Conclusions

Children prenatally exposed to alcohol and other substances were found to be at an increased risk of mental health problems in multiple domains, impacting their daily life functioning, when compared to a reference group. This increased risk may be related to prenatal substance exposure, or to other known and unknown risk factors, or most likely to an interaction between several factors. Prenatally substance-exposed children also had a high risk of foster care placement and were often provided with supportive measures, which could be a result of health problems influencing their needs for care and supportive measures. While this study was not able to demonstrate a direct causal relationship between prenatal drug exposure and the risk of mental health problems and the increased use of supportive measures, nevertheless, it highlights the key issues affecting children prenatally exposed to drugs—notably their increased risk of mental health problems, their propensity for out-of-home placement and the high rate of these children receiving supportive measures. Moreover, in this study, the children's specific needs were not evaluated, and so the provision of supportive measures may not necessarily reflect the children's actual needs for care and support. Further research is therefore needed in this area. Overall, this study would help provide a clear focus on the setting up and provision of optimized and appropriate health and care plans for this group of children, with minimal intervention delay.

5.7 Clinical implications

Children prenatally exposed to substances have an increased risk of mental health problems, which may impact on their daily life functioning. It is recommended that mental health assessment of children prenatally exposed to substances is conducted when this group of children are referred to health-care providers. In addition, caregivers should

be aware of the range of mental health symptoms associated with prenatal substance exposure, and supportive measures should be put in place accordingly.

5.8 Future challenges and perspectives

Due to stigmatization and the illegal nature of substance use during pregnancy, it is challenging to obtain an accurate picture of the extent of the problem of prenatal substance exposure. Therefore, further studies on a wider and more general population, i.e. not restricted to hospital-based settings, are warranted. Establishing a national register of all children with known prenatal substance exposure, including sampling of biomarkers of prenatal substance exposure, could contribute to improving the quality of data available for further studies. However, a high proportion of cases of prenatal substance exposure are likely to remain undetected.

Routine monitoring for substance use in pregnant women is essential, and can be carried out within the current guidelines for antenatal care. These women are entitled to increased support and follow-up during pregnancy. In cases of known or suspected maternal substance use and dependency, there could be established routine urine and/or blood sampling from pregnant women and the newborn children.

Finally, also of crucial importance is careful evaluation of the care and support needs of children prenatally exposed to substances, as well as the care and supportive measures that have been initiated in response to these needs. The ultimate aim is for these children's needs to be adequately and appropriately met by optimized care and supportive measures in place.

6. Errata

Paper II, page 3, last paragraph under the subheading "Participant categorization according to prenatal substance exposure": "Also, if a child met the criteria for FASD" – corrected to "Also, if a child met the criteria for FAS".

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I

Mental Health in School-Aged Children Prenatally Exposed to Alcohol and Other Substances

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ABSTRACT: Prenatal exposure to substances can possibly influence a child's neurodevelopment and may impact on subsequent mental health. We investigated the mental health status of school-aged children referred to a pediatric hospital with a history of prenatal exposure to alcohol or other substances. Mental health was assessed using the Strengths and Difficulties Questionnaire and compared with a reference group. A total of 105 of 128 (82%) eligible children prenatally exposed to substances participated in the study, with 48 children exposed to alcohol and 57 to other substances. Strengths and Difficulties Questionnaire subscale mean scores, total difficulties scores, and total impact scores were statistically significantly higher in the group of exposed children, compared with the reference group. In this hospital-based population of school-aged children prenatally exposed to alcohol or other substances, the exposed group had an increased risk of mental health problems, compared with the reference group.

KEYWORDS: Mental health, development, alcohol exposure, drug effects, child development

Introduction

Background

Alcohol, opiates, and most illicit drugs cross the placenta and can affect the fetus through direct effects on fetal development and indirectly through pharmacological effects on the pregnant mother.[1–5] Prenatal substance exposure may result in neurodevelopmental impairments through adverse effects on the fetal brain and can possible impact on subsequent mental health outcomes.[2–4,6,7] Substance exposure in pregnancy represents a public health problem.[1] Furthermore, it is difficult to estimate the prevalence due to inconsistent reporting from pregnant women and the illegal nature of illicit drug use.[1,8,9]

Prenatal exposure to alcohol

Alcohol is a well-known teratogenic substance, and alcohol exposure during pregnancy may result in fetal alcohol spectrum disorders (FASD).[1,10,11] Fetal alcohol spectrum disorder comprises a spectrum of conditions presenting with mild to severe neurodevelopmental consequences such as cognitive impairment and an increased risk of specific learning disabilities, attention-deficit/hyperactivity disorder (ADHD), and anxiety and mood disorders.[1,10–12] Other important sequelae associated with prenatal alcohol exposure include an increased risk of miscarriage, preterm birth, prenatal and postnatal growth restriction, and sudden death

infant syndrome, as well as effects on various organ systems such as the cardiovascular, musculoskeletal, renal, ocular, and auditory systems.[1,12] The impact of maternal alcohol use on fetal development depends on a variety of factors, including the timing and level of alcohol exposure and genetic background.[13] Recent research exploring the epigenetic mechanisms involved in fetal exposure to alcohol suggests a link between the genetic background, environmental factors, and neurodevelopmental outcomes.[13]

Prenatal exposure to substances other than alcohol

Prenatal substance exposure also includes exposure to opioids, amphetamine, methamphetamine, cocaine, and cannabis and the illegal use of benzodiazepines. Exposure to these substances is associated with low birthweight, preterm births, and, particularly in the case of opioids, neonatal abstinence syndrome (NAS).[1,14,15] Systematic reviews of children exposed to substances other than alcohol have reported an increased risk of cognitive and behavioral impairments later in preschool age.[3,6] Furthermore, some longitudinal studies found that cognitive difficulties in preschool-aged children persisted into school and adolescence age, and a recent study reported effects in children of exposure to substances other

than alcohol on cognition increasing over time, compared with nonexposure.[6,7,16,17] Less is known about the mental health outcomes of prenatal exposure to other substances in school-aged children.[3]

Genetics and environmental factors affecting mental health

Children prenatally exposed to substances are influenced by several risk factors, including biological, genetic, environmental, and socioeconomic factors that are associated with mental health outcomes.[6,18–21] Parental substance use increases the risk of poverty, family stress, low level of parental education, poor prenatal care, and family instability, as well as being a risk factor for placement of children into foster care.[22,23] Exposure to inadequate caregiving conditions earlier in life may affect the mental health later in life, and optimizing care conditions is likely to have a positive effect on mental health outcomes.[23,24] For youth placed in foster care in western countries, the prevalence of mental disorders has been estimated to be higher than that for the general population.[23,25]

Aim of the study

The aim of this hospital-based follow-up study was to assess mental health in school-aged children prenatally exposed to alcohol and other substances, in comparison with a reference group as control. We hypothesized that prenatal exposure to substances would result in higher mean scores on the Strength and Difficulties Questionnaire (SDQ) in exposed children, compared with controls. Furthermore, given the known teratogenic effects of alcohol, we expected higher mean SDQ scores in children mainly exposed to alcohol, compared with those mainly exposed to other substances.

Methods

Participants

The study included a hospital-based population of children referred to the pediatric department at Haukeland University Hospital in Bergen, Norway, between January 1997 and December 2012. Referral criteria included the presence of developmental impairments and a concomitant past medical history of prenatal alcohol or other substance exposure. Referrals to the pediatric department were from healthcare providers, social workers, and physicians in primary community care units and pediatric and child psychiatric units.

A follow-up study on mental health status was conducted at school age. At this point, in the study, 128 children aged between 6 and 14 years were invited to participate; of whom, 111 gave informed written consent (87%). Of the 111 children, 105 (95%) had their caregivers complete the SDQ questionnaire.

The reference group

The reference group consisted of children participating in the Bergen Child Study (BCS), which is a longitudinal population-based study. There were no exclusion criteria,[26] and all children attending grades 2 to 4 at 79 schools in a geographically delineated area in the academic years of 2002 and 2003 were invited to participate in the study (n = 9430). Parent SDQ questionnaires were completed for about two-thirds of the participating children (n = 6297).[26] Of the participating children in BCS, about 2 out of 3 lived in a family categorized as having good or very good family economy, and about 50% of the mothers and fathers had higher education.[27] More details about the reference group are presented in the papers by Heiervang et al,[26] Boe et al,[27] and Stormark et al.[28] In this study, participants from the first 2 waves were included. The first wave of the BCS, conducted in autumn 2002, comprised a target population of 9430 primary school children aged 7 to 9 years, and informed consent to participate was received from 7007 (74%) parents prior to study inclusion. The second wave was conducted 4 years later during spring 2006, comprising 5683 children aged 11 to 13 years (60% of the original target population). For every participating child in the hospital-based group of children prenatally exposed to substances, 3 children from the BCS population, who were sex and age matched (±0.9 years), were randomly selected into the reference group. Three controls were included for each case to improve the robustness of the analyses.[29] As we considered age to be an important matching factor in this study, we used a relatively narrow matching criterion of ±0.9 years, which hence allows 3 eligible controls from the BCS. We considered that a 3:1 ratio worked best with the available data, as to achieve a 4:1 ratio between the controls and cases would require the age matching criterion to be extended to about ±2 years.

Ethics

The study was approved by the Regional Committee for Medical Research Ethics in Norway. For children prenatally exposed to substances, informed written consent was obtained from all participating caregivers: biological parents for children living in their biological home and foster parents for children living in foster care. For children in foster care, the social welfare office legally responsible for the participating child also gave written consent. Children 12 years and older, gave their independent consent to participate in the study. For the reference group, children's caregivers gave informed written consent.

Care situation

The following data were collected from medical records and questionnaires completed by the caregivers: the present care situation and age at time of placement in cases where the child was placed in a foster home before and after 1 year of age.

Participant categorization according to prenatal substance exposure

Children with confirmed prenatal exposure to substances, including alcohol, illicit drugs, illegal use of prescription drugs, and opioids used in opioid management treatment (OMT) programs, were included in the study. History of exposure was confirmed by information obtained from the mothers and obstetric or pediatric records, including data from referring units and medical reports of neonatal withdrawal symptoms after birth. Data were systematically recorded based on the mother's main drug of use during pregnancy, and the children were categorized into 2 groups: (1) prenatal exposure to alcohol (FASD group) and (2) prenatal exposure to other substances. No valid information was available on doses of substance used in pregnancy, including the number of units of alcohol consumed or the exact timing of exposure during pregnancy.

If there was evidence from the data collected that a child had been exposed to both alcohol and other substances, the child was placed in the FASD group if alcohol was the main drug of use by the mother and if there were reported regular, or more often than occasional, episodes of alcohol use during pregnancy. Also, if a child met the criteria for FASD, he or she was automatically placed in the FASD group, which meant that no children in the other substances group met the FASD criteria.

Fetal alcohol spectrum disorders. The FASD group included cases of both fetal alcohol syndrome (FAS) and FASD. The diagnosis of FAS or FASD was given after evaluation of the medical history and clinical examination by a pediatrician with relevant specialized training and neuropsychological testing. Differential diagnoses were considered in all cases, and pediatricians specially trained in the field, including pediatric endocrinologists, were consulted in cases of uncertain diagnosis. Fetal alcohol syndrome was diagnosed if a child with confirmed prenatal alcohol exposure met all of the following Centers for Disease Control and Prevention (CDC) criteria:[10] (1) presence of facial dysmorphic features, (2) growth restriction, and (3) central nervous system (CNS) impairment. Children who did not fulfill all 3 FAS criteria were diagnosed with FASD.

Central nervous system impairment was defined as the presence of learning disabilities (defined as an IQ below 85) or having ADHD. Intellectual level was determined using either the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) test or the Wechsler Intelligence Scale for Children-Revised (WISC-R) test. An IQ below 70 was defined as intellectual disability and an IQ of 70 to 84 as low IQ. Attention-deficit/hyperactivity disorder was diagnosed by a pediatrician and a child psychiatrist according to the International Classification of Diseases, Tenth Revision criteria.

Prenatal exposure to other substances. This group included children exposed to street drugs and polydrug use, as well as those exposed to opioids as part of the national OMT (the latter including 9 children). The most common "other substances" reported in this group were opiates and polydrug use. Children in this group either had a medical history of prenatal drug exposure to one or more drugs or were diagnosed with NAS after birth. None of the children in this group met the criteria for FASD. Although nondocumented (ie, unknown) use of alcohol could not be totally excluded, but the mother's main drug of use included substances other than alcohol. Any involvement of the mother in the national OMT during pregnancy was also recorded.

Mental health

The SDQ is a behavioral screening questionnaire for 4 to 17-year-old children.[30–32]

In this study, the SDQ questionnaire was completed by the children's caregivers. It consists of 25 items describing positive and negative attributes of the children, and it is divided into 5 subscales: (1) emotional problems, (2) hyperactivity problems, (3) conduct problems, (4) peer problems, and (5) prosocial behavior. For subscales other than the prosocial behavior subscale, a higher score represents more mental health problems. A total difficulties score (TDS) was computed by adding the first 4 subscale scores. Each item is scored on a 3-point scale, ie, "not true," "somewhat true," and "certainly true," with total subscale scores ranging from 0 to 10 and TDS from 0 to 40.[30]

The impact supplement of the SDQ is activated by a positive response to one screening item, indicating difficulties in areas of emotions, concentration, behavior, or social skills. The impact supplement of the SDQ examines overall distress and social impairment at home, with friends, at school, and with leisure activities. Each item is rated on a 4-point scale, rating difficulties as "not at all," "only a little," "quite a lot," and "a great deal." This is summed up to a total impact score with a maximum score of 10. If the child is not considered to have a problem, the impact score is scored as 0.[30]

The SDQ is widely used in groups of at-risk children such as children with chronic illness, those with intellectual disabilities, and those prenatally exposed to substances.[7,30,33–35] Its use as a screening instrument for mental health disorders in foster children has been previously validated.[36]

Statistical analyses

First, independent *t* tests were used to compare mean scores on symptom subscales, TDS, and total impact scores between the group of children prenatally exposed to alcohol or other substances and the reference group. Cohen *d* was used to quantify the differences between the groups, and standard interpretation was used (0.20 = small, 0.50 = moderate, and 0.80 = large). Second, the FASD group and the group of children exposed to substances other than alcohol were each compared with the reference group, and third, the FASD group and the group of children exposed to other substances

Table 1. Sample characteristics of a hospital-based population of school-aged children exposed to drugs during pregnancy and of a reference group.

	REFERENCE GROUP (N = 313)	TOTAL SUBSTANCE-EXPOSED GROUP (N = 105)	FASD[a] (N = 48)	SUBSTANCES OTHER THAN ALCOHOL[b] (N = 57)			
Mean age in years (SD)	10.5 (2.0)	10.6 (2.2)	10.8 (2.2)	10.3 (2.2)			
Gender (boys) (%)	188 (60)	63 (60)	27 (56)	36 (63)			
COMPARING SUBGROUPS OF CHILDREN WITH FASD AND CHILDREN EXPOSED TO SUBSTANCES OTHER THAN ALCOHOL					MD	95% CI	*P*
Mean IQ (SD)		88 (21)	80 (20)	94 (20)	13 (MD)	5.1–21	.001
In foster care (%)		90 (86)	36/48 (75)	54/57 (95)	2.0 (OR)	0.04–0.63	.004
In foster care ≤1 year (%)		29/90 (32)	9/36 (25)	20/54 (37)	1.4 (OR)	0.7–2.8	.200

Abbreviations: CI, confidence interval; FASD, fetal alcohol spectrum disorder; MD, mean difference; OR, odds ratio.
[a]Fetal alcohol spectrum disorders.
[b]Opioids, amphetamine, methamphetamine, cocaine, cannabis, and benzodiazepines.

were compared with each other. The characteristics of the 2 groups (ie, FASD group and group exposed to other substances) were analyzed using a χ² test for gender and care situation. Finally, a regression analysis for the substance was performed, with the TDS as the dependent variable and gender, age, IQ, drug group, and care situation as independent variables. Information about care situation and IQ was not available for the reference group. We also used the Mann-Whitney *U* test to assess if this test affected the statistical significance when comparing the groups. This test is suitable for small-sized samples and where the distribution is not normal. IBM SPSS version 22 for Windows was used for all analyses. The significance level was set at $P \leqslant .05$.

Results
Participants

The mean age of substance-exposed children was 10.6 years and comparable with the reference group (Table 1). Of the 105 children exposed to substances, 48 had FASD and 57 were exposed to substances other than alcohol.

Of the 48 children in the FASD group, 20 (42%) met all 3 CDC criteria and were given a diagnosis of FAS. The remaining 28 children in the FASD group had some of the dysmorphic facial features associated with FAS but did not fulfill all the CDC criteria for dysmorphic facial features, although they all met the other CDC criteria for growth restriction and CNS impairment.

Of the 57 children in the group exposed to substances other than alcohol, 41 (72%) had symptoms of NAS, 5 were reported as not having symptoms of NAS, whereas no valid information about the NAS status was available for the remaining 11 children.

Overall, 3 children were living with their biological families, 12 were adopted, and 90 were in foster care. In all, 11 children were placed in foster care at birth, a further 18 within the first

year, and 61 after 1 year of age. There were no significant gender or age differences between the 2 groups. Compared with the FASD group, the mean IQ was significantly higher ($P = .001$) in the group exposed to substances other than alcohol. The mean IQ of the 20 children diagnosed with FAS was 75 (SD: 17.6, 95% CI = 67-83), with a median IQ of 70, whereas the mean IQ for the remaining 28 children in the FASD group was 85 (SD: 20.9, 95% CI = 76-92), with a median IQ of 85. There were no statistically significant differences ($P = .13$) between the groups.

Mental health in the substance-exposed group compared with the reference group

Mean scores for the SDQ subscales, TDS, and total impact scores for the substance-exposed group, compared with the reference group, are presented in Table 2. There were statistically significant differences in all 5 SDQ subscales, TDS, and total impact scores between the group of alcohol-exposed and substance-exposed children and the reference group. A large effect size was obtained for all subscales and TDS ($d \geqslant 0.80$), with the greatest difference noted for the hyperactivity subscale between the group prenatally exposed to substances and the reference group ($d = 2.29$). After accounting for multiple testing and using the Bonferroni correction (critical $P = .05$/number of tests), we found that the group differences remained statistically significant for all tests. Use of the Mann-Whitney *U* test to compare SDQ scores between the groups did not change the statistical significance of the results.

When comparing the FASD group and the group of children exposed to other substances, no statistically significant differences were found in any of the 5 SDQ subscale scores, TDS, or total impact scores (Table 3).

Within the group exposed to other substances, 9 children were born to mothers in the national OMT. There were no differences in mean scores on any of the SDQ subscales between these children and the other 48 children in the group.

Table 2. Mental health problems based on Strengths and Difficulties Questionnaire scores in a hospital-based population of school-aged children prenatally exposed to substances, compared with a reference group.

	TOTAL SUBSTANCE-EXPOSED GROUP[a] (N = 105)	REFERENCE GROUP (N = 313)	MD	95% CI	P	COHEN D[b] (CI)
Emotional problems (SD)	4.0 (2.5)	1.3 (1.7)	−2.7	−3.1 to −2.3	<.01	1.93 (0.92–1.59)
Conduct problems (SD)	3.6 (2.3)	1.0 (1.3)	−2.6	−3.0 to −2.3	<.01	1.61 (1.18–1.76)
Hyperactivity problems (SD)	7.6 (2.3)	2.5 (2.2)	−5.0	−5.5 to −4.5	<.01	2.29 (1.85–2.54)
Peer problems (SD)	3.6 (2.5)	1.1 (1.6)	−2.5	−3.0 to 2.1	<.01	1.34 (0.86–1.52)
Prosocial behavior (SD)	6.4 (2.4)	8.5 (1.5)	2.0	−1.6 to −2.4	<.01	1.19 (1.02–1.65)
Total difficulties (SD)	18.9 (6.7)	5.9 (5.0)	−12.9	−14.2 to −11.7	<.01	2.37 (1.09–2.93)
Impact score[c] (n = 87) (SD)	4.2 (3.0)	0.4 (1.4)	−3.8	−4.3 to −3.4	<.01	1.97 (1.40–2.13)

Abbreviations: CI, confidence interval; FASD, fetal alcohol spectrum disorder; MD, mean difference.
[a]Clinical population of children exposed to alcohol and other substances.
[b]Cohen *d*: 0.20 = small, 0.50 = moderate, 0.80 = large.
[c]n for FASD = 45; n for other substances = 42.

Mental health and care situation in the substance-exposed group

Among the 90 children living in foster care, there were no statistically significant differences in the mean TDS between those taken in foster care at birth, those placed before 1 year of age, and those placed after 1 year of age (mean TDS: 17, 18, and 20, respectively; *P* = .30).

In a regression analysis with the TDS as the dependent variable and referral age, gender, IQ, substance group, and care situation as independent variables, only low IQ was a significant factor explaining a variance of 6% (adjusted R^2 = 0.06; 95% CI = 16-32; *P* = .01).

Discussion

In this hospital-based study of school-aged children prenatally exposed to alcohol and other substances, we found that the exposed children were at increased risk of mental health problems, compared with the reference group. In addition, mental health problems had a more marked impact on daily life functioning in the exposed group, in comparison with the reference group.

In this study, most of the prenatally exposed children had mental health problems affecting their daily life functioning; both the FASD group and the group of children exposed to other substances had high SDQ scores. This indicated an increased risk of mental health problems, compared with the reference group, with no statistically significant differences between the 2 study groups. The increased risk of mental health problems is in agreement with other studies of prenatally exposed children.[4,6,7,20,37]

The greatest mean difference between the exposed group and the reference group was obtained in the hyperactivity SDQ subscale, which is consistent with previous studies that reported high scores of hyperactivity symptoms both in the

FASD group as well as in the group of children exposed to substances other than alcohol.[1,6,37–39] When comparing the exposed group with the reference group, the mean difference in the hyperactivity subscale could only partly explain the mean difference in the TDS between the groups, indicating that children exposed to substances present with a wider range of mental problems. Irner et al[7] who, also using the SDQ, reported a higher proportion of hyperactivity in a group of prenatally exposed children, compared with British norms.

Children may be genetically predisposed to ADHD, and a recent review highlighted that ADHD may develop as a result of a complex process involving both genetic and nongenetic factors.[40] Studies of adults having substance use disorder have found a higher rate of ADHD symptoms, with ADHD itself as an independent risk factor for substance abuse.[41] Other previous studies have also described an association between maternal mental health and behavioral problems in their children.[42,43] However, we were not able to investigate this issue in our study because most of the children were not living with their biological parents.

The increased risk of mental health problems in children prenatally exposed to alcohol and other substances may thus be due to factors other than the direct or indirect effects of alcohol and other substances on the developing brain. This is supported by findings from previous studies showing that factors such as children's socioeconomic status, caregiving environment, and learning disabilities influence mental health outcomes.[18,21,23,27] In this study, we found an association between cognitive impairments and poorer mental health status, in line with previous reports.[18] Furthermore, numerous studies have found that a high proportion of children prenatally exposed to alcohol and other substances were placed in foster homes and that changes in care environment could affect the mental

Table 3. Mental health problems based on SDQ scores in the group of children prenatally exposed to alcohol (FASD[a]) and the group of children prenatally exposed to substances other than alcohol[a], compared with the reference group and with each other.

Mean SDQ scores (SD)	REFERENCE GROUP (N=313)	FASD[a] (N=48)	OTHER SUBSTANCES[b] (N=57)	FASD COMPARED WITH REFERENCE GROUP			CHILDREN EXPOSED TO OTHER SUBSTANCES[a] COMPARED WITH REFERENCE GROUP			FASD GROUP COMPARED WITH GROUP OF CHILDREN EXPOSED TO OTHER SUBSTANCES[a]		
				d	95% CI	P	d	95% CI	P	d	95% CI	P
Emotional problems	1.3 (1.7)	4.5 (2.4)	3.6 (2.5)	1.8	1.1–2.0	<.01	1.3	0.6–1.44	<.01	0.4	−0.3 to 1.0	.07
Conduct problems	1.0 (1.3)	3.4 (2.1)	3.7 (2.4)	1.7	1.1–1.8	<.01	1.8	1.2–1.9	<.01	0.1	−0.7 to 0.5	.50
Hyperactivity problems	2.5 (2.2)	7.8 (2.1)	7.4 (2.5)	2.4	1.8–2.7	<.01	2.2	1.5–2.4	<.01	0.2	−0.4 to 0.8	.30
Peer problems	1.1 (1.7)	4.0 (2.5)	3.3 (2.6)	1.6	0.9–1.8	<.01	1.2	0.5–1.4	<.01	0.3	−0.4 to 1.0	.10
Prosocial behavior	8.5 (1.5)	6.3 (2.4)	6.5 (2.4)	1.3	1.2–2.0	<.01	1.2	1.0–1.8	<.01	0.1	−0.8 to 0.5	.70
Total difficulties	5.9 (5.0)	19.6 (5.8)	18.2 (7.4)	2.7	1.0–3.2	<.01	2.3	0.3–2.8	<.01	0.2	−1.4 to 2.1	.30
Impact score[c] (n=87)	0.4 (1.4)	4.8 (2.9)	3.8 (3.0)	2.7	1.8–2.8	<.01	2.0	1.1–2.2	<.01	0.3	−0.5 to 1.3	.07

Abbreviations: d, Cohen d; CI, confidence interval; FASD, fetal alcohol spectrum disorders; SDQ, Strengths and Difficulties Questionnaire; Cohen d: 0.20=small, 0.50=moderate, 0.80=large.
[a]Fetal alcohol spectrum disorders.
[b]Opioids, amphetamine, methamphetamine, cocaine, cannabis, and benzodiazepines.
[c]n for FASD=45; n for other substances=42.

health status.[44–46] In our study population, an increased risk of mental health problems was found in school-aged children, with no statistically significant differences between children placed in foster care before and those placed after 1 year of age. It has been suggested that prenatally drug-exposed children are biologically vulnerable to the effects of poor caretaking and a poor caregiving environment and that optimizing care conditions may thus improve developmental outcome.[19,47–49]

In this study, there were no differences in mental health outcomes between children prenatally exposed to alcohol and those exposed to substances other than alcohol. This suggests that exposure to other substances may also affect neurodevelopment and mental health, as also suggested by earlier studies.[1,3,4,7,50] In addition, mental health problems impaired the children's daily life functioning, irrespective of the main type of substance exposure and environmental factors, to such an extent that it calls for special focus for this group of children. These findings indicate a need for mental health assessment of children prenatally exposed to alcohol and other substances to provide early intervention if necessary.

Our study results should be interpreted with caution due to some limitations. One limitation was our inability to verify the accuracy of the types of substances used and to which the fetus was exposed, as reported by the children's mothers. This underlines the potential risk of underestimating the actual prenatal exposure to specific substances. Previous studies have reported many mothers in OMT with an illicit polydrug use while on the opioid maintenance program, highlighting the complexity of accurately measuring actual drug exposure.[51,52] In this study, it was not possible to ascertain that mothers to children prenatally exposed to other substances had not consumed any alcohol, in addition to other substances, during their pregnancy. Thus, we relied on obstetric and pediatric records, as well as reports from mothers, and in cases showing any confirmation or evidence of a greater number of single episodes of alcohol exposure, the children were categorized in the FASD group. None of the children in the group of prenatal exposure to other substances met the criteria for FASD. Our initial hypothesis was that given the known teratogenic effects of alcohol, alcohol-exposed children had a higher risk of mental health problems, compared with children exposed to substances other than alcohol. However, we found this was not the case in this study and suggest that children with a positive medical record of prenatal substance exposure have an increased risk of mental health problems, irrespective of the mother's main substance of use.

Another limitation is that although nicotine exposure is also a known risk factor affecting a child's neurodevelopment,[1,6] data on maternal use of tobacco and nicotine were not available in our study. A further limitation is that the study has a hospital-based study design, which likely resulted in selection bias of participants meaning that our hospital-based study population represented mainly the most severely affected

children. This has a major impact on the generalizability of our study findings, and hence, the results should be interpreted with caution. Therefore, further studies on a wider and more general population, ie, not restricted to hospital-based settings, are warranted.

It is possible that the statistical models presented in this study could raise some methodological concerns using of IQ scores as a variable when exploring neurodevelopmental outcomes.[53] For our purpose, we found it appropriate to include the IQ scores when comparing the subgroups of exposed children because the scores are a measure of global cognitive function according to the diagnostic criteria of FASD.[10]

We consider the SDQ suitable for our study to identify the risk of mental health problems in prenatally exposed children, given that most of these children were taken into foster care. Indeed, a study examining the properties of the SDQ in children placed in foster care in Norway supports the use of the SDQ when screening children in foster care for mental health problems, compared with the diagnostic interview of Developmental and Well-Being Assessment.[36]

Conclusions

In this study of a hospital-based population of school-aged children prenatally exposed to alcohol or other substances, we found that these children were at increased risk of mental health problems affecting their daily life functioning, with no difference between whether the mother's main drug of use during pregnancy was alcohol or other substances.

Clinical implications

Given the increased risk of mental health problems, we recommend the performance of mental health assessment for this group of children when referring to healthcare providers. We believe this approach to be important in establishing an optimized healthcare plan, with minimal intervention delay, for this group of children, and more research to evaluate the treatment measures on mental health outcomes in this group is needed.

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Author Contributions

LBS, IBE, MH, and SAN conceived and designed the experiments and contributed to the writing of the manuscript. LBS, IBE, and MR analyzed the data. LBS and MR wrote the first draft of the manuscript. LBS, IBE, MH, MR, and SAN agreed with manuscript results and conclusions. LBS, IBE, and MH jointly developed the structure and arguments for the paper. MH, IBE, and SAN made critical revisions and approved the final version. All authors reviewed and approved the final manuscript.

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III

Symptoms Associated With Attention Deficit/Hyperactivity Disorder and Autism Spectrum Disorders in School-Aged Children Prenatally Exposed to Substances

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ABSTRACT: Prenatal exposure to substances may influence a child's neurodevelopment and impact on subsequent mental health. In a hospital-based population of school-aged children prenatally exposed to opiates and a number of illicit substances (n = 57), we evaluated mental health symptoms associated with attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorders (ASD) using the Swanson, Nolan, and Pelham Questionnaire, revision IV (SNAP-IV) and the Autism Spectrum Screening Questionnaire (ASSQ) and compared the scores to a reference group which comprised children from the population-based Bergen Child Study (n = 171). Prenatally exposed children had significantly higher SNAP-IV scores associated with ADHD symptoms in both areas of inattention and hyperactivity/impulsivity and also reported a higher ASSQ score related to an increased number of symptoms associated with ASD, compared with the reference group. Of tested predictors of mental health outcomes in the exposed group, the intelligence quotient was a strong predictor of most mental health outcomes, and neonatal abstinence syndrome was a predictor of inattention. In conclusion, prenatally exposed children had more mental health symptoms associated with ADHD and ASD, compared with the reference group.

KEYWORDS: Mental health, development, drug effects, child development, prenatal substance exposure

Introduction

Prenatal exposure to opiates and illicit drugs may influence neurodevelopment in children,[1] including mental health.[2–6] Earlier studies of prenatal substance exposure have reported neurodevelopmental impairments in school-aged children and adolescents.[7–11] However, it may be difficult to distinguish between long-term outcomes of prenatal substance exposure and outcomes of other influencing factors on a child's development.[3,12,13] Previous research suggested that in addition to prenatal substance exposure, genetic and epigenetic factors,[14] gender,[15,16] cognitive functioning,[17,18] and environmental conditions, including the quality of caregiving environment in early childhood,[10,11,19–23] are all associated with mental health outcomes in children and adolescents. Parental substance abuse is associated with an increased risk for foster care, heightening the risk for placement in foster care for the group of prenatal substance-exposed children.[24,25] Furthermore, it has been suggested that optimization of caregiving environments, including placement in foster care, may improve developmental outcomes in children prenatally exposed to substances.[9,11,20] Regardless of the different factors affecting children's neurodevelopment, it is important to examine the mental health status and describe potential challenges for the group of prenatally substance-exposed children.[26]

It is difficult to obtain a true estimate of the prevalence of prenatal substance exposure in children, due to stigmatization and the illegal nature of illicit drug use.[2,27] However, it is clear that the incidence has increased over the past decade in the United States and Western European countries, with an increasing number of neonates diagnosed with withdrawal symptoms.[28] Children prenatally exposed to substances, in particular opiates, are at risk for withdrawal symptoms and neonatal abstinence syndrome (NAS).[28,29] Neonatal abstinence syndrome is a complex disorder affecting various organs, and clinical manifestations range from mild, such as irritability and mild tremors, to severe such as seizures, excessive weight loss, and fever.[28,29] Neonatal abstinence syndrome occurs in 55% to 94% of children prenatally exposed to

Table 1. Characteristics of a hospital-based population of school-aged children prenatally exposed to substances, compared with a reference group.

	EXPOSED GROUP (N = 57)	REFERENCE GROUP (N = 171)
Mean age in years (SD)	10.4 (2.2)	10.3 (2.0)
Gender (boys), N (%)	37 (65)	111 (65)
Mean IQ (SD)	93.5 (20.4)	
Neonatal abstinence symptoms, N (%)	41 (72)	
NAS, N (%)	18/41 (44)	
Out of biological home at age ≤1 yearª, N (%)	22 (39)	

Abbreviations: IQ, intelligence quotient; NAS, neonatal abstinence syndrome; SD, standard deviation.
ªAdopted or in foster care (n = 56) at age ≤1 year.

opioids.[28–30] A follow-up study of children with NAS also found an increased risk for rehospitalization due to maltreatment, trauma, mental health problems, and behavioral disorders when compared with controls.[5]

Overall, substance-exposed children seem to be vulnerable, having several risk factors for developing mental health problems. Interestingly, some studies have suggested that cumulative risk factors, including prenatal substance exposure and the caregiving environment, may exert a greater impact on development than prenatal substance exposure itself.[31,32]

A recent review of alcohol-exposed children found the rate of attention deficit/hyperactivity disorder (ADHD) to be 15 times higher, and autism spectrum disorders (ASD) twice higher, compared with the general population.[33] Moreover, it is well established that children prenatally exposed to substances other than alcohol have an increased risk for hyperactivity.[2,3,8] A recent study, using the Strengths and Difficulties Questionnaire (SDQ), reported that children exposed to alcohol and other substances had a higher risk for mental health problems, compared with controls, including hyperactivity problems as well as other domains of mental health problems.[26] Based on the above, it is of interest to examine in more details specific mental health outcomes in children exposed to substances during pregnancy.

The aims of this study are as follows: (1) to evaluate symptoms of ADHD and ASD in children prenatally exposed to substances other than alcohol, compared with a reference group and (2) to determine relevant predictors of mental health outcomes in substance-exposed children. We hypothesized that children prenatally exposed to substances would display a higher number of symptoms of ADHD and ASD, compared with the reference group.

Methods

Study participants

This study included children aged 6 to 14 years, prenatally exposed to opiates and a number of illicit drugs, who were referred to the Pediatric Department at Haukeland University Hospital in Bergen, Norway, from January 1997 to December 2012. The study population is hospital-based, including children referred to the pediatric department at the hospital, and referral criteria included symptoms of developmental impairment in the presence of a medical history of prenatal exposure to drugs. Some of the children were hospitalized after birth due to abstinence symptoms; others were referred later in childhood when suspecting developmental impairments.

Referrals were by health care providers, social workers, and physicians in primary health care, as well as in pediatric units and child psychiatric units. Of a total number of 128 children referred, informed written consent was provided for 87% (n = 111). Children mainly exposed to alcohol (n = 50) were excluded from the study. Of 61 children exposed to substances other than alcohol, 57 (93%) completed relevant questionnaires assessing the mental health status and care situation (Table 1). The questionnaires were distributed when the child was included in the study, earliest at 6 years of age. The mean age of the child at completion of the questionnaires is given in Table 1, and the current caretakers were the informants.

The reference group

This group consisted of children participating in the longitudinal population-based Bergen Child Study (BCS). All children attending grades 2 to 4 at 79 schools in a geographically restricted area during the academic years of 2002/2003 were invited to participate in the study (N = 9430); there were no exclusion criteria.[34] Parent questionnaires were completed for about two-thirds of the participating children (N = 6297).[34] Of the participating children in the BCS, about 2 out of 3 lived in a family categorized as with good or very good family economy, and about 50% of the mothers and fathers had higher education.[35] More details about the reference group are presented in the papers by Heiervang et al,[34] Bøe et al,[35] and Stormark et al.[36] This study included participants from the first two waves of the BCS. The first wave, conducted in autumn 2002, was composed of a target population of 9430 primary schoolchildren aged 7 to 9 years, and informed consent to

participate was obtained from 7007 (74%) parents prior to study inclusion. The second wave was conducted 4 years later during spring 2006, comprising 5683 children aged 11 to 13 years (60% of the original target population).

For every participating child in the hospital-based group of children prenatally exposed to substances included in this study, 3 children from the BCS population, who were sex- and age-matched (±0.9 years), were randomly selected into the reference group. Three controls were added for each case to improve the quality of the analyses.[37] As we considered age to be an important matching factor in this study, we used a relatively narrow matching criterion of ±0.9 years, which therefore allowed 3 eligible controls from the BCS. As we would have to considerably expand the age-matching criterion (to about ±2 years) to achieve a 4:1 ratio between controls and cases, we considered a 3:1 ratio to best use the available data.

Exposure to substances

Children with confirmed prenatal exposure to substances were included in the study. Substance exposure was defined as prenatal exposure to opiates and a number of illicit drugs and illicit use of prescribed drugs with psychoactive or sedative effects. In addition, children were included in the study if they were exposed to opioids as part of the national opioid maintenance treatment program (OMT) and/or they presented with neonatal withdrawal symptoms or NAS after birth. Prenatal exposure was confirmed by information obtained from mothers and obstetric or pediatric records, including details from referring units and reports of neonatal withdrawal symptoms.

In cases involving exposure to both alcohol and other substances, the mother's main substance of use was taken into account to determine a child's eligibility for inclusion in the study. In cases involving a greater number of single episodes of alcohol exposure, or if a child met the criteria of fetal alcohol spectrum disorders (FASD), the child was excluded from the study.

Withdrawal symptoms and NAS

The presence of withdrawal symptoms in children was assessed for and recorded, and abstinence symptoms were scored using a modified version of the Finnegan abstinence score.[29] Abstinence scores of 8 or above were classified as NAS.

Care situation

Based on the medical records and questionnaires completed by the children's respective caregivers, data on the current care situation were obtained, as well as age at first placement outside of the biological home (before or after 1 year of age). Early placement in an adopted home or foster care was defined as placement before 1 year of age.

Cognitive functioning

Cognitive functioning in exposed children was evaluated using either the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) test[38] or the Wechsler Intelligence Scale for Children–Revised (WISC-R).[39]

Mental health

Mental health assessment was based on 2 different questionnaires—the Swanson, Nolan, and Pelham Questionnaire, revision IV (SNAP-IV) and the Autism Spectrum Screening Questionnaire (ASSQ), both comprising items scored on a 3-point scale (0-2). The questionnaires were completed by the current caregivers.

The Swanson, Nolan, and Pelham Questionnaire, revision IV. The SNAP-IV is a screening tool for ADHD.[40] It contains 9 items on inattention and 9 items on hyperactivity/impulsivity, which correspond to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition; DSM-IV) criteria for ADHD.[41] Scores ranged from 0 to 18 for each scale. The SNAP Combined variables consisted of the sum of all 18 items. Reliability of SNAP-IV as a screening tool has been reported as good.

The Autism Spectrum Screening Questionnaire. The ASSQ consists of 27 items covering symptoms of ASD, ie, social interaction and communication, motor clumsiness, tics, and restricted and repetitive behavior.[43–45] In this study, one of the items (item 9 related to involuntary sounds and words) was inadvertently omitted for the reference group and therefore not included.[44] Scores ranged from 0 to 52.

For further description of symptoms reported in ASSQ, the 26 items were computed into 3 subscales, as suggested in Ryland et al[46]: (1) social difficulties, including items related to difficulties with friendship, prosocial behavior, and social communication; (2) motor/tics/obsessive–compulsive disorder (OCD), including items related to repetitive, stereotype behavior, and autism-associated symptoms such as motor difficulties and tics; and (3) autistic style, including items related to characteristics often seen in high-functioning individuals with ASD. The specific items included in each subscale are as follows: (1) social difficulties: lives in own world, no social fit in language, lacks empathy, naive remarks, deviant style of gaze, fails to make friends, sociable on own terms only, lacks best friend, lacks common sense, poor at games and own rules, and bullied by other children; (2) motor/tics/OCD: different voice/speech, clumsy, involuntary movements, compulsory repetition, insists on no change, idiosyncratic attachment, unusual facial expression, and unusual posture; and (3) autistic style: old-fashioned or precocious, eccentric professor, accumulates facts, literal understanding, robot-like language, idiosyncratic words, and uneven abilities.[46]

Statistical analyses

Descriptive analyses were used to describe the sample (mean, standard deviation, and frequency). Group differences were analyzed using the *t*-test. Levene's test was used to test homogeneity of variances. If variances were found to be statistically unequal, the *t*-test not assuming equal variances was used.[47] Effect sizes were estimated by Cohen's *d*. IBM SPSS version 24 was used for all analyses.[48]

Regarding the use of ASSQ, it has been recommended a cutoff score of 17 or more is optimal in screening for ASD.[45] We therefore used a cutoff value of ≥17 as high score in our analyses comparing child placement outside of the biological home before and after 1 year of age. Due to skewness in outcome variables in the reference group, the program Mplus version 7.4 was used with the maximum likelihood robust (MLR) estimator and corrected standard errors for sensitivity analyses.[49,50] This analysis strategy does not assume equal variances when comparing the groups. Spearman correlation was used when analyzing the relationship between SNAP-IV and ASSQ scores.

In the group of children prenatally exposed to substances, multiple regression analysis was used to predict the outcome variables SNAP Combined, SNAP Inattention, and SNAP Hyperactivity/impulsivity and ASSQ Total score, ASSQ Social difficulties, ASSQ Motor/tics/OCD, and ASSQ Autistic style. Predictors were age, gender, intelligence quotient (IQ), NAS, and child placement outside of the biological home before or after 1 year of age based on earlier studies of prenatal substance exposure and mental health in children.[5,10,11,14–18,20,23]

For 21 children in the exposed group, one or more responses on the ASSQ were missing. For missing data, the variables were replaced with imputed data based on the expectation–maximization method and ASSQ total scores computed.[51]

Ethics

The study was approved by the Regional Committee for Medical Research Ethics in Norway (approval number 2010/3301). For children prenatally exposed to substances, informed written consent was obtained from all participating caregivers. These included biological parents if the child was living in the biological home, adoptive parents, or foster parents if relevant for the care situation. For children in foster care, the social welfare office legally responsible for the participating child also gave written consent. In addition to the caregivers and social welfare office, children 12 years and older gave their independent consent to participate in the study. For the reference group, the caregivers gave informed written consent.

Results

Study participants

The characteristics of the hospital-based population of children prenatally exposed to substances and the reference group are presented in Table 1. Almost 2 in 3 participants were boys,

and the mean IQ was within the normal range for the entire study sample. In the exposed group, all, except 1 child, lived in foster care (n = 54) or with adopted parents (n = 2), and of the children adopted or in foster care (n = 56), more than 1 in 3 were placed outside of their biological home before the age of 1 year. The mean age at follow-up was approximately 10 years, with age normally distributed and approximately 95% of the sample in the age range of 6.3 to 14.4 years. However, a weak positive skewness may reflect more children being older than expected under the assumption of perfect normality. Symptoms compatible with neonatal abstinence were reported in 41 of the exposed children, of whom 18 were diagnosed with NAS. Five children were reported without abstinence symptoms, and for 11 children, there was no valid information regarding abstinence symptoms.

Mental health outcomes

Mental health outcomes are presented in Table 2. For the exposed group, the caregivers reported significantly higher scores of ADHD symptoms combined ($P < .001$) and Cohen's *d* was large ($d = 2.08$). The SNAP-IV scores were high in areas of both inattention and hyperactivity/impulsivity. Caregivers also reported an increased number of symptoms associated with ASD, with the largest Cohen's *d* in the subscale "social difficulties." For the ASSQ, 21 of the 56 (37%) of the children had high scores (≥17) in the exposed group, compared with 5 of the 162 (3%) in the reference group (odds ratio [OR] = 17.44, 95% confidence interval [CI] = 6.1-49.6, $P < .05$). However, there was no significant difference in high ASSQ scores between the group of children placed into foster care before and those after 1 year of age ($P = .083$). The effect sizes for the outcome variables were in the range of 0.44 to 3.60. Effects for the mental health outcomes were above the threshold for large effects. Mplus sensitivity analyses correcting for standard errors due to skewness in some variables confirmed that all differences were statistically significant ($P < .001$).

Predictors of mental health outcomes

Regression analyses were performed to evaluate possible predictors of mental health outcomes available in this study. Seven mental health measures were chosen as dependent variables, and predictors were age, gender, IQ, the presence or absence of NAS, and child placement outside of their biological home before or after the age of 1 year. The standardized regression coefficients for the independent variables are given in Table 3. IQ was a statistically significant factor in 5 of the 7 regression models, whereby higher IQ scores predicted lower levels of mental health problems. Furthermore, NAS was a significant predictor of the SNAP Inattention scale.

When analyzing the correlation between ASSQ Total score and SNAP, we found a moderate to strong correlation between high ASSQ scores and high SNAP scores, with the strongest

Table 2. Mental health outcomes in a hospital-based population of children prenatally exposed to substances, compared with a reference group.

	EXPOSED GROUP (N = 57)	REFERENCE GROUP (N = 171)	t	P	d^a
	MEAN (SD)	MEAN (SD)			
SNAP Combined	19.65 (9.06)	4.13 (5.37)	12.22	*	2.08
SNAP Inattention	10.79 (4.63)	2.72 (3.49)	12.05	*	1.97
SNAP Hyperactivity/impulsivity	8.86 (5.26)	1.42 (2.41)	10.31	*	1.82
ASSQ total	14.00 (7.98)	3.57 (4.51)	9.36	*	1.61
ASSQ Social difficulties	7.74 (4.99)	1.47 (2.61)	9.07	*	1.57
ASSQ Motor/tics/OCD	2.37 (2.22)	0.36 (1.06)	6.59	*	1.16
ASSQ Autistic style	3.89 (2.65)	1.83 (2.06)	5.37	*	0.87

Abbreviations: ASSQ, Autism Spectrum Screening Questionnaire; OCD, obsessive–compulsive disorder; SD, standard deviation; SNAP, Swanson, Nolan, and Pelham Questionnaire, revision IV (SNAP-IV).
[a]*d*: Cohen's *d*; *t*-test is corrected when Levene's test shows unequal variances.
*$P < .001$.

Table 3. Mental health outcomes in a hospital-based population of children prenatally exposed to substances (n = 57) and possible predictors of mental health.

	SNAP COMBINED	SNAP INATTENTION	SNAP HYPERACTIVITY/ IMPULSIVITY	ASSQ TOTAL	ASSQ SOCIAL DIFFICULTIES	ASSQ MOTOR/ TICS/OCD	ASSQ AUTISTIC STYLE
	β	β	β	β	β	β	β
Age	−0.03	0.05	−0.09	0.01	0.01	−0.17	0.14
Gender	−0.22	−0.12	−0.26	0.02	0.06	0.06	−0.12
Early placement[a]	0.20	0.22	0.16	0.10	0.10	0.11	0.02
NAS	0.22	0.29*	0.12	0.09	0.09	0.22	−0.08
IQ	−0.38**	−0.48***	−0.22	−0.35*	−0.40**	−0.40**	0.02
R^2 (adjusted)	0.23 (0.16)	0.28 (0.21)	0.17 (0.09)	0.12 (0.03)	0.15 (0.07)	0.18 (0.10)	0.04 (0.00)

Abbreviations: ASSQ, Autism Spectrum Screening Questionnaire; IQ, intelligence quotient; NAS neonatal abstinence syndrome; SNAP, Swanson, Nolan, and Pelham Questionnaire, revision IV (SNAP-IV).
Results from multiple regression analysis for SNAP Combined, SNAP Inattention, and SNAP Hyperactivity/impulsivity, and ASSQ Total, ASSQ Social difficulties, ASSQ Motor/tics/OCD, and ASSQ Autistic style. Relations are given by beta-weights (β) and model fit by explained variance.
[a]Placement in adopted home or foster care before 1 year of age.
*$P < .05$; **$P < .01$; ***$P < .001$.

correlation between ASSQ Social difficulties and both SNAP Inattention ($r = .702, P \leq .01$) and SNAP Hyperactivity/impulsivity ($r = .714, P \leq .01$).

Discussion

In our hospital-based population of children prenatally exposed to substances, we found that exposed children had more symptoms associated with ADHD and ASD, compared with the reference group. Using the standardized instrument SNAP-IV and ASSQ, high symptom scores were obtained in the areas of inattention and hyperactivity/impulsivity, and in addition, the exposed children presented with an increased number of symptoms in all 3 ASSQ subscales. Of the available predictors of mental health outcomes in the exposed group of children, only

the IQ could explain variances in some of the mental health scales and NAS only for ADHD/inattention problems. Gender, age, or early placement in an adopted home or foster care was not found to be predictive of mental health outcomes in the group of exposed children.

In line with earlier research in children prenatally exposed to substances,[2,3] caregivers in this study reported an increased number of ADHD symptoms in the exposed group, with higher symptom scores for both hyperactivity/impulsivity and inattention, compared with the reference group. Attention deficit/hyperactivity disorder is a complex disorder and may result from processes involving both genetic and nongenetic factors.[52] A previous study found adults with substance use disorder to have a higher rate of ADHD symptoms and suggested ADHD

as an independent risk factor for substance abuse.[53] Therefore, it is possible that prenatally exposed children may be genetically predisposed to ADHD, which could explain the increased number of ADHD symptoms in this group of children.

Mean level of symptoms associated with ASD was increased in the exposed group of children, compared with the reference group, with more than 1 in 3 exposed children having high ASSQ scores, mainly on the "social difficulties" subscale. In children with prenatal alcohol exposure, an increased risk for both ADHD and ASD has been described.[33] Autism spectrum disorder is characterized by symptoms of social impairment, as are other mental health disorders such as reactive attachment disorder (RAD), and therefore, diagnostic assessment is necessary to distinguish between these disorders.[41,54,55] Reactive attachment disorder may result from inadequate caregiving and can develop when a child's caregiving environment fails to address the child's care needs.[41,54–56] This study did not demonstrate any association between early placement in an adopted home or foster care and symptoms of ASSQ. We suggest future studies to evaluate possible associations between quality of the caregiving environment, as well as the timing, duration, and number of placements in foster care, and the development of mental health problems in prenatally exposed children.

In this study, IQ and NAS were the only predictors of mental health outcomes. The protective effect of a higher IQ against mental health problems is in line with findings from previous studies investigating other risk factors such as prematurity[57] and chronic illness.[58] In this study, the presence of NAS was a predictor of later inattention problems, suggesting a potential vulnerability for neurodevelopmental disorders in children with NAS; however, more research is needed to investigate this further.[5] Furthermore, children with overlapping symptoms of ADHD and ASD were found in the exposed group, which lends support to the suggested neurodevelopmental vulnerability in exposed children.

In summary, our study found that children prenatally exposed to substances presented with symptoms in more than one area of mental health problems. Although exposed children may not necessarily fulfill the diagnostic criteria of a specific psychiatric disorder, they may present with a range of symptoms associated with ADHD and ASD. The extent of these symptoms strongly suggests a functional impact on daily living for many of these exposed children, and this calls for more attention focused on follow-up programs.

This study has limitations. We were unable to confirm the accuracy of the types of substances to which the fetus was exposed, based on information reported by the biological mothers. It is possible this resulted in an underestimation of the actual prenatal exposure to specific substances, e.g., alcohol. Previous studies reported some concurrent illicit polydrug use by mothers while undergoing OMT, emphasizing the complexity of accurately measuring actual exposure.[59,60] In this study, it was not possible to ascertain whether the mothers had consumed alcohol, in addition to other substances during pregnancy, and we relied on obstetric

and pediatric records, as well as reports from mothers. If there was confirmation or evidence of a greater number of single episodes of alcohol exposure, the children were excluded from this study, based on the known teratogenic effects of alcohol. Another limitation is that although nicotine exposure is a risk factor known to affect a child's neurodevelopment,[2,3] data on tobacco and nicotine use by mothers during pregnancy were not available in our study. Furthermore, the study design likely produced selection bias, as a hospital-based population tends to include the most severely affected children, which therefore has a major impact on the generalizability of the study findings. Also, it would have been useful to include mental health data collected from different settings, such as from teachers' reports, but due to ethical considerations, it was not possible to invite teachers to participate in the study. Another limitation of this study was that we did not have information about IQ and foster care for the children in the reference group. As the reference group was drawn from a population with parents reporting having relatively good family economy, and about 50% reported having higher education, this could lead the reference group to consist of more well-adjusted children than the general population. This should be taken into account when interpreting the findings from this study.

Important strengths of this study are the relatively large population of children prenatally exposed to substances and the use of standardized, validated screening tools to assess mental health symptoms. Also, the reference group consisted of children mainly from the same geographical area as the exposed group, which could contribute to the robustness of result comparability between the 2 groups, although there was no information on prenatal substance exposure for the reference group.

Conclusions

Findings from our hospital-based study show that children prenatally exposed to substances presented with an increased number of symptoms associated with ADHD and ASD, compared with the reference group. In light of increased mental health symptoms in children prenatally exposed to substances and referred to the hospital, early mental health assessment is suggested for this population. Moreover, caregivers should be educated on the range of symptoms associated with mental health problems for which exposed children are at risk. There is a need for increased awareness of, and further research on, the impact of prenatal substance exposure on mental health outcomes and functioning of exposed children within the family, at school, and in the wider society.

Author Contributions

LBS, IBE, and SAN conceived and designed the experiments. LBS, SKEF, and RG analyzed the data. LBS, SKEF, and IBE wrote the first draft of the manuscript. LBS, SKEF, SAN, TB, RG, and IBE contributed to the writing of the manuscript.

LBS, SKEF, SAN, TB, RG, SH, and IBE agree with the manuscript results and conclusions. LBS, TB, SH, and IBE jointly developed the structure and arguments for the paper. LBS, SKEF, SAN, TB, RG, SH, and IBE made critical revisions and approved final version. All authors reviewed and approved the final manuscript.

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