Tampere University

NIINA-MARIA NISSINEN

Secondary Disabilities in Finnish Youth with Prenatal Substance Exposure

A longitudinal register-based cohort study on secondary education, financial difficulties and mood and neurotic disorders in youth with prenatal substance exposure

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ACADEMIC DISSERTATION
To be presented, with the permission of
the Faculty of Social Sciences
of Tampere University,
for public discussion in the auditorium D11
of the Main Building, Kalevantie 4, Tampere,
on 13 October 2023, at 12 o'clock.

ACADEMIC DISSERTATION
Tampere University, Faculty of Social Sciences
Folkhälsan Research Center, Helsinki
Finland

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The originality of this thesis has been checked using the Turnitin OriginalityCheck service.

Cover design: Roihu Inc.

ISBN 978-952-03-3067-5 (print)
ISBN 978-952-03-3068-2 (pdf)
ISSN 2489-9860 (print)
ISSN 2490-0028 (pdf)
http://urn.fi/URN:ISBN:978-952-03-3068-2

Carbon dioxide emissions from printing Tampere University dissertations have been compensated.

PunaMusta Oy – Yliopistopaino
Joensuu 2023

ACKNOWLEDGEMENTS

Finalising this doctoral dissertation would not have occurred without the support from various experts, colleagues, friends, and family. First and foremost, I would like to express my deepest gratitude towards my supervisors Professor (emerita) Arja Rimpelä, Adjunct Professor Anne Maarit Koponen and Adjunct Professor Kirsimarja Raitasalo. Thank you for your invaluable advice, continuous support, and patience during this journey.

I'm sincerely grateful to the pre-examiners Dr. Raja Mukherjee and Professor Marjo-Riitta Järvelin for their careful review and insightful remarks, which have helped me to improve the dissertation at the final stage. I also wish to express my warmest gratitude to Professor Timo Harrikari for kindly agreeing to be the opponent at the public defence of this dissertation.

I'm particularly grateful for the ADEF Helsinki research group, including Anne Maarit Koponen as well as Taisto Sarkola, Hanna Kahila, Mika Gissler and Ilona Autti-Rämö. I want to thank you for initiating and starting the work of ADEF Helsinki research and for accepting me to join the research group as a young doctoral student. I'm grateful for your continuous support and advice during the process. Your vast expertise in terms the subject area and for research has been the greatest help during this journey, and your guidance has carried me throughout the process. Without your patience and commitment, this dissertation would not have been completed.

I want to extend my thanks to Åse Fagerlund and Mika Gissler for serving as a supportive follow-up group. I also want to express my thanks to Folkhälsan Research Center for being the research base of this dissertation.

I'm also grateful for the collaborations I have had during this journey. Jenny Rangmar, thank you for welcoming me as a visiting researcher at Gothenburg University in Sweden and for the enjoyable collaboration we have had. I'm thankful to Kehitysvammaliitto for our collaboration and the joint effort to foster FASD knowledge and work in Finland. I would also like to thank the Nordic Welfare Center for the collaboration and work we did towards improving knowledge of FASD in the Nordic countries. I would particularly like to thank Nadja for our collaboration and our

achievements. I'm also grateful that our collaboration has led to a personal friendship. I'm looking forward to seeing what our plans will bring.

I'm thankful for all my colleagues at Folkhälsan Research Center and at any other workplaces during this journey. Marja and Mari, I'm genuinely thankful that our work friendship turned into a personal friendship. You have been my greatest support during this process and when life has tried to challenge us. I'm grateful to have such warm, loving, and supportive friends in my life. I can always rely on you.

I'm also thankful for the teachers at Tampere University and the other doctoral students I've met during this process. I would particularly like to thank my friends and PhD peers, Salla and Bertina, for their friendship and peer support, not only during this journey but also in the world outside academia. Salla, I remember our trips to Tampere University and the courses we completed together with great warmth. These shared experiences have made this journey more enjoyable and fun. Bertina, my dearest friend, even though there is an ocean between us, it's not big enough to affect our friendship. Thank you for always being there. I'm looking forward to seeing where the world takes us next.

In addition, I would like to express my thanks to all my other friends not mentioned here by name. I consider myself lucky to have you in my life. Thank you for your encouragement and support during this journey. I would also like to express thanks to all the people whose paths came across mine during this journey.

I would also like to highlight the importance of hobbies during this journey and express thanks to the people I have met in the gym and dance classes. One should not underestimate the power of sports on one's wellbeing. The hobbies have offered an escape and a break from work when needed. Additionally, the hobbies have also been the place to learn determination, commitment, and perseverance, which I personally consider particularly important skills during the doctoral studies.

Finally, I owe my deepest gratitude to my family, especially my parents. Thank you for your patience and continuous support, no matter what plans or adventures I come up with. Thank you also for reminding me about the power of laughter in life. I love you.

Helsinki,
9 September 2023

Niina-Maria Nissinen

ABSTRACT

Exposure to substances (i.e.alcohol and/or illicit drugs) during pregnancy imposes a significant risk for fetal development, especially for the central nervous system (CNS) and brain development. Impairments in the CNS can manifest as various deficits in cognitive and behavioural functioning, commonly referred to as primary disabilities in the context of prenatal substance exposure. The primary disabilities can predispose an individual with prenatal substance exposure to other challenges in various areas of life, including mental health, education, employment and financial self-supporting. These disabilities prenatally substance exposed individuals may encounter are commonly termed secondary disabilities. In addition to risk factors occurring during the prenatal period, psychosocial factors of the caregiving environment can also influence one's developmental trajectories. The postnatal caregiving environment of children with prenatal substance exposure is often characterised by adversities, and a high proportion of these children are placed in out-of-home care (OHC) in early childhood. Thus, secondary disabilities in youth with prenatal substance exposure may result from this double jeopardy. However, we know relatively little about the secondary disabilities in youth with prenatal substance exposure and the influence of other risk factors (especially adversities and caregiving instability in the postnatal caregiving environment) on these secondary disabilities.

The overall aim of this dissertation was to study secondary disabilities in Finnish youth aged 15 to 24 years old with prenatal substance exposure. More specifically, the aim was to investigate: (1) completed secondary education (Study I), (2) financial difficulties measured as the recipiency of long-term financial social assistance (FSA), and (3) mood and neurotic disorders measured as specialised healthcare episodes (i.e. inpatient or outpatient hospital care) for mood and neurotic disorders -related diagnosis (Study III) among youth with prenatal substance exposure. In all the sub-studies, the aim was also to study associations between prenatal substance exposure, youth characteristics, and adverse maternal characteristics and OHC, and the studied secondary disabilities.

This dissertation was based on the ADEF Helsinki (Alcohol and/or Drug Exposure During Fetal Life) study, which is a longitudinal register-based cohort study. The overall study population consisted of 615 youth with prenatal exposure to substances (i.e. the

exposed cohort) and 1787 matched unexposed youth (i.e. the unexposed cohort). The youth in the exposed cohort were born in 1992–2001 to mothers whose pregnancies were followed up at the special antenatal clinics (i.e. HAL clinics) in the Helsinki metropolitan area due to identified substance abuse during pregnancy. Youth in the unexposed cohort were born in 1992–2001 to mothers with no registered evidence of substance use one year before the birth of the offspring or at the time of birth in the national health and social care registers. The cohorts were matched for five maternal characteristics including maternal age at the time of offspring's birth, parity, number of fetuses, month of birth, and delivery hospital of the index child. Register data were collected identically for the exposed and unexposed mother-child dyads from birth until the end of follow-up in 2016.

Multivariable logistic regression analysis was applied in Study I to investigate completed secondary education, whereas financial difficulties in Study II were studied using generalised linear models and mediation analysis. Mood and neurotic disorders in Study III were studied using multivariable Cox's proportional hazard regression analysis and mediation analyses.

Overall, the results of this dissertation showed that youth with prenatal substance exposure had an increased likelihood of experiencing secondary disabilities compared with unexposed youth. More specifically, the results of the descriptive and unadjusted analyses showed that compared to unexposed youth, youth with prenatal substance exposure had: (1) delayed completion of secondary education and an overall lower secondary education completion rate (Study I), (2) higher likelihood of financial difficulties (Study II) and (3) a two-fold higher likelihood of being in specialised healthcare for mood and neurotic disorders (Study III).

Furthermore, the results of this dissertation showed: (4) maternal prenatal substance abuse was interlinked with an accumulation of adversities in the postnatal caregiving environment, and a high proportion of prenatally substance-exposed youth had been placed in OHC in early childhood. These factors had a strong influence on secondary disabilities apart from on secondary education completion. The results of the adjusted analyses showed: (5) prenatal substance exposure was not independently associated with a lack of secondary education, and different forms of youth mental/behavioural disorders independently reduced the likelihood of completed secondary education. (6) Prenatal substance exposure was not independently associated with youth's financial difficulties, and these difficulties were influenced by youth's mental/behavioural disorders and lack of secondary education in addition to maternal financial difficulties and OHC. Maternal financial difficulties and OHC also mediated a large proportion of the association between prenatal substance exposure and youth's financial difficulties.

(7) The association between prenatal substance exposure and mood and neurotic disorders was attenuated to a non-significant level when the influence of other predictors was controlled for. Accumulation of adverse maternal characteristics and OHC in addition to female sex were associated with an increased likelihood of mood and neurotic disorders. OHC also mediated a large proportion of the association between prenatal substance exposure and youth's mood and neurotic disorders.

In light of the research findings, youth with prenatal substance exposure seem to be a group vulnerable to various avoidable secondary disabilities in the youth period, especially when considering the accumulation of postnatal risk factors in these populations and their associations with secondary disabilities.

The dissertation sheds light on areas where further research is needed, including studies on secondary disabilities incorporating information on primary disabilities in prenatally substance-exposed youth. This information could provide a better understanding of risk factors that increase susceptibility to secondary disabilities, and providing directions for the prevention of secondary disabilities in these youth. The study also highlights the need for studies including more detailed information on the characteristics of the postnatal caregiving environment and their associations with secondary disabilities in youth with prenatal substance exposure. The results also indicated implications for public health and prevention and the need for multiprofessional preventative measures at different levels: from the prevention of substance use during pregnancy to the early and long-term individualised support for the affected individual and their family. This also calls for more comprehensive knowledge and adequate training of professionals. The results also highlight the need for preventative measures to secure a safe and stable postnatal caregiving environment, especially among children and youth in OHC.

TIIVISTELMÄ

Altistuminen päihteille (ml. alkoholi ja laittomat huumeet) raskaudenaikana on merkittävä riskitekijä sikiön kehitykselle, erityisesti sikiön keskushermoston ja aivojen kehitykselle. Altistuksen aiheuttamat keskushermostovauriot voivat ilmetä erilaisina häiriöinä kognitiivisissa taidoissa ja käyttäytymisessä. Näitä häiriöitä kutsutaan yleisesti englanninkielisellä termillä "primary disabilities", suomennettuna primaariset häiriöt. Nämä häiriöt voivat altistaa päihteille raskaudenaikana altistuneen lapsen muille haasteille nuoruudessa, kuten mielenterveyden ongelmille, koulutuksen haasteille, sekä haasteille itsenäistymisessä. Näitä nuoruusiällä ilmeneviä haasteita kuvataan englanninkielisellä termillä "secondary disabilities", suomennettuna sekundaariset häiriöt.

Raskaudenaikaisten riskitekijöiden lisäksi myös lapsuusajan kasvuympäristön psykososiaalisilla tekijöillä on vaikutuksia yksilön kasvuun ja kehitykseen. Lapset, jotka ovat altistuneet äidin merkittävälle päihteidenkäytölle raskaudenaikana, altistuvat usein myös muille epäsuotuisille ja huono-osaisuutta kuvaaville tekijöille lapsuuden kasvuympäristössä ja suuri osa näistä lapsista on sijoitettu kodin ulkopuolelle jo varhaislapsuudessa. Toisin sanoen, sekundaariset häiriöt päihteille raskaudenaikana altistuneilla nuorilla voivat siis kuvastaa eri riskitekijöiden kasautumista. Tutkimustietoa sekundaarisista häiriöistä päihteille raskaudenaikana altistuneilla nuorilla sekä siitä, miten muut riskitekijät, erityisesti kasvuympäristön epäsuotuisuutta ja huono-osaisuutta kuvaavat tekijät, ja kodin ulkopuolinen sijoitus ovat yhteydessä sekundaarisiin häiriöihin, on vain vähän.

Tämän tutkimuksen päätavoitteena oli tutkia sekundaarisia häiriöitä suomalaisilla nuorilla, jotka ovat altistuneet päihteille raskaudenaikana. Tavoitteena oli tutkia päihteille raskaudenaikana altistuneiden nuorten (1) toisen asteen koulutuksen suorittamista (osatutkimus 1), (2) taloudellisia vaikeuksia, jotka määriteltiin pitkäaikaisena toimeentulotuen tarpeena (osatutkimus 2), sekä (3) mielialahäiriöitä ja neuroottisia häiriöitä, jotka määriteltiin erikoissairaanhoidon hoitojaksona (ml. vuodeosasto ja poliklinikka) mielialahäiriötä tai neuroottisia häiriötä kuvaavalla diagnoosilla. Kaikissa osatutkimuksissa tavoitteena oli lisäksi tutkia raskaudenaikaisen päihdealtistuksen, nuorta kuvaavien tekijöiden, sekä äitiin liittyvien epäsuotuisaa

kasvuympäristöä ja huono-osaisuutta kuvaavien tekijöiden ja kodin ulkopuolisen sijoituksen yhteyttä tutkittuihin sekundaarisiin häiriöihin.

Tämä tutkimus pohjautui ADEF Helsinki (Alcohol and/or Drug Exposure During Fetal Life) -tutkimukseen, joka on pitkittäinen, rekisteriaineistoon pohjautuva kohorttitutkimus. Tutkimusjoukko koostui 615 päihteille raskaudenaikana altistuneesta nuoresta (altistunut kohortti) sekä 1787 kaltaistetusta verrokkinuoresta, joilla ei ollut rekisterimerkintää, joka viittaisi raskaudenaikaiseen päihdealtistukseen (verrokkikohortti). Päihteille raskaudenaikana altistuneet nuoret syntyivät vuosina 1992–2001 naisille, joiden raskautta seurattiin pääkaupunkiseudun HAL-äitiyspoliklinikoilla tunnistetun merkittävän raskaudenaikaisen päihteidenkäytön vuoksi. Verrokkinuoret syntyivät vuosina 1992–2001 naisille, joilla ei ollut rekisteröityä tietoa päihteidenkäytöstä vuosi ennen lapsen syntymää tai lapsen syntymähetkellä. Kohortit kaltaistettiin viiden äitiin liittyvän tekijän mukaan. Näitä tekijöitä olivat äidin ikä lapsen syntymähetkellä, parityteetti, sikiöiden lukumäärä, lapsen syntymäkuukausi sekä synnytyssairaala indeksilapsen mukaan. Rekisteriaineistoa kerättiin identtisesti molempien kohorttien äiti-lapsi-pareille lapsen syntymästä seurannan loppuun saakka vuoteen 2016.

Kaikissa osajulkaisuissa käytössä olivat monimuuttuja-analyysit. Osajulkaisussa 1 toisen asteen koulutuksen suorittamista tutkittiin logistisella regressioanalyysillä. Osajulkaisussa II taloudellisia vaikeuksia tutkittiin yleistetyllä lineaarisella mallilla sekä mediaatioanalyysilla. Mielialahäiriöitä ja neuroottisia häiriöitä tutkittiin osajulkaisussa III Coxin regressionanalyysillä sekä mediaatioanalyysilla.

Tutkimuksen tulokset osoittivat, että päihteille raskaudenaikana altistuneilla nuorilla oli suurentunut todennäköisyys sekundaarisille häiriöille verrokkinuoriin verrattuna. Kuvailevien ja univariaatti analyysitulosten mukaan verrokkinuoriin verrattuna: (1) päihteille raskausaikana altistuneet nuoret suorittivat toisen asteen koulutus myöhemmin ja yleisesti koulutuksen suorittaneiden määrä oli vähäisempi (osajulkaisu I), (2) heillä oli suurentunut taloudellisten vaikeuksien todennäköisyys (osajulkaisu II) ja (3) he olivat kaksi kertaa useammin erikoissairaanhoidossa mielialahäiriöistä ja neuroottisista häiriöistä johtuen (osajulkaisu III).

Tulokset myös osoittivat, että: (4) äidin merkittävä raskaudenaikainen päihteidenkäyttö oli yhteydessä epäsuotuisaa kasvuympäristöä ja äidin huono-osaisuutta kuvaavien tekijöihin kasautumiseen ja suuri osa raskaudenaikana päihteille altistuneista lapsista oli sijoitettu kodin ulkopuolelle varhaislapsuudessa. Näillä tekijöillä oli merkittävä yhteys tutkittuihin sekundaarisiin häiriöihin, pois lukien toisen asteen koulutus. Monimuuttuja-analyysien tulokset myös osoittivat: (5) raskaudenaikainen päihdealtistus ei ollut itsenäisesti yhteydessä toisen asteen koulutuksen suorittamiseen,

kun muiden koulutusta ennustavien tekijöiden vaikutus vakioitiin. Nuoren mielenterveyden ja käyttäytymisen häiriöt itsenäisesti vähensivät toisen asteen koulutuksen suorittamisen todennäköisyyttä. (6) Raskaudenaikainen päihdealtistus ei itsenäisesti selittänyt nuoren taloudellisia vaikeuksia ja merkittävinä selittävinä tekijöinä nuoren taloudellisille vaikeuksille olivat nuoren mielenterveyden ja käyttäytymisen häiriöt ja toisen asteen koulutuksen puuttuminen, sekä äidin taloudelliset vaikeudet ja kodin ulkopuolinen sijoitus, joka myös medioi merkittävän osan raskaudenaikaisen päihdealtistuksen ja nuoren taloudellisten vaikeuksien välisestä yhteydestä. (7) Raskaudenaikainen päihdealtistus ei ollut itsenäisesti yhteydessä mielialahäiriöihin ja neuroottisiin häiriöihin vaan mielialahäiriöiden ja neuroottisten häiriöiden riskiä selittivät äitiin liittyvien huono-osaisuutta kuvaavien tekijöiden kasautuminen ja kodin ulkopuolinen sijoitus sekä naissukupuoli. Kodin ulkopuolinen sijoitus medioi merkittävän osan raskaudenaikaisen päihdealtistuksen ja tutkittujen häiriöiden välisestä yhteydestä.

Tutkimuksen tulosten valossa päihteille raskausaikana altistuneet nuoret näyttävät olevan erityisen haavoittuvat ryhmä vältettävissä oleville sekundaarisille häiriöille, ottaen huomioon riskitekijöiden kasautumisen näissä populaatioissa sekä eri riskitekijöiden yhteydet sekundaarisiin häiriöihin.

Tutkimus osoitti jatkotutkimustarpeita, kuten tarpeen sekundaarisia häiriöitä käsitteleville tutkimuksille, joissa tietoa kerätään myös primaarisista häiriöistä ja näiden häiriöiden yhteyksistä nuoruusiän sekundaarisiin häiriöihin. Lisäymmärrys eri tekijöistä, jotka lisäävät sekundaaristen häiriöiden riskiä, antaisi suuntaviivoja näiden häiriöiden ennaltaehkäisyyn. Tutkimus osoitti myös tarpeen lisätutkimuksille, joissa tietoa kerätään lapsuusajan kasvuympäristön eri tekijöistä ja näiden tekijöiden yhteyksistä sekundaarisiin häiriöihin. Tutkimuksen tulokset osoittivat myös tarpeen moniammatillisille ehkäiseville toimenpiteille eri tasoilla. Toimia tarvitaan niin raskaudenaikaisen päihteidenkäytön ehkäisemiseksi kuin varhaisen ja pitkäkestoisen, yksilön tarpeet huomioon ottavan tuen edistämiseksi. Tämä vaatisi myös eri ammattiryhmien osaamisen ja tietämyksen lisäämistä ja kouluttamista. Tulokset myös korostavat ennaltaehkäisevien toimenpiteiden tarvetta turvallisen ja vakaan lapsuusajan kasvuympäristön turvaamiseksi, erityisesti lapsilla ja nuorilla, jotka ovat olleet sijoitettuina kodin ulkopuolelle.

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ABBREVIATIONS

ADHD	Attention Deficits Hyperactivity Disorders
AHR	Adjusted Hazard Ratio
AOR	Adjusted Odds Ratio
APGAR	Appearance, Pulse, Grimace, Activity, and Respiration
ARBD	Alcohol-Related Birth Defects
ARND	Alcohol-Related Neurodevelopmental Disorders
AUDIT	Alcohol Use Disorders Identification Test
CD	Conduct Disorder
CNS	Central Nervous System
CI	Confidence Interval
DUDIT	Drug Use Disorders Identification Test
FSA	Financial Social Assistance
FASD	Fetal Alcohol Spectrum Disorders
FAS	Fetal Alcohol Syndrome
HAL	Huumeet, alkoholi, lääkkeet
HPA	Hypothalamic-Pituitary-Adrenal
HR	Hazard Ratio
HUS	The Hospital District of Helsinki and Uusimaa
ICD	International Statistical Classification of Diseases and Related Health Problems
IQ	Intelligence Quotient
NAS	Neonatal Abstinence Syndrome
ODD	Oppositional Defiant Disorders
OHC	Out-of-Home Care
OR	Odds Ratio
pFAS	Partial Fetal Alcohol Syndrome
THL	Finnish Institute for Health and Welfare
UN	United Nations
WHO	World Health Organization

ORIGINAL PUBLICATIONS

Publication I Nissinen, N.M. Gissler, M., Sarkola, T., Kahila, M., Autti-Rämö, I., & Koponen, A.M. (2021). Completed secondary education among youth with prenatal substance exposure: A longitudinal register- based matched cohort study. Journal of Adolescence, 86: 15−27. DOI: 10.1016/j.adolescence.2020.11.006

Publication II Nissinen, N.M., Rangmar, J., Autti-Rämö, I., Gissler, M., Kahila, H., Raitasalo, K.., & Sarkola, T. (2023). Financial difficulties among youth prenatally exposed to substances: a longitudinal register-based cohort study. Drugs: Education, Prevention and Policy. DOI: 10.1080/09687637.2023.2176285

Publication III Nissinen, N.M, Sarkola, T., Autti-Rämö, I., Gissler, M., Kahila, H., & Koponen, A.M. (2022). Mood and neurotic disorders among youth with prenatal substance exposure: A longitudinal register-based cohort study. Journal of Affective Disorders, 1(308): 328−336. DOI: 10.1016/j.jad.2022.04.039

1 INTRODUCTION

1.1 Prenatal substance exposure and lifelong concerns for child development and wellbeing

An individual's health and developmental trajectories are defined in a complex process, and many factors can influence development directly or indirectly at different stages during the life course. Exposure to various risk factors can have adverse effects on later development. These risk factors can include biological exposures (e.g. exposure to substances) and exposure to psychosocial factors (e.g. maternal stress and altered health) during the prenatal period, and exposure to psychosocial factors (e.g. socioeconomic characteristics of the family, parenting behaviours, adverse experiences, and trauma) in the postnatal period (Maggi et al., 2010; Anda et al., 2006). There are also critical periods of development during the life course in which exposures can have especially harmful influences on later developmental trajectories.

Pregnancy is a critical period of development, and of the prenatal risk factors, exposure to alcohol and/or illicit drugs (hereinafter referred to as substances) during pregnancy imposes a significant risk for fetal development, causing lifelong impairments (Behnke et al., 2013; Irner, 2012; Riley et al., 2011; Staton-Tindall et al., 2013). Of the substances, alcohol as a teratogen has the most detrimental effects on fetal and child development (Behnke et al., 2013). Exposure to alcohol during the prenatal period has been recognized as the leading cause of developmental disabilities and birth defects in Western societies (Hoyme et al., 2016). The effects of prenatal alcohol exposure on fetal and child development were first discovered in the research literature in the 1960s and 1970s (Jones & Smith, 1973; Lemoine et al., 1968). Since then, a vast body of research has shown how prenatal alcohol exposure is associated with a wide range of lifelong developmental impairments of varying severity and complexity, often described under the non-diagnostic umbrella term, Fetal Alcohol Spectrum Disorders (FASD) (Riley et al., 2011).

The most profound effects of prenatal substance exposure are on central nervous system (CNS) development. Prenatal exposure to substances affects brain development via numerous pathways increasing the likelihood of subsequent deficits in cognitive and behavioural functioning – often termed primary disabilities (Mattson et al., 2011; Pyman et al., 2021; Ross et al., 2015).

Because of these primary disabilities, an individual with prenatal substance exposure can encounter challenges in various areas of life, including education, mental health, independent living and self-supporting, social welfare dependency, delinquent behaviours, inappropriate sexual behaviours, and problems with substance use. In the research literature, the terms secondary disabilities or secondary conditions are used to describe these avoidable conditions (Streissguth, 1996). The earliest research on secondary disabilities originates in the clinic-based work done by Streissguth et al. (1996) in the mid-1990s. Since then, accumulating research from across countries using clinical and register data has documented high rates of various secondary disabilities in individuals with prenatal alcohol exposure. These secondary disabilities can be especially common during the youth period (i.e. from 15 to 25 years old (United Nations, n.d.)), which is a critical and sensitive period of development characterising the transition from childhood to adult independence.

Most of the research on secondary disabilities has been carried out among prenatally alcohol-exposed individuals, particularly among individuals with a condition within the FASD spectrum. The results show that 94.0% of individuals with FASD have experienced at least one mental health problem during their lifetime, and 61.0% have experienced educational challenges. Furthermore, 60.0% of these individuals have a history of delinquent behaviours, 49.0% have experienced inappropriate sexual behaviours, and 35.0% have had issues with problematic use of substances (Petrenko et al., 2014).

Secondary disabilities in the youth period can predispose individuals to further challenges in adult life. Furthermore, these disorders can place a burden on individuals with prenatal substance exposure and their families, and society (Greenmyer et al., 2018, 2020). However, secondary disabilities among youth with prenatal substance exposure, and factors predisposing to secondary disabilities during the life course, are still poorly studied.

1.2 Prevalence of substance use during pregnancy

Alcohol is a legal and widely used psychoactive substance in Finnish society, and approximately 85.0% of Finnish women drink alcohol (Mäkelä, 2018). In conjunction with the increased use of alcohol, harmful drinking patterns have also been increasing and are most common among women aged 15 to 29 years, followed by women aged 30 to 49 years (Mäkelä, 2018), that is, among women of childbearing age.

The use of drugs including psychostimulants (e.g. methamphetamine, cocaine), empathogens (e.g. ecstasy), cannabinoids (e.g. cannabis (marijuana)), and non-medical use of opiates (e.g. buprenorphine, methadone, fentanyl, oxycontin) is illegal in Finland. Cannabis is the most used illicit drug in Finland, and although its use is more common among men, its use has been increasing among women. The use of cannabis by women is most common from the age of 15 to 34 years (that is, women of childbearing age). The use of other illicit drugs (including ecstasy and cocaine as well as the non-medical use of opiates) has also been increasing in Finland. A common characteristic of illicit drug use in Finland is the use of multiple substances (i.e. polysubstance use) and it has been estimated that half of the individuals using illicit drugs also use other substances such as alcohol and tobacco (Karjalainen, 2020).

Accurately defining the prevalence of substance use during pregnancy is difficult due to the challenge of identifying and confirming maternal substance use during pregnancy retrospectively. The prevalence of substance use in Finland during pregnancy has not been accurately determined. Existing studies can provide estimates of the prevalence, however, it's likely that the prevalence estimates are underestimated. Older estimates suggest that approximately 600−3600 children are born every year in Finland with impairments caused by prenatal exposure to alcohol (Fagerlund, 2013). In a Finnish study published in 2022, Voutilainen et al. reported that 26.0% of the 14,822 pregnant women in the study reported stopping consuming alcohol after pregnancy recognition, while 4.5% reported using alcohol during pregnancy (Voutilainen et al., 2022). Higher estimates of alcohol consumption among pregnant women in Finland ranging between 14.0% and 15.7% have been suggested in other studies (Mårdby et al., 2017; Popova et al., 2017). However, these studies have several limitations, including clinically referred high-risk populations and self-reported use of alcohol use during pregnancy, and therefore, the suggested

higher prevalence estimates should be interpreted with caution. Globally, approximately 10.0% of women in the general population are estimated to consume alcohol during pregnancy (Popova et al., 2017).

Similar national or global prevalence estimates of the use of illicit drugs among pregnant women are not available. However, the increase in the use of illicit drugs especially among women of childbearing age in Finland (Karjalainen, 2020) implies a possible increase among pregnant women, too.

Substance abuse during pregnancy commonly includes polysubstance use, and tobacco smoking, in particular, is common among pregnant women who use substances (Esper & Furtado, 2014; McQuire et al., 2020). A positive development has been observed in the prevalence of tobacco smoking among pregnant women in Finland. The prevalence has decreased from 15.5% in 2010 to 7.9% in 2021 (Kiuru et al., 2022). Despite this positive development, the high prevalence warrants attention, considering the wealth of evidence demonstrating the long-term negative consequences of prenatal exposure to tobacco smoking for fetal development (Abbott & Winzer-Serhan, 2012; Bublitz & Stroud, 2012).

Despite the lack of accurate estimates, the estimated prevalence of substance use among pregnant women is worrying. The high prevalence of alcohol use before pregnancy recognition (26.0%) found by Voutilainen et al. (2022) also warrants attention, as a relatively high number of first pregnancies in Finland are unplanned (40.0% among women under 30 years of age, 18.0% among women age 30 years and older) (Klemetti et al., 2014). Thus, the use of substances before pregnancy recognition imposes a risk of fetal exposure during the early stages of pregnancy, which is a sensitive period, especially for the development of the CNS (Maier & West, 2001; Moore et al., 2014).

1.3 No safe level for substance use during pregnancy

The mechanism of how alcohol exposure during pregnancy influences fetal development and subsequent developmental trajectories is influenced by several factors including the dose, frequency, and timing of alcohol use (Lees et al., 2020; May et al., 2013; Sood et al., 2001). Exposure to heavy drinking during pregnancy (i.e. alcohol abuse) most likely leads to adverse fetal outcomes (Flak et al., 2014; May et al., 2013; Patra et al., 2011), while the evidence of the effects of low to moderate

prenatal alcohol exposure is limited and inconsistent (Flak et al., 2014; Mamluk et al., 2017; Römer et al., 2020). However, research suggests that exposure to even low levels of alcohol use during pregnancy could lead to negative developmental trajectories (Lees et al., 2020; Long & Lebel, 2022; Mamluk et al., 2017).

The research evidence indicates that the effects of prenatal exposure to illicit drugs seem to also depend on the dose, frequency, and timing of use, with heavy use (i.e. abuse) leading to the most harmful effects (Baía & Domingues, 2022; Ross et al., 2015). The evidence of the effects of prenatal exposure to illicit drugs mainly comes from studies investigating the effects of a single illicit drug. As the use of illicit drugs during pregnancy commonly includes the use of multiple drugs and/or other substances, the effects of exposure to a single illicit drug can be confounded by the use of other substances, making it challenging to draw conclusions about the effects of specific drugs (Mravčík et al., 2020; Ross et al., 2015).

In light of the research evidence, a safe period during pregnancy when any amount of any substances could be consumed without risking fetal development cannot be established. Therefore, as precaution, women should be advised to abstain from using substances while pregnant and preferably already when planning to become pregnant (Maier & West, 2001; Mamluk et al., 2017).

1.4 Adversities in the postnatal caregiving environment and long-term effects on child health and development

A child's health and developmental trajectories result from a complex interplay between genetics, prenatal, and postnatal factors. In addition to prenatal exposures, psychosocial factors in the postnatal caregiving environment can also influence a child's health and development in the long term (Maggi et al., 2010). Adversities or adverse experiences during childhood such as physical, emotional and sexual abuse, neglect in caregiving and household dysfunction are particularly significant risk factors for a child's long-term developmental trajectories and wellbeing (Anda et al., 2006; Felitti et al., 1998; Norman et al., 2012).

In children with prenatal exposure to maternal substance abuse, the postnatal caregiving environment and the early years of life are often characterised by an accumulation of adversities and caregiving instability (Flannigan et al., 2021; Lebel et al., 2019; Price et al., 2017). The adverse characteristics of the postnatal caregiving

environment and problems in parenting domains are also reflected in a high proportion of these children being placed in out-of-home (OHC) care during the early years of life (Flannigan et al., 2021; Price et al., 2017; Sarkola et al., 2007). These adversities can place these children and youth at high risk of poor developmental outcomes and secondary disabilities (Chu et al., 2020; Henry et al., 2007; Kambeitz et al., 2019). However, research on the associations between adverse postnatal caregiving characteristics and caregiving instability, and secondary disabilities in youth with prenatal substance exposure is still limited.

This dissertation adds to the current literature by providing knowledge about secondary disabilities in youth with a history of prenatal substance exposure. Furthermore, this dissertation aims to bring knowledge about the influences of youth characteristics, characteristics of the postnatal caregiving environment and caregiving instability on secondary disabilities in these youth.

2 REVIEW OF THE LITERATURE

In the following sections, the literature on the key concepts applied in this dissertation is reviewed. The review of the literature is narrative, and systematic methods for the review were not applied. Considering the heterogeneous manifestation of the effects of prenatal substance exposure, specific criteria for the study population or methods used in the studies were not set. Furthermore, due to the limited number of studies on secondary disabilities in youth, a specific time frame for the included studies was not set. The primary focus was on studies conducted on human data.

2.1 Prenatal substance exposure and the effects on fetal development

In the following section, the effects of prenatal substance exposure on fetal development are described separately for alcohol and illicit drugs.

2.1.1 Prenatal exposure to alcohol

When a pregnant woman consumes alcohol (ethanol), it enters the maternal bloodstream. The alcohol easily crosses the placenta and passes into the fetus's bloodstream and fetal organs (Behnke et al., 2013; Paintner et al., 2012). Alcohol is also excreted into the amniotic fluid through fetal urine, and due to fetal breathing movements, amniotic fluid is transferred to the fetal lungs. Within minutes of drinking, the blood alcohol concentration is similar in the mother, the fetus, and the amniotic fluid (Paintner et al., 2012). The fetus has a limited capacity to metabolise alcohol, and the majority of the alcohol metabolism occurs in the maternal metabolic system (Burd et al., 2007; Heller & Burd, 2014). Consequently, the fetus is exposed to higher concentrations of alcohol than the mother and to alcohol's teratogenic effects for a long period (Behnke et al., 2013; Paintner et al., 2012).

Many different mechanisms of alcohol teratogenicity have been proposed, and prenatal alcohol exposure can affect several aspects of fetal development (Gupta et al., 2016). One aspect relates to epigenetic modifications (Kaminen-Ahola, 2020). Research has indicated how prenatal exposure to alcohol in early pregnancy can influence fetal development by modifying epigenetic pathways. The effects of prenatal alcohol exposure have been identified in epigenetic marks, including DNA methylation, histone modifications, and non-coding RNAs (Ciafrè et al., 2020; Gutherz et al., 2022; Wallén et al., 2021). Studies also suggest that exposure to alcohol in early pregnancy may interfere with epigenetic reprogramming and potentially change the formation of epigenetic marks (Ciafrè et al., 2020; Gutherz et al., 2022; Wallén et al., 2021). Nevertheless, it has been stated that more research is needed to increase the understanding of epigenome's role in prenatal alcohol-induced molecular alterations and the aetiology of neurodevelopmental disorders in prenatally alcohol-exposed individuals (Wallén et al., 2021).

Prenatal alcohol consumption can also influence the fetus by impairing placental functioning. Alcohol exposure can increase the risk of placental insufficiency and placental abruption and alter uteroplacental blood flow. Consequently, the delivery of oxygen and nutrients to the fetus can be impaired (Burd et al., 2007; Steane et al., 2021). Placental dysfunction can further increase the risk of intrauterine growth restrictions, including the risk of low birth weight, which on the other hand, can increase the risk of developmental delays (Steane et al., 2021). Placental dysfunction is also associated with pregnancy complications including miscarriage, prematurity, and perinatal mortality (Burd et al., 2007; Steane et al., 2021).

Exposure to alcohol during pregnancy can increase the risk of congenital malformations in the fetal face and organs such as the heart, kidneys, liver, and endocrine systems (Feldman et al., 2012; O'Leary et al., 2010). In terms of facial dysmorphism, a distinct pattern of facial anomalies stemming from prenatal alcohol exposure has been identified. These facial anomalies include short palpebral fissures, smooth philtrum, and thin upper lip vermillion. These facial anomalies are also part of the diagnostic criteria of Fetal Alcohol Syndrome (FAS) discussed later in this section. These facial anomalies appear to be linked to exposure to alcohol during the first trimester, and only a minority of prenatally alcohol-exposed children represent these facial abnormalities (del Campo & Jones, 2017).

The most profound effects of prenatal alcohol exposure are found on fetal central nervous system (CNS) development, including brain development (Goodlett &

Horn, 2001; Moore et al., 2014). Prenatal alcohol exposure can affect several stages of brain development in a complex way (e.g. disrupt neuronal proliferation, and migration, cause cell death) and can cause structural and functional alternations in the developing fetal brain throughout the pregnancy (Guerri et al., 2009; Moore et al., 2014). Some brain areas or groups of brain cells seem to be more vulnerable to alcohol's effects than others (e.g. the corpus callosum, cerebellum, basal ganglia, and hippocampus) (Goodlett & Horn, 2001; Guerri et al., 2009; Inkelis et al., 2020; Nuñez et al., 2011). Although brain abnormalities have been reported in diverse populations with prenatal alcohol exposure (Goodlett & Horn, 2001; Moore et al., 2014) and among children exposed to a low level of alcohol during pregnancy (Long & Lebel, 2022), it is noteworthy that the amount of alcohol consumed during the pregnancy and the timing of exposure are likely to be associated with the observed effects on brain development (Lebel et al., 2011).

Studies using neuroimaging techniques have documented an overall reduction in brain volume (smaller head size and small brain) in alcohol-exposed children relative to control children, with frontal, temporal, and parietal lobes, and the cerebellum showing the most pronounced effects (Donald et al., 2015; Lebel et al., 2008). The decreased brain volume seems to be particularly associated with exposure to heavy alcohol use during pregnancy (Mattson et al., 2019). The smaller head size is also one of the indications of CNS dysfunction in the diagnostic criteria for FAS discussed later in this section. Overall, these effects on brain development and functioning can extend into adulthood (Inkelis et al., 2020; Sullivan et al., 2020).

In terms of specific brain regions vulnerable to the effects of prenatal alcohol exposure, neuroimaging studies have consistently shown abnormalities in the corpus callosum (Donald et al., 2015; Lebel et al., 2011; Nuñez et al., 2011) – the largest white matter track with primary function to integrate and transfer information between the two hemispheres to process high-level cognitive signals, and sensory and motor signals (Lebel et al., 2011). Observed abnormalities in the corpus callosum (e.g. complete/partial agenesis, hypoplasia, displacement in posterior regions, and variability in shape) can manifest as impairments in cognitive functions including intellectual functioning, reading, learning, working memory, and executive functions including attention (Norman et al., 2009).

Another area affected by prenatal alcohol exposure is the cerebellum (Archibald et al., 2001; Autti-Rämö et al., 2002; Nuñez et al., 2011). The cerebellum is involved particularly in motor movement regulation and balance control, as well as cognitive

and executive functions (Donald et al., 2015). Prenatal alcohol exposure induced impairments in the cerebellum (e.g. reduced volume, displacement of the anterior vermis of the cerebellum), which can manifest as functional deficits in motor functions, including balance and coordination as well as impairments in attention regulation (Spadoni et al., 2007).

Studies have also reported a decreased volume of basal ganglia, which are primarily responsible for movement control. Basal ganglia also play a role in functions such as decision-making and working memory (Archibald et al., 2001; Donald et al., 2015; Norman et al., 2009). Another brain area especially affected by heavy prenatal alcohol exposure is the hippocampus, which plays a role in memory formation, storage, and retrieval. Alterations in the hippocampus can contribute to cognitive deficits, including deficits in memory and learning (Mattson et al., 2001; Norman et al., 2009).

Besides these brain regions, studies have also indicated the effects of prenatal alcohol exposure on specific areas of the frontal lobe (Lebel et al., 2011). Studies have indicated thicker cortex in frontal lobes in prenatally alcohol exposed individuals relative to unexposed controls (Infante et al., 2017; Kable & Coles, 2017; Malisza et al., 2005). However, also contradicting evidence exist on the cortical thickness and the prenatal alcohol exposure's effects on cortical thickening or thinning seem to depend on the timing and dose of exposure (Norman et al., 2009; Nuñez et al., 2011; Robertson et al., 2016). Studies have also shown smaller volumes and decreased white and grey matter volumes of frontal lobe subregions (e.g. prefrontal cortex and orbitofrontal cortex). The prefrontal cortex is a brain region that develops from early pregnancy to late adolescence. Prefrontal cortex operations provide the goal-directed organisation and top-down regulation of behaviour, actions, thoughts, and emotions (i.e. executive functions) through connection with other brain regions. The orbitofrontal cortex, on the other hand, also has a role in regulating emotions. Impairments in these brain areas can manifest as various impairments in executive functioning (Jones & Graff-Radford, 2021).

Another neurological system affected by prenatal alcohol exposure is the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis represents the interaction between the hypothalamus, pituitary gland, and adrenal glands, and it has an important role in the physiological response to stressful stimuli (Sheng et al., 2021; Smith & Vale, 2006). The development of the HPA axis begins in the prenatal period, and prenatal exposures (including prenatal alcohol exposure), has been

associated with dysregulation of the HPA axis (Ciafrè et al., 2020; Hellemans et al., 2008, 2010; Weinberg et al., 2008). On the other hand, this can impair the brain's stress-response system and increase sensitivity to stressors (Hellemans et al., 2008, 2010; Weinberg et al., 2008). The HPA axis and its role in depression and anxiety, are further discussed in Section 2.3.1.

2.1.1.1 Fetal Alcohol Spectrum Disorders

The range of fetal outcomes resulting from prenatal alcohol exposure is encompassed under the non-diagnostic term, Fetal Alcohol Spectrum Disorder (FASD). FASD has a highly heterogeneous manifestation, as the effects of prenatal alcohol exposure can be influenced by several factors, including drinking patterns, amount of alcohol consumed, timing of exposure as well as genetic susceptibility and maternal metabolism (May et al., 2013; Popova et al., 2023). FASD includes the categories of FAS, partial FAS (pFAS), Alcohol-Related Neurodevelopmental Disorders (ARND) and Alcohol-Related Birth Defects (ARBD) (Hoyme et al., 2016).

No single medical test can be used to diagnose conditions within the FASD spectrum, and the diagnostic process is a rather complex medical assessment requiring a multiprofessional team. Several diagnostic schemas have been established for diagnosing conditions within the FASD spectrum (Astley, 2004, 2013; Chudley et al., 2005; Hoyme et al., 2016). There are differences between the diagnostic schemas. For example, the Institute of Medicine (IOM) Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders (Hoyme et al., 2016) considers FASD as a non-diagnostic umbrella term that includes four categories (i.e. FAS, pFAS, ARND, and ARBD, described in detail below), whereas other guidelines (e.g. Australian guidelines (Bower et al., 2016)) consider FASD as a diagnostic term.

Despite differences in the diagnostic schemas, most of them rely on the following three areas in diagnosing FAS (Riley et al., 2011):

a) Characteristic pattern of facial anomalies (i.e. short palpebral fissures, a smooth philtrum, and/or a thin upper vermillion border of the upper lip)

b) Prenatal and/or postnatal growth deficiency (e.g. low birth weight for gestational age, height and/or weight ≤ 10th percentile (plotted on a racially and ethnically appropriate growth curve, if available))

c) CNS dysfunction (e.g. evidence of structural brain anomaly, head circumference below the 10th percentile, or evidence of neurological or other CNS dysfunction)

In addition to these common criteria, a FAS diagnosis typically requires a confirmed history of prenatal alcohol exposure (Riley et al., 2011). However, in some diagnostic schemas, the diagnosis can be given without a confirmed history of maternal alcohol use during pregnancy (e.g. the IOM Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders (Hoyme et al., 2016)).

The FAS diagnosis is rather narrow and captures only a small fraction of those affected by prenatal alcohol exposure falling within the FASD spectrum. Not all exposed individuals display the characteristic patterns of facial anomalies required for FAS diagnosis. In the IOM Updated Clinical Guidelines for Diagnosing Fetal Alcohol Spectrum Disorders (Hoyme et al., 2016), the exposed individual may be identified as having the other conditions under the umbrella term, FASD. The terms pFAS, ARBD, and ARND are not medical diagnoses but describe conditions a child may exhibit. The term pFAS can be used when an individual exhibits a symptom of FAS but not to the full extent. pFAS can be used even when a history of prenatal alcohol exposure cannot be confirmed (Hoyme et al., 2016).

Both ARBD and ARND require confirmation of prenatal alcohol exposure. ARBD is used to describe minor or major structural anomalies in exposed individuals who display normal growth and intellectual functioning. ARND is used to describe children exhibiting a specific pattern of cognitive and behavioural deficits with normal growth and structural development. For a full description, see Hoyme et al. (2016).

Diagnosing conditions within the FASD spectrum is a complex medical process; thus, FASD is often an undiagnosed and misdiagnosed disorder (Lange et al., 2013). A study from the United States showed that nearly 80.0% of children who meet the criteria for FAS were undiagnosed and 7.0% were misdiagnosed (Chasnoff et al., 2015). Thus, FASD represents an unseen public health issue, even though its

prevalence seems to exceed other birth defects, including Down syndrome (Popova et al., 2017; World Health Organization, 2022).

2.1.2 Prenatal exposure to illicit drugs

Illicit drugs including psychostimulants (e.g. cocaine, amphetamine), cannabis (marijuana), and opiates (e.g. buprenorphine, methadone) easily cross the placenta and the blood-brain barrier and therefore can disrupt fetal growth and CNS development (Ross et al., 2015). Exposure to psychostimulants, cannabis, and opiates has been associated with an increased risk of placental insufficiency, pregnancy complications, and preterm birth (Graeve et al., 2022; Ross et al., 2015). Studies have also reported an association between prenatal exposure to psychostimulants, cannabis, and opiates and fetal growth restrictions including low birth weight and smaller head circumference (Gouin et al., 2011; Ladhani et al., 2011; Marchand et al., 2022). Also contradicting evidence exist on the association between prenatal cannabis exposure and birth outcomes (Gunn et al., 2016). Studies indicate that the fetal growth restrictions linked with prenatal cannabis exposure could be confounded by other factors including maternal sociodemographic factors and polysubstance use (Nashed et al., 2021).

A consistent pattern of dysmorphology among prenatally drug-exposed infants has not been identified, and simultaneous use of other substances including alcohol can confound these findings (Behnke et al., 2001; Minnes et al., 2006). However, some studies have indicated congenital abnormalities among neonates with exposure to psychostimulants or opiates (Ross et al., 2015; Wang et al., 2022), and organ-specific abnormalities (e.g. cardiac anomalies and musculoskeletal abnormalities) among neonates with exposure to psychostimulants (Ladhani et al., 2011; Ross et al., 2015).

Prenatal exposure to illicit drugs (e.g. psychostimulants, cannabis, opiates) can also cause abnormal infant neurobehaviour including lower arousal, non-optimal reflexes (e.g. increased startles and tremors), jitteriness, and poorer quality of movements (Wouldes & Woodward, 2020). Prenatal opiate exposure, in particular, is associated with Neonatal Abstinence Syndrome (NAS), which includes the physiological and neurobehavioural signs of withdrawal, including irritability, increased muscle tone and activity, and feeding problems (Jones et al., 2010; Kocherlakota, 2014).

Prenatal exposure to illicit drugs has also been associated with harmful effects on fetal brain development, including reduced overall brain volume, as well as structural and functional brain abnormalities (Caritis & Panigrahy, 2019; Etemadi-Aleagha & Akhgari, 2022; Martin et al., 2016). Studies have indicated that specific brain areas, such as the frontal lobes, cerebellum, and basal ganglia, are vulnerable to the effects of illicit drugs (e.g. cocaine, psychostimulants, and cannabis) (Derauf et al., 2009). Also, connectivity between different brain areas can be influenced by prenatal exposure to illicit drugs (e.g. psychostimulants) (Morie et al., 2019). Prenatal exposure to illicit drugs (e.g. psychostimulants, polysubstance exposure) has also been associated with abnormalities in grey and white matter volumes in specific brain regions (Ackerman et al., 2010). It is noteworthy, that the brain abnormalities seem to be influenced by the illicit drug the fetus has been exposed to as well as the amount of substance exposure (Ackerman et al., 2010). The observed alterations in brain structure and functioning can manifest as varying cognitive and behavioural deficits later in life (Nygaard et al., 2018; Sheinkopf et al., 2009)

The use of illicit drugs during pregnancy is often linked with polysubstance use (e.g. alcohol use and tobacco smoking) and other risk factors, including the risk of infection, poor nutrition, and other psychosocial risk factors (Mravčík et al., 2020; Ross et al., 2015). Thus, the effects of prenatal exposure to illicit drugs can be confounded by these co-occurring risk factors (Morie et al., 2019).

2.2 Prenatal substance exposure and the effects on child cognitive and behavioural functioning

CNS impairments induced by prenatal substance exposure can manifest as impairments in cognitive and behavioural functioning, often termed primary disabilities (Mattson et al., 2011; Pyman et al., 2021; Ross et al., 2015). Impairments in these domains can become apparent in childhood or at school age when demands increase and tasks become more difficult and require more complex cognitive and behavioural functioning abilities. In the following sections, research findings on the associations between prenatal substance exposure and a child's cognitive functioning, executive functioning, and externalising disorders and adaptive functioning are described separately for alcohol and illicit drugs.

2.2.1 Cognitive functioning

Cognitive functioning refers to mental processes and activities such as intellectual abilities, language, memory, reasoning, and problem-solving, which are essential in acquiring and processing information. Cognitive functioning, especially in childhood, typically concerns the development of learning and understanding (Pound, 2013).

One aspect of cognitive functioning is an individual's intellectual abilities: abilities that are required to manage everyday life. Intellectual abilities are typically measured by the Intelligence Quotient (IQ) (Pound, 2013). The IQ includes a population mean score of 100 with a standard deviation of 15, and a score under 70 indicates an intellectual deficit (World Health Organization, 1992). Studies done among prenatally alcohol-exposed children show diminished intellectual capacity across the FASD spectrum (Ferreira & Cruz, 2017). However, studies also indicate that intellectual capacity seems to be most impaired among individuals with a FAS diagnosis (Chasnoff et al., 2010; Ferreira & Cruz, 2017). Despite the diminished intellectual capacity, studies indicate that a majority of prenatally alcohol-exposed individuals do not have an IQ score under 70 and thus are not considered to have an intellectual disability (Chasnoff et al., 2010). The diminished intellectual capacity appears to remain the same over time among prenatally alcohol-exposed populations (Kodituwakku, 2007).

The results regarding the influence of prenatal exposure to illicit drugs on general intelligence are inconsistent. Lower intelligence test scores have been reported in a study of 6-year-old children with prenatal exposure to cannabis (marijuana), even after controlling for important confounders (i.e. maternal IQ, home environment, and social support) (Goldschmidt et al., 2008). Some studies have not shown an association between prenatal cannabis exposure and a child's intelligence (Fried & Smith, 2001; Smid et al., 2022), although other aspects of cognitive functioning appear to be affected (Behnke et al., 2013; Fried & Smith, 2001). Studies on prenatal exposure to psychostimulants (cocaine) have shown that although prenatal exposure is linked with poorer cognitive performance, the exposure does not independently increase the risk of low intelligence, and associated risk factors including low birth weight, prematurity, and an adverse postnatal caregiving environment contribute to lower intelligence scores (Lambert & Bauer, 2012; Pulsifer et al., 2008; Ross et al.,

2015). In terms of prenatal opiate exposure, studies have shown that the exposure is associated with deficits in intellectual functioning (Balalian et al., 2023).

Concerning language development, studies conducted among prenatally alcohol-exposed children show deficits in language development across social and linguistic contexts and with varying doses and duration of prenatal alcohol exposure (Hendricks et al., 2019; Subramoney et al., 2018). Deficits in language development have been observed during the first three years of life (Hendricks et al., 2019), whereas studies among older children indicate that the delays in language development may be confounded by postnatal environmental factors such as low maternal education or socioeconomic status (Coggins et al., 2007; Hendricks et al., 2019).

Research findings regarding associations between prenatal exposure to illicit drugs and language development seem to be influenced by the type of illicit drug the child has been exposed to. Studies conducted among children with prenatal exposure to cannabis show no effect on language skills (Behnke et al., 2013; Sharapova et al., 2018), whereas prenatal exposure to opiates has been associated with a negative effect on language outcomes, even after adjusting the analysis for important confounders including child sex, maternal education, other prenatal substance use, maternal pregnancy nutrition, and prenatal depression (Kim et al., 2021). In terms of psychostimulants, prenatal exposure to methamphetamine does not seem to be associated with language deficits (Smith et al, 2011), whereas studies on prenatal exposure to cocaine indicate language deficits from childhood through early adolescence (Bandstra et al., 2011; Lambert & Bauer, 2012; Martin et al., 2016). Contradictory evidence has also been found (Betancourt et al., 2011). Some studies show an independent association between prenatal exposure to cocaine and language delays (Bandstra et al., 2002; Lambert & Bauer, 2012; Lewis et al., 2004), while other studies indicate that the observed language impairments are subtle after controlling for the influence of environmental factors (Ackerman et al., 2010). The results suggest that a stimulating environment that enriches a child's linguistic environment (e.g. adoption or foster care) can improve a child's language functioning and protect children with prenatal exposure to cocaine from exhibiting language delays (Lambert & Bauer, 2012; Lewis et al., 2004).

In terms of memory, research findings have indicated that prenatally alcohol-exposed children display deficits with working memory, relative to controls, manifested as difficulties in holding and manipulating information in memory

(Connor et al., 2000; Rasmussen, 2005). Deficits have also been seen in spatial working memory, with deficits becoming more pronounced with increasing task complexity (Malisza et al., 2005). These deficits in working memory can be linked to the commonly observed learning difficulties in these populations (Mattson et al., 2019). Willford et al. (2004) observed deficits in memory and learning, especially in the verbal domains, among 14-year-old children exposed to moderate levels of alcohol during pregnancy.

The results regarding the association between prenatal exposure to illicit drugs and memory deficits in children are inconsistent and the associations vary by the illicit drug the child has been exposed to. Sharapova et al. (2018) suggested a potential adverse effect of prenatal cannabis exposure on memory, whereas in a review, Nashed et al. (2021) reported an association between prenatal cannabis exposure and memory deficits. In terms of psychostimulants, Minnes et al. (2011), showed an association between prenatal cocaine exposure and memory deficits at the age of 12 years (Minnes et al., 2011). In contrast, in a systematic review, Cruz-Bermúdez et al. (2020) did not show any statistically significant differences in working memory between children exposed to cocaine relative to control children. Studies on children exposed to methamphetamine have shown a negative influence on verbal and long-term memory (Chang et al., 2004; Ross et al., 2015). In terms of prenatal exposure to opiates, an association between the exposure and child's memory deficits has been suggested (Ross et al., 2015).

In terms of motor development, studies have indicated that prenatal alcohol exposure can have a negative effect on infants' and children's fine and gross motor development (Lucas et al., 2014). However, the impairments appear to be influenced by the dose and frequency of exposure (Doney et al., 2014; Lucas et al., 2014). Particularly prenatal exposure to heavy alcohol use and for a longer duration of alcohol use during pregnancy seem to be associated with deficits in motor development (Bay & Kesmodel, 2011; Lucas et al., 2014), whereas the results regarding lower exposure levels are inconsistent (Bay & Kesmodel, 2011; Doney et al., 2014; Lucas et al., 2014). However, the research findings indicate that the deficits in motor abilities appear to persist into adulthood (Connor et al., 2006).

With respect to the associations between prenatal exposure to illicit drugs and child motor functioning, some studies indicate a negative effect of prenatal exposure to psychostimulants (methamphetamine) on children's motor skills (Ross et al., 2015). In a study, Smith et al. (2011) found a subtle effect of prenatal

methamphetamine exposure on fine motor skills among 1-year-old children, with the poorest performance observed among children exposed to heavy use. However, differences in motor performance between exposed children and comparison children were not observed at the age of 3 years (Smith et al., 2011). Motor impairments have also been reported in children with prenatal opiate exposure (Hunt et al., 2008).

2.2.2 Executive functioning and externalising disorders

Executive functioning refers to higher-order cognitive abilities involved in goal-directed behaviour. Executive functioning comprises skills including working memory, problem-solving and planning abilities, cognitive flexibility, attention, and inhibitory control (Mitchell & Ziegler, 2013). Executive function abilities are relevant in executing daily activities as well as in social interaction and academic functioning (Anderson, 2010). Deficits in executive functioning are associated with externalising disorders such as Attention Deficit Hyperactivity Disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD) (Mitchell & Ziegler, 2013). These externalizing disorders are typically characterised by problematic behaviour related to poor impulse control and can include rule-breaking, aggression, impulsivity, and inattention. Many factors contribute to these disorders, including male sex, genetics, environmental factors, and the interaction between these risk factors (Carneiro et al., 2016; Samek & Hicks, 2014). The disorders can span throughout the life course and have a major burden on an individual's health, wellbeing, and academic and social functioning (Gundel et al., 2018; Esch et al., 2014). These disorders are often linked with other comorbidities, including internalising disorders (Gundel et al., 2018; Riglin et al., 2021).

The research literature shows significant deficits in several domains of executive functioning in children exposed to alcohol during pregnancy across the FASD spectrum compared to control children (Kingdon et al., 2016; Rasmussen, 2005). However, studies also indicate that the effects seem to be more profound in children exposed to heavy alcohol use during pregnancy (Khoury et al., 2018). Studies indicate that alcohol-exposed children and adolescents have impairments in behavioural and emotional self-regulation, problem-solving and planning abilities (Green et al., 2009). Furthermore, deficits in cognitive flexibility also referred to as set-shifting have been observed among children with prenatal alcohol exposure, potentially predicting

some of the behavioural problems observed in exposed populations (Khoury et al., 2018; Tsang et al., 2016). As discussed in Section 2.2.1, deficits in working memory are also observed (Mattson et al., 2019). Studies also indicate that deficits in the executive functioning domains can extend into adulthood (Rangmar, Sandberg, et al., 2015; Rockhold et al., 2021).

Furthermore, attention problems are frequently reported among prenatally alcohol-exposed children, and ADHD is shown to be a highly prevalent co-occurring behavioural disorder in individuals exposed to alcohol during pregnancy (Lange et al., 2018; Sayal, et al., 2014). In a systematic review, Weyrauch et al. (2017) reported that 50.0% of individuals with FASD had a diagnosis of ADHD. Earlier studies have suggested an even higher co-occurrence of FASD and ADHD, although in different ethnic groups (Fryer et al., 2007; Rasmussen et al., 2010). Although ADHD is a highly co-occurring disorder among individuals with FASD, the etiological pathways to FASD and ADHD may differ (Vaurio et al., 2011). In addition, the pattern of deficits in attention and executive functioning has shown to differ between prenatally alcohol-exposed children and unexposed children with ADHD (Peadon & Elliott, 2010). However, in a meta-analysis, Khoury et al. (2018) indicated that although children and adolescents with prenatal alcohol exposure exhibit more behavioural problems than those with ADHD, the differences between these groups were not statistically significant. Khoury et al. (2018) also reported that contextual factors (e.g. home placement, family's socioeconomic status) can moderate the association between prenatal alcohol exposure and externalising disorders. In addition to ADHD, studies have also reported an association between prenatal alcohol exposure and ODD and CD (Lange et al., 2018; Ruisch et al., 2018).

Deficits in executive functioning have also been reported among children exposed to illicit drugs during pregnancy (Minnes et al., 2011; Nygaard et al., 2016). Studies on prenatal exposure to cannabis have shown associations between exposure and executive functioning deficits and externalising disorders including inattention, hyperactivity, impulsivity, and aggression among children (Cioffredi et al., 2022; Fried & Smith, 2001; Rompala et al., 2021) and young adults (Smith et al., 2016). However, co-occurrence with ADHD seems to be unclear (Tchuente et al., 2022). Studies on children exposed to psychostimulants (cocaine) during pregnancy show deficits in specific areas of executive functioning, including inhibitory control, visual-perceptual ability, attention, and aggressive behaviours (Ackerman et al., 2010; Lambert & Bauer, 2012). Studies have also described that in some areas of executive

functioning, the independent effects of prenatal cocaine exposure appear to be subtle, and other factors (including the child's age and sex and the caregiving environment) can influence the observed difficulties with executive functioning (Ackerman et al., 2010; Lambert & Bauer, 2012). Prenatal exposure to methamphetamine has been shown to be associated with some areas of executive functioning, including attention, and exposure has also been linked to co-occurrence of ADHD and ODD (Kiblawi et al., 2013; LaGasse et al., 2012). In terms of prenatal exposure to opiates, studies have indicated associations between the exposure and child's externalising behaviours including attention issues and higher likelihood of ADHD relative to controls (Balalian et al., 2023).

2.2.3 Adaptive functioning

Adaptive functioning refers to the development of personal and social skills that are essential in performing daily activities. Furthermore, adaptive functioning refers to skills that gradually enable independent living, maintaining social relationships, and becoming an active member of society (Anderson, 2010). Adaptive skills are age-related and can be conceptualised in the domains of communication (receptive, expressive and written communication), daily living skills (e.g. how an individual is able to use time and money, perform household tasks, and perform at work). and socialisation (e.g. how an individual is able to interact with others) (Anderson, 2010).

Research on adaptive functioning has been conducted among prenatally alcohol-exposed children and adolescents with a diagnosis within the FASD spectrum, whereas studies conducted among children with prenatal exposure to illicit drugs are lacking. The existing studies on children and adolescents exposed to alcohol during pregnancy show deficits in different domains of adaptive functioning (Kautz-Turnbull & Petrenko, 2021; Mattson et al., 2019). The deficits in adaptive functioning seem to persist event when compared to children with comparable IQ levels and learning difficulties (Fagerlund et al., 2012) or with children with ADHD (Crocker et al., 2009). The research findings from Crocker et al. (2009) and Fagerlund et al. (2012) also demonstrated that deficits in adaptive functioning can become more pronounced with increasing age, as the adaptive tasks expected of an individual are more difficult and involve more complex executive functioning abilities. Consequently, prenatally alcohol-exposed children and adolescents may not be able to function at an optimal level, which can negatively impact their capacity to adapt

to environmental demands. Research results have indicated a decline, especially in socialisation skills with increasing age in the FASD group compared to control groups (Crocker et al., 2009; Fagerlund et al., 2012). A similar association between adaptive behaviour and age was not observed by Hammond et al. (2022). Research suggests that prenatal alcohol exposure does not alone explain the impairments in adaptive functioning, but it is also influenced by caregiving factors (Fagerlund et al., 2012).

2.3 The postnatal caregiving environment and the effects on child health and development

The characteristics of the postnatal caregiving environment and caregiving can have a significant influence on child's health, functioning and development. In particular, adversities or traumatic events occurring during childhood as well as compromised parenting behaviours (e.g. neglect in caregiving) can have a harmful influence on a child's development and increase the likelihood of developmental concerns (Anda et al., 2006; Felitti et al., 1998; Norman et al., 2012).

The following sections describe the research literature on the postnatal caregiving environment and the effects on a child's health and development. First, early life adversities and underlying factors reflecting the associations with inferior developmental outcomes are discussed. Next, the attachment relationship between the caregiver and its role in a child's development are described. Finally, the research literature on the associations between out-of-home care and a child's development is described. The focus is on the context of maternal prenatal substance abuse.

2.3.1 Maternal substance abuse and adversities in the postnatal caregiving environment

Adversities or adverse experiences in childhood can be defined as any act or series of acts by a caregiver that can cause harm or threaten a child (Felitti et al., 1998). Adversities can include a child's physical, emotional, or sexual abuse and neglect of care, reflecting a failure to provide for the shelter, safety, supervision, and nutritional needs of the child. Adversities can also include the loss of a parent or close relative,

and life difficulties or household dysfunction, including parental separation, parental financial difficulties, substance use or mental health issues, domestic violence, and criminality (Anda et al., 2006; Lebel et al., 2019; Norman et al., 2012). The adversities tend to be interlinked and co-occur. Thus, exposure to a cumulative number of adversities appears to be common among individuals who have been exposed to one type of childhood adversity (Felitti et al., 1998; Turney & Wildeman, 2017).

Children born to mothers with prenatal substance abuse often face a double jeopardy. Not only are their health and development influenced by the teratogenic effects of prenatal substance exposure, but they are also at a heightened risk of experiencing an accumulation of adversities in the postnatal caregiving environment (Esper & Furtado, 2014; Flannigan et al., 2021; Lebel et al., 2019; McQuire et al., 2020). Adversities that are often observed in mothers with prenatal substance use include maternal low educational level, financial difficulties, single parenthood, co-occurring health conditions (including physical and mental health issues), and care instability (Esper & Furtado, 2014; Flannigan et al., 2021; Havens et al., 2009; Holmila et al., 2017). These adversities in the postnatal caregiving environment can manifest as a chaotic caregiving environment, harming a child's safety and increasing the risk of neglect of care (Walsh et al., 2003). In addition, maternal life difficulties or depression can affect parenting behaviours and limit the mother's ability to respond to the child's physical and/or emotional needs sensitively and responsively or limit her ability to socially engage with the child (Conners et al., 2009; Coyne & Thompson, 2011; Monk et al., 2012).

It is well-documented that exposure to early life adversities is associated with a child's health and developmental concerns. The underlying mechanisms explaining these associations are complex. Many indirect and direct pathways have been proposed, and many factors can mediate the link between early life adversities and later outcomes. These factors can include individual variations in sensitivity to stressors influenced by the interaction between genetics and environment, the developmental timing of exposure, the type of adversity the child has been exposed to, and the availability of supportive relationships (Boyce et al., 2021; Cassiers et al., 2018; Morgart et al., 2021). Studies indicate that particularly repeated and prolonged exposure to adversities in the early years of life without the protection of a supportive relationship can disrupt the development of the brain and other organ systems (Boyce et al., 2021; Shonkoff & Garner, 2012). These disruptions can manifest as impairments in cognitive and socioemotional functioning, produce maladaptive

behaviours, and increase susceptibility to various mental health disorders (Boyce et al., 2021; Drevets et al., 2008; Nelson et al., 2020; Shonkoff & Garner, 2012).

One of the underlying mechanisms relates to neuroplastic alternations in the brain structure and functioning induced by exposure to stressors (Cassiers et al., 2018; Hart & Rubia, 2012). From the neurobiological perspective, the plasticity of the brain in the early years of life and the maturation of the different brain regions until adolescence makes the brain vulnerable to the influence of stress (Bick & Nelson, 2016; Hart & Rubia, 2012; Lupien et al., 2009). Prolonged and repeated stress, and even acute exposure to stressors, can increase the risk of lasting structural and functional impairments in specific brain areas and the connectivity between different brain areas. The prefrontal cortex and the limbic region (including the hippocampus and amygdala) appear to be particularly vulnerable to the effects of stress (Bick & Nelson, 2016; Cassiers et al., 2018; Shonkoff & Garner, 2012).

As described in Section 2.1.1, the prefrontal cortex has a role in top-down regulations of behaviour, actions, thoughts, and emotions (Jones & Graff-Radford, 2021). Studies have shown that exposure to psychological stress can lead to impairments in the structures and functioning of the prefrontal cortex and its subregions (e.g. decreased activity) and connectivity to other brain areas (e.g. to the amygdala) (Negrón-Oyarzo et al., 2016; Woo et al., 2021). The effects of stress have been found in cognitive functioning that relies on the prefrontal cortex, including working memory, attention, and decision-making, as well as with emotion regulation. Furthermore, studies show that stress-induced prefrontal cortex dysfunction (e.g. in the medial cortex – subregion of the prefrontal cortex) may underlie various neurological disorders, including depression and anxiety (Chen et al., 2022; Chocyk et al., 2013).

The prefrontal cortex is also interconnected with amygdala −another brain area vulnerable to the effects of stress (Cassiers et al., 2018). The amygdala has a major role in evaluating sensory information from different brain regions and inducing an appropriate response. The amygdala also plays a role in detecting a threat and triggering a response to the perceived threat in the brain and body. During stress, the amygdala is hyperactive and hyperreactive (Shackman et al., 2016). Studies have shown that exposure to prolonged and repeated stress (or even acute stress) in early years of life can lead to structural and functional changes in the amygdala and greater reactivity to emotional information (Etkin & Wager, 2007). This can affect a child's socio-emotional outcomes (e.g. emotional responses) and later psychopathology

(Etkin & Wager, 2007; Miguel et al., 2019). Studies have shown larger amygdala volumes and increased amygdala activity in children and adolescents with anxiety relative to typically developing controls (Etkin & Wager, 2007; Shackman et al., 2016).

Another interconnected region vulnerable to the effects of stress is the hippocampus, which is primarily involved in memory but also stress regulation, as described in Section 2.1.1 (Shonkoff & Garner, 2012). Exposure to early-life stress has been shown to alter the structure and functioning of the hippocampus and can thus lead to memory impairments and alterations in mood related functions (Kim et al., 2015).

These interconnected brain regions (i.e. the prefrontal cortex, amygdala, and hippocampus) are also interlinked with HPA axis activation through communication with the hypothalamus (which has a role in maintaining body's homeostasis) (Smith & Vale, 2006). The HPA axis represents the interaction between the hypothalamus, pituitary gland, and adrenal glands. These organs have a role in producing chemicals that help the body respond to stress. When a perceived stress stimulus occurs, the hypothalamus releases a corticotrophin-releasing hormone that sends a signal to the pituitary gland. The pituitary gland then releases an adrenocorticotropic hormone. This triggers the adrenal glands to release cortisol, which prepares the body to either flee or fight the stressor. After initiation of the stress response, the increased cortisol level can act on the hypothalamus and pituitary and inhibit the production of the corticotrophin-releasing hormone and the adrenocorticotropic hormone. This is termed a negative feedback loop (Sheng et al., 2021; Smith & Vale, 2006). Research has shown that exposure to prolonged stress early in life can alter HPA axis development and functioning and lead to chronic activation of the HPA axis (Sheng et al., 2021). Inappropriate regulation of stress responses and dysregulation of HPA axis activity can increase vulnerability to immune system dysfunction, various health conditions (including diabetes and cardiovascular diseases), and mental health disorders (including anxiety and depression) (Hellemans et al., 2008, 2010; Smith & Vale, 2006; Weinberg et al., 2008).

Early life adversities can be especially harmful in the prenatally substance-exposed populations due to prenatal substance exposure-induced abnormalities in the brain structure and functioning (Guerri et al., 2009; Moore et al., 2014; Nuñez et al., 2011) and impaired development of the body's stress-response system, including the HPA axis (McLachlan et al., 2016; Weinberg et al., 2008). Research findings have

demonstrated that children exposed to both alcohol during pregnancy and early life adversities are at high risk of poor developmental outcomes (Kambeitz et al., 2019). Henry et al. (2007) compared children exposed to traumatic experiences with or without prenatal alcohol exposure. The results indicated that children in both groups exhibited neurodevelopmental deficits, but the deficits were more severe in the prenatally alcohol-exposed group (Henry et al., 2007). Studies done among children with prenatal exposure to illicit drugs also show that characteristics of the caregiving environment have a major influence on developmental outcomes (Chu et al., 2020; Karpova et al., 2021). The results of a study by Karpova et al. (2021) indicated that adolescents (males in particular) with prenatal exposure to cocaine and high environmental risk were at risk of poorer functioning relative to non-exposed controls.

The increased vulnerability to stress combined with exposure to early life adversities in the postnatal caregiving environment can further increase exposed children's vulnerability to health and developmental concerns in the youth period (McLachlan et al., 2016). However, there is a paucity of studies on long-term health and developmental outcomes in prenatally substance-exposed youth populations with exposure to various early life adversities.

The associations between adversities in the postnatal caregiving environment and long-term health and developmental outcomes among the general youth population have been well-documented in the research literature (Bradley & Corwyn, 2003; Felitti et al., 1998; McKay et al., 2022; Shonkoff et al., 2009). Several studies describe the association between exposure to various early life adversities and increased risk of physical and mental/behavioural disorders in youth (e.g, ADHD, mood disorder, anxiety) (Björkenstam et al., 2016, 2017; McKay et al., 2022; Raitasalo et al., 2017, 2019). Studies have also reported that exposure to early life stress is associated with depression severity and earlier onset of depression (Nelson et al., 2017). The type of early life adversity may also affect the risk of developing a mental health disorder (McKay et al., 2022; Nelson et al., 2017). In addition, associations have been found between various early life adversities and low educational attainment (Berg et al., 2016; Raitasalo et al., 2021), employment difficulties, and risky behaviour, including early initiation of alcohol use (Christoffersen & Soothill, 2003).

2.3.2 Maternal substance abuse and attachment relationship with the child

Another crucial aspect of the influences of the postnatal caregiving environment on a child's health and development relates to the caregiving and caregiver-child attachment. A caregiver's responses to a child's cues for care in a sensitive, responsive, and predictable way and healthy caregiver-child interaction are essential for a child's healthy development. The quality of the primary caregiver's caregiving behaviours, often maternal caregiving, plays a critical role in a child's cognitive and socioemotional development and psychopathology (Bick & Nelson, 2016; DeKlyen & Greenberg, 2016; Groh et al., 2017).

The theory of attachment, proposed by John Bowlby in the 1950s (Bowlby, 1969) characterises the attachment relationship between an infant and a caregiver. An attachment relationship describes the emotional connectedness, bond, or tie between two people who both attempt to maintain closeness to the other and ensure a lasting relationship (Bowlby, 1969).

The first attachment bonds are established in infancy, and according to Bowlby, the attachment is formed through four developmental phases from birth to the final stage when the child is 24–30 months old (Bowlby, 1969). The caregiver (i.e. attachment figure) has an important role in offering comfort and protection for the child in a predictable way when they are stressed. This, in turn, enhances the development of an attachment relationship between the child and the caregiver (Ainsworth et al., 2015). In other words, the caregiver is the infant's secure base in times of distress, and the early interaction between the infant and the primary caregiver influences the child's ability to express and regulate emotions (Brumariu, 2015; Cassidy, 2016). Thus, the Attachment relationship form the framework for a child's socio-emotional development and the development of psychopathological conditions (Bick & Nelson, 2016; DeKlyen & Greenberg, 2016; Groh et al., 2017).

In the 1970s, Ainsworth and colleagues discovered different patterns of attachment between an infant and primary caregiver following the responses during the Strange Situation study − an observational procedure to characterise the security of attachment when the infant is under stress (Ainsworth et al., 1978). Based on the results of the Strange Situation study, the following attachment styles have been described: Secure Attachment, Insecure-Avoidant Attachment, Insecure-Resistant Attachment, and Insecure-Disorganised Attachment (Ainsworth et al., 1978).

Secure attachment is typically characterised by safety and by sensitive and responsive caregiver interaction with the child. In a secure caregiver-child attachment relationship, the caregiver also encourages the child to express different emotions (Brumariu, 2015). Securely attached children are confident in exploring their surroundings and returning to their attachment figure when feeling frightened. Secure attachment has been associated with emotion-regulation abilities and positive socioemotional development from infancy to adolescence (Brumariu, 2015; Groh et al., 2017). Furthermore, securely attached children tend to be more socially competent, have better abilities to form and sustain friendships, and have better self-esteem and peer competence (Groh et al., 2017).

By contrast, insecure attachment, often linked with difficult parental life situations and adversities in the postnatal caregiving environment, is related to fewer interactions with the child and rigid, unresponsive, inconsistent, or demanding reactions from the caregiver (Kobak et al., 2016). Maternal depression can also affect the mother's ability to respond to her child's cues for care predictably and sensitively, thus, increasing the risk of insecure attachment (Barnes & Theule, 2019). Consequently, an infant's negative emotional states can last for long periods of time. This can cause alterations in the biochemistry of the immature brain (Schore, 2001). Insecure attachment, especially disorganised attachment, has been associated with long-term negative outcomes including poor social skills and peer relationships, externalising disorders, and attention problems (Fearon et al., 2010; Groh et al., 2012; Kobak et al., 2016; Pallini et al., 2019). Furthermore, studies have shown associations between insecure attachment and a child's impaired capabilities to regulate emotions and cope with stress. Impaired emotion-regulation abilities have been associated with an increased risk of internalising disorders in childhood and youth, including anxiety and depression (Cooke et al., 2019; Groh et al., 2012; Schore, 2001).

Research shows that maternal substance abuse and associated adversities can affect the mother's ability to take care of the child's physical and emotional needs in a predictable and responsive way, thus forming a risk for an unhealthy attachment relationship between the mother and child (Walsh et al., 2003). Furthermore, studies show that interaction with the child is often disturbed among mothers with substance abuse (Frigerio et al., 2019; Pajulo et al., 2001; Salo et al., 2009), and the attachment relationship between the mother and child is often characterised as unhealthy and insecure (O'Connor et al., 2002; Staton-Tindall et al., 2013).

2.3.3 Out-of-home care in prenatally substance-exposed children

Maternal prenatal and postnatal substance abuse and the highly prevalent and co-occurring life difficulties (Esper & Furtado, 2014; Flannigan et al., 2021; Havens et al., 2009) can indicate severe risks for the child's wellbeing and safety, thus reflecting the need for child welfare services. If reasonable efforts have been made and concerns for the child's safety still exist, the child can be placed in out-of-home care (OHC) (Christoffersen & Soothill, 2003; Sarkola et al., 2007). Research shows that a high proportion of children exposed to maternal prenatal substance abuse are placed in OHC during early childhood (Flannigan et al., 2021; Kambeitz et al., 2019; Price et al., 2017; Sarkola et al., 2007). In addition, studies of children in OHC show a relatively high prevalence of children with a history of prenatal exposure to alcohol and/or illicit drugs and thus a high proportion of undiagnosed or misdiagnosed FASD in children in OHC (Chasnoff et al., 2015; Lange et al., 2013; Tenenbaum et al., 2020).

Few studies have studied the developmental outcomes of children with prenatal substance exposure placed in OHC. Current evidence shows poor developmental outcomes in the areas of cognitive and behavioural functioning (Bada et al., 2008; Fagerlund et al., 2011; Koponen et al., 2009) and increased vulnerability to challenges in the youth period or adulthood (Streissguth et al., 2004). A few studies have also shown that characteristics of OHC (including instability of the child's living situations, age at placement outside the biological home, and type of care) can be associated with the observed poor developmental outcomes (Bada et al., 2008; Koponen et al., 2022; Streissguth et al., 2004). Bada et al. (2008), for example, showed that instability in the child's living situation – including number of moves, changes in the caretaker, duration of child protective service involvement, and other characteristics of the household – was a significant predictor of observed behavioural problems and poorer scores in adaptive functioning among 3-year-old children with prenatal exposure to cocaine or opiates (Bada et al., 2008). Parallel to these findings, Fagerlund et al. (2011) also showed that childhood environments, especially residential care, exert a strong influence on behavioural outcomes in children and adolescents with FASD. The results of the study showed that the time spent in residential care was the most significant risk factor for internalising, externalising, and total behavioural problems in the studied population with FASD (Fagerlund et al., 2011).

Studies have also indicated a protective effect of an early placement in OHC. In a qualitative study, Koponen et al. (2013) compared the socio-emotional development of children with a diagnosis within the FASD spectrum in two groups within long-term foster family care. The first group included children taken into care at birth (n=7). The second group included children who had lived their first years of life with their biological parents and were placed into long-term foster family care at an older age (n=27). The results indicated that children in both groups displayed somatic and neuropsychological disabilities linked to prenatal alcohol exposure, but concentration and hyperactivity problems seemed to be more severe in the second group. Furthermore, the results showed that children in the second group had more socio-emotional problems and were more difficult to foster. In addition, these children had serious behavioural and attachment problems and developmental delays (Koponen et al., 2013). In another study, Koponen et al. (2009) showed that early placement was associated with fewer attention problems among children with prenatal alcohol exposure compared to children with prenatal alcohol exposure placed at an older age.

Research among older children or youth with prenatal substance exposure and OHC history is limited. In a register-based study based on the same data from the ADEF Helsinki study as this dissertation, Koponen et al. (2022) explored whether the type of OHC and number of OHC placements were associated with mental and behavioural disorders among 15–24-year-old youths with prenatal substance exposure in comparison to matched unexposed controls. The results showed that the youth with prenatal substance exposure had entered OHC at a younger age, had been placed in OHC for a longer period, had a higher number of separate OHC placements, and had been placed in family-type OHC more often than their unexposed age-mates. The results showed that a higher number of separate OHC placements was associated with an increased likelihood of mental and behavioural problems in both groups (Koponen et al., 2022).

Several studies have investigated the developmental outcomes of children and youth with an OHC history without information on prenatal substance exposure (Brännström et al., 2017; Côté et al., 2018; Egelund & Lausten, 2009; Kääriälä et al., 2018, 2019, 2021; Lehmann et al., 2013; Vinnerljung & Sallnäs, 2008). Like the studies conducted among prenatally substance-exposed children, these studies show impairments in cognitive, executive, and socioemotional functioning and an increased likelihood of externalising and internalising symptoms (Bick & Nelson,

2016; Loman et al., 2013; Wiik et al., 2011). The characteristics of the OHC (e.g. type of care, time spent in care) can also influence the outcomes (Bick & Nelson, 2016).

Often children and youth leave OHC at the age of emancipation before they are fully able to support themselves. Thus, many youths with an OHC history can encounter difficulties when they leave OHC and enter independent adulthood (Bronsard et al., 2016; Kääriälä & Hiilamo, 2017). Studies show poor youth outcomes in many domains, including overall wellbeing and life satisfaction (Ikonen et al., 2020), mental health and behaviour, including substance use (Bronsard et al., 2016; Egelund & Lausten, 2009; Ikonen et al., 2020; Lehmann et al., 2013; Turney & Wildeman, 2016), education (Kääriälä et al., 2018, 2019), employment and financial self-supporting (Brännström et al., 2017; Kääriälä et al., 2019; Vinnerljung & Sallnäs, 2008), and criminality (Côté et al., 2018). Research has suggested that these outcomes are not only influenced by the adversities these children and youth have been exposed to during childhood and adolescence preceding OHC but also by characteristics of the OHC (Jones et al., 2011), as previously described.

2.4 Youth period

The years from the late teens to the twenties describe a developmental phase of exploration, change, and importance. There is no single definition for this period. Following the definition of the UN (United Nations, n.d.), the term youth is used here to refer to this phase of life and years (i.e. the ages from 15 to 24 years).

Youth is a critical developmental phase that describes the transition from childhood to independent adulthood. The transition phase is characterised by significant parallel developmental phases including physical, cognitive, emotional, and social development. In addition, the youth period is also characterised by neurobiological changes and includes continuing brain development and maturation, especially the brain regions involved in behaviour and emotion regulation and executive functioning (Arain et al., 2013; Arnett, 2000; Ravindranath et al., 2023). Youth can also be a sensitive developmental phase and a period for the onset of various forms of mental/behavioural disorders (Kessler et al., 2007; Ravindranath et al., 2023).

The youth period can include several markers of the achievement of adult independence and becoming self-sufficient. These markers can include obtaining

higher education, the transition from family living into independent living, the transition from education to work, obtaining economic self-sufficiency, and establishing relationships (Arnett, 2000).

The youth period and transition to independent adulthood can be a period characterised by challenges, especially among individuals with disabilities, including individuals with intellectual disabilities or deficits in adaptive functioning abilities (Floyd et al., 2009; Gray et al., 2014). The transition period can also be challenging due to highly prevalent mental health disorders, including anxiety and depression, potentially challenging the ability to establish adult independence (Austin et al., 2018; Kessler et al., 2007).

For these reasons, the transition phase can be especially challenging for individuals with prenatal substance exposure. The CNS dysfunction that ensues from prenatal substance exposure and the subsequent deficit in cognitive, behavioural, and adaptive functioning can predispose these individuals to challenges in everyday life, thus, making youth with prenatal substance exposure vulnerable to challenges during the youth period (Korkman et al., 2003; McLachlan et al., 2020; Spohr et al., 2007; Streissguth, 2007). Furthermore, exposure to adverse experiences and caregiving instability among prenatally substance-exposed youth (Flannigan et al., 2021; Koponen et al., 2020b; Price et al., 2017) can add to this and further increase the vulnerability to poor developmental trajectories during the sensitive youth.

2.5 Prenatal substance exposure and its association with secondary disabilities in youth

The effects of prenatal substance exposure on CNS dysfunction and the primary disabilities can predispose exposed individuals to other challenges in life. In the research literature, these challenges are termed secondary disabilities or secondary conditions (Streissguth, 1996).

Secondary disabilities represent challenges in different areas of life, including mental health, education, alcohol and/or other substance use, independent living and employment, and delinquent behaviour. Challenges in these areas of life have been observed particularly among prenatally alcohol-exposed individuals (Easey et al., 2019; Fast & Conry, 2009; Flannigan et al., 2018; Lynch et al., 2017; Rangmar et

al., 2017; Rangmar, Hjern, et al., 2015; Streissguth, 2007), whereas studies conducted among youth with prenatal exposure to illicit drugs or polysubstance use are scarce.

In the following section, research findings on the secondary disabilities of interest of this dissertation, i.e. internalising disorders (mood and neurotic disorders), educational outcomes in secondary education, and financial difficulties (receipt of financial social assistance) and other aspects of adult independence − will be reviewed. The focus is on secondary disabilities in the youth period. However, results from child or adult populations are also briefly described.

2.5.1 Internalising disorders

Internalising disorders or internalising behaviours including mood disorders (e.g. depressive disorders and bipolar affective disorders) and neurotic disorders (e.g. anxiety disorders, panic disorders, and obsessive-compulsive disorder) are mental health disorders with self-directed symptoms. These mental health disorders typically co-occur, with a typical onset in youth or young adulthood (Kessler et al., 2007; Solmi et al., 2021). These disorders are associated with increased morbidity and mortality, and they have a high likelihood to recur (Patel et al., 2007; Thapar et al., 2012).

It has been estimated that approximately 15.0% to 25.0% of Finnish youth have experienced some sort of mental health disorder; mood and neurotic disorders are some of the most commonly observed (Marttunen & Kaltiala, 2021). Also, the results from the Finnish School Health Promotion study from 2019 show similar estimates. Approximately 20.0% of Finnish youth aged 14 to 17 years had experienced moderate or severe symptoms of anxiety during the last two weeks, while the corresponding proportion in 2021 during the COVID-19 pandemic was approximately 30.0%. The results from 2019 showed that approximately 25.0% of these youth had experienced symptoms of depression during the last two weeks. The proportion was higher in 2021 (approximately 30.0%) (Finnish Institute for Health and Welfare, 2021).

Typically, these disorders are more often observed among females than males (Kuehner, 2003; Rapee et al., 2009). Other factors contributing to these disorders include prenatal risk factors such as exposure to alcohol during pregnancy and parental psychopathology (Andre et al., 2020; Basu & Banerjee, 2020; Essex et al.,

2006; Su et al., 2021). Furthermore, psychosocial factors, including exposure to adverse and traumatic experiences in early life (in particular, prolonged and repeated exposure to stressors) can lead to neurobiological alterations in the brain and HPA axis and stress-induced internalising disorders (Cassiers et al., 2018) (See Section 2.3.1). Parenting behaviours and caregiver-child interaction are also shown to influence offspring's likelihood of developing internalising disorders (Rapee et al., 2009; Reising et al., 2013; Staton-Tindall et al., 2013) (See Section 2.3.1).

The association between prenatal substance exposure and internalising disorders is a complex research area. These associations have been mainly studied among children with prenatal alcohol exposure and as part of other mental/behavioural disorders (including externalising disorders). Furthermore, the existing studies have used varying study designs and methods to assess child or youth symptoms (e.g. clinical or parental assessment of a child's symptoms). These studies also vary in terms of exposure assessment, follow-up times, and study populations. Also, the inclusion of comparison groups varies between the studies as well as methods used to adjust for potential confounders. These methodological differences may reflect the slight variation observed in the research findings.

Studies from child populations indicate a high prevalence of various forms of internalising disorders (including depression, anxiety, panic attacks, and emotional problems) and sleep disturbances in prenatally alcohol-exposed children either with or without a diagnosis within the FASD spectrum (O'Connor & Kasari, 2000; O'Connor & Paley, 2006, 2009; Walthall et al., 2008). Some studies indicate a higher rate of various internalising disorders in the prenatally alcohol-exposed group compared to a control group (e.g. Fryer et al., 2007), while other studies (e.g. Sood et al., 2001; Walthall et al., 2008) have not observed differences in the internalising disorders in exposed children relative to controls. Furthermore, some studies from child populations have shown an association between prenatal alcohol exposure and children's symptoms of internalising disorders even after covariate adjustments (Lees et al., 2020), while other studies show small or no associations after controlling for the influence of other risk factors (Walthall et al., 2008). Studies have also indicated that factors including the child's sex and maternal depression (O'Connor & Kasari, 2000) and adverse experiences during childhood (including the mother-child relationship and parenting) are linked to a child's symptoms of internalising disorders (O'Connor & Paley, 2006).

There is a limited number of studies on internalising disorders in prenatally alcohol-exposed populations extending to the youth period. In a meta-analysis, Khoury et al. (2018) stated that age moderates the association between prenatal alcohol exposure and internalising disorders. That is, internalising disorders tend to peak in adolescence, and therefore, due to the focus on child populations, we may not have a clear understanding of the extent of internalising disorders in youth in these populations (Khoury et al., 2018).

The limited number of studies on internalising disorders in prenatally alcohol-exposed youth populations are described in Table 1 (listed in publication order). Despite methodological differences, most of these studies have indicated a high prevalence of internalising disorders in prenatally alcohol-exposed youth (Easey et al., 2020; Famy et al., 1998; Fryer et al., 2007). However, there is a variation in the findings, which possibly reflects methodological differences.

Starting from the earliest work, Streissguth et al. (1996) reported that in the overall sample that include individuals aged 6 to 51 years with a diagnosis within the FASD spectrum, 94.0% reported mental health problems. The most observed mental health problems among participants aged 12 to 20 years were attention deficit problems followed by depression. Among participants aged 21 to 51 years, the most common mental health problems were depression followed by suicide threats. The first sign of mental health problems among participants aged 12 or more was typically related to depression (Streissguth et al., 1996) (Table 1).

Studies that include a comparison group have shown varying results. The observed differences between exposed youth and a control group seem to vary by the studied internalising disorder and/or the level of prenatal alcohol exposure. Barr et al. (2006) reported an increased likelihood of various psychiatric disorders in young adults exposed to binge drinking in mid-pregnancy. However, the difference was not statistically significant compared to the unexposed group. In a more recent study, Duko et al. (2021), on the other hand, reported a higher likelihood of depression in youth exposed to heavy alcohol use during pregnancy than in non-exposed youth, even after a covariate adjustment. However, differences in the likelihood of depression compared with non-exposed youth were not observed among youth with exposure to light or moderate alcohol use during pregnancy in either univariate or adjusted analysis (Duko et al., 2021). In another study, Duko et al. (2022) assessed anxiety symptoms among youth with prenatal alcohol exposure compared to non-exposed youth. Although the results suggested an increase in the

symptoms of anxiety with increasing levels of alcohol exposure during pregnancy in comparison with unexposed youth, the associations were not statistically significant, either in the univariate or adjusted analysis (Duko et al., 2022) (Table 1).

The studies also suggest that the association between prenatal alcohol exposure and youth internalising disorder may not be direct but rather influenced by other factors. Hill et al. (2000) reported an association between maternal prenatal alcohol use and offspring childhood/adolescent anxiety disorder and depressive disorder. However, the association was non-significant after covariate adjustments. Easey et al. (2020) also showed an association between maternal alcohol use at 18 weeks of gestation and offspring's diagnosis of depression at the age of 18 years. However, the association was slightly attenuated after controlling for the influence of socioeconomic factors and maternal behaviours (Easey et al., 2020).

A few studies on internalising disorders extend beyond youth period (Coles et al., 2022; Famy et al., 1998; Rangmar et al., 2017). These studies include small samples mainly including individuals who meet the criteria for FAS, thus potentially reflecting internalising disorders in more severely affected individuals. Overall, these studies from the adult population show that adults with FAS or Fetal Alcohol Effect[1] report a high rate of internalising disorders − including major depressive disorders, psychotic symptoms, bipolar disorder and anxiety disorder − and symptoms requiring psychiatric treatment or hospitalization in a psychiatric institution (Coles et al., 2022; Famy et al., 1998; Rangmar et al., 2017). Rangmar et al. (2017) reported a higher rate of self-reported psychiatric problems, including depression and anxiety (among other problems) in the FAS group compared with the comparison group. However, group differences were not observed in psychiatric problems measured with the Beck Anxiety Inventory or Beck Depression Inventory. Coles et al. (2022), on the other hand, reported higher rates of depression, bipolar disorder, anxiety disorder, and ADHD in alcohol-exposed groups (including the alcohol-exposed/Fetal Alcohol Effect group and FAS group) compared with the non-exposed. Coles et al. (2022) also accounted for the influence of other factors, and the results of the study showed that the association between prenatal alcohol exposure and the studied mental health disorders was not direct but rather indirect

[1] Fetal Alcohol Effect is a previously used term to describe deficits in intellectual abilities and behavioural problems in children with prenatal alcohol exposure.

mediated by environmental factors including adverse childhood experiences and an adult's social and economic status (Coles et al., 2022).

Studies on internalising disorders among individuals exposed to illicit drugs are limited and mainly conducted among children. To the best of my knowledge, only one study extends to youth (Nygaard et al., 2020) (Table 1).

The studies conducted among children with prenatal exposure to illicit drugs include children exposed to cannabis/marijuana, opioids, or polysubstance use. These studies have used various methods to evaluate symptoms of internalising disorders. The results of Paul et al. (2021) showed that prenatal exposure to cannabis before and after maternal knowledge of pregnancy was associated with higher child-reported psychotic-like experiences and internalizing and externalizing problems among other measured mental/behavioural outcomes in children at the age of 8 to 9 years. In the covariate-adjusted analysis, prenatal exposure to cannabis after maternal knowledge of pregnancy was associated with an increased likelihood of child-reported psychotic experiences and internalizing and externalizing problems among other mental/behavioural outcomes relative to those without exposure and those with prenatal cannabis exposure before maternal knowledge of pregnancy (Paul et al., 2021). Rompala et al. (2021) also showed a positive association between prenatal cannabis exposure and childhood anxiety and other measured externalising behaviours (e.g. aggression and hyperactivity) among 3−6-year-old children. In a study, Gray et al. (2005) also showed a positive association between marijuana use during the first trimester and a child's depressive symptoms at the age of 10 years, even after controlling for other pre- and postnatal confounding factors. On the contrary, marijuana use during the second trimester was not associated with a child's depressive symptoms (Gray et al., 2005). El Marroun et al. (2019) on the other hand reported no association between prenatal cannabis exposure and childhood internalising disorders.

The study by Nygaard et al. (2020) investigated mental health outcomes among 45 children exposed to illicit drugs during pregnancy who were mainly placed in permanent foster or adoptive homes in early infancy in comparison to 48 unexposed youth at the ages of 17–22 years (Table 1). For internalising disorders, the results showed that the exposed groups had a higher prevalence of major depressive disorders and anxiety disorders than the unexposed group. After adjusting the analysis for gender, age, and caregiver education, only the association between prenatal drug exposure and major depressive episodes remained statistically

significant. The results from the self-reported responses indicated no statistically significant differences between the groups (Nygaard et al., 2020).

Table 1. A summary of studies investigating internalising disorders (including mood and neurotic disorders) in youth with prenatal exposure to substances

Authors, year, study country	Study title	Study population	Assessment of mental health outcomes	Main findings related to mental health outcomes including internalizing disorders
Prenatal alcohol exposure				
Streissguth et al., 1996, United States	Understanding the occurrence of secondary disabilities in clients with Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE): final report	415 participants, all with diagnosed FAS, Fetal Alcohol Effect, partial Fetal Alcohol Effect or ARND. 57.0% of the participants were male. At the time of interview, 39.0% were 6–11 years old, 39.0% were 12–20 years old, and 22.0% were over 21 years.	Mental health outcomes were assessed using a Life History Interview. The interview was administered by telephone to caretakers/informants of the study participants. The interview covered behaviour management and mental health issues among other items (e.g. independent living and financial management, education, and employment). Mental health problems were recorded if the participant described ever having had any mental health problems, had gone to a psychiatrist, psychotherapist or counselor for mental health problems, or had been hospitalized in a psychiatric or mental health hospital.	In the overall sample (*n*=415), 94.0% reported mental health problems. A variation in the mental health problems was observed by age. Among participants aged 6 to 11 years, the most common mental health problems were attention deficit problems (60.0%). Among participants aged 12 to 20 years, the most common mental health problems were attention deficit problems (~60.0%) followed by depression (over 40.0%), suicide threats (~40.0%) and panic attacks (over 20.0%). Among participants aged 21 to 51 years, the most common mental health problems were depression (over 50.0%), followed by suicide threats (over 40.0%), attention deficit problems (over 40.0%), and panic attacks (over 30.0%). Among participants aged 12 years and older, the first sign of mental health problems was typically related to depression. The most common reason for obtaining outpatient mental health treatment was attention problems followed by depression whereas the most common reasons for inpatient treatment were suicide threats and depression.

Authors, year, study country	Study title	Study population	Assessment of mental health outcomes	Main findings related to mental health outcomes including internalizing disorders
Hill et al., 2000, United States	Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders	150 children/adolescents (ages 8–18 years) at high or low risk of developing alcoholism. Maternal drinking history during pregnancy was available for each child. Most women reported decreased alcohol use by the second and third trimesters. Drinking alcohol during pregnancy was more common among children in the high-risk group (62.9% than among those in the low-risk group (31.1%).	The Schedule for Affective Disorders and Schizophrenia for School-Aged Children was administered to all children. The following disorders were assessed: depression (major depression and dysthymia), phobia, anxiety disorders (panic disorder, separation anxiety, overanxious disorder), attention deficit hyperactivity disorder (ADHD), conduct disorder, substance abuse/dependence disorders, and oppositional disorder.	In terms of internalising disorders, the results from the univariate analyses showed that maternal prenatal alcohol use was associated with an increased likelihood offspring developing childhood/adolescent anxiety disorder and depressive disorder. The adjusted analysis showed no significant associations between maternal prenatal substance use and the studied internalising disorders.
Barr et al., 2006, United States	Binge drinking during pregnancy as a predictor of psychiatric disorders in the structured clinical interview for DSM-IV in young adult offspring	400 offspring with a mean age of 25.7 years at the time of assessment (53.0% male). IQ at the age of 21 years ranged from 70 to 114 (mean IQ of 103). Prenatal alcohol exposure was assessed from maternal self-reports for the two periods of early pregnancy (before pregnancy recognition) and mid-pregnancy. Alcohol exposure was dichotomized into none and one or more binge episodes during mid-pregnancy.	Structured Clinical Interview for DSM-IV was used to assess Axis I psychiatric disorders grouped into nine primary classes: depressive, manic, psychotic, anxiety, somatoform, mood, adjustment, eating, and substance (alcohol or drug) disorder. The Structured Clinical Interview for DSM-IV Personality Disorder was used to assess 14 personality disorders or traits that do not meet the diagnosis criteria but are considered as interfering with life.	In terms of Axis I disorders, group differences between offspring exposed to binge drinking versus offspring not exposed to binge drinking during pregnancy were not observed in any of the disorders except for somatoform disorders and substance abuse or dependence, the odds of these disorders being higher in the offspring with exposure to binge drinking during pregnancy. In terms of Axis II disorders, group differences were only observed in paranoid disorders, passive-aggressive disorders, and antisocial disorders, the odds of these disorders being higher in the offspring with exposure to binge drinking during pregnancy.

Authors, year, study country	Study title	Study population	Assessment of mental health outcomes	Main findings related to mental health outcomes including internalizing disorders
Easey et al., 2020, the United Kingdom	Association of prenatal alcohol exposure and offspring depression: A negative control analysis of maternal and partner consumption	Sample of 13,480 adolescents assessed at the age of 18 years. Of the adolescents' mothers, 16.0% reported drinking at least one drink per week during the first trimester, and 17.0% reported binge drinking at least 1 to 2 days per month at 18 weeks of gestation.	Adolescents' depression was assessed by using the computerised version of the Clinical Interview Schedule-Revised. The interview is used to diagnose mental health disorders and the presence of depressive episodes from the ICD-10 category F32.	Maternal alcohol use at 18 weeks of gestation increased the offspring's likelihood of having a diagnosis of depression at age 18. The observed association between maternal alcohol use at 18 weeks of gestation and offspring's depression was attenuated slightly after controlling for the influence of socioeconomic factors and maternal behaviours. The results also suggested a linear trend between the amount of alcohol the mother consumed during pregnancy and the offspring's risk of depression. The results from the sensitivity analysis assessing offspring depression at the age of 24 years showed similar but slightly weaker results for depression compared to the result observed at the age of 18 years.
Duko et al., 2021, Australia	Prenatal alcohol and tobacco use and the risk of depression in offspring at the age of 17 years: findings from the Raine study	1168 youth from the Raine study assessed at age 17. Maternal alcohol use during pregnancy assessed at 18 and 34 weeks of gestation. Prenatal alcohol use during the first and third trimester categorised as nonuse, light use (1−2 standard drinks/week), moderate use (3−5 standard drinks/week) and heavy use (≥ 6 standard drinks/week).	Youth's depressive symptoms were assessed using the Beck Depression Inventory for Youth.	23.3% of the youth were exhibiting depressive symptoms at the age of 17 years. The results from the univariate analysis showed that youth in the heavy prenatal alcohol exposure group were more likely to have depressive symptoms than those in the non-use group. The adjusted analyses showed an increased risk of depressive symptoms in the heavy prenatal alcohol exposure group compared to the non-exposed group. Similar associations were not observed in the light or moderate exposure groups in univariate or the adjusted analyses.

Authors, year, study country	Study title	Study population	Assessment of mental health outcomes	Main findings related to mental health outcomes including internalizing disorders
Duko et al., 2022, Australia	Prenatal tobacco and alcohol exposures and the risk of anxiety symptoms in young adulthood: A population-based cohort study	1190 youth from the Raine study assessed at the age of 20 years. Maternal alcohol use during pregnancy assessed at 18 and 34 weeks of gestation. Prenatal alcohol use categorised as non-drinker (Group 1), up to three standard drinks per week (Group 2), 4 ≥ standard drinks per week (Group 3), separately for the first and third trimesters.	Youth's anxiety symptoms were assessed by a short form of the Depression Anxiety Stress Scale.	The results from the unadjusted analysis showed that the associations between first or third trimester alcohol exposure and youth's anxiety symptoms were not statistically significant. The results suggested an increase in the risk of anxiety symptoms with increasing levels of prenatal alcohol exposure. However, the association was not statistically significant. The results remained the same after covariate adjustments.
Prenatal exposure to illicit drugs				
Nygaard et al., 2020, Norway	Mental health in youth prenatally exposed to opioid and poly-drugs and raised in permanent foster/adoptive homes: A prospective longitudinal study	Exposed group: 45 youth with prenatal drug exposure (aged 17 to 22 years) mainly raised in foster or adoptive homes. Nonexposed group: 48 nonexposed youth (aged 17 to 22 years) raised by their biological parents.	Diagnostic interview using the extended version of the Norwegian translation of the Mini International Neuropsychiatric Interview. Self-reported assessment by using the Achenbach Adult Self-Report form, Cantril's Ladder of Life Satisfaction Scale.	According to the results from the diagnostic interview, a higher proportion of the individuals in the exposed group had experienced a major depressive episode after taking into account differences in gender, age, and caregiver education. The self-reported results indicated that participants in the exposed group were more often above the cut-off for the clinical level of problems compared to the non-exposed group. However, no significant group differences were observed after taking into account the differences in gender, age, and caregiver education.

Note: ADHD; Attention Deficit Hyperactivity Disorders, ARND; Alcohol-Related Neurodevelopmental Disorder, DSM-IV; Diagnostic and Statistical Manual of Mental Disorders, FAS; Fetal Alcohol Syndrome, ICD; International Statistical Classification of Diseases and Related Health Problems, IQ; Intelligence quotient. The table provides a summary of the studies. For full details, please refer to the publication.

2.5.2 Secondary education

In Finland, the nine-year comprehensive education is compulsory and publicly funded. Comprehensive education is typically completed at the age of 16 years, and approximately 90.0% of Finnish youth continue to upper secondary education (i.e. secondary education) without gap. Publicly funded secondary education was voluntary in Finland until 2021. The new legislation that came into force in 2021 extended compulsory education until the completion of secondary education or the age of 18 years (Oppivelvollisuuslaki 1214/2020, 2020). Secondary education is typically completed within three years. The number of individuals without secondary education has remained relatively similar over the years. For example, 14.0% of the individuals born in 1995 had no secondary education at the age of 24 years (Suomen virallinen tilasto, 2019). Secondary education is considered crucial for youth's successful participation in further education and work life (Lamb & Markussen, 2011). Youth without secondary education can have a heightened risk of unemployment and financial difficulties (Sipilä et al., 2011), critical for a successful transition to adult independence.

Studies on the educational outcomes among prenatally substance-exposed individuals have mainly been carried out among prenatally alcohol-exposed populations with a diagnosis within the FASD spectrum. These studies have largely focused on school performance and learning in children or special education needs among various age groups. The available studies have indicated difficulties in various areas of learning (including mathematics, reading, and writing) and school performance (Sayal et al., 2014; Streissguth, 1996) and the need for special education (Brownell et al., 2013; Popova et al., 2016). These challenges observed in children can persist into adolescence and later adulthood when the tasks and demands of education increase, thus increasing susceptibility to inferior educational outcomes in youth (McLachlan et al., 2020; Streissguth et al., 1996). However, there is only a limited number of studies on educational outcomes in the youth population.

Table 2 summarises the studies assessing educational outcomes, including secondary education completion in youth with prenatal substance exposure (listed in publication order). The studies described in Table 2 come from various countries with different educational systems. Most of these studies have also measured other

secondary disabilities. These results are also provided in Table 2 and discussed in Section 2.5.3.

The available studies of educational outcomes among prenatally alcohol-exposed youth show challenges with educational attainment. Starting from the earliest work, Streissguth et al. (1996) studied secondary disabilities among individuals with a diagnosis within the FASD spectrum. Concerning the educational outcomes, 60.0% of participants aged 12 years and older had disrupted school experiences, which were more common in the older age groups. The results also showed that individuals with FAS or Fetal Alcohol Effect completed high school education less frequently than other students. After the age of 21, only 30.0% of the participants had gone into post-secondary education. Disrupted school experiences correlated with learning and behavioural problems, and 40.0% of the participants were in special education (Streissguth, 1996) (Table 2).

Similarly, other studies have also indicated a relatively low number of completed secondary (McLachlan et al., 2020; Landgren et al., 2019; Spohr et al., 2007) or post-secondary education (Landgren et al., 2019; Rangmar, Hjern, et al., 2015) among prenatally alcohol-exposed populations with a diagnosis within the FASD spectrum. In a 20-year follow-up of 37 individuals with a diagnosis within the FASD spectrum, Spohr et al. (2007) indicated low levels of completed primary (38.0%) and secondary education (5.0%) (Spohr et al., 2007). However, over half of the participants had borderline intelligence or mental retardation. Thus, the results from Spohr et al. (2007) likely reflect educational outcomes in more severely affected individuals.

Similarly, Freunscht & Feldmann (2011) reported a low level of completed secondary education (10.0%) among individuals with FAS or Fetal Alcohol Effect, with a mean age of 24 years (Table 2). In a register-based study, Rangmar, Hjern, et al. (2015) did not report differences in the rate of completed secondary education between adults (aged 18 to 47 years) with FAS and unexposed adults. However, of the adults with FAS, a higher proportion had primary education as the highest education compared with the unexposed, and post-secondary education was completed by only 4.9% of the individuals with FAS compared with 44.9% of the unexposed group (Rangmar, Hjern, et al., 2015) (Table 2).

Landgren et al. (2019) studied adoptees with a diagnosis within the FASD spectrum at the age of 22 years. Of the participants, 25.0% had primary education as the highest completed education, while secondary education was completed by 31.0%. Only 5.0% had sought a university degree (Landgren et al., 2019) (Table 2).

The results by McLachlan et al. (2020) showed that 18.0% of the overall sample including individuals with prenatal alcohol exposure in three age groups (12–17 years, 18–24 years, and 25–60 years), had experienced school disruptions, defined as suspension or expulsion from school. The educational challenges were most often observed among the youngest study participants. The results regarding academic achievement measured by standardised tests in reading, mathematics, and/or written language indicated that 61.0% of the total sample experienced impairments in these domains, the impairments being most observed in a subgroup that included individuals with FASD with sentinel facial features, likely reflecting individuals more severely affected by prenatal alcohol exposure (McLachlan et al., 2020) (Table 2).

There is a scarcity of studies on educational outcomes among children or youth exposed to illicit drugs during pregnancy. The current evidence stems from studies investigating school performance among children with prenatal exposure to amphetamine (Eriksson et al., 2000) and cannabis (marijuana) (Goldschmidt et al., 2004). These studies indicated problems in reading and spelling and overall school performance, including being a year behind in school for their age (Eriksson et al., 2000; Goldschmidt et al., 2004).

In contrast to studies done among prenatally alcohol-exposed individuals, studies conducted among children with prenatal exposure to illicit drugs have also assessed other factors associated with inferior educational outcomes. Levine et al. (2012) reported that the need for special education in children aged 11 years with prenatal cocaine exposure was partly explained by the child's internalising and externalising disorders (Levine et al., 2012). Goldschmidt et al. (2004) found poorer school performance among prenatally marijuana-exposed children even after adjusting for potential confounders. The results suggested that a child's mental and behavioural disorders can influence the association between prenatal exposure and school performance (Goldschmidt et al., 2004). Hurt et al. (2005), on the other hand, found no differences in school performance among 62 cocaine-exposed fourth graders compared to 73 unexposed controls. The results indicated that a better home environment and a higher IQ predicted better school performance scores regardless of prenatal cocaine exposure (Hurt et al., 2005).

To the best of my knowledge, the only study extending beyond childhood is a study done by Goldschmidt et al. (2012). In the study, Goldschmidt et al. (2012) studied school achievement at the age of 14 years among prenatally marijuana-exposed adolescents. The results showed that the association between first-trimester

marijuana exposure and a child's school achievement at the age of 14 years was mediated by the effects of marijuana exposure on a child's IQ, attention problems, depressive symptoms, and early age of marijuana initiation (Goldschmidt et al., 2012). Studies extending into youth or adulthood are lacking.

Table 2. A summary of studies investigating educational outcomes or other secondary disabilities in youth with prenatal substance exposure

Author, year, study country	Study title	Study population	Assessment of outcomes	Main findings: educational outcomes	Main findings: other secondary disabilities including outcomes reflecting adult independence
Prenatal alcohol exposure					
Streissguth et al., 1996, United States	Understanding the occurrence of secondary disabilities in clients with Fetal Alcohol Syndrome (FAS) and Fetal Alcohol Effects (FAE): final report	415 participants, all with diagnosed FAS, Fetal Alcohol Effect, partial Fetal Alcohol Effect or ARND. Of the participants, 57.0% were male. At the time of the interview, 39.0% were 6–11 years old, 39.0% were 12–20 years old, and 22.0% were over 21 years old.	Secondary disabilities were assessed using the Life History Interview. The interview was administered by telephone to caretakers/informants of the study participants. The interview covered items such as independent living and financial management, education, and employment. Disrupted school experiences were recorded if the participant had ever been suspended or expelled from school or dropped out of school. Dependent living was recorded if the participant was not independent. Independence was defined as the ability to handle daily living activities without help, live without a caregiver, and pay at least some of their own expenses. Problems with employment were recorded if the participant was not effectively employed.	In the overall sample, 60.0% had disrupted school experiences. In the age group of 12–20 years, approximately 50.0% had been suspended, 30.0% had been expelled and more than 25.0% had dopped out of school. The corresponding proportions in the age group of 21-51 years were approximately 40.0%, 20.0%, and 40.0%, respectively. Individuals with FAS or Fetal Alcohol Effect graduated from high school less often than other students, and 30.0% had gotten some type of post-secondary education (55.0% of other students). In the overall sample, the most frequently reported learning problems were attention problems followed by repeatedly incomplete schoolwork. Nearly half had failed a grade in school. The most frequently reported behaviour problems were peer problems followed by disruptive behaviour in the	In the sample of 21–51-year olds (*n*=89), over 80.0% were living dependently. The daily activities requiring intensive help or supervision most often included managing money (over 80.0%), making decisions (nearly 80.0%) and getting social services (~70.0%). The most often reported social problems included poor judgment, poor organisational skills, lack of initiative, and losing one's temper. Regarding employment problems, nearly 80.0% of the study participants aged 21 years and older had problems with employment. Difficulty in holding a job was reported by more than 60.0% of the participants, while getting hired or fired was reported by 50.0%. The most reported employment problems while employed included being

Author, year, study country	Study title	Study population	Assessment of outcomes	Main findings: educational outcomes	Main findings: other secondary disabilities including outcomes reflecting adult independence
				classroom. Of the participants with FAS or Fetal Alcohol Effect approximately 40.0% were in special education. The reported protective factors against disrupted school experiences included early diagnosis, longer duration in living situations, longer duration in a stable and nurturing home, and living in a good quality home.	easily frustrated (~65.0%), poor task comprehension (nearly 60.0%), poor judgment (~55.0%), and social problems (~55.0%).
Spohr et al., 2007, Germany	Fetal Alcohol Spectrum Disorders in young adulthood	37 individuals with a diagnosis within the FASD spectrum (originally diagnosed with FAS or Fetal Alcohol Effect) (median follow-up time of 20.5 years). Of the participants, 12 were with normal intelligence (IQ>85), 10 with borderline intelligence (IQ 70 to 85) and 15 with mental retardation (IQ < 70).	Physical examinations with special emphasis on characteristic craniofacial malformations and growth. A coded item list based on an interview with the subject's caregiver or closest relative assessing academic and occupation career, domestic arrangements, and independent living. The Young Adult Behaviour Checklist was used to assess emotional and behavioural problems.	Of the study participants, 49.0% had received special education only, 38.0% of the participants had passes primary school, and 13.0% had a secondary school education.	Regarding occupational outcomes, 13.0% had held an ordinary job, 69.0% had received preparatory job training and 58.0% had started or progressed to formal occupational training. 19.0% had terminated job training. Regarding domestic arrangements, 27.0% lived in institutions, and 35.0% were in a dependent living situation requiring assistance from others. Of the youth, 14.0% lived independently alone, 8.0% lived with a partner, 8.0% had a family of their own, and 8.0% lived with their father and a mother surrogate.

Author, year, study country	Study title	Study population	Assessment of outcomes	Main findings: educational outcomes	Main findings: other secondary disabilities including outcomes reflecting adult independence
Freunscht & Feldmann, 2011, Germany	Young adults with fetal alcohol syndrome (FAS): Social, emotional, and occupational development	60 individuals: 57 with FAS and 3 with suspected FAS (33 men, 27 women), aged 18 – 39 years (mean age of 24.2 years).	A structured caregiver interview included adoptive parents (*n*=25), foster parents (*n*=18), biological parents (*n*=5) and caregivers (*n*=2). Ten of the study participants had no relatives or caregivers to answer on their behalf. The following items were covered by the interview: living situation, education and occupation, social contacts, health, social problems, and consumption of alcohol and other drugs.	Of the participants, 60.0% had enrolled in school at the age of 7 years and 2 out of 3 attended regular schools. 25.0% had no educational qualifications, 43.0% had completed elementary school, 10.0% secondary school and 3.0% grammar school. Special education was attended mainly due to learning disabilities. In terms of vocational education, 31 participants were in training. Of these 31, 28.0% had completed vocational training, 26.0% had started vocational training and 46.0% had no education or job training. Nearly 50.0% of the training positions were in sheltered workshops. Educational dropout was reported by 37.0% of the participants.	Regarding current occupation, 42 of the study participants were no longer in training. Of these, 24.0% reported having no occupation, 33.0% attended sheltered workshops, and 24.0% were employed.
Rangmar, Hjern et al., 2015, Sweden	Psychosocial outcomes of Fetal Alcohol Syndrome in adulthood	FAS group: 79 individuals with diagnosed FAS (63.0% men, 37.0% women), mean age of 32 years (age range 18 to 47 years). Of these adults, 75 were alive and living in Sweden in 2011. Comparison group: 3160	Education as recorded in the register data	In the FAS group 25.3% had attended special education (1.6% in the comparison group and 26.7% had primary school as the highest completed education (12.2% in the comparison group). Statistically significant differences were not observed between the FAS and comparison groups in terms of completed secondary education (45.7% and 46.1%, respectively). In the FAS	A larger proportion of individuals in the FAS group were unemployed (51.0% vs. 15.0%) and had received disability pensions (31.0% vs. 3.0%) compared with the comparison group. The FAS group also differed from the comparison group in terms of received social welfare (27.9% vs. 3.4%).

Author, year, study country	Study title	Study population	Assessment of outcomes	Main findings: educational outcomes	Main findings: other secondary disabilities including outcomes reflecting adult independence
		individuals matched with the FAS group on age, gender and place of birth. A comparison group of 122 individuals placed in state care as children.		group, 4.9% had postsecondary education as the highest completed education (44.9% in the comparison group). Those in the FAS group were more likely to receive special education than those in the comparison group (25.05% and 2.0%, respectively).	The proportions of individuals with criminal offences were similar in both groups. The FAS group had a higher rate of hospital admissions for alcohol abuse (9.0% vs. 2.0%) and psychiatric disorders (33.0% vs. 5.0%), and the proportion of individuals with prescribed psychotropic drugs (57.0% vs 27.0%) was higher than in the control group.
Landgren et al., 2019, Sweden	Fetal alcohol spectrum disorders from childhood to adulthood: a Swedish population-based naturalistic cohort study of adoptees from Eastern Europe	37 adoptees with a diagnosis within the FASD spectrum were evaluated at the age of 22 years (age range 18–28 years).	A structured interview evaluating educational attainment and current social circumstances. Psychiatric evaluations included the Mini International Neuropsychiatric Interview 6.0.0 and Adult ADHD Self-Report Scale 1.1. The Leiter-Revised non-verbal test and Leiter-R Attention and Memory Battery were used in psychological evaluations. Medical examination and ophthalmological evaluations were also conducted.	Of the participants, 36 had information on educational outcomes. Of these 36, 39.0% had received special education, 25.0% had primary school (9 years) as the highest completed education, while secondary school (12 years) was the highest completed education among 31.0%. 5.0% had attempted university studies.	Of the 36 participants with information available on income and compensation, 31.0% were working, 28.0% were dependent on social welfare, 28.0% received disability pension, and 14.0% were students.

Author, year, study country	Study title	Study population	Assessment of outcomes	Main findings: educational outcomes	Main findings: other secondary disabilities including outcomes reflecting adult independence
McLachlan et al., 2020, Canada	Difficulties in daily living experienced by adolescents, transition-aged youth, and adults with Fetal Alcohol Spectrum Disorder	726 individuals with confirmed prenatal alcohol exposure from various ethnocultural backgrounds. Of the participants, 443 (61.0%) were 12 to 17 years old, 135 (19.0%) were 18 to 24 years old, and 148 (20.0%) were 25 to 60 years old. 306 (43.0%) of the participants were females.	The following difficulties with daily living were evaluated: suspension or expulsion from school (school disruption), employment problems, needing help with independent living (independent living needs), needing sheltered or assisted housing (housing problems), legal problems with victimization, legal problems with offending, incarceration, alcohol misuse, and misuse of other substances. The above-mentioned aspects of daily living were assessed using the Canadian FASD Diagnostic Guidelines. In addition, 10 domains of neurodevelopment were assessed, including academic achievement (test scores in reading, math, and/or written language).	In the overall sample, 18.0% had experienced school disruption. School disruptions were more commonly observed among the youngest participants (12–17 years old) than among the oldest participants (25–60 years old) (26.0% vs. 5.0%) and among males compared to females (23.0% vs. 12.0%). The results regarding academic achievement indicated that 61.0% of the participants (*n*=707) showed impairments in this domain. The impairments were most profound in the FASD group with sentinel facial features (83.0%), followed by the FASD group without sentinel facial features (72.0%), the group at risk of neurodevelopmental disorder/FASD (40.0%) and the non-diagnosed group (25.0%).	In the overall sample, 37.0% had experienced employment problems, 63.0% needed help with independent living, and 21.0% needed sheltered or assisted housing. The employment problems and housing problems varied between age groups. Alcohol misuse was reported by 38.0% and substance misuse by 46.0%. In terms of legal problems, 4.0% had legal programs with victimization, 30.0% had legal problems with offending, and incarceration was reported by 3.0%.

Note: ADHD; Attention Deficit Hyperactivity Disorders, ARND; Alcohol-Related Neurodevelopmental Disorder, FASD; Fetal Alcohol Spectrum Disorders, FAS; Fetal Alcohol Syndrome, IQ; Intelligence quotient. The table provides a summary of the studies. For full details, please refer to the publication

2.5.3 Financial difficulties

Temporary financial difficulties are typical among youth during the transition phases (Ilmakunnas & Moisio, 2019). In Finland, one important indicator of financial difficulties is the receipt of financial social assistance (FSA) (Ristikari et al., 2018). In Finland, FSA is the last resort of financial assistance for individuals and families who live or are residents in Finland and whose income and assets do not otherwise cover the necessary expenses. FSA is intended to help the recipient to overcome temporary financial difficulties. It takes into consideration all the applicant's income and assets, including other social security benefits. Therefore, FSA is considered a means-tested benefit, i.e. only accessible for individuals and families whose income or other assets fall below a pre-determined threshold.

The receipt of FSA is relatively common among youth (Ilmakunnas, 2018; Raittila et al., 2018). A Finnish study showed that 30.0% of youth aged 18 to 24 years in Finland had received FSA for at least one month during their study period (Haula & Vaalavuo, 2021). An estimate from 2017 suggests that 19.0% of Finnish youth aged 18 to 24 years had received FSA for at least one month (Raittila et al., 2018). The duration of FSA receipt among youth is typically short and aimed at helping to overcome temporary financial difficulties (Ilmakunnas, 2018; Raittila et al., 2018). Long-term receipt of FSA, on the other hand, can indicate financial difficulties and challenges in establishing financial self-support. Financial difficulties can also increase the risk of further problems in being an active member of society (Ilmakunnas & Moisio, 2019; Kauppinen et al., 2014). Risk factors increasing the likelihood of FSA in youth include parental receipt of FSA, youth's lower educational level, and moving from parental care to independence at a young age. The youth's mental health issues can also predict FSA receipt in youth (Haula & Vaalavuo, 2021; Ilmakunnas & Moisio, 2019; Kauppinen et al., 2014; Vaalavuo et al., 2020).

Research on financial difficulties among prenatally substance-exposed youth is still scarce. Existing studies have mainly focused on studying other aspects of secondary disabilities including employment and independent living and the need for social welfare or a disability pension. The variation in the studied outcomes may reflect the differences in the study countries and their welfare systems. The existing evidence comes primarily from studies carried out among prenatally alcohol-exposed populations with a diagnosis within the FASD spectrum. These studies are described

in Table 2 (listed in publication order). The results are also provided for other studied outcomes (e.g. alcohol/drug abuse, legal problems) but these results are only described in Table 2.

Overall, the studies indicate that prenatally alcohol-exposed youth or adults experience challenges in achieving adult independence (Rangmar, Hjern, et al., 2015; Spohr et al., 2007; Streissguth, 1996) (Table 2). In the earliest study on secondary disabilities, Streissguth (1996) reported that most of the participants with diagnosed FAS or Fetal Alcohol Effect (aged 21 to 51 years) were living dependently. The daily activities most often requiring assistance from others included managing money, making decisions, and getting social services. In terms of employment, nearly 80.0% of the participants had problems with employment (Streissguth, 1996) (Table 2).

In a German study, the long-term sequelae of prenatal alcohol exposure were studied among 37 adults with FAS or Fetal Alcohol Effect (Spohr et al., 2007). The results indicated serious late sequelae, including behavioural difficulties, which led to limited vocational qualifications and dependency on care in adulthood. Of the study participants, 14.0% lived independently alone, 27.0% lived in institutions and 35.0% were in a dependent-living situation and required assistance from others. In terms of occupational outcomes, 13.0% had held an ordinary job (Spohr et al., 2007) (Table 2). Similar inferior occupational outcomes were reported in another German study by Freunscht & Feldmann (2011) which included individuals with FAS or suspected FAS.

In a register-based study from Sweden, Rangmar, Hjern, et al. (2015) studied secondary disabilities among 79 adults with a FAS diagnosis compared to unexposed adults (aged 18 to 47 years). In terms of employment, 51.0% of the adults with FAS were unemployed (15.0% among the unexposed). Rangmar, Hjern et al. (2015) pointed out that nearly half of the adults in the FAS group were employed. However, the results on disposable income indicated that these adults were employed in lower-paid jobs and their income was supplemented by welfare benefits. The results also indicated that adults in the FAS group were more often dependent on disability pensions and social welfare compared with a matched comparison group (Rangmar, Hjern, et al., 2015).

In a Swedish observational population-based cohort study, Landgren et al. (2019) studied 37 young adults (aged 18 to 28 years) adopted from orphanages in Eastern Europe and with a diagnosis within the FASD spectrum. Concerning the social circumstances of these young adults, 14.0% were students, 31.0% were working, and

56.0% were dependent on social support, of which 28.0% were dependent on social welfare and 28.0% on a disability pension (Landgren et al., 2019).

Lastly, McLachlan et al. (2020) studied difficulties in daily living among individuals with confirmed prenatal alcohol exposure. In the overall sample, 37.0% had employment problems, 63.0% needed assistance with independent living and 21.0% were in sheltered or assisted housing (McLachlan et al., 2020). To the best of my knowledge, no studies on financial difficulties or on other aspects of adult independence have been conducted in youth with prenatal exposure to illicit drugs.

3 SUMMARY OF PREVIOUS RESEARCH FINDINGS

Exposure to substances (i.e. alcohol and/or illicit drugs) during pregnancy is a significant risk factor for fetal development and is associated with lifelong developmental concerns (Behnke et al., 2013; Ross et al., 2015). Substances can influence the fetus throughout the pregnancy. However, the fetal effects are influenced by several factors, including the type and amount of substance(s) used during pregnancy, timing of exposure, epigenetic alterations, genetic susceptibility and maternal metabolism (May et al., 2013; Popova et al., 2023).

The most profound effect of prenatal substance exposure is on fetal CNS and brain development (Etemadi-Aleagha & Akhgari, 2022; Goodlett & Horn, 2001; Guerri et al., 2009; Moore et al., 2014). The CNS dysfunction ensuing from prenatal substance exposure can manifest as primary disabilities, i.e. deficits in cognitive, executive, and adaptive functioning (Behnke et al., 2013; Goodlett & Horn, 2001; Mattson et al., 2011; Pyman et al., 2021). The research findings on the association between prenatal alcohol exposure and primary disabilities are consistent, whereas research evidence on the association between prenatal exposure to illicit drugs and primary disabilities is inconsistent. The results seem to be influenced by the type of illicit drug the fetus has been exposed to during pregnancy and by other pre- and postnatal risk factors (Behnke et al., 2013; Ross et al., 2015).

The prenatal substance exposure induced CNS dysfunction and primary disabilities can predispose the exposed individuals to other challenges in various areas of life, including mental health issues, disrupted school experiences, challenges with independent living and employment, and need for social welfare (Easey et al., 2019; Flannigan et al., 2018; Lynch et al., 2017; Rangmar et al., 2017; Rangmar, Hjern, et al., 2015). In the research literature, the term secondary disabilities is used to describe these challenges (Streissguth, 1996). These disorders can place a burden on the individual with prenatal substance exposure and their families, and also society (Greenmyer et al., 2018).

These secondary disabilities can be especially common during the youth period. The youth period is a critical developmental phase and characterises the transition

period from childhood to independent adulthood. The youth period can be especially challenging for individuals with prenatal substance exposure, considering the primary disabilities and potential functional impairments, as well as the highly prevalent externalising and internalising disorders (Easey et al., 2019; Kautz-Turnbull & Petrenko, 2021; Korkman et al., 2003; McLachlan et al., 2020; Streissguth, 2007).

The current research evidence on secondary disabilities stems mainly from studies conducted among prenatally alcohol-exposed individuals, particularly from populations with a diagnosis within the FASD spectrum or with diagnosed FAS. Thus, the current research evidence may reflect secondary disabilities in more severely affected individuals. The available studies vary in terms of study design, data, exposure assessment, and measures employed to assess the outcomes of interest or other developmental domains. Moreover, the studies vary in terms of the inclusion of a control group and covariate adjustments.

Regardless of these methodological differences, the current evidence indicates that individuals with prenatal alcohol exposure exhibit various secondary disabilities at a high rate, including internalising disorders (e.g. mood and neurotic disorders), low levels of completed secondary education and difficulties in achieving adult independence (e.g. the need for social welfare, challenges with employment and independent living). Studies including an unexposed control group indicate that exposed individuals experience secondary disabilities (e.g. internalising disorders) at a higher rate relative to controls. However, there is a variation between the studies whether these groups differences remain significant after covariate adjustment. The evidence on specific secondary disabilities such as educational outcomes in secondary education or financial difficulties in youth relative to unexposed controls is still scarce. In addition, the current evidence on the effects of prenatal exposure to illicit drugs on child development mainly extends to childhood or adolescence (Eriksson et al., 2000; Goldschmidt et al., 2004; Gray et al., 2005). Thus, we know relatively little about secondary disabilities in youth with prenatal exposure to illicit drugs or polysubstance use.

As illustrated in Figure 1, the secondary disabilities in youth with prenatal substance exposure are multifaceted, and several factors during childhood and youth can increase the susceptibility to these disorders. In addition to prenatal substance exposure and the lifelong impartments that ensue, the characteristics of the postnatal caregiving environment, parenting, and caregiving instability also have a significant

influence on child development in the long term (Anda et al., 2006; Felitti et al., 1998).

Several studies have shown that children exposed to substances during pregnancy often face a double jeopardy. That is, the health and development of these children are not only influenced by the teratogenic effects of prenatal substance exposure but also by an accumulation of adversities and caregiving instability in the postnatal caregiving environment (Carta et al., 2001; Conners et al., 2009). Maternal prenatal substance abuse typically co-occurs with interlinked risk factors, including maternal low socioeconomic status, financial difficulties, single parenthood, postnatal substance use, and comorbid health conditions, including mental health disorders (Esper & Furtado, 2014; Flannigan et al., 2021; Lebel et al., 2019; McQuire et al., 2020). The use of illicit drugs and polysubstance use can include additional risk factors that can endanger maternal wellbeing and child health and development (Mravčík et al., 2020; Ross et al., 2015).

A wealth of research evidence indicates that exposure to early life adversities and repeated and prolonged stress can have lasting effects on a child's brain development and functioning (including the prefrontal cortex, amygdala, and hippocampus) and the body's stress-response systems (including the HPA axis) (Cassiers et al, 2018; Sheng et al., 2021). These alterations can negatively influence a child's subsequent cognitive, behavioural, and socio-emotional development (Cassiers et al., 2018; Morgart et al., 2021). The stress-induced neurobiological alterations can also underlie various mental health disorders, including internalising disorders (Bick & Nelson, 2016; Hart & Rubia, 2012; Shonkoff & Garner, 2012). Parenting also plays a significant role in child development. Parenting seems to be challenged among mothers with pre- and postnatal substance abuse, and often the attachment relationship between the mother and child is characterised as unhealthy and insecure. This can harm the caregiver-child attachment relationship that is important for a child's socioemotional development and later mental health and behavioural functioning (Frigerio et al., 2019; Pajulo et al., 2001; Walsh et al., 2003).

The adversities in the postnatal caregiving environment and caregiving difficulties can also be indications for child welfare interventions (Sarkola et al., 2007). A large number of children exposed to maternal substance abuse during pregnancy are placed in OHC during early childhood (Flannigan et al., 2021; Price et al., 2017; Sarkola et al., 2007). The disruptions in caregiving and caregiving instability and exposure to early life adversities among children in OHC can manifest as poor

outcomes in various developmental domains (Bada et al., 2008; Fagerlund et al., 2011; Koponen et al., 2009), and challenges during the youth period (e.g. mental/behavioural disorders, lower educational attainment, and financial social assistance needs) (Bronsard et al., 2016; Kääriälä & Hiilamo, 2017; Vinnerljung & Sallnäs, 2008). However, research on the associations between early life adversities (including OHC) and secondary disabilities in prenatally substance exposed youth is still scarce.

To conclude, the current evidence on secondary disabilities among youth with prenatal substance exposure is still limited. We know relatively little about the likelihood of secondary disabilities in prenatally substance exposed youth relative to unexposed controls. Furthermore, the secondary disabilities among youth with prenatal substance exposure can be multifaceted. In addition to the prenatal-substance-exposure-induced structural and functional brain abnormalities and the primary disabilities that ensue, exposure to adversities during childhood can also interfere with the development placing these individuals at risk of secondary disabilities in the youth period (Figure 1). However, research on the influences of adversities in the postnatal caregiving environment and caregiving instability (including OHC) on secondary disabilities in youth with prenatal substance exposure is limited. This dissertation aims to fill the knowledge gap by studying the secondary disabilities among youth with prenatal substance exposure and among matched unexposed youth. Further, the influences of youth characteristics, characteristics of the postnatal caregiving environment, and caregiving instability on secondary disabilities are studied in this longitudinal register-based cohort study.

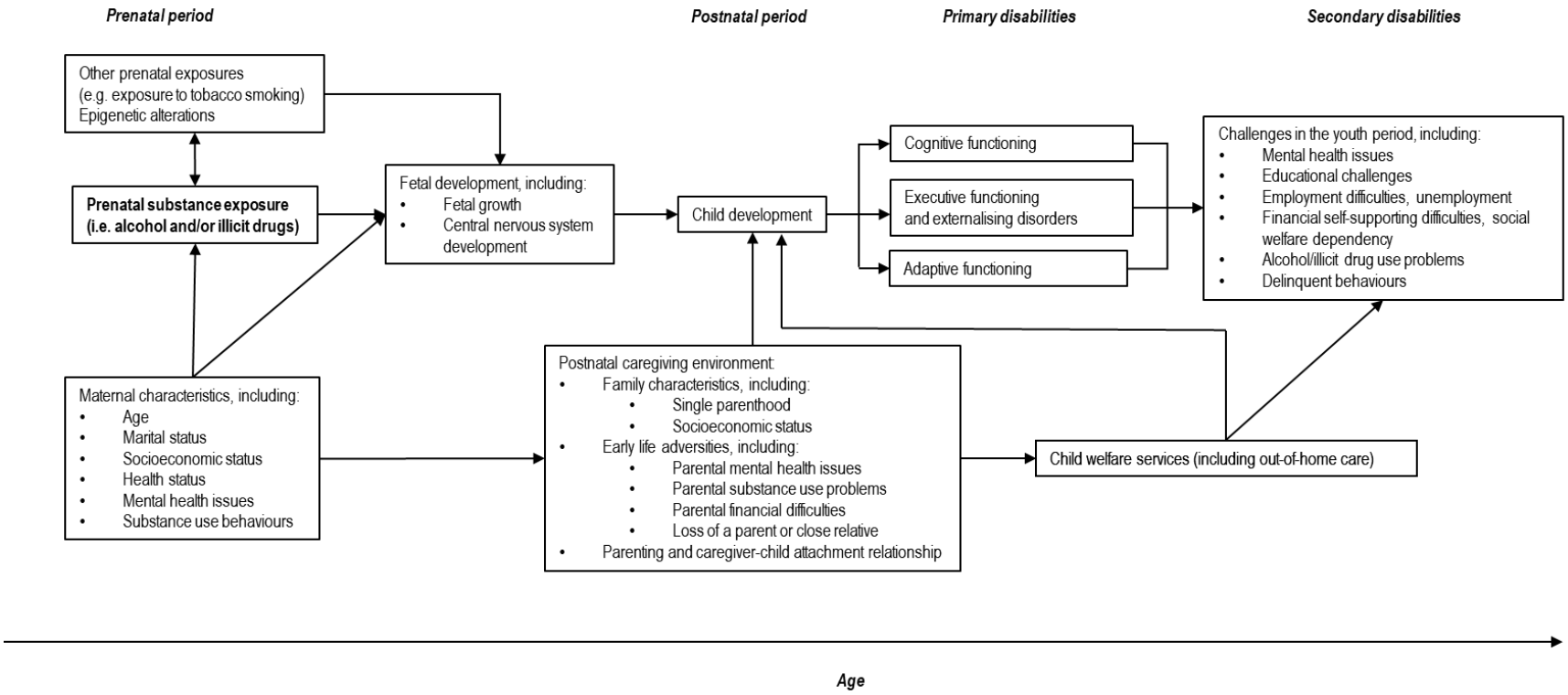


Figure 1. Potential risk factors in the prenatal and postnatal periods and their pathways to the primary and secondary disabilities in individuals with prenatal substance exposure

4 AIMS OF THE STUDY

The overall aim of this dissertation was to investigate secondary disabilities in Finnish youth with prenatal substance exposure. More specifically, the aim was to study completed secondary education, financial difficulties, and mood and neurotic disorders in this youth population. In addition, the aim was to study the influence of a variety of youth characteristics, adverse maternal characteristics, and out-of-home care (OHC) on the studied secondary disabilities. Adverse maternal characteristics and OHC were used as a proxy to describe adversities and caregiving instability in the postnatal caregiving environment.

The specific aims of the sub-studies were the following:

Study I: The aim was to investigate completed secondary education among youth with prenatal substance exposure. In addition, the aim was to investigate the associations between prenatal substance exposure, youth characteristics (i.e. sex, gestational exposure to tobacco smoking, and mental/behavioural disorders), adverse maternal characteristics (i.e. low socioeconomic status and cumulative childhood adversity score), OHC, and completed secondary education.

Study II: The aim was to investigate financial difficulties among youth with prenatal substance exposure. Further, the aim was to investigate associations between prenatal substance exposure, youth characteristics (i.e. sex, mental/behavioural disorders, land ack of secondary education), and adverse maternal characteristics (i.e. maternal mental/behavioural disorders, substance use, and long-term financial social assistance receipt), OHC, and youth's financial difficulties.

Study III: The aim was to investigate mood and neurotic disorders among youth with prenatal substance exposure. In addition, the aim was to investigate the associations between prenatal substance exposure, youth characteristics (i.e. sex),

adverse maternal characteristics (i.e. cumulative childhood adversity score), OHC, and youth's mood and neurotic disorders.

5 DATA AND METHODS

5.1 Study design and population

This study is a longitudinal register-based matched cohort study. Data from the ADEF Helsinki[2] (Alcohol and/or Drug Exposure During Fetal Life) study is used in this dissertation. The cohort profile of the ADEF Helsinki study was published by Koponen et al. (2020a).

This study includes two matched cohorts, i.e. exposed and unexposed cohorts representing youth born in 1992–2001 in the Helsinki metropolitan area. The cohorts are described in detail in the following sections. The youth of the cohorts were followed up from birth (1992−2001) until the end of 2016 when the youth were 15−24 years old.

Data from several national health and social care registers were collected identically for both cohorts. Data linkages were made by using the identification number assigned to every Finnish citizen at birth or migration. The registers used in this study are described in Table 3, Table 4, and Table 5 for studies I, II, and III, respectively.

ADEF Helsinki is the second follow-up for these offspring. The first follow-up continued from birth (1992−2001) until the end of 2007 when the offspring were 6−15 years old. The results of the first follow-up were published by Sarkola et al. (2007, 2011, 2012) and Kahila et al. (Kahila et al., 2010).

5.1.1 Defining the exposed cohort

The exposed cohort (n=640) represents offspring born in 1992−2001 to mothers (n=524) with intensified pregnancy follow-up at special tertiary care antenatal clinics (i.e. HAL clinics) in the Helsinki metropolitan area due to identified substance abuse

[2] Please refer to Koponen, et al. (2020a) for further details about the ADEF Helsinki study.

during pregnancy. HAL clinics (abbreviation for illicit drugs, alcohol and medication for the central nervous system with misuse potential) are special outpatient clinics for pregnant women with substance abuse problems. The clinics offer intensified support and easy access to addiction treatment and psychiatric care for the women. In the ADEF Helsinki study, the pregnancies of women with identified prenatal substance abuse were followed-up in the following HAL clinics in the Hospital District of Helsinki and Uusimaa (HUS): Women's Hospital (in Finnish: Naistenklinikka) in Helsinki, Kätilöopisto Hospital in Helsinki, and Jorvi Hospital in Espoo. At Jorvi Hospital, the clinic is named ETU. However, the term HAL clinic is used here to refer to all these clinics.

The referral to the HAL clinics was made by public health nurses at the antenatal care. The public health nurses were trained and advised to refer pregnant women with identified substance abuse to HAL clinics. The identification of substance use was based on test results from the Alcohol Use Disorder Identification Test (AUDIT) (score ≥ 8 points), ongoing maternal opioid maintenance treatment, drug use, or non-medical use of central nervous system medication.

At the HAL clinic, the pregnancies of the women with identified substance abuse were followed up in multiprofessional service settings from daily visits to one visit every 2 to 4 weeks, based on individual needs. The multiprofessional team included an obstetrician, a nurse, a midwife, a psychiatric nurse, and a social worker with experience in addiction treatment. Maternal substance abuse, including alcohol, cannabis, amphetamine, heroin, buprenorphine, and other drugs, was monitored at each visit by self-report, voluntary urine toxicology screenings, and conventional blood tests reflecting alcohol consumption (Sarkola et al., 2000). Most of the deliveries (~97.0%) took place in hospitals in the Helsinki metropolitan area including Helsinki University Central Hospital in Helsinki, Kätilöopisto Hospital in Helsinki, and Jorvi Hospital in Espoo. Only a minority (~3.0%) of the deliveries took place in a hospital outside the Helsinki metropolitan area.

The first follow-up from birth until the end of 2007[3] included 638 children of which 2 had a missing personal identification number and 7 had died in infancy. In the second follow-up, of the 631 exposed living children, 16 were missing[4]. Thus,

[3] The results of the first follow-up are published by Sarkola et al. (2007, 2011, 2012) and Kahila et al. (Kahila et al., 2010).

[4] Information of the offspring could not be traced due to incomplete, missing, or incorrect personal identification number.

the exposed cohort of the ADEF Helsinki study and this dissertation includes 615 offspring. The exposed cohort represent approximately 0.4% of children born in the Helsinki metropolitan area (Sarkola et al., 2007).

5.1.2 Matching an unexposed cohort

Matching is a technique used to avoid confounding in study design. In cohort studies, matching is used to ensure an equal distribution of the variables believed to be confounding in the studied cohorts. Matching can be done to match each study subject with one or more control study subjects on one or more potential confounders (Vittinghoff et al., 2012).

In the ADEF Helsinki study, the matched unexposed cohort was obtained from the Medical Birth Register maintained by the Finnish Institute for Health and Welfare (THL). The unexposed cohort (*n*=1914) represents offspring born in 1992−2001 to women (*n*=1792) with no registered evidence of substance use one year before or at the time of the offspring's birth in the national healthcare registers. Maternal substance use was defined as the presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary or secondary diagnosis following International Statistical Classification of Diseases and Related Health Problems (ICD)[5] 9th revision (ICD-9) codes 291−292, 303−305, 357.0, 425.5, 535.3, 571.0, 571.1−571.3, 648.3, 655.5, 965.0, and 969.6-969.7, or the 10th revision (ICD-10) codes E24.4, F10−F16, F18-F19, G31.2, G40.5, G40.51, G40.52, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, K86.08, O35.4−O35.5, P04.4, R78.0-R78.5, T40, T43.6, T50.2−T50.3, T51, Z71.4, and Z72.1−Z72.2 (no, yes).

Three unexposed mother-offspring dyads were collected for each exposed mother-offspring dyad. The cohorts were matched individually based on five maternal characteristics, including maternal age at the time of offspring's birth, parity, number of fetuses, month of birth, and delivery hospital of the indexed child.

[5] In Finland, ICD-9 codes were used from 1 January 1987 until the end of 1995. ICD-10 codes were in use since 1 January 1996 until the end of the study period.

The first follow-up from birth (1992–2001) until the end of 2007[6] included 1914 unexposed offspring, of which 8 had died during infancy. In the second follow-up, of these 1906 living offspring, 119 were missing[7], and thus the unexposed cohort of the ADEF Helsinki study and this dissertation includes 1787 unexposed offspring.

5.1.3 Study population: Study I

The study population of Study I comprised 283 exposed and 820 unexposed youth aged 18–23 years old in 2015, i.e. the year from which the latest information on secondary education was available (i.e. offspring born in 1992–1997) from the ADEF Helsinki study. Figure 2 displays in detail the inclusion and exclusion criteria applied in Study I.

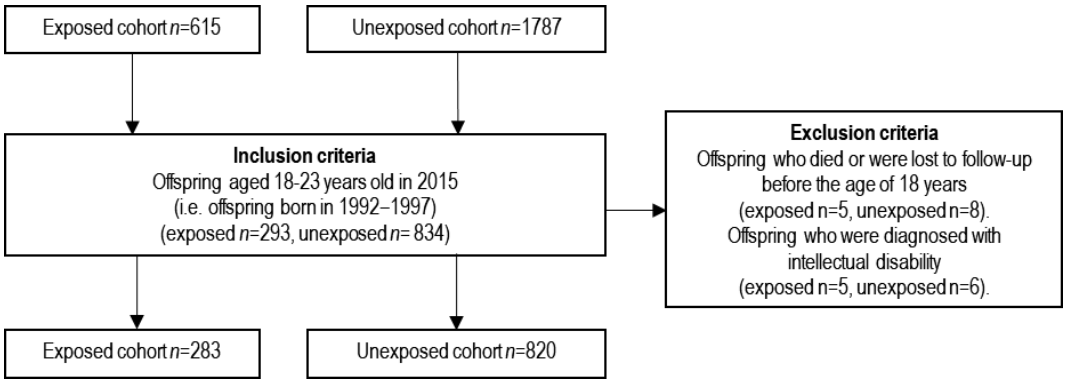


Figure 2. Flow diagram of the exposed and unexposed youth included in Study I

Note: Intellectual disability was defined as at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) from birth until the end of follow-up in 2016 with a primary diagnosis following ICD-9 codes 317–319 or ICD-10 codes F70–F79.

[6] The results of the first follow-up are published by Sarkola et al. (2007, 2011, 2012) and Kahila et al. (2010).

[7] Information on the offspring could not be traced due to an incomplete, missing, or incorrect personal identification number.

5.1.4 Study population: Study II

The study population of Study II comprised 355 exposed and 1011 unexposed youth aged 18–24 years old from the ADEF Helsinki study[6]. Figure 3 displays in detail the inclusion and exclusion criteria applied in Study II.

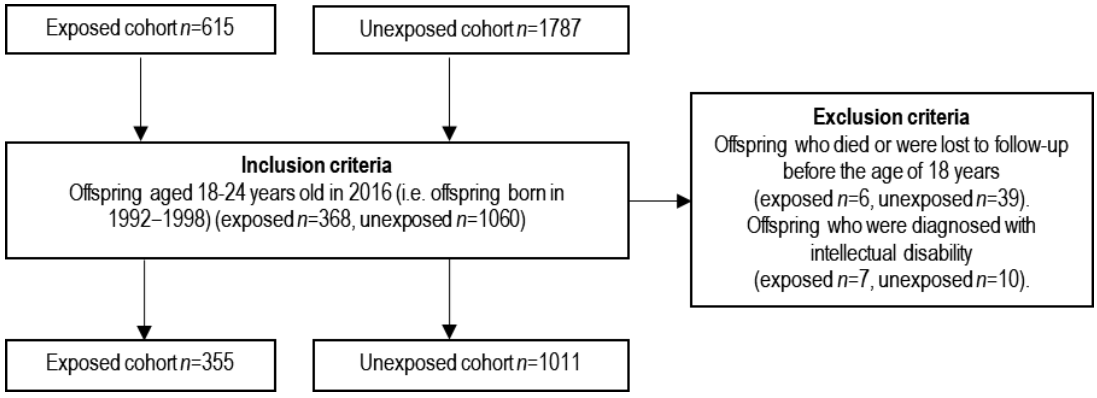


Figure 3. Flow diagram of the exposed and unexposed youth included in Study II

Note: Intellectual disability was defined as at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) from birth until the end of follow-up in 2016 with a primary diagnosis following ICD-9 codes 317–319 or ICD-10 codes F70–F79.

5.1.5 Study population: Study III

The study population of Study III comprised 594 exposed and 1735 unexposed youth from the ADEF Helsinki study. Figure 4 displays in detail the exclusion criteria applied in Study III.

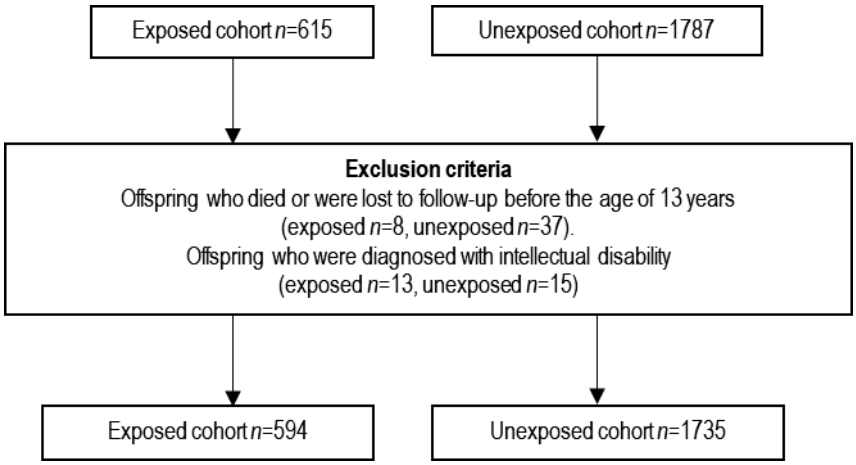


Figure 4. Flow diagram of the exposed and unexposed youth included in Study III

Note: Intellectual disability was defined as at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) from birth until the end of follow-up in 2016 with a primary diagnosis following ICD-9 codes 317−319 or ICD-10 codes F70−F79.

5.2 Outcome measures

The assessment and operationalisation of the outcome measures (i.e. secondary education completion, financial difficulties, and mood and neurotic disorders) are described in the following sections.

5.2.1 Completed secondary education

The Finnish educational system consists of a comprehensive nine-year education period commonly starting during the year a child turns seven years old. Secondary education is post-comprehensive education, and the most common options are general upper secondary school and vocational education. The typically three-year general upper secondary education leads to a matriculation examination and qualifies for further higher education. Vocational education is more practice-oriented education and provides similarly general eligibility for further higher education.

During the study period, secondary education was non-mandatory. In August 2021, the new Compulsory Education Act (Oppivelvollisuuslaki 1214/2020) came

into force extending compulsory education until the person turns 18 years old unless a person has gotten a secondary education degree before turning 18.

The main outcome variable in Study I was the completion of secondary education analysed as a dichotomised variable (no, yes). Additional information on the level of completed education including general upper secondary school, vocational education, and a bachelor's degree from a university or university of applied sciences, was included in the descriptive results. Information on secondary education was available from the beginning of 2010 until the end of 2015 and was obtained from the Register of Education maintained by Statistics Finland (Table 3).

5.2.2 Financial difficulties

The main outcome of interest in Study II was the youth's financial difficulties measured as the receipt of long-term financial social assistance (FSA) (no, yes) (Table 4).

In Finland, FSA is the last resort of financial assistance for individuals and families who live or are resident in Finland and whose income and assets do not otherwise cover the necessary expenses. FSA is intended to help the recipient to overcome temporary financial difficulties. FSA takes into consideration all the applicant's income and assets, including other social security benefits. FSA is a means-tested benefit and is usually granted for one month at a time.

In FSA, the household is the benefit unit, and therefore the data does not differentiate whether the recipient of social assistance is the sample individual, their spouse, or a member of the household. If a person receiving FSA is 18 years or older, FSA is considered their benefit unit in the Finnish social assistance system. Therefore, only individuals aged 18 years and older were included to distinguish that FSA receipt reflects the study participant's FSA receipt and not the recipiency of their parent.

In Study II, primary FSA was studied, including basic FSA and supplementary FSA. Basic FSA is intended to cover expenses arising from daily necessities such as food, clothing, transportation, and the Internet. Supplementary FSA is intended to cover expenses arising from special needs (e.g. pharmaceuticals) or circumstances (e.g. sudden financial needs).

Studies define long-term FSA receipt in varying ways. According to the Act of Rehabilitative Work (Laki Kuntouttavasta Työtoiminnasta 189/2001), youth under

25 years old can be referred to rehabilitative work if they have received FSA for more than 4 months during a calendar year. Therefore, following the law (Laki Kuntouttavasta Työtoiminnasta 189/2001), receipt of long-term FSA among youth was defined as receipt of FSA for four months or longer during a calendar year at least once after the 18th birthday (no, yes). This operationalisation excludes brief 1–3-month FSA provided during educational summer breaks.

Additional information was also included in the descriptive analysis on other characteristics of youth's long-term FSA receipt. This information included the age in years at the first long-term FSA receipt and the cumulative number of years for which long-term FSA was granted.

Information on FSA was available from 2010 until the end of 2016, and the information was obtained from the Register of Social Assistance maintained by THL (Table 4).

5.2.3 Mood and neurotic disorders

The main outcome variable in Study III was youth's mood and neurotic disorders (Table 5), which are considered internalising disorders. This was defined by at least one care episode in specialised healthcare covering inpatient and outpatient hospital care for mood or neurotic disorders (no, yes).

Mood disorders were defined by ICD-10 codes F30–F39 while neurotic disorders were defined by ICD-10 codes F40–F48. Codes F30–F39 (i.e. mood (affective) disorders) include the following categories: manic episode (F30), bipolar affective disorder (F31), depressive episode (F32), recurrent depressive episode, recurrent (F33), persistent mood (affective) disorders (F34), other mood disorders (affective disorders) (F38), and unspecified mood (affective) disorders (F39). Codes F40–F48 (i.e. neurotic, stress-related and somatoform disorders) include the following disorders with specific ICD-10 codes: phobic anxiety disorders (F40), other anxiety disorders (F41), obsessive-compulsory disorder (F42), reaction to severe stress, and adjustment disorders (F43), dissociative (conversation) disorders (F44), somatoform disorders (F45), and other neurotic disorders (F48).

Diagnoses were collected from birth, but as these disorders typically evolve in youth (Kessler et al., 2007; Patel et al., 2007), the focus was on episodes from 13 years of age until the end of follow-up in 2016 when participants were 15–24 years

old. In the analysis, the onset age of mood and neurotic disorders was based on the first diagnosis in specialised healthcare after the 13th birthday.

Additional information on the specialised healthcare episodes for these disorders was also provided in the descriptive analysis. This information included the age at the first episode in inpatient or outpatient hospital care, the number of days spent in inpatient hospital care, and the number of care episodes in outpatient hospital care for the studied disorders. In addition, information was also provided for the specialised healthcare episodes (i.e. inpatient or outpatient hospital care) for each of the ICD-10 category included within codes F30-F39 and F40-F48 from the 13th birthday until the end of follow-up.

Information was obtained from the Care Register for Health Care maintained by the THL. Data on inpatient hospital care is available from 1992 to 2016 and outpatient hospital care in public hospitals from 1998 to 2016 (Table 5).

5.3 Covariates

The selection of covariates was based on prior research that has shown associations with the studied outcomes and maternal prenatal substance abuse (e.g. Basu & Banerjee, 2020; Flannigan et al., 2021; Lebel et al., 2019; Mravčík et al., 2020), as well as data availability in the ADEF Helsinki study. The studied youth and maternal characteristics are described in the following sections. Table 3, Table 4, and Table 5 comprise the information on the youth and maternal covariates, operationalisation of the covariates, and the data sources for studies I, II and III, respectively.

5.3.1 Youth characteristics

The characteristics of the exposed and unexposed youth and the operational definitions are detailed in Table 3, Table 4, and Table 5 for studies I, II, and III, respectively. The youth's demographic characteristics included birth year, sex, and mother language.

Youth characteristics also included gestational age at birth, birth weight, gestational exposure to maternal tobacco smoking, and Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score at 1 minute. Youth characteristics also included information on the intellectual disability, which was defined as at least one

specialised healthcare episode (i.e. inpatient or outpatient hospital care) from birth until the end of follow-up in 2016 with a primary diagnosis following ICD-9 codes 317−319 or ICD-10 codes F70−F79. Information was also collected on diagnose within the FASD spectrum for exposed youth (i.e. diagnosis or free text), and Neonatal Abstinence Syndrome (NAS) (i.e. diagnosis or free text).

Information on youth mental/behavioural disorders was based on the presence of at least one care episode in specialist healthcare (i.e. inpatient or outpatient hospital care) and included ICD-10 codes F00−F99 (excluding categories F17 Mental and behavioural disorders due to use of tobacco and F70−F79 Mental retardation). The codes F00−F99 includes the following sub-categories: F00−F09 Organic, including symptomatic mental disorders; F10−F19 Mental and behavioural disorders due to psychoactive substance use; F20−F29 Schizophrenia, schizotypal and delusional disorders; F30−F39 Mood (affective) disorders; F40−F48 Neurotic, stress-related and somatoform disorders; F50−F59 Behavioural syndromes associated with physiological disturbances and physical factors; F60−F69 Disorders of adult personality and behaviour; F80−F80 Disorders of psychological development; F90−F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence (including ADHD); and F99 Unspecified mental disorder. Please refer to Table 3 (for Study I), Table 4 (for Study II), and Table 5 (for Study III) for further details.

5.3.2 Maternal characteristics

The maternal characteristics and operational definitions are detailed in Table 3, Table 4, and Table 5 for studies I, II, and III, respectively. Information on maternal characteristics was collected at the time of the offspring's birth as well as during the follow-up. Maternal age at the time of the offspring's birth was one of the matching criteria for the cohorts, and therefore the information was only reported as a background characteristic. Other maternal characteristics included information on marital status at the time of the offspring's birth and socioeconomic status based on maternal occupation during pregnancy.

Maternal characteristics also included mental/behavioural disorder and substance use, maternal receipt of financial social assistance reflecting financial difficulties, maternal criminal convictions, and the death of the mother. These maternal

characteristics were used as a proxy to describe potential adversities in the postnatal caregiving environment. The operational definitions of these maternal characteristics are described in Table 3, Table 4, and Table 5 for studies I, II, and III, respectively.

As prior research indicates (e.g. Carta et al., 2001; Conners et al., 2009; Koponen et al., 2020b), adversities tend to co-occur, and therefore, a cumulative childhood adversity score was created for studies I and III. The cumulative childhood adversity score summed together the occurrence of five maternal characteristics. These adversities included maternal mental/behavioural disorder and substance use, maternal receipt of long-term financial social assistance, maternal criminal conviction and the death of the mother. In Study I, the occurrence of these maternal characteristics was considered until the offspring's 18th birthday, whereas in Study III, the occurrence was considered until the offspring's 13th birthday. The cumulative childhood adversity score was analysed as a categorical variable (0 adversities, 1 adversity, 2 adversities, 3 to 5 adversities).

5.3.3 Out-of-home care

In Finland, out-of-home care (OHC) is the last resort of municipal child protective service and is provided if supportive child welfare measures are insufficient. A child can be taken into care if their health or development is endangered by the child's home environment or if the child endangers their own health or development. A child is taken into care only if the substitute care is seen as being in the best interest of the child. In Finland, the Child Welfare Act safeguards a child's health and development (Lastensuojelulaki 417/2007).

Indications for OHC among small children typically include family financial difficulties, internal conflicts and domestic violence, parental substance use, or mental health problems. Indications for OHC among older children and youth typically involve problems in school participation or youth's problematic behaviour reflected as substance use, mental health problems, or delinquent behaviour. The reasons among older children can also include conflicts with parents (Heino et al., 2016).

In this dissertation, information on OHC was based on the information provided by the Child Welfare Register. The information on OHC included information on OHC episodes from birth to the age of 18 years, age at the first OHC episode,

cumulative lifetime duration of OHC episodes (in years), and number of separate OHC episodes. See Table 3, Table 4, and Table 5 for studies I, II, and III, respectively, for further details and operational definitions.

Table 3. Summary of the outcome variables, covariates, and data sources used in Study I

Variables	Definition and classification	Data Source (maintained by)	Years covered
Main outcome variable			
Completed secondary education	Completion of general upper secondary education (no, yes)	Education Register (Statistics Finland)	2010–2015
Other characteristics of youth's secondary education	Level of completed secondary education indicated as completion of general upper secondary education, vocational education, or bachelor's degree from a university or university of applied science (no, yes).	Education Register (Statistics Finland)	2010–2015
Covariates			
Youth characteristics			
Sex	Female, male	Medical Birth Register (THL)	1992–2016
Language	Mother language (Finnish, Swedish, other)	Digital And Population Data Services Agency	1992–2016
Gestational age at birth	< 37 weeks, ≥ 37 weeks	Medical Birth Register (THL)	1992–2016
Birth weight	< 2500g, ≥2500g	Medical Birth Register (THL)	1992–2016
APGAR score at 1 minute	Appearance, Pulse, Grimace, Activity, and Respiration score (0–6, 7–10 points)	Medical Birth Register (THL)	1992–2016
Gestational exposure to tobacco smoking	Exposure to maternal tobacco smoking during any trimester (no, yes)	Medical Birth Register (THL)	1992–2016
Fetal Alcohol Spectrum Disorder (FASD)	Diagnosis within the Fetal Alcohol Spectrum Disorder (FASD) continuum (no, yes) defined as the presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary diagnosis following ICD-9 code 760.71 or ICD-10 code Q86.0, or registered evidence of FAS, FAE, ARND, ARBD diagnoses or free text in the Register of Congenital Malformations. Assessed at any time during the follow-up.	Register of Congenital Malformations (THL), Hospital Discharge Register (THL)	ICD-9: 1992–1995; ICD-10; 1996–2016
Neonatal Abstinence Syndrome (NAS)	Registered evidence of NAS in the Medical Birth Register or in the Hospital Chart from the HAL clinics (as free text) (yes, no). The presence of at least one specialised healthcare episode (i.e. inpatient or	Medical Birth Register (THL), Hospital Discharge Register (THL) or the Care Register for Health Care, Hospital Chart from the HAL clinics	1992–2016

Variables	Definition and classification	Data Source (maintained by)	Years covered
	outpatient hospital care) with a primary diagnosis following ICD-9 code 779.5 or the ICD-10 code P96.1 (primary diagnosis) (no, yes).		
Mental/behavioural disorders	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary diagnosis with ICD-9 codes 290–316 or ICD-10 codes F00–F99 (F17 Mental and behavioural disorders due to use of tobacco and F70-F79 Mental retardation excluded) prior to the youth's 18th birthday (no, yes). Mental and/or behavioural disorders categorised as no psychiatric (F10–F60 or the corresponding ICD-9 codes) or neuropsychological disorders (F80–F99 or the corresponding ICD-9 codes), psychiatric disorder only (F10–F60 or the corresponding ICD-9 codes), neuropsychological disorder only (F80–F99 or the corresponding ICD-9 codes), dual psychiatric and neuropsychological disorder (both F10–F60 and F80–F99 diagnosis or the corresponding ICD-9 codes).	Hospital Discharge Register (THL) or the Care Register for Health Care,	1992–2016
Maternal characteristics			
Maternal age	Maternal age at the time of the offspring's birth analysed as a continuous variable.	Medical Birth Register (THL)	1992–2016
Maternal marital status	Marital status at the time of the offspring's birth (unmarried, married). Unmarried indicated single, widowed, or divorced.	Medical Birth Register (THL)	1992–2016
Maternal socioeconomic status	Socioeconomic status based on maternal occupation during pregnancy (low, high). Low status indicated by manual workers/students/pensioners/others, high status indicated by lower-/upper-level employees/self-employed.	Medical Birth Register (THL)	1992–2016
Maternal mental/behavioural disorder	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary diagnosis following ICD-9 codes 290 and 293–319 (291, 292, 303–305 excluded) or ICD-10 codes F00–F09 and F20–F99 (no, yes). Assessed prior to offspring's 18th birthday.	Hospital Discharge Register or the Care Register for Health Care (THL)	ICD-9: 1987–1995; ICD-10: 1996–2016
Maternal substance use	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary diagnosis following ICD-9 codes 291–292, 303–305, 357.0, 425.5, 535.3, 571.0, 571.1–571.3, 648.3, 655.5, 965.0, and 969.6–969.7 or ICD-10 codes	Hospital Discharge Register or the Care Register for Health Care (THL)	ICD-9: 1987–1995; ICD-10: 1996–2016

Variables	Definition and classification	Data Source (maintained by)	Years covered
	E24.4, F10–F16, F18–F19, G31.2, G40.5, G40.51, G40.52, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, K86.08, O35.4–O35.5, P04.4, R78.0-R78.5, T40, T43.6, T50.2–T50.3, T51, Z71.4, Z72.1–Z72.2 (no, yes). Assessed prior to offspring's 18th birthday.		
Maternal financial social assistance receipt	Receipt of financial social assistance (including basic and supplementary financial social assistance) at least once. Based on the maximum number of months of financial social assistance during a calendar year. Analysed in three categories: no, short-term, and long-term. Short-term financial social assistance indicated as receipt of financial social assistance for 1 to 9 months during a calendar year and long-term indicated as 10 to 12 months during a calendar year. Assessed prior to offspring's 18th birthday.	Register of Social Assistance (THL)	2002–2016
Maternal criminality	Sentenced at least once for conditional or unconditional imprisonment (no, yes). Assessed prior to offspring's 18th birthday.	Criminal Records (Legal Register Centre)	1985–2018
Death of mother	Death of mother (no, yes). Assessed prior to offspring's 18th birthday.	Cause of Death Register (Statistics Finland)	1992–2016
Cumulative childhood adversity score	Cumulative exposure to adverse maternal characteristics including maternal mental/behavioural disorder, substance use, receipt of long-term financial social assistance, criminality, death prior to offspring's 18th birthday. Analysed in four categories (0, 1, 2, 3 to 5).		
Out-of-home care (OHC)			
At least one OHC episode	At least one OHC episode before the offspring's 18th birthday (no, yes)	Child Welfare Register (THL)	1992–2016
Age at the first OHC episode	Offspring's age in years at the first OHC episode.	Child Welfare Register (THL)	1992–2016
Cumulative lifetime duration of OHC episodes	Cumulative duration of separate OHC episodes in years.	Child Welfare Register (THL)	1992–2016
Number of separate OHC episodes	Number of separate OHC episodes.	Child Welfare Register (THL)	1992–2016

Note: ICD; International Statistical Classification of Diseases and Related Health Problems, THL; Finnish Institute for Health and Welfare

Table 4. Summary of the outcome variables, covariates, mediators, and data sources used in Study II

Variables	Definition and classification	Data Source (maintained by)	Years covered
Main outcome variable			
Youth's long-term financial social assistance receipt	Receipt of financial social assistance for at least four months during a calendar year at least once between the ages of 18 and 24 years (no, yes).	Register of Social Assistance (THL)	2010–2016
Other characteristics of youth financial social assistance receipt	Age in years at the first long-term financial social assistance receipt, cumulative number of years for which long-term financial social assistance was granted.	Register of Social Assistance (THL)	2010–2016
Mediator variables			
Youth characteristics			
Mental/behavioural disorders	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with primary or secondary diagnosis following ICD-9 codes 290–316 (292 excluded) or ICD-10 codes F00–F99 (F17 Mental and behavioural disorders due to use of tobacco, F70–F79 Mental retardation excluded (no, yes). Assessed prior to youth's 18th birthday.	Hospital Discharge Register or Care Register for Health Care (THL)	1992–2016
Completed secondary education	Record of completed upper secondary education by the end of 2015 (no, yes).	Education Register (Statistics Finland)	2010–2015
Maternal characteristics			
Maternal mental/behavioural disorder	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary or secondary diagnosis following ICD-9 codes 290 and 293–319 (303–305 excluded), or the ICD-10 codes F00–F09 and F20–F99 (no, yes). Assessed prior to offspring's 18th birthday.	Hospital Discharge Register or Care Register for Health Care (THL)	ICD-9 1987–1995 ICD-10 1996–2016
Maternal substance use	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary diagnosis following ICD-9 codes 291–292, 303–305, 3570, 4255, 5353, 5710, 5711–5713, 6483, 6555, 9650, and 9696–9697, or ICD-10 codes E24.4, F10-F16, F18–F19, G31.2, G40.5, G40.51,	Hospital Discharge Register or Care Register for Health Care (THL)	ICD-9 1987–1995 ICD-10 1996–2016

Variables	Definition and classification	Data Source (maintained by)	Years covered
	G40.52, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, K86.08, O35.4–O35.5, P04.4, R78.0–R78.5, T40, T43.6, T50.2–T50.3, T51, Z71.4 and Z72.1–Z72.2 (no, yes). Assessed prior to offspring's 18th birthday.		
Maternal long-term financial social assistance receipt	The presence of at least one receipt of financial social assistance (including basic and supplementary financial social assistance) for at least four months during a calendar year at least once (no, yes). Assessed prior to offspring's 18th birthday.	Register of Social Assistance (THL)	2002–2016
Out-of-home care (OHC)			
At least one OHC episode	At least one OHC episode before the offspring's 18th birthday (no, yes),	Child Welfare Register (THL)	1992–2016
Age at the first OHC episode	Offspring's age in years at the first OHC episode.,	Child Welfare Register (THL)	1992–2016
Cumulative lifetime duration of OHC episodes	Cumulative duration of separate OHC episodes in years.	Child Welfare Register (THL)	1992–2016
Covariates			
Youth's sex	Female, male	Medical Birth Register (THL)	1992–2016

Note: ICD; International Statistical Classification of Diseases and Related Health Problems, THL; Finnish Institute for Health and Welfare. The table is an adapted version of the table reported in Nissinen et al. (2022).

Table 5. Summary of the outcome variables, covariates, mediators, and data sources used in Study III

Variables	Definition and classification	Data Source (maintained by)	Years covered
Main outcome variable			
Youth's mood and neurotic disorders	The presence of at least one specialist healthcare episode (i.e. inpatient or outpatient hospital care) after the age of 13 years until the end of follow-up in 2016 with a primary diagnosis for mood disorders (ICD-10 codes F30–F39) or neurotic disorders (ICD-10 codes F40–F48) (no, yes).	Hospital Discharge Register or the Care Register for Health Care (THL)	1992–2016
Other characteristics of youth's mood or neurotic disorders	Age at the first care episode in inpatient or outpatient hospital care. Number of days spent in inpatient hospital care. Number of care episodes in outpatient hospital care for the mood or neurotic disorders. At least one care episode in specialised healthcare (i.e. inpatient or outpatient hospital care) after the age of 13 years with a primary diagnosis for a specific mood or neurotic disorder included in the ICD-10 codes F30–F39 and F40–F48.		
Covariates			
Youth characteristics			
Sex	Female, male	Medical Birth Register (THL)	1992–2016
Gestational age at birth	< 37 weeks, ≥ 37 weeks	Medical Birth Register (THL)	1992–2016
Birth weight	< 2500g, ≥2500g	Medical Birth Register (THL)	1992–2016
Gestational exposure to tobacco smoking	Exposure to maternal tobacco smoking during any trimester (no, yes)	Medical Birth Register (THL)	1992–2016
Fetal Alcohol Spectrum Disorder (FASD)	Diagnosis within the Fetal Alcohol Spectrum Disorder (FASD) continuum (no, yes) defined as the presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with primary diagnosis following ICD-9 code 760.71 or ICD-10 code Q86.0, or registered evidence of FAS, FAE, ARND, ARBD diagnoses or free text in the Register of Congenital Malformations.	Register of Congenital Malformations (THL), Hospital Discharge Register (THL)	ICD-9: 1992–1995; ICD-10; 1996–2016
Maternal characteristics			

Variables	Definition and classification	Data Source (maintained by)	Years covered
Maternal age	Maternal age at the time of the offspring's birth analysed as continuous variable.	Medical Birth Register (THL)	1992–2016
Maternal marital status	Maternal marital status at the time of the offspring's birth (unmarried, married). Unmarried indicated single, widowed, or divorced.	Medical Birth Register (THL)	1992–2016
Maternal socioeconomic status	Socioeconomic status based on maternal occupation during pregnancy (low, high). Low status indicated by manual workers/students/pensioners/others, high status indicated by lower-/upper-level employees/self-employed.	Medical Birth Register (THL)	1992–2016
Maternal mental/behavioural disorder	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary diagnosis following ICD-9 codes 290 and 293–319 (291, 292, 303–305 excluded) or ICD-10 codes F00–F09 and F20–F99 (F10–F19 excluded) (no, yes). Assessed prior to offspring's 13th birthday.	Hospital Discharge Register or the Care Register for Health Care (THL)	ICD-9: 1987–1995; ICD-10: 1996–2016
Maternal substance use	The presence of at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care) with a primary diagnosis following ICD-9 codes 291–292, 303–305, 357.0, 425.5, 535.3, 571.0, 571.1–571.3, 648.3, 655.5, 965.0, and 969.6–969.7 or ICD-10 codes E24.4, F10–F16, F18–F19, G31.2, G40.5, G40.51, G40.52, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, K86.08, O35.4–O35.5, P04.4, R78.0–R78.5, T40, T43.6, T50.2–T50.3, T51, Z71.4, Z72.1–Z72.2 (primary diagnosis) (no, yes). Assessed prior to offspring's 13th birthday.	Hospital Discharge Register or the Care Register for Health Care (THL)	ICD-9: 1987–1995; ICD-10: 1996–2016
Maternal financial social assistance receipt	Receipt of financial social assistance (including basic and supplementary financial social assistance) at least once before the offspring's 18th birthday. Based on the maximum number of months of financial social assistance during a calendar year. Analysed in three categories: no, short-term, and long-term. Short-term financial social assistance indicated as receipt of financial social assistance for 1 to 9 months during a calendar year and long-term indicated as 10 to 12 months during a calendar year. Assessed prior to offspring's 13th birthday.	Register of Social Assistance (THL)	2002–2016

Variables	Definition and classification	Data Source (maintained by)	Years covered
Maternal criminality	Sentenced at least once for conditional or unconditional imprisonment (no, yes). Assessed prior to offspring's 13th birthday.	Criminal Records (Legal Register Centre)	1985–2018
Death of mother	Death of mother (no, yes). Assessed prior to offspring's 13th birthday.	Cause of Death Register (Statistics Finland)	1992–2016
Cumulative childhood adversity score	Cumulative exposure to adverse maternal characteristics including maternal mental/behavioural disorder, substance use, receipt of long-term financial social assistance, criminality, death prior to offspring's 13th birthday. Analysed in four categories (0, 1, 2, 3 to 5).		
Out-of-home care (OHC)			
At least one OHC episode	At least one OHC episode before or after the offspring's 13th birthday. Analysed in three categories (no OHC episodes, first OHC episode before the age of 13 years, first OHC episode after the age of 13 years)	Child Welfare Register (THL)	1992–2016
Age at the first OHC episode	Offspring's age in years at the first OHC episode.	Child Welfare Register (THL)	1992–2016
Cumulative lifetime duration of OHC episodes	Cumulative duration of separate OHC episodes in years.	Child Welfare Register (THL)	1992–2016

Note: ICD; International Statistical Classification of Diseases and Related Health Problems, THL; Finnish Institute for Health and Welfare. The table is an adapted version of the table reported in Nissinen et al. (2022).

5.4 Statistical methods

The statistical methods used in studies I, II and III are described in the following sections and summarised in Table 6. Descriptive statistical methods were used across all studies, whereas logistic regression analyses were performed in Study I, generalised linear models in Study II, and Cox proportional hazard regression analysis in Study III. Mediation analyses were performed in studies II and III.

Table 6. Summary of the statistical methods and programs used in studies I, II, and III

	Statistical methods	Statistical program
Study I	Pearson's chi-square test, Mann-Whitney U-test, multivariable logistic regression	IBM SPSS Statistics version 25
Study II	Pearson's chi-square test, independent samples t-test, univariate and multivariable generalised linear models, mediation analysis	IBM SPSS Statistics version 28, R, the mediation package for R[1]
Study III	Pearson's chi-square test, Mann-Whitney U-test, multivariable Cox Proportion Hazards regression, mediation analysis	IBM SPSS Statistics version 28, R, the mediation package for R[1]

Note: IBM; International Business Machines Corporation, SPSS; Statistical Package for the Social Sciences. [1] Tingley et al. (2014).

5.4.1 Descriptive statistical methods

Descriptive statistical methods (frequencies, means, standard deviations (SD), medians, and interquartile ranges (IQR)) were used in all studies to describe the characteristics of the exposed and unexposed cohorts. Descriptive statistical methods were also used to describe the prevalence of completed secondary education (Study I), receipt of financial social assistance (Study II) and the utilisation of specialised healthcare for mood and neurotic disorders (Study III) in the cohorts. The results were reported as counts and percentages for categorical variables and means and SDs or medians and IQRs for continuous variables.

The statistical comparison of the characteristics of the exposed and unexposed cohorts was based on Pearson's chi-square test (χ^2) test for categorical variables (or Fisher's exact test if the expected frequencies in each cell were < 5) and on the Mann-Whitney U-test or independent samples t-test for continuous variables, as appropriate,

given the normality of the distribution of the data. In this study, the cohorts were analysed as independent samples.

In the study, the absence of register data (e.g. on diagnosis code, completed secondary education, or financial social assistance receipt) was interpreted as the absence of register data for the study participant, and not as missing data. For variables where the absence of register data can be considered as representative of missingness (e.g. data collected from the Medical Birth Register, including gestational age and APGAR score), the missing values (n and % relative to the total) were reported as their own category. Imputations of missing values were not undertaken in the study and the statistical comparison was based on non-missing values. The descriptive analyses were computed with IBM SPSS Statistics (Statistical Package for the Social Sciences) version 25 (Study I) or version 28 (Study II, Study III).

5.4.2 Logistic regression analysis and generalised linear models

Logistic regression is a model in which a binary outcome is predicted by binary, ordinal, or continuous predictors. The logistic regression produces odds ratios (OR), which is the exponential of the regression coefficient B. Odds ratios indicate the changes in the likelihood of the outcome to occur resulting from a unit change in the predictor. An OR of 1 indicates that the predictor does not affect the odds of the outcome occurring. An OR > 1 indicates that a unit increase in the predictor increases the odds of the outcome occurring. Conversely, an OR < 1 indicates that a unit increase in the predictor decreases the odds of the outcome occurring (Vittinghoff et al., 2012).

Logistic regression was used in Study I. Multivariable stepwise logistic regression models were constructed to study the associations between prenatal substance exposure and the outcome and the influence of covariates stepwise in six models. The covariates included youth characteristics (sex, exposure to tobacco smoking during gestation, mental/behavioural disorders), maternal characteristics (maternal socioeconomic status and cumulative childhood adversity score), and OHC. The results of the unadjusted model (Model 1) are reported as OR with 95% Confidence Intervals (CIs), and the results from the adjusted models (models 2 to 6) are reported as adjusted odds ratios (AOR) with 95% CIs. All analyses of Study I were computed with IBM SPSS Statistics version 25.

Generalised linear models, a class of models similar to linear and logistic models (Rothman, 2012; Vittinghoff et al., 2012), were used in Study II in a similar way as the

logistic regression analysis. First, bivariate associations were calculated to study the associations between prenatal substance exposure, selected covariates, and the outcome of interest (i.e. youth's receipt of long-term FSA). Next, a multivariable generalised linear model was constructed in which all the studied variables were included simultaneously. The adjusted model was also adjusted for follow-up time to account for the differences in the follow-up time between birth years and thus for the likelihood of long-term financial social assistance receipt between birth years. The results from the bivariate analyses were reported as parameter estimates (*b*) with standard error (SE), odds ratios (OR) and p-values, while the results from the adjusted multivariable model were reported as parameter estimates with SE, adjusted odds ratios (AOR), and p-values. The analyses were performed with generalised linear models with R.

5.4.3 Cox proportional hazard regression analysis

Cox proportional hazard regression (i.e. Cox regression) is a method for investigating the association between predictor(s) and a right-censored, time-to-event outcome. The dependent variable is binary, whereas the independent variable can be binary, ordinal, or continuous (Vittinghoff et al., 2012).

Cox regression produces hazard ratios (HR), which indicate the probability of the outcome of interest occurring at any point in the specified time. An HR of 1 indicates that a unit increase in the predictor does not affect the event of interest. An HR > 1 indicates that a unit increase in the predictor increases the hazard of the event (positive association with the event probability). Conversely, an HR < 1 indicates that a unit increase in the predictor decreases the hazard of the event (negative association with the event probability) (Vittinghoff et al., 2012).

In Cox regression, time refers to the length of time for the event of interest to occur before the study is terminated. For participants who obtained the event of interest, time records the survival time until the event of interest occurs. For participants who did not obtain the event of interest, time indicates survival time during the follow-up. Participants who do not obtain the event of interest during the follow-up are censored. Information on these participants' event-free time during the follow-up is included in the analysis. Among other reasons, censoring can also occur if the study participant is lost to follow-up during the follow-up time or withdraws from the study during the follow-up for reasons such as death (Vittinghoff et al., 2012).

Cox regression analysis was used in Study III. In the analyses, time was calculated to begin from the youth's 13th birthday and continued until the event of interest occurred (i.e. first inpatient or outpatient hospital care episode for mood or neurotic disorders), death or end of the follow-up in 2016.

In the analysis, five multivariable Cox regression models were constructed to study the association between prenatal substance exposure and mood and neurotic disorders and the influence of covariates stepwise. The covariates included youth characteristics (sex), maternal characteristics (cumulative childhood adversity score) and OHC. The results of the unadjusted model (Model 1) were reported as an HR with 95% CIs, whereas the results of the adjusted models (models 2 to 5) were reported as adjusted hazard ratios (AHR) with 95% CIs. The analyses of Study III were conducted using IBM SPSS Statistics version 28.

5.4.4 Mediation analysis

Mediation analysis is a statistical method to study how and to what extent a third variable (i.e. mediator, M) explains the association between an independent variable (X) and a dependent variable (Y) (Hayes, 2013).

In the mediation analysis (Figure 5), the pathway from X to Y (without the effect of M) (c') is termed a direct effect. The second pathway from X to Y that goes through M (ab) is termed an indirect effect. The total effect (c) sums the direct and indirect effects. The proportion mediated indicates the proportion of the path from X to Y that is explained by M. Other pathways calculated in mediation analysis are those from X to M (a) and from M to Y (b) (Figure 5) (MacKinnon, 2008).

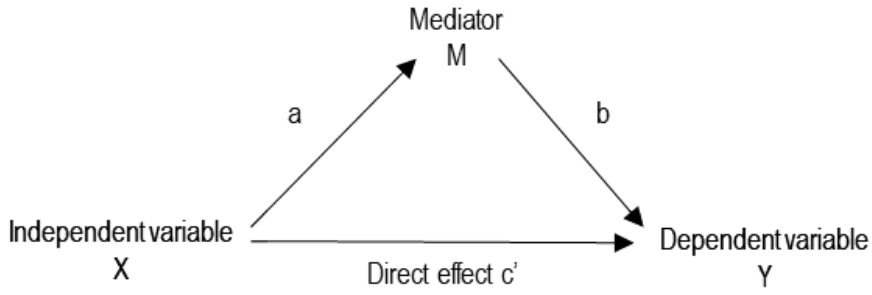


Figure 5. Illustration of the pathways of the mediation analysis

Mediation is said to occur if the strength of the relationship between X and Y is reduced when the mediator is included. Perfect mediation occurs if c' is zero, i.e. the relationship between X and Y is completely removed by including the mediator in the model (Hayes, 2013).

Mediation analyses were used in studies II and III. In Study II, the mediating effect of youth characteristics (including mental/behavioural disorders and lack of secondary education, maternal receipt of long-term FSA and OHC) on the association between prenatal substance exposure and youth's long-term FSA receipt was studied. In Study III, mediation analysis was used to study the mediating effect of OHC on the association between prenatal substance exposure and youth's mood and neurotic disorders.

The results of the mediation analysis were reported as parameter estimates (*b*) with standard errors (SE), 95% CIs, and p-values. Mediation analyses were performed using a bootstrapping method that included one thousand simulations and was conducted using the mediation package for R (Tingley et al., 2014).

5.5 Ethical considerations

The local ethical committee of the Hospital District of Helsinki and Uusimaa (Nro 333/E8/02) approved the study. Permission for data linkages was obtained from all authorities maintaining the registers. The Finnish Institute for Health and Welfare performed the register linkages and pseudonymised the data prior to analyses to ensure anonymity. Study participants were neither involved in the study nor contacted, and register data was only collected for research purposes. Therefore, informed consent from the study participants was not required, following Finnish legislation. In addition, the data are presented only on the group level to ensure that individual study participants cannot be identified. Only researchers with research permission provided by the register authorities have access to the anonymised data. The data are considered highly confidential and stored on protected servers at Folkhälsan Research Centre.

6 RESULTS

6.1 Characteristics of the exposed and unexposed cohorts

A description of the characteristics of the study population is presented in Table 7 for the total study population in the ADEF Helsinki study. The characteristics of the study population in Study I, Study II, and Study III are presented in Table 8, Table 11, and Table 15, respectively.

In the total study population in the ADEF Helsinki study (Table 7) including 615 exposed and 1787 unexposed youth, the median follow-up time among exposed and unexposed was 18.7 and 18.6 years, respectively (p=0.337). Of the exposed, 1.3% had died during the follow-up compared with 1.1% of the unexposed (p=0.630). The sex distribution of the cohorts did not differ and approximately half of the youth in both cohorts were males. A majority of youth in the exposed and unexposed cohorts had Finnish as their mother language. However, a slightly larger number of the unexposed had Swedish or other languages as the mother language compared with the exposed.

The cohorts did not differ in gestational age at birth or APGAR score at 1 minute. However, differences between the cohorts were found in birth weight, and a higher proportion of the exposed had a birth weight of less than 2500g, indicating low birth weight compared to the unexposed (12.5% vs. 6.7%, p<0.001). A significantly higher proportion of the exposed youth had been exposed to gestational tobacco smoking compared to the unexposed (76.9% vs. 19.3%, p<0.001). A minority of the exposed youth (7.5%) had received a diagnosis within the FASD spectrum, and 8.1% had registered evidence of NAS. Of the exposed youth, 2.1% were diagnosed with intellectual disability compared to 0.8% among the unexposed (p=0.011) (Table 7).

The cohorts were matched for maternal age at the time of the offspring's birth, and thus differences in the maternal age were not found between the exposed and unexposed cohorts. Differences between the cohorts were also not observed in terms of other maternal matching criteria (data not shown). Regarding other maternal characteristics assessed during pregnancy or at the time of the offspring's birth, the

mothers of the exposed offspring were more often unmarried and from a lower socioeconomic status group than the mothers of the unexposed offspring (Table 7).

A comparison of other maternal characteristics that occurred before the offspring's 18th birthday between the cohorts showed that the mothers of the exposed offspring were more likely to have specialised healthcare episodes (i.e. outpatient or inpatient hospital care episodes) for mental/behavioural disorders and substance use. Furthermore, the mothers of the exposed offspring had more often been recipients of FSA and sentenced for a criminal conviction. A higher proportion of the mothers of the exposed offspring had also died before the offspring's 18th birthday compared to the mothers of the unexposed offspring (Table 7).

When the maternal characteristics that occurred before the offspring's 18th birthday (i.e. mental/behavioural disorders, substance use, receipt of long-term FSA receipt, criminality, death) were analysed as a cumulative childhood adversity score, a higher proportion of the exposed offspring had been exposed to childhood adversities compared to the unexposed. The median number of adversities the exposed youth had experienced prior to their 18th birthday was also higher compared to the unexposed (2.0 vs. 0.0, $p<0.001$) (Table 7).

With respect to OHC, a higher proportion of the exposed offspring had been placed in OHC at least once before their 18th birthday compared to the unexposed (63.9% vs. 8.2%, $p<0.001$). Among the exposed offspring, the first OHC episode occurred at a younger age compared to the unexposed. The exposed also had more separate OHC episodes, and the cumulative lifetime duration of OHC was longer in the exposed cohort compared to the unexposed (Table 7).

Table 7. Descriptive characteristics of the exposed and unexposed cohorts in the ADEF Helsinki study

	Exposed ***n*=615**	**Unexposed** ***n*=1787**	**p-value**
Follow-up time from birth until the end of 2016 (in years) (median, IQR)	18.7 (16.6; 21.0)	18.6 (16.5; 20.9)	0.337
Youth characteristics			
Died during the follow-up time, *n* (%)	8 (1.3)	19 (1.1)	0.630
Sex, *n* (%)			0.308
Male	303 (49.3)	923 (51.7)	
Female	312 (50.7)	864 (48.3)	
Language, *n* (%)			<0.001
Finnish	587 (95.4)	1526 (85.4)	
Swedish	19 (3.1)	113 (6.3)	
Other	9 (1.5)	148 (8.3)	

Gestational age at birth, *n* (%)			0.985
< 37 weeks	55 (8.9)	162 (9.1)	
≥ 37 weeks	552 (89.8)	1621 (90.7)	
Missing	8 (1.3)	4 (0.2)	
Birth weight, *n* (%)			<0.001
< 2500g	77 (12.5)	120 (6.7)	
≥ 2500g	538 (87.5)	1664 (93.3)	
Birth weight (mean, SD)	3189.5 (607.6)	3454.9 (622.5)	<0.001
APGAR score at 1 minute, *n* (%)			0.409
0 to 6 points	25 (4.1)	60 (3.4)	
7 to 10 points	588 (95.6)	1724 (96.5)	
Missing	2 (0.3)	3 (0.2)	
Gestational exposure to tobacco smoking, *n* (%)			<0.001
No	142 (23.1)	1443 (80.7)	
Yes	473 (76.9)	344 (19.3)	
A diagnosis within the FASD spectrum, *n* (%)	46 (7.5)	0 (0.0)	<0.001
Neonatal Abstinence Syndrome, *n* (%)	50 (8.1)	0 (0.0)	<0.001
Intellectual disability, *n* (%)	13 (2.1)	15 (0.8)	0.011
Maternal characteristics (assessed during pregnancy or at the time of offspring's birth)			
Maternal age at the time of offspring's birth (mean, SD)	27.4 (6.5)	27.5 (6.4)	0.717
Maternal marital status, *n* (%)			<0.001
Unmarried (single/widowed/divorced)	490 (79.7)	728 (40.7)	
Married	125 (20.3)	1059 (59.3)	
Maternal socioeconomic status, *n* (%)			<0.001
Low (manual workers/students/pensioners/others)	425 (69.1)	821 (45.9)	
High (lower-/upper-level employees, self-employed)	190 (30.9)	966 (54.1)	
Maternal characteristics (assessed before the offspring's 18th birthday)			
Maternal mental/behavioural disorder, *n* (%)			<0.001
No	303 (49.3)	1480 (82.8)	
Yes	312 (50.7)	307 (17.2)	
Maternal substance use, *n* (%)			<0.001
No	293 (47.6)	1731 (96.9)	
Yes	322 (52.4)	56 (3.1)	
Maternal financial social assistance receipt, *n* (%)			<0.001
No	58 (9.4)	1188 (66.5)	
Short-term (1 to 9 months during a calendar year)	118 (19.2)	336 (18.8)	
Long-term (10 to 12 months during a calendar year)	439 (71.4)	263 (14.7)	
Maternal criminality, *n* (%)			<0.001
No	555 (90.2)	1775 (99.3)	
Yes	60 (9.8)	12 (0.7)	
Death of mother, *n* (%)			<0.001
No	548 (89.1)	1776 (99.4)	
Yes	67 (10.9)	11 (0.6)	
Cumulative childhood adversity score, *n* (%)			<0.001

0 adversity	50 (8.1)	1291 (72.2)	
1 adversity	126 (20.5)	334 (18.7)	
2 adversities	175 (28.5)	109 (6.1)	
3 to 5 adversities	264 (42.9)	53 (3.0)	
The number of adversities (median, IQR)	2.0 (1.0, 3.0)	0.0 (0.0, 1.0)	<0.001
Out-of-home care (OHC)			
At least one OHC episode before offspring's 18th birthday, *n* (%)			<0.001
No	222 (36.1)	1640 (91.8)	
Yes	393 (63.9)	147 (8.2)	
Age at the first OHC episode (in years) (median, IQR)	2.0 (2.1; 15.0)	10.0 (4.0; 14.0)	<0.001
Number of separate OHC episodes (median, IQR)	3.0 (2.0; 3.0)	2.0 (1.0; 3.0)	<0.001
Cumulative lifetime duration of OHC episodes (in years) (median, IQR)	9.3 (2.1; 15.0)	1.1 (0.2; 4.6)	<0.001

Note: FASD; Fetal Alcohol Spectrum Disorders, IQR; Interquartile Range, SD: Standard Deviation. p-values based on the χ^2 test or Fisher's exact test for categorical variables, independent samples t-test or Mann-Whitney test for continuous variables, as appropriate. The cumulative childhood adversity score includes the sum of the occurrences of the following maternal characteristics before the offspring's 18th birthday: maternal mental/behavioural disorders, maternal substance use, maternal recipiency of long-term financial social assistance, maternal criminality, and death of mother.

6.2 Completed secondary education (Study I)

In Study I, completed secondary education was studied among the exposed (*n*=283) and unexposed (*n*=820) youth aged 18 years and older at the end of the follow-up in 2015 (i.e. the year from which the latest information on secondary education was obtained). The descriptive characteristics of the exposed and unexposed youth included in Study I are described in Table 8.

Table 8. Descriptive characteristics of 18–23-year-old exposed and unexposed youth in Study I

	Exposed ***n*=283**	**Unexposed** ***n*=820**	**p-value**
Follow-up time from birth until the end of 2015 (in years) (median, IQR)	20.2 (18.8; 22.2)	20.1 (18.8; 22.1)	0.769
Youth characteristics			
Sex, *n* (%)			0.626
Male	144 (50.9)	431 (52.6)	
Female	139 (49.1)	389 (47.4)	
Language, *n* (%)			<0.001
Finnish	273 (96.5)	705 (86.0)	
Swedish	8 (2.8)	55 (6.7)	
Other	2 (0.7)	60 (7.3)	
Gestational age at birth, *n* (%)			0.705

< 37 weeks	29 (10.2)	91 (11.1)	
≥ 37 weeks	253 (89.4)	729 (88.9)	
Missing	1 (0.4)	0 (0.0)	
Birth weight, *n* (%)			<0.001
< 2500g	42 (14.8)	55 (6.7)	
≥ 2500g	241 (85.2)	765 (93.9)	
APGAR score at 1 minute, *n* (%)			0.296
0 to 6 points	11 (3.9)	22 (2.7)	
7 to 10 points	270 (96.1)	798 (97.3)	
Gestational exposure to tobacco smoking, *n* (%)			<0.001
No			
Yes	224 (79.2)	163 (19.9)	
A diagnosis within the FASD spectrum, *n* (%)	31 (11.0)	0 (0.0)	<0.001
Neonatal Abstinence Syndrome, *n* (%)	14 (4.9)	0 (0.0)	<0.001
Categorised mental and/or behavioural disorders, *n* (%)			<0.001
No psychiatric or neuropsychological disorder	118 (41.7)	589 (71.8)	
Psychiatric disorder only	54 (19.1)	87 (10.6)	
Neuropsychological disorder only	57 (20.1)	80 (9.8)	
Dual psychiatric and neuropsychological disorder	54 (19.1)	64 (7.8)	
Maternal characteristics (assessed during pregnancy or the time of offspring's birth)			
Maternal age at the time of offspring's birth (mean, SD)	27.7 (6.5)	27.9 (6.5)	0.644
Maternal marital status, *n* (%)			<0.001
Unmarried (single/widowed/divorced)	217 (76.7)	288 (35.1)	
Married	66 (23.3)	532 (64.9)	
Maternal socioeconomic status, *n* (%)			<0.001
Low (manual workers/students/pensioners/others)	173 (66.0)	320 (40.0)	
High (lower-/upper-level employees, self-employed)	89 (34.0)	481 (60.0)	
Maternal characteristics (assessed before the offspring's 18th birthday)			
Maternal mental/behavioural disorder, *n* (%)			<0.001
No	161 (56.9)	693 (84.5)	
Yes	122 (43.1)	127 (15.5)	
Maternal substance use, *n* (%)			<0.001
No	139 (49.1)	795 (97.0)	
Yes	144 (50.9)	25 (3.0)	
Maternal financial social assistance receipt, *n* (%)			<0.001
No	34 (12.0)	596 (72.7)	
Short-term (1 to 9 months during a calendar year)	54 (19.1)	126 (15.4)	
Long-term (10 to 12 months during a calendar year)	195 (68.9)	98 (12.0)	
Maternal criminality, *n* (%)			<0.001
No	254 (89.8)	818 (99.8)	
Yes	29 (10.2)	2 (0.2)	
Death of mother, *n* (%)			<0.001
No	251 (88.7)	815 (99.4)	
Yes	32 (11.3)	5 (0.6)	

Cumulative childhood adversity score, *n* (%)			<0.001
0 adversity	38 (13.4)	627 (76.5)	
1 adversity	82 (20.9)	144 (17.6)	
2 adversities	70 (24.7)	34 (4.1)	
3 to 5 adversities	23 (8.1)	15 (1.8)	
Out-of-home care (OHC)			
At least one OHC episode before offspring's 18th birthday, *n* (%)			<0.001
No	102 (36.0)	769 (93.8)	
Yes	181 (64.0)	51 (6.2)	
Age at the first OHC episode (in years) (median, IQR)	3.0 (1.0; 7.0)	12.0 (7.0; 14.0)	<0.001
Number of separate OHC episodes (median, IQR)	3.0 (3.0; 2.0)	2.0 (1.0; 2.0)	<0.001
Cumulative lifetime duration of OHC episodes (in years) (median, IQR)	10.8 (2.7; 16.1)	1.9 (0.3; 5.0)	<0.001

Note: FASD; Fetal Alcohol Spectrum Disorders, IQR; Interquartile Range, SD: Standard Deviation. P-values based on the χ^2 test for categorical variables, independent samples t-test or Mann-Whitney test for continuous variables, as appropriate. The cumulative childhood adversity score includes the sum of the occurrences of the following maternal characteristics before the offspring's 18th birthday: maternal mental/behavioural disorders, maternal substance use, maternal recipiency of long-term financial social assistance, maternal criminality, and death of mother. The table is an adapted version of the table reported in Nissinen et al. (2021).

In terms of completed secondary education, the results showed a delay in secondary education completion (Figure 6) and a lower education completion rate in the exposed youth compared with the unexposed (37.8% vs. 51.0%, respectively, p<0.001) (Table 9). The proportion of youth with completed secondary education increased with increasing age in both cohorts (data not shown). Among youth aged 23 years at the end of follow-up in 2015, 56.1% of the exposed had completed secondary education compared to 74.8% among the unexposed (p=0.027).

The results also showed differences in the level of completed secondary education between the exposed and unexposed youth. Among the exposed, the most common type of completed secondary education was vocational education (26.9%), followed by general upper secondary school (10.6%). Among the unexposed, the most commonly completed education was general upper secondary school (27.6%) followed by vocational education (22.4%). Of the exposed, only 0.4% (n=1) had a bachelor's degree compared to 1.1% (n=9) among the unexposed (p<0.001) (Table 9).

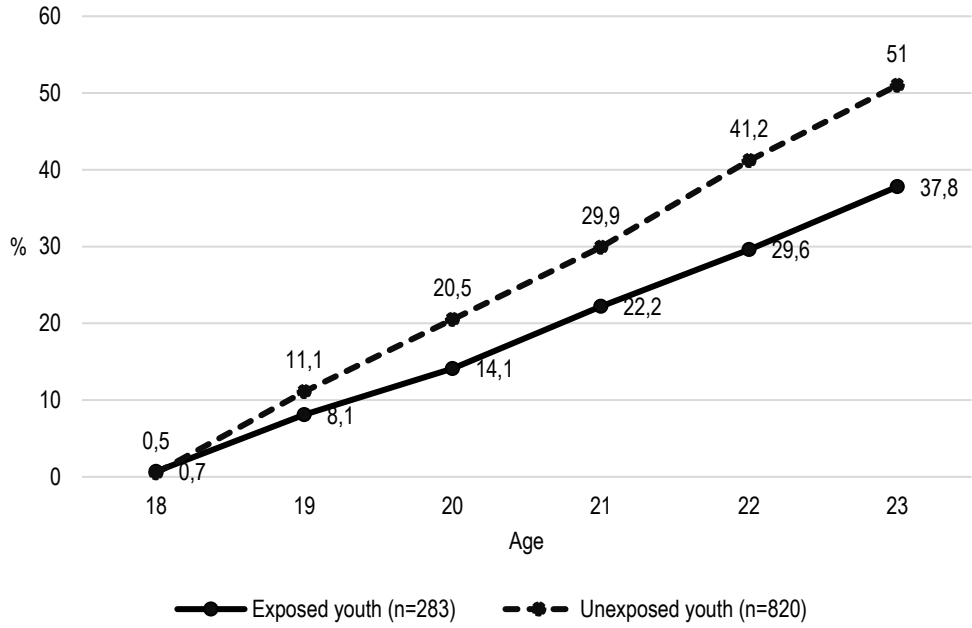


Figure 6. Cumulative proportions of exposed and unexposed youth with completed secondary education at the age of 18–23 years.

Note: The figure is an adapted version of the figure reported in Nissinen et al. (2021)

Table 9. Comparison of completed secondary education among 18–23-year-old exposed and unexposed youth

	Exposed *n*=283	**Unexposed *n*=820**	**p-value**
Secondary education, *n* (%)			<0.001
No completed secondary education	176 (62.2)	402 (49.0)	
Completed secondary education	107 (37.8)	418 (51.0)	
Level of completed secondary education, *n* (%)			<0.001
Vocational education	76 (26.9)	184 (22.4)	
General upper secondary school	30 (10.6)	225 (27.4)	
Bachelor's degree	1 (0.4)	9 (1.1)	

Note: p-values based on the χ^2 test. The table is an adapted version of the table reported in Nissinen et al. (2021).

6.2.1 Factors associated with completed secondary education, adjusted multivariable analysis

Table 10 displays the results from the unadjusted and adjusted multivariable logistic regression analysis. The results of the unadjusted model (Model 1) showed that the exposed youth were less likely to have completed secondary education (OR 0.59, 95% CI 0.44; 0.77) than the unexposed youth. However, the difference in completed secondary education between the cohorts was attenuated to non-significant levels following the stepwise adjustments for youth characteristics, maternal characteristics, and OHC in models 2 to 6. The results of Model 6, in which all covariates were included simultaneously, showed that prenatal substance exposure was not statistically associated with completed secondary education (AOR 0.93, 95% CI 0.61; 1.43), and the different domains of youth's mental/behavioural disorders were independently associated with secondary education completion. None of the other variables showed a statistically significant association with secondary education completion. Of the youth's mental/behavioural disorders, psychiatric disorders (AOR 0.65, 95% CI 0.45; 0.96), neuropsychological disorders (AOR 0.35, 95% CI 0.23; 0.54), and dual psychiatric and neuropsychological disorders (AOR 0.29, 95% CI 0.18; 0.48) were associated with reduced likelihood of completed secondary education (Table 10).

Table 10. Unadjusted Odds Ratios (OR) and adjusted Odds Ratios (AOR) with 95% Confidence Intervals (Cis) and p-values for completed secondary education in six multivariable logistic regression models (N=1103)

	Model 1 (unadjusted model)		Model 2		Model 3		Model 4		Model 5		Model 6	
	OR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value	AOR (95% CI)	p-value
Prenatal substance exposure												
Unexposed (ref)	1		1		1		1		1		1	
Exposed	0.59 (0.44; 0.77)	<0.001	0.70 (0.51; 0.97)	0.034	0.72 (0.51; 1.02)	0.061	0.85 (0.57; 1.27)	0.429	0.91 (0.60; 1.38)	0.656	0.93 (0.61; 1.43)	0.745
Youth's sex												
Male (ref)			1		1		1		1		1	
Female			1.07 (0.85; 1.36)	0.559	1.05 (0.82; 1.34)	0.695	1.05 (0.82; 1.34)	0.696	1.05 (0.82; 1.34)	0.714	0.95 (0.74; 1.23)	0.703
Gestational exposure to tobacco smoking												
No (ref)			1		1		1		1		1	
Yes			0.73 (0.54; 0.98)	0.038	0.79 (0.59; 1.08)	0.137	0.83 (0.61; 1.13)	0.226	0.84 (0.62; 1.15)	0.277	0.80 (0.58; 1.11)	0.177
Maternal socioeconomic status												
High (ref)					1		1		1		1	
Low					0.80 (0.62; 1.03)	0.081	0.83 (0.64; 1.07)	0.150	0.83 (0.64; 1.07)	0.150	0.83 (0.64; 1.08)	0.168
Cumulative childhood adversity score												
0 adversity (ref)							1		1		1	
1 adversity							0.80 (0.57; 1.12)	0.196	0.83 (0.59; 1.16)	0.272	0.94 (0.66; 1.33)	0.714
2 adversities							0.73 (0.44; 1.19)	0.205	0.81 (0.48; 1.38)	0.434	0.92 (0.53; 1.59)	0.770
3 to 5 adversities							0.70 (0.41; 1.19)	0.189	0.79 (0.45; 1.40)	0.421	0.79 (0.44; 1.41)	0.421
At least one out-of-home care (OHC) episode												
No (ref)									1		1	
Yes									0.78 (0.51; 1.20)	0.257	1.17 (0.73; 1.86)	0.515
Youth's mental and/or behavioral disorder												
No psychiatric or neuropsychological disorder (ref)											1	
Psychiatric disorder only											0.65 (0.45; 0.96)	0.031
Neuropsychological disorder only											0.35 (0.23; 0.54)	<0.001
Dual psychiatric and neuropsychological disorder											0.29 (0.18; 0.48)	<0.001

Note: Maternal socioeconomic status indicated as low (manual workers/students/pensioners/others) and high (lower-/upper-level employees, self-employed). The cumulative childhood adversity score includes the sum of the occurrences of the following maternal characteristics before the offspring's 18th birthday: maternal mental/behavioural disorders, maternal substance use, maternal recipiency of long-term financial social assistance, maternal criminality, and death of mother. The table is an adapted version of the table reported in Nissinen et al. (2021).

6.3 Financial difficulties (Study II)

Study II investigated financial difficulties measured by the receipt of long-term FSA among 355 exposed and 1011 unexposed youth aged 18 to 24 years. The descriptive characteristics of the exposed and unexposed youth included in Study II are described in Table 11.

Table 11. Descriptive characteristics of 18−24-year-old exposed and unexposed youth in Study II

	Exposed ***n*=355**	**Unexposed** ***n*=1011**	**p-value**
Follow-up time from birth until the end of 2016 (in years) (median, IQR)	20.5 (19.2; 22.7)	20.4 (19.2; 22.5)	0.770
Youth characteristics			
Sex, *n* (%)			0.411
Female	175 (49.3)	524 (51.8)	
Male	180 (50.7)	487 (48.2)	
Mental/behavioural disorders, *n* (%)			<0.001
No	152 (42.8)	723 (71.5)	
Yes	203 (57.2)	288 (28.5)	
Completed secondary education, *n* (%)			<0.001
No	248 (69.9)	592 (58.7)	
Yes	107 (30.1)	418 (41.3)	
Maternal characteristics (assessed before the offspring's 18th birthday)			
Maternal mental/behavioural disorder, *n* (%)			<0.001
No	184 (51.8)	836 (82.7)	
Yes	171 (48.2)	175 (17.3)	
Maternal substance use, *n* (%)			<0.001
No	175 (49.3)	981 (97.0)	
Yes	180 (50.7)	30 (3.0)	
Maternal long-term financial social assistance receipt, *n* (%)			<0.001
No	56 (15.8)	806 (79.7)	
Yes (≥ 4 months in a calendar year at least once)	299 (84.2)	205 (20.3)	
Out-of-home care (OHC)			
At least one OHC episode before offspring's 18th birthday, *n* (%)			<0.001
No	126 (35.5)	940 (93.0)	
Yes	229 (64.5)	71 (7.0)	
Age at the first OHC episode (in years) (median, IQR)	3.2 (1.2; 7.5)	12.9 (6.8; 14.7)	<0.001
Cumulative lifetime duration of OHC episodes (in years) (median, IQR)	10.6 (2.6; 16.0)	1.6 (0.2; 5.0)	<0.001

Note: P-values based on the χ^2 test. The table is an adapted version of the table reported in Nissinen et al. (2023).

The comparison of long-term FSA receipt between the exposed and unexposed showed that the exposed youth received long-term FSA nearly three times as often as the unexposed youth (50.4% vs. 17.2%, p<0.001). The exposed youth were slightly younger when they first received long-term FSA than the unexposed youth (18.8 years vs. 19.3 years, p<0.001). There were also minor differences in the years for which long-term FSA was granted between the exposed and unexposed youth (2.5 years vs. 2.1 years, p=0.039) (Table 12).

Table 12. Comparison of long-term financial social assistance receipt among 18−24-year-old exposed and unexposed youth

	Exposed *n*=355	**Unexposed *n*=1011**	**p-value**
Main outcome variable			
Receipt of long-term financial social assistance, *n* (%)	179 (50.4)	174 (17.2)	<0.001
Other characteristics of youth's receipt of financial social assistance			
Age at first long-term financial social assistance receipt (mean, SD)	18.8 (0.97)	19.3 (1.39)	<0.001
Cumulative number of years for which long-term financial social assistance was granted (mean, SD)	2.5 (1.6)	2.1 (1.4)	0.039

Note: Youth long-term financial social assistance is defined as receipt of financial social assistance for at least 4 months during a calendar year at least once during the follow-up, SD: Standard Deviation. P-values based on the $\chi 2$ test for categorical variables and the independent Samples t-test for continuous variables. The table is an adapted version of the table reported in Nissinen et al. (2023).

6.3.1 Factors associated with financial difficulties, adjusted multivariable analysis

Table 13 displays the results from the unadjusted and adjusted generalised linear models. The results of the unadjusted analysis showed that exposed youth were nearly five times more likely to receive long-term FSA (OR 4.89, 95% CI 3.76; 6.37) than the unexposed youth. The results also indicated that all of the studied covariates except sex were associated with an increased likelihood of long-term FSA.

In the multivariable model, adjustments were made for the effects of youth and maternal characteristics and OHC simultaneously. Adjustments were also made for the follow-up time to account for the differences in the follow-up times between birth years. The results of the adjusted multivariable model showed that the crude difference in long-term FSA receipt between the exposed and unexposed youth was attenuated to non-significant levels following the adjustments (AOR 1.33, 95% CI

0.89; 1.98). Of the youth characteristics, mental/behavioural disorders (AOR 2.28, 95% CI 1.68; 3.10) and lack of secondary education (AOR 5.39, 95% CI 3.55; 8.17) increased the likelihood of long-term FSA receipt. Of the maternal characteristics, maternal long-term FSA receipt showed a positive association with youth's long-term FSA receipt (AOR 3.09, 2.13; 4.48). OHC was also associated with an increased likelihood of youth's long-term FSA receipt (AOR 3.39, 95% CI 2.20; 5.23) (Table 13).

Table 13. Unadjusted and adjusted parameter estimates of long-term financial social assistance receipt among 18– 24-year old exposed and unexposed youth (N=1366)

	Unadjusted				Adjusted*			
	b	**SE**	**OR (95% CI)**	**p-value**	***b***	**SE**	**OR (95% CI)**	**p-value**
Prenatal substance exposure	1.59	0.14	4.89 (3.76; 6.37)	<0.001	0.28	0.21	1.33 (0.89; 1.09)	0.167
Youth characteristics								
Male sex	0.16	0.12	1.17 (0.92; 1.49)	0.200	0.15	0.15	1.17 (0.87; 1.57)	0.312
Mental/behavioural disorders	1.48	0.13	4.38 (3.39; 5.65)	<0.001	0.82	0.16	2.28 (1.68; 3.10)	<0.001
Lack of secondary education	0.68	0.14	1.97 (1.51; 2.57)	<0.001	1.68	0.21	5.39 (3.55; 8.17)	<0.001
Maternal characteristics								
Maternal mental/behavioural disorders	0.75	0.14	2.11 (1.61; 2.76)	<0.001	0.01	0.18	1.01 (0.70; 1.44)	0.979
Maternal substance use	1.36	0.16	3.88 (2.82; 5.34)	<0.001	-0.27	0.25	0.76 (0.47; 1.24)	0.274
Maternal long-term financial social assistance receipt	1.78	0.13	5.93 (4.56; 7.72)	<0.001	1.13	0.19	3.09 (2.13; 4.48)	<0.001
Out-of-home care (OHC)								
At least one OHC episode	2.09	0.15	8.07 (6.08; 10.72)	<0.001	1.22	0.22	3.39 (2.20; 5.23)	<0.001

Note: Youth and maternal long-term financial social assistance is defined as receipt of financial social assistance for at least 4 months during a calendar year at least once during the follow-up. Unadjusted and adjusted parameter estimates (b) with standard error (SE), odds ratios (OR) and adjusted odds ratios (AOR) with 95% Confidence Intervals (CIs) and p-values reported for univariate and multivariable generalised linear models. *Adjusted for prenatal substance exposure, youth characteristics, maternal characteristics, and OHC. The table is an adapted version of the table reported in Nissinen et al. (2023).

6.3.2 Mediating effects of youth and maternal characteristics and out-of-home care

The variables associated with youth's long-term FSA receipt in the adjusted multivariable model were selected for the mediation analysis. Therefore, in the mediation analysis, the mediating effect of youth's mental/behavioural disorders and lack of secondary education, maternal long-term FSA receipt, and child OHC on the

association between prenatal substance exposure and youth's long-term FSA receipt were studied (Table 14, Figure 7).

In terms of youth characteristics, prenatal substance exposure was positively associated with youth's mental/behavioural disorders (b=1.21, p<0.001). The direct effect between prenatal substance exposure and youth's long-term FSA receipt (b=0.26, 95% CI 0.20; 0.32) was stronger than the indirect effect of the mediator (i.e. youth's mental/behavioural disorders) (b=0.07, 95% CI 0.05; 0.10). The results showed that 21.0% (95% CI 0.14; 0.30) of the association between prenatal substance exposure and youth's long-term FSA receipt was mediated by the youth's mental/behavioural disorders. Prenatal substance exposure was also positively associated with a lack of secondary education (b=0.49, p<0.001). Similarly, the direct effect of prenatal substance exposure on youth's long-term FSA receipt (b=0.32, 95% CI 0.26; 0.38) was stronger than the indirect effect of the mediator (i.e. lack of secondary education) (b=0.01, 95% CI 0.004; 0.02). Consequently, the mediating effect of lack of secondary education was minor, and only 3.0% (95% CI 0.01; 0.07) of the association between exposure and receipt of long-term FSA was mediated by the mediator.

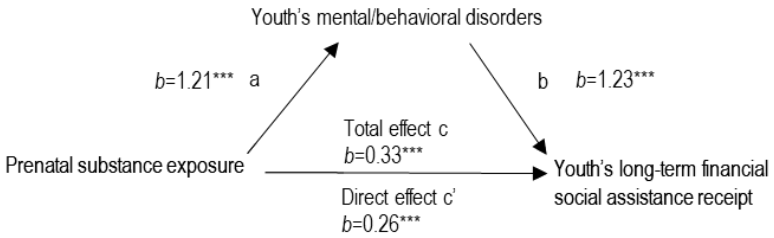
Prenatal substance exposure also showed a positive association with maternal long-term FSA receipt (b=2.70, p<0.001). The direct effect (b=0.17, 95% CI 0.10; 0.24) was nearly the same as the indirect effect of the mediator (i.e. maternal long-term FSA receipt) (b=0.16, 95% CI 0.12; 0.20), and 48.0% (95% CI 0.35; 0.64) of the association between prenatal substance exposure and youth's long-term FSA receipt was mediated by maternal long-term FSA receipt.

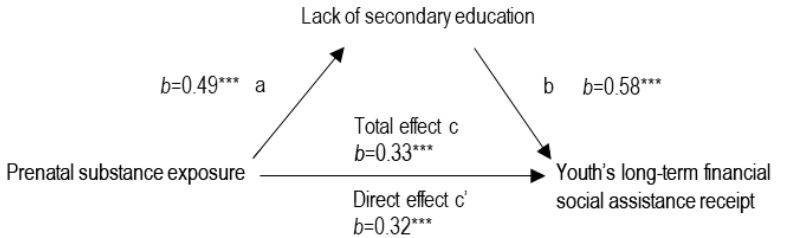
Of the studied variables, child OHC showed the strongest mediation effect on the association between prenatal substance exposure and youth's long-term FSA receipt. Prenatal substance exposure was positively associated with OHC (*b*=3.18, p<0.001). The direct effect of prenatal substance exposure on youth's long-term FSA receipt (b=0.12, 95% CI 0.05; 0.20) was smaller than the indirect effect of OHC (b=0.20, 95% CI 0.16; 0.26). Of the association between prenatal substance exposure and youth's long-term FSA receipt, 63.0% (95% CI 0.47; 0.83) was mediated by OHC.

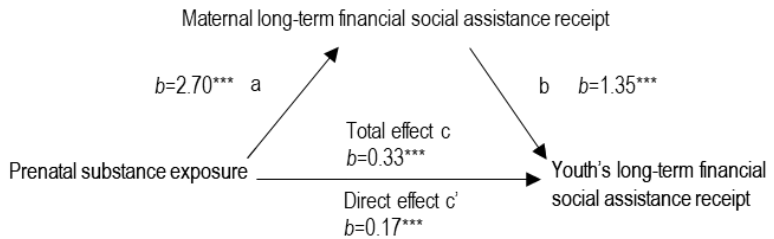
Table 14. Mediating effect of youth characteristics (mental/behavioural disorders, lack of secondary education), maternal receipt of long-term financial social assistance, and child out-of-home care on the association between prenatal substance exposure and youth's receipt of long-term financial social assistance (FSA). Parameter estimates (b) with standard error (SE), 95% Confidence Intervals (CIs) and p-values (N=1366)

	Mediators															
	Youth characteristics								Maternal characteristics				Out-of-home care			
	Mental/behavioural disorder				Lack of secondary education				Long-term financial social assistance receipt				Child out-of-home care			
	b	SE	95% CI	p-value	*b*	SE	95% CI	p-value	*b*	SE	95% CI	p-value	*b*	SE	95% CI	p-value
Prenatal substance exposure and mediator (a)	1.21	0.13		<0.001	0.49	0.13		<0.001	2.70	0.15		<0.001	3.18	0.17		<0.001
Mediator and youth's long-term FSA receipt (b)	1.23	0.14		<0.001	0.58	0.14		<0.001	1.35	0.16		<0.001	1.69	0.18		<0.001
Indirect effect (ab)	0.07		0.05; 0.10	<0.001	0.01		0.004; 0.02	<0.001	0.16		0.12; 0.20	<0.001	0.20		0.16; 0.26	<0.001
Direct effect (c')	0.26		0.20; 0.32	<0.001	0.32		0.26; 0.38	<0.001	0.17		0.10; 0.24	<0.001	0.12		0.05; 0.20	<0.001
Proportion mediated (ab/(ab+c'))	0.21		0.14; 0.30	<0.001	0.03		0.01; 0.07	0.004	0.48		0.35; 0.64	<0.001	0.63		0.47; 0.83	0.002
Total effect (c)	0.33		0.28; 0.39	<0.001	0.33		0.28; 0.39	<0.001	0.33		0.28; 0.39	<0.001	0.32		0.27; 0.39	<0.001

Note: Youth long-term financial social assistance is defined as receipt of financial social assistance for at least 4 months during a calendar year at least once during the follow-up. The table is an adapted version of the table reported in Nissinen et al. (2023).







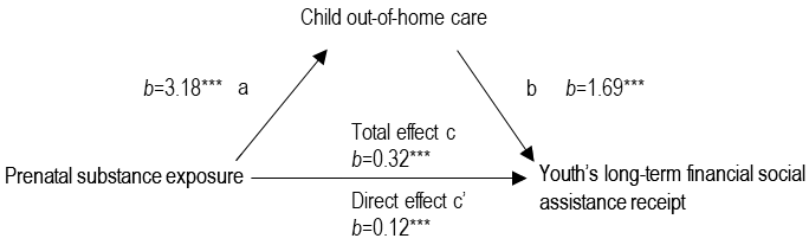


Figure 7. Mediating effect of youth's mental/behavioural disorders, lack of secondary education, maternal receipt of long-term financial social assistance and child out-of-home care on the association between prenatal substance exposure and youth's receipt of long-term financial social assistance. Parameter estimates (b) with p-value ***p<0.001.

Note: Youth's long-term financial social assistance receipt defined as receipt of financial social assistance for at least 4 months during a calendar year at least once during the follow-up. The figure is an adapted version of the figure reported in Nissinen et al. (2023).

6.4 Mood and neurotic disorders (Study III)

Study III investigated mood and neurotic disorders among 594 exposed and 1735 unexposed youth. Table 15 displays the descriptive characteristics of the exposed and unexposed youth included in Study III.

Table 15. Descriptive characteristics of exposed and unexposed youth in Study III

	Exposed *n*=594	**Unexposed *n*=1735**	**p-value**
Follow-up time from birth until the end of 2016 (in years) (median, IQR)	18.8 (16.7; 21.0)	18.6 (16.7; 20.9)	0.713
Youth characteristics			
Sex, *n* (%)			0.475
Male	296 (49.8)	894 (51.5)	
Female	298 (50.2)	841 (48.5)	
Gestational age at birth, *n* (%)			0.790
< 37 weeks	48 (8.1)	148 (8.5)	
≥ 37 weeks	538 (90.6)	1584 (91.3)	
Missing data	8 (1.3)	3 (0.2)	
Birth weight, *n* (%)			<0.001
< 2500 g	70 (11.8)	109 (6.3)	
≥ 2500 g	524 (88.2)	1624 (93.6)	
Missing data	0 (0.0)	2 (0.1)	
Gestational exposure to tobacco smoking, *n* (%)			<0.001
No	138 (23.2)	1400 (80.7)	
Yes	456 (76.8)	335 (19.3)	
A diagnosis within the FASD spectrum, *n* (%)	41 (6.9)	0 (0.0)	<0.001
Maternal characteristics (assessed during pregnancy or at the time of offspring's birth)			
Maternal age at the time of offspring's birth (mean, SD)	27.3 (6.5)	27.6 (6.5)	0.449
Maternal marital status, *n* (%)			<0.001
Unmarried (single/widowed/divorced)	474 (79.8)	705 (40.6)	
Married	120 (20.2)	1030 (59.4)	
Maternal socioeconomic status, *n* (%)			<0.001
Low (manual workers/students/pensioners/others)	409 (68.9)	789 (45.5)	
High (lower-/upper-level employees, self-employed)	185 (31.1)	946 (54.5)	
Maternal characteristics (assessed before the offspring's 13th birthday)			
Maternal mental/behavioural disorder, *n* (%)			<0.001
No	318 (53.5)	1491 (85.9)	
Yes	276 (46.5)	244 (14.1)	
Maternal substance use, *n* (%)			<0.001

No	300 (50.5)	1701 (98.0)	
Yes	294 (49.5)	34 (2.0)	
Maternal financial social assistance receipt, *n* (%)			<0.001
No	65 (10.9)	1207 (69.6)	
Short-term (1 to 9 months during a calendar year)	140 (23.6)	322 (18.6)	
Long-term (10 to 12 months during a calendar year)	389 (65.5)	206 (11.9)	
Maternal criminality, *n* (%)			<0.001
No	549 (92.4)	1727 (99.5)	
Yes	45 (7.6)	8 (0.5)	
Death of mother, *n* (%)			<0.001
No	542 (91.2)	1729 (99.7)	
Yes	52 (8.8)	6 (0.3)	
Cumulative childhood adversity score, n (%)			<0.001
0 adversity	90 (15.2)	1353 (78.0)	
1 adversity	161 (27.1)	289 (16.7)	
2 adversities	173 (29.1)	73 (4.2)	
3 to 5 adversities	170 (28.6)	20 (1.2)	
Out-of-home care (OHC)			
At least one OHC episode, *n* (%)			<0.001
No	213 (35.9)	1594 (91.9)	
Yes, occurred < 13 years of age	344 (57.9)	86 (5.0)	
Yes, occurred ≥ 13 years of age	37 (6.2)	55 (3.2)	
Age at the first OHC episode (in years) (median, IQR)	2.9 (1.0; 6.9)	10.8 (5.3; 14.3)	<0.001
Cumulative lifetime duration of OHC episodes (in years) (median, IQR)	9.2 (2.1; 15.0)	1.1 (0.2; 4.1)	<0.001

Note: FASD; Fetal Alcohol Spectrum Disorders, IQR; Interquartile Range, SD: Standard Deviation. P-values based on the χ^2 test or Fisher's exact test for categorical variables, independent samples t-test or Mann-Whitney test for continuous variables, as appropriate. The cumulative childhood adversity score includes the sum of the occurrences of the following maternal characteristics before the offspring's 13th birthday: maternal mental/behavioural disorders, maternal substance use, maternal recipiency of long-term financial social assistance, maternal criminality, and death of mother. The table is an adapted version of the table reported in Nissinen et al. (2022).

In terms of the care episodes in inpatient and outpatient hospital care for mood and neurotic disorders (Table 16), the median age at the first care episode in inpatient or outpatient hospital care did not differ between the exposed and unexposed youth. Neither the median number of days spent in inpatient hospital care nor the median number of care episodes in outpatient hospital care differed between the exposed and unexposed youth.

However, differences between the exposed and unexposed youth were observed in the number of care episodes per 1000 people in inpatient (60.6 episodes/1000 people vs. 16.7 episodes/1000 people, $p<0.001$) or outpatient hospital care (210.4 episodes/1000 people vs. 95.1 episodes/1000 people, $p<0.001$), the number being

significantly higher among the exposed compared to the unexposed youth. When the care episodes in inpatient or outpatient hospital care were combined and analysed as care episodes in specialised healthcare, the number of care episodes per 1000 people was over twice as high in the exposed cohort compared to the unexposed (208.8/1000 people vs. 95.7/1000 people, p<0.001). Overall, 20.9% of the exposed youth had been in specialised healthcare for mood and neurotic disorders after the age of 13 years compared to 9.6% of the unexposed (p<0.001) (Table 16).

Table 16. Specialised healthcare episodes for mood and neurotic disorders among the exposed and unexposed youth

	Exposed ***n*=594**	**Unexposed** ***n*=1735**	**p-value**
Inpatient hospital care			
Care episodes (≥ 13 years of age) per 1000 people	60.6	16.7	<0.001
First care episode by age, n (%)			<0.001
No care episodes	548 (92.3)	1700 (98.0)	
< 13 years of age	10 (1.7)	6 (0.3)	
≥ 13 years of age	36 (6.1)	29 (1.7)	
Age at the first care episode (median, IQR)	15.6 (13.2; 17.1)	16.5 (14.6; 17.9)	0.173
Cumulative number of days spent in inpatient hospital care ≥ 13 years of age (median, IQR)	12.0 (3.0; 28.0)	12.0 (3.5; 22.5)	0.861
Outpatient hospital care			
Care episodes (≥ 13 years of age) per 1000 people	210.4	95.1	<0.001
First care episode by age, n (%)			<0.001
No care episodes	431 (72.6)	1529 (88.1)	
< 13 years of age	38 (6.4)	41 (2.4)	
≥ 13 years of age	125 (21.0)	165 (9.5)	
Age at the first care episode (median, IQR)	14.5 (13.3; 16.7)	15.1 (13.5; 16.8)	0.112
Cumulative number of care episodes ≥ 13 years of age (median, IQR)	14.0 (5.0; 32.0)	13.0 (2.0; 35.0)	0.386
Inpatient or outpatient hospital care			
Care episodes (≥ 13 years of age) per 1000 people	208.8	95.7	<0.001
First care episode by age, n (%)			<0.001
No care episodes	429 (72.2)	1525 (87.9)	
< 13 years of age	41 (6.9)	44 (2.5)	
≥ 13 years of age	124 (20.9)	166 (9.6)	

Note: Specialised healthcare episodes for mood and neurotic disorders based on International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) categories F30–F39 or F40–F48. p-values based on χ^2 test for categorical variables and Mann-Whitney U-test for continuous variables. IQR; Interquartile Range. The table is an adapted version of the table reported in Nissinen et al. (2022).

Table 17 shows the number and percentage of exposed and unexposed youth with at least one specialised healthcare episode (i.e. inpatient or outpatient hospital care)

for mood and neurotic disorders by specific ICD-10 categories within codes F30−F39 (for mood (affective disorders) and F40−F48 (for neurotic, stress-related and somatoform disorders). The specialised healthcare episodes for the disorders were assessed at any time from the 13th birthday until the end of follow-up in 2016. The same person may be included in multiple ICD-10 categories due to the possibility of multiple specialised healthcare episodes for different disorders.

In terms of specific categories of mood disorders (ICD-10 codes F30−F39), exposed youth were more likely to have been in specialised healthcare due to bipolar affective disorder (1.7% vs. 0.3%, p=0.002), depressive episode (13.5% vs. 6.2%, p<0.01), and persistent mood disorders (1.5% vs. 0.3%, p=0.05) than the unexposed youth. In terms of specific categories of neurotic disorders (ICD-10 codes F40−F48), the exposed youth were more likely to have been in specialised healthcare due to other anxiety disorders (10.9% vs. 4.9%, p<0.001), reaction to severe stress and adjustment disorder (7.2% vs. 2.7%, p<0.001), and dissociative disorders (1.3% vs. 0.2%, p<0.001) than the unexposed youth (Table 17).

Table 17. Specialised healthcare episodes for mood and neurotic disorders among exposed and unexposed youth by specific ICD-10 categories

	Exposed *n*=594	**Unexposed *n*=1735**	**p-value**
Mood (affective) disorders, n (%)			
F30 Manic episode	2 (0.3)	0 (0.03)	0.065
F31 Bipolar affective disorder	10 (1.7)	6 (0.3)	0.002
F32 Depressive episode	80 (13.5)	108 (6.2)	<0.001
F33 Recurrent depressive episode	12 (2.0)	22 (1.3)	0.187
F34 Persistent mood [affective] disorders	9 (1.5)	6 (0.3)	0.05
F38 Other mood (affective) disorders	0 (0.0)	0 (0.0)	NA
F39 Unspecified mood [affective] disorders	0 (0.0)	1 (0.1)	1.000
Neurotic, stress-related and somatoform disorders, n (%)			
F40 Phobic anxiety disorder	12 (2.0)	19 (1.1)	0.089
F41 Other anxiety disorders	65 (10.9)	85 (4.9)	<0.001
F42 Obsessive-compulsory disorder	2 (0.3)	4 (0.2)	0.649
F43 Reaction to severe stress, and adjustment disorder	43 (7.2)	47 (2.7)	<0.001
F44 Dissociative [conversation] disorders	8 (1.3)	3 (0.2)	<0.001
F45 Somatoform disorders	0 (0.0)	1 (0.1)	1.000
F48 Other neurotic disorders	0 (0.0)	0 (0.0)	NA

Note: ICD-10; International Statistical Classification of Diseases and Related Health Problems, 10th revision, NA: not applicable. Specialised healthcare episodes include inpatient and outpatient hospital care. p-values based on χ^2 test or Fisher's exact test, as appropriate.

6.4.1 Factors associated with mood and neurotic disorders, adjusted multivariable analysis

Table 18 shows the results from the unadjusted and adjusted multivariable Cox regression analysis. The results of the unadjusted model (Model 1) indicated that the exposed youth had a two-fold higher likelihood of being in specialised healthcare for mood and neurotic disorders (HR 2.34, 95% CI 1.86; 2.95) than the unexposed youth. This difference remained unchanged when the model was adjusted for youth's sex in Model 2 (AHR 2.34, 95% CI 1.85; 2.95) but was attenuated to nonsignificant levels when the effects of childhood adversity score and OHC were accounted for in models 3 to 5. The results of Model 5, in which adjustments were made for all the studied covariates simultaneously (i.e. youth's sex, cumulative childhood adversity score, and OHC) showed no statistically significant association between prenatal substance exposure and mood and neurotic disorders (AHR 1.08 95% CI 0.78; 1.49). The results showed that female sex (AHR 2.44, 95% CI 1.90; 3.12), cumulative childhood adversity score, and OHC were associated with an increased likelihood of mood and neurotic disorders. The likelihood of these disorders was similar across several adversities, the likelihood spanning from AHR 1.83 (95% CI 1.33; 2.51) for 1 adversity (p=0.067), AHR 1.90 (95% 1.25; 2.87) for 2 adversities to AHR 2.00 (95% CI 1.24; 3.22) for 3 to 5 adversities. Youth with an OHC history had a higher likelihood of mood and neurotic disorders, with AHR ranging from 1.77 (95% CI 1.22; 2.55) among those placed in OHC before the age of 13 years to AHR 5.12 (95% CI 3.53; 7.43) among those placed in OHC at the age of 13 year or older (Table 18)

Table 18. Unadjusted Hazard Ratio (HR) and adjusted Hazard Ratios (AHR) with 95% Confidence Intervals (CIs) and p-values for care episode in specialised healthcare for mood and neurotic disorders. Follow-up starts from the 13th birthday and continues until the first care episode in specialised healthcare for the disorders, death, or end of follow-up in 2016 (N=2329)

	Model 1 (Unadjusted model)		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value
Prenatal substance exposure										
Unexposed (ref)	1		1		1		1		1	
Exposed	2.34 (1.86; 2.95)	<0.001	2.34 (1.85; 2.95)	<0.001	1.30 (0.96; 1.77)	0.095	1.36 (0.99; 1.85)	0.055	1.08 (0.78; 1.49)	0.648
Youth characteristics										
Sex										
Male (ref)			1		1		1		1	
Female			2.35 (1.83; 3.00)	<0.001	2.34 (1.83; 2.99)	<0.001	2.44 (1.91; 3.13)	<0.001	2.44 (1.90; 3.12)	<0.001
Maternal characteristics										
Cumulative childhood adversity score										
0 adversity (ref)					1				1	
1 adversity					2.17 (1.60; 2.96)	<0.001			1.83 (1.33; 2.51)	0.067
2 adversities					2.60 (1.76; 3.83)	<0.001			1.90 (1.25; 2.87)	0.002
3 to 5 adversities					2.66 (1.71; 4.15)	<0.001			2.00 (1.24; 3.22)	0.005
Out-of-home care (OHC)										
At least one OHC episode										
No OHC episodes							1		1	
Yes, occurred < 13 years of age							2.34 (1.66; 3.29)	<0.001	1.77 (1.22; 2.55)	0.002
Yes, occurred ≥ 13 years of age							5.97 (4.14; 8.60)	<0.001	5.12 (3.53; 7.43)	<0.001

Note: Specialised healthcare includes inpatient or outpatient hospital care. Mood and neurotic disorders based on International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) categories F30−F39 or F40−F48. The cumulative childhood adversity score includes the sum of the occurrences of the following maternal characteristics before the offspring's 13th birthday: maternal mental/behavioural disorders, maternal substance use, maternal recipiency of long-term financial social assistance, maternal criminality, and death of mother. The table is an adapted version of the table reported in Nissinen et al. (2022).

6.4.2 Mediating effect of out-of-home care

Mediation analysis was conducted to study the mediating effect of OHC on the association between prenatal substance exposure and mood and neurotic disorder. The results showed that the direct effect of prenatal substance exposure on mood and neurotic disorders was minor (b=0.04, 95% CI 0.01; 0.08) and the indirect effect of the mediator (i.e. OHC) was stronger (b=0.07, 95% CI 0.05; 0.08). OHC mediated 61.0% (95% CI 0.41; 0.94) of the association between prenatal substance exposure and mood and neurotic disorders (Table 19, Figure 8).

Table 19. Mediating effect of child out-of-home care on the association between prenatal substance exposure and youth's mood and neurotic disorders. Parameter estimates (*b*) with standard error (SE), 95% Confidence Intervals (CIs) and p-value (N=2329)

	Child out-of-home care			
	b	**SE**	**95% CI**	**p-value**
Prenatal substance exposure and mediator (a)	0.59	0.02		<0.001
Mediator and youth's mood and neurotic disorder (b)	0.94	0.11		<0.001
Indirect effect (ab)	0.07		0.05; 0.08	<0.001
Direct effect (c')	0.04		0.01; 0.08	0.028
Proportion mediated (ab/(ab+c'))	0.61		0.41; 0.94	<0.001
Total effect (c)	0.11		0.07; 0.14	<0.001

Note: Mood and neurotic disorders based on International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) codes F30–F39 and F40–F48. The table is an adapted version of the table reported in Nissinen et al. (2022).

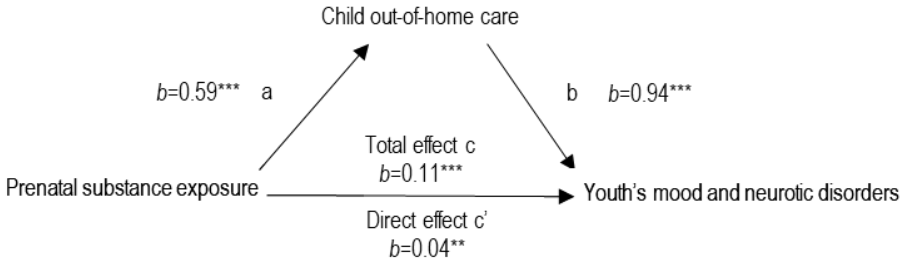


Figure 8. Mediating effect of child out-of-home care on the association between prenatal substance exposure and youth's mood and neurotic disorders. Parameter estimates (b) with p-value ***p<0.001, **p<0.05

Note: Mood and neurotic disorders based on International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) categories F30–F39 and F40–F48. The figure is an adapted version of the figure reported in Nissinen et al. (2022).

7 DISCUSSION

7.1 Main findings

The overall aim of this dissertation was to investigate secondary disabilities among Finnish youth with prenatal substance exposure. More specifically, the aim was to study completed secondary education (Study I), financial difficulties (Study II), and mood and neurotic disorders (Study III) in these youth.

To answer the overall aim, the main findings of the dissertation showed that youth with a history of exposure to maternal prenatal substance abuse had an increased likelihood of secondary disabilities. More specifically, the results of the descriptive and unadjusted analyses showed: (1) Delayed completion of secondary education and an overall lower secondary education completion rate in youth with prenatal substance exposure compared to the unexposed youth (Study I). (2) Financial difficulties, measured as the receipt of long-term financial social assistance (FSA), were more common among youth with prenatal substance exposure compared to the unexposed youth (Study II). (3) Youth with prenatal substance exposure were twice as likely to be in specialised healthcare for mood and neurotic disorders as the unexposed youth (Study III).

The aim of this dissertation was also to study the influence of youth characteristics as well as adverse maternal characteristics and OHC on the studied secondary disabilities. Adverse maternal characteristics and OHC were used as a proxy to describe adversities and care instability in the postnatal caregiving environment. To answer the aim, the main findings were: (4) Maternal prenatal substance abuse was interlinked with an accumulation of adversities in the postnatal caregiving environment and a high proportion of prenatally substance-exposed youth had been placed in OHC in early childhood. These factors had a strong influence on secondary disabilities, apart from secondary education completion. The results further indicated: (5) Prenatal substance exposure was not independently associated with the lack of secondary education, and different forms of youth mental/behavioural disorders independently reduced the likelihood of completed secondary education (Study I). (6) Prenatal substance exposure

was not independently associated with youths' financial difficulties, and these difficulties were associated with youths' mental/behavioural disorders and lack of secondary education in addition to maternal financial difficulties and OHC. Maternal financial difficulties and OHC also mediated a large proportion of the association between prenatal substance exposure and youth's financial difficulties (Study II). (7) The association between prenatal substance exposure and mood and neurotic disorders was attenuated to a non-significant level when the influence of other predictors was controlled for. Accumulation of adverse maternal characteristics and OHC in addition to female sex were associated with an increased likelihood of mood and neurotic disorders. OHC also mediated a large proportion of the association between prenatal substance exposure and youth mood and neurotic disorders (Study III). These findings are discussed further in the following sections.

7.1.1 Prenatal substance exposure and its association with secondary disabilities in youth

The results of this dissertation showed that youth with prenatal substance exposure experienced secondary disabilities at a higher rate compared to the matched unexposed youth. Starting with secondary education, the results of Study I showed a lower rate of completed secondary education in youth with prenatal substance exposure compared to the unexposed youth. The proportion of youth with completed secondary education increased with increasing age (data not shown). Among the oldest youth (i.e. youth aged 23 years old at the end of follow-up in 2015), 56.1% of the exposed had completed secondary education compared to 74.8% among the unexposed. The proportion of unexposed youth with completed secondary education at the age of 23 years is somewhat similar to the estimates from the general population (Suomen virallinen tilasto, 2019), whereas the proportion of exposed youth with completed secondary education at the age of 23 years is significantly lower.

Prior studies on educational outcomes in youth or adults with prenatal substance exposure have primarily been conducted among prenatally alcohol-exposed individuals, particularly among individuals with FAS. These studies have shown a low rate of completed secondary education in individuals with FAS. However, it is noteworthy that these findings most likely reflect educational difficulties in more severely affected individuals (Freunscht & Feldmann, 2011; Rangmar, Hjern, et al., 2015; Spohr etal., 2007). Despite the study population related differences, the results of this dissertation

are in accordance with prior studies and indicate challenges and delays in completing secondary education in prenatally substance-exposed youth.

Similar studies on secondary education completion among youth with prenatal exposure to illicit drugs are lacking, and the current evidence comes from studies investigating school performance among children and adolescents with prenatal exposure to marijuana or amphetamines. The results of these studies have shown poorer school performance in the exposed populations (Eriksson et al., 2000; Goldschmidt et al., 2004). The challenges in school performance observed in children exposed to illicit drugs during pregnancy may predispose these children to challenges in secondary education when the level of difficulty of tasks and the demand for independence increase. However, future studies are needed to confirm this, since the effects of a specific illicit drug on secondary education were not studied here.

Overall, the findings from Study I add to the research literature on secondary education outcomes by including a prenatally substance-exposed youth population with the minority with a diagnosis within the FASD spectrum, and by including an unexposed control group. Thus, the results increase the reliability and validity of the prior findings. Although the results of this dissertation likely reflect educational outcomes in a more heterogeneous population compared to studies conducted among individuals with FAS, it is noteworthy that the severity of the effects of prenatal substance exposure and associations with secondary education were not studied in this dissertation. There may be a variation in the secondary education outcomes in the exposed cohort when assessed by the severity. Studies are needed to further explore whether the educational outcomes vary in individuals, considering the severity of the effects of prenatal substance exposure, or whether educational challenges occur across the FASD spectrum.

The underlying reasons behind the low rate of completed secondary education among prenatally substance-exposed youth could be linked to the primary disabilities affecting learning and school performance (Mattson et al., 2011; Pyman et al., 2021; Ross et al., 2015; Tsang et al., 2016). The commonly observed difficulties with executive functioning and externalising disorders, including attention and impulse control relevant to academic functioning (Anderson, 2010) and the highly prevalent ADHD (Ackerman et al., 2010; Kingdon et al., 2016; Lange et al., 2018; Nygaard et al., 2016; Weyrauch et al., 2017), among prenatally substance-exposed populations could challenge their learning and performance in secondary education. Although the data in this dissertation did not include detailed information on primary disabilities, including executive

functioning and externalising behaviours, the results of Study I showed that all the studied domains of youth mental/behavioural disorders, especially neuropsychological disorders (including ADHD, ODD, and CD) or dual psychiatric and neuropsychological disorders, independently reduced the likelihood of completing secondary education.

Prior studies on secondary education among prenatally substance-exposed youth and young adults have not studied the influence of youth mental/behavioural disorders on educational outcomes. However, studies conducted among children and adolescents with prenatal exposure to illicit drugs have shown that a child's educational outcomes and school performance are influenced by mental/behavioural disorders and IQ (Goldschmidt et al., 2004; Goldschmidt et al., 2012; Hurt et al., 2005; Levine et al., 2012). The results by Goldschmidt et al. (2004, 2012) showed that a child's mental/behavioural disorders and IQ mediated the association between prenatal exposure to marijuana and school performance. Furthermore, a study by Hurt et al. (2005) showed that a child's IQ and better home environment predicted better school performance regardless of prenatal cocaine exposure. Findings from the general youth population also support the association between mental/behavioural disorders and educational challenges (Brännlund et al., 2017; Jangmo et al., 2019; Polderman et al., 2010). Thus, this study adds to the research literature by showing that youth's mental/behavioural disorders are an important factor in increasing the likelihood of inferior educational outcomes in secondary education among prenatally substance-exposed youth.

Mental/behavioural disorders can include symptoms that can cause severe impairment to emotional, cognitive, and social functioning, or challenges stemming from difficulties with behaviour, self-regulation, concentration, attention, and executive functioning, thus affecting an individual's overall wellbeing and abilities to carry out academic or vocational activities, as previously described (Brännlund et al., 2017; Howell et al., 2006; Jangmo et al., 2019; Polderman et al., 2010). Different forms of mental/behavioural disorders can affect educational outcomes differently. An individual with external disorders directs negative feelings (e.g. anger and frustration) towards others and disruptive behaviours, attention problems, difficulties with social adjustment, and frustration can increase the likelihood of academic failure and dropping out of school. On the other spectrum, an individual with internalising disorders can direct negative emotions towards themselves and may experience educational challenges due to social phobia, including feeling nervous or anxious in the classroom or while

carrying out educational activities (Esch et al., 2014; van Ameringen et al., 2003). The high prevalence of various externalising and internalising disorders among prenatally substance-exposed populations (Easey et al., 2019; Kingdon et al., 2016) and the co-occurrence of these disorders (Gundel et al., 2018; Riglin et al., 2021) can predispose these individuals at high risk of educational challenges in secondary education as also reflected by the results of this dissertation. Studies are needed to explore the associations between specific mental/behavioural disorders and secondary education in youth with prenatal substance exposure.

Educational challenges and interlinked mental/behavioural disorders can further increase the risk of challenges in other areas of life including employment and financial self-supporting during the youth period (Esch et al., 2014; Gariépy et al., 2022; Hakulinen, Musliner, et al., 2019; Haula & Vaalavuo, 2021). The results of Study II add to the current literature by showing a higher rate of financial difficulties measures as a receipt of long-term financial social assistance among exposed youth than among their unexposed age-mates. Similar studies on financial difficulties or financial self-supporting among prenatally substance-exposed youth are lacking. The few available studies on other aspects of adult independence have shown that a higher proportion of adults with FAS are dependent on disability pension or social welfare than are unexposed controls (Rangmar, Hjern, et al., 2015). Studies have also indicated that individuals with a diagnosis within the FASD spectrum experience challenges in employment or independent living (Landgren et al., 2019; Rangmar, Hjern, et al., 2015; Spohr et al., 2007; Streissguth, 1996) and at a higher rate than for the unexposed controls (Rangmar, Hjern, et al., 2015). These findings can potentially reflect challenges in establishing adult independence and the inability to support oneself financially. To the best of my knowledge, similar studies conducted among youth or young adults with prenatal exposure to illicit drugs are lacking.

Studies on FSA needs conducted among the general youth population in Finland have shown that receipt of FSA is relatively common among youth, but its duration is often short. A study by Haula & Vaalavuo (2021) showed that 30.0% of Finnish youth aged 18−24 years had received FSA for at least one month during the study period. An estimate from 2017 suggested that 19.0% of Finnish youth within the same age range had been recipients of FSA for at least one month (Raittila et al., 2018). Although Study II focused on studying long-term FSA, the results of Study II showed that 50.4% of the exposed youth had received FSA long-term at least once – the estimate was significantly

higher compared to the proportion of FSA receipts in the unexposed cohort (17.2%) or the estimates reported above from the general Finnish youth population.

The challenges in financial self-supporting or in establishing adult independence among youth with prenatal substance exposure can reflect the delays and challenges in many areas of development and mental/behavioural functioning (Easey et al., 2019; Kingdon et al., 2016) and thus the inability to support themselves at the age of 18 years old when legally considered an adult. One important predictor for financial difficulties found in Study II was the lack of secondary education. Prior studies on FSA needs in the general youth population in Finland have also shown that a lower educational level can increase the likelihood of FSA needs (Haula & Vaalavuo, 2021; Ilmakunnas & Moisio, 2019; Kauppinen et al., 2014; Vaalavuo et al., 2020). Despite the observed association between the lack of secondary education and financial difficulties, the mediating effect of lack of secondary education on the association between prenatal substance exposure and financial difficulties was minor. This may be due to no observed differences in the completed secondary education between exposed and unexposed recipients of long-term FSA, as reported by Nissinen et al. (2023). Furthermore, this may be due to the relatively young age of the exposed and unexposed cohorts and the low proportion of completed secondary education as found in Study I. However, the delays in secondary education completion in the exposed youth compared with the unexposed youth (Study I) could increase long-term FSA needs later in adulthood. Research extending into later adulthood is needed to confirm these potential associations among prenatally substance-exposed individuals.

The results of Study II also indicated that youth's mental/behavioural disorders were an important predictor associated with an increased likelihood of youth's financial difficulties. These disorders also showed a strong mediating effect, and one-fifth of the association between prenatal substance exposure and youth's financial difficulties was mediated by these disorders. The existing studies on other aspects of adult independence in individuals within the FASD spectrum have not studied the influence of mental/behavioural disorders, and thus, the results of study II add to the research literature. A similar association between mental/behavioural disorders and receipt of FSA has also been reported in a Finnish study investigating the receipt of FSA in the general youth population (Haula & Vaalavuo, 2021). As described earlier, the youth period is a sensitive developmental phase and mental/behavioural disorders occurring in this period can influence overall wellbeing and increase challenges during the transition to adult independence (Gariépy et al., 2022).

Although the data did not include detailed information on specific areas of mental health or behavioural functioning that can affect financial self-supporting abilities, the mental/behavioural disorders could also reflect difficulties with adaptive functioning often seen in prenatally alcohol-exposed children and youth (Fagerlund et al., 2012; Kautz-Turnbull & Petrenko, 2021; Mattson et al., 2019), while studies of adaptive functioning among individuals with prenatal exposure to illicit drugs are lacking. Adaptive functioning refers to the age-appropriate skills necessary for completing tasks in everyday life, and behaviours important for being able to live independently (Anderson, 2010). Thus, deficits in adaptive functioning could predispose youth to challenges in obtaining education or employment, which may also be reflected as heightened FSA needs. However, studies are needed to investigate potential associations.

Furthermore, as discussed earlier, mental/behavioural disorders can include symptoms in the externalising and internalising continuum. Various mental/behavioural disorders can affect an individual's ability to support themselves, get an education, or obtain employment (e.g. Brännlund et al., 2017; Gariépy et al., 2022; Hakulinen, Elovainio, et al., 2019) and thus potentially being reflected as long-term FSA needs. However, future studies are needed to confirm associations between specific mental/behavioural disorders (e.g. adaptive functioning abilities, externalising disorders, internalising disorders) and financial self-supporting abilities in prenatally substance-exposed populations.

In terms of mental/behavioural disorders, the results of this dissertation showed that mental/behavioural disorders were common among youth with prenatal substance exposure. Over 50.0% of the youth in the exposed cohort in studies I and II had been in specialised healthcare for mental/behavioural disorders compared to approximately 29.0% in the unexposed cohort. A high prevalence of mental/behavioural disorders in children and youth with prenatal substance exposure has also been reported in prior studies, although in different study populations (including individuals with a diagnosis within the FASD spectrum). The observed disorders range from emotional adjustment and attachment issues to complex psychiatric comorbidities, disorders on both the internalising and externalising continua, and intellectual disability (e.g. Duko et al., 2021, 2022; Easey et al., 2019; Khoury et al., 2018; Lange et al., 2018; Nygaard et al., 2020).

The estimates of mental/behavioural disorders among the exposed youth are significantly higher than the estimates among the general youth population, whereas the estimates for the unexposed youth are more aligned with the Finnish national estimates.

Marttunen and Kaltiala (2021), for example, have estimated that 15.0% to 25.0% of Finnish youth have experienced some sort of mental health disorder, with mood and neurotic disorders being the most observed. Mental/behavioural disorders, particularly internalising disorders (including mood and neurotic disorders) are common disorders with a typical onset age in youth or young adulthood (Kessler et al., 2007; Solmi et al., 2021). Despite these disorders being relatively common during the youth period, the high occurrence of these disorders among exposed youth raises concerns, especially considering the effects of these disorders on secondary education (Study I) and financial difficulties (Study II).

Specific mental disorders on the internalising continuum, i.e. mood and neurotic disorders, were studied in Study III. The results of Study III showed that youth with prenatal substance exposure were twice as likely to be in specialised healthcare for mood and neurotic disorders as the unexposed youth. The results from the descriptive analysis showed that in terms of specific mood disorders, exposed youth had been in specialised healthcare more often for bipolar affective disorders, depressive episodes, persistent mood disorders, and other anxiety disorders. In terms of neurotic disorders, the occurrence of specialised healthcare episodes was higher in exposed cohorts than in unexposed youth for conditions that include reaction to severe stress and adjustment disorders as well as dissociative (conversational) disorders. The most common reasons for hospitalisation were depressive episodes and other anxiety disorders. However, the associations between prenatal substance exposure and specific mood or neurotic disorders were not studied further in this dissertation. Therefore, research is needed to confirm whether prenatal substance exposure increases the susceptibility to specific disorders on the internalising continuum.

Although these are methodological variations across studies assessing internalising disorders in exposed populations, the results are in line with prior research findings that indicate a high prevalence of these disorders among youth with prenatal exposure to alcohol (with or without a diagnosis within the FASD spectrum) or illicit drugs (e.g. Duko et al., 2021, 2022; Easey et al., 2020; Nygaard et al., 2020). However, the occurrence of these disorders relative to unexposed controls appears to vary between studies. Duko et al. (2021) reported a higher likelihood of depression in youth with prenatal exposure to heavy alcohol use relative to unexposed controls even after adjusting the model for other risk factors. In contrast, other studies (Barr et al., 2006; Duko et al., 2022; Easey et al., 2020; Hill et al., 2000) have not found differences between exposed and unexposed either in unadjusted or adjusted analysis. In Study III,

the results from the unadjusted analysis indicated significant differences between the exposed and unexposed cohorts; however, such differences were no longer observed in the fully adjusted model. These findings are further discussed in Section 7.1.3.

As reflected by the findings of Study III, mood and neurotic disorders (among other mental/behavioural disorders) in the prenatally substance-exposed populations are multifaceted and can involve multiple risk factors occurring during the prenatal period, childhood, and youth. The vulnerability for these disorders can stem from the association between prenatal substance exposure and CNS dysfunction, and the structural and functional abnormalities in different brain regions, particularly in the brain areas sensitive to stress including the prefrontal cortex, amygdala, and hippocampus (Andre et al., 2020; Drevets et al., 2008). In addition, of the substances, prenatal alcohol exposure has been associated with disturbances in the functioning of the HPA axis, which has an important role in altering the body's responses to stressors (Hellemans et al., 2010). HPA dysfunction has been shown to be an underlying risk factor for the development of mood and neurotic disorders (Hellemans et al., 2008, 2010; Weinberg et al., 2008). Furthermore, the highly prevalent externalising disorders can also increase the susceptibility of mood and neurotic disorders in youth and adult life (Riglin et al., 2021). However, these associations were not studied in this dissertation. Therefore, studies are needed to explore these associations in more detail.

Nevertheless, as shown by the results of Study III, prenatal substance exposure was not independently associated with the increased likelihood of mood and neurotic disorders when the influence of other factors was controlled for. As found in other studies (Kuehner, 2003; Rapee et al., 2009), female sex increased the likelihood of these disorders. In addition, exposure to cumulative number of adverse maternal characteristics and OHC showed strong associations between the studied disorders. Thus, other mechanisms that seem to underlie mental/behavioural disorders in prenatally substance-exposed populations can relate to the caregiver-child attachment relationship and other adverse characteristics of the postnatal caregiving environment, which will be further discussed in Section 7.1.3.

To conclude, as shown by the results, youth with prenatal substance exposure experienced secondary disabilities at a higher rate than unexposed youth. The results also showed that mental/behavioural disorders, including mood and neurotic disorders, were more common among the exposed youth than among the unexposed, and the influence of various forms of mental/behavioural disorders on secondary disabilities was found to be significant in studies I and II. Mental/behavioural disorders occurring

in childhood and youth tend to recur (Thapar et al., 2012). Therefore, these disorders can predispose individuals with prenatal substance exposure to other challenges and health concerns during the transition to adult independence and challenges later in adult life (Hakulinen, Elovainio, et al., 2019; Hakulinen, Musliner, et al., 2019). However, it is also important to understand the risk factors increasing the vulnerability to mental/behavioural disorders, as well as the other risk factors increasing the susceptibility to the studied secondary disabilities in prenatally substance-exposed youth populations.

7.1.2 Accumulation of adversities and out-of-home care in youth with prenatal substance exposure

The results of this dissertation showed that adverse maternal characteristics tended to accumulate among youth born to mothers with prenatal substance abuse. An accumulation of adversities in children born to mothers with prenatal substance abuse has also been reported in prior studies (Carta et al., 2001; Flannigan et al., 2021; Price et al., 2017). As shown by the results, the mothers of the exposed youth were more often unmarried and had lower socioeconomic status. Furthermore, postnatal substance use, mental/behavioural disorders, financial difficulties, and criminality were observed more often among mothers of the exposed youth than among mothers of the unexposed youth. In addition, a higher proportion of the mothers of the exposed youth had died during the follow-up compared to only a marginal proportion of the mothers of the unexposed youth (10.9% and 0.6%, respectively). When these adversities were analysed as a sum score, the exposed youth had been exposed to on average two adversities (median 0 among the unexposed). Thus, the results reflect difficult life situations among mothers of exposed youth. The maternal difficult life situation may also be reflected as a high proportion of exposed individuals being placed in OHC.

The results of this dissertation also showed that a significant proportion (63.9%) of exposed youth had a history of OHC (8.2% in the unexposed cohort). Although the proportion represents the cumulative proportion in the exposed cohort during the follow-up, the proportion is significantly higher than the number of children in OHC in Finland reported by the THL, or in other Finnish studies. According to the THL, in 2021, 1.6% of Finnish children and youth aged 0 to 18 years had been placed in OHC (Forsell & Kuoppala, 2022). Kääriälä et al. (2021) on the other hand indicated that 5.7% of the study children born in 1997 (n=57 174) had experienced OHC before their 18th

birthday. The differences in the proportion of children placed in OHC in this study compared to the unexposed youth or the other estimates indicate that the exposed cohort of this study represents a high-risk population in need of child welfare services.

The results of this dissertation also showed that youth with prenatal substance exposure were placed in OHC during early childhood (median age of 2 years) and for a long lifetime duration (median duration of 9.3 years). In contrast, the unexposed were placed in OHC at a median age of 10 years, and the cumulative duration of OHC was short (median duration of 1.1 years). These differences could reflect different reasons for OHC.

In Finland, indications for OHC among small children typically include family difficulties in terms of finance, internal conflicts and domestic violence, and parental substance use and mental health problems, which can endanger the child's health and safety (Heino et al., 2016). Indications for OHC among older children can involve youth's problematic behaviour (e.g. substance use or mental/behavioural problems, delinquent behaviours), problems in school participation or conflict with parents (Heino et al., 2016). Unfortunately, the data of this dissertation did not include information on reasons for OHC. However, the results on the accumulation of adversities in the postnatal caregiving environment among exposed youth could reflect maternal challenging life situations endangering a child's health and development and thus the need for child welfare services and OHC in early childhood. In contrast, in the unexposed cohort, older age at the first OHC episode can indicate challenges in the child's behaviour or school participation, which per se can be associated with problems in the youth period. However, due to the lack of data on specific OHC indications, strong conclusions should be avoided. The influence of OHC on the studied secondary disabilities will be further discussed in the following section.

7.1.3 Adversities in the postnatal caregiving environment and out-of-home care, and their associations with secondary disabilities in youth with prenatal substance exposure

The results of this dissertation add to the research literature by studying the influence of maternal characteristics and OHC, used as a proxy of postnatal caregiving adversities and caregiving instability, on secondary disabilities among prenatally substance-exposed youth. The results indicated that although the exposed cohort had a higher likelihood of secondary disabilities, the direct effect of prenatal substance exposure on the studied

secondary disabilities was attenuated to non-significant levels when the influence of other predictors was controlled for. In addition to the specific youth characteristics described earlier, adverse maternal characteristics and OHC were associated with an increased likelihood of secondary disabilities.

However, there was a variation in how adversities and OHC were associated with the studied secondary disabilities. The results of Study I indicated that exposure to a cumulative number of adversities and OHC were not associated with completed secondary education in any of the multivariate regression analyses. Prior studies on secondary education among prenatally substance-exposed populations have not considered the influence of the characteristics of the postnatal caregiving environment. However, these findings are in contrast with prior studies conducted among the general youth population. These studies have shown a negative association between adversities in the postnatal caregiving environment (e.g. parental alcohol abuse), OHC, and offspring's educational outcomes (Berg et al., 2016; Kääriälä et al., 2018; Raitasalo et al., 2021). One explanation for the differing results could be that prenatal substance exposure is strongly correlated with the studied adversities and OHC; thus, these variables – when their independent effect is studied – do not show a statistically significant association with secondary education. In addition, the mitigating support from the population-based mandatory comprehensive Finnish education system could somewhat reduce the influence of childhood caregiving adversities and caregiving instability on educational outcomes in the exposed population. However, future studies are needed to confirm these speculations.

In studies II and III, adverse maternal characteristics and OHC were important predictors of the studied secondary disabilities. The results of Study II showed that in addition to the studied youth characteristics (i.e. lack of secondary education, mental/behavioural disorders), maternal financial difficulties and OHC were associated with an increased likelihood of youth's financial difficulties. The results of the mediation analysis also showed that maternal financial difficulties and OHC mediated a large proportion of the association between prenatal substance exposure and youth's financial difficulties. These findings are supported by studies from the general youth population, which have shown that family characteristics, especially a disadvantaged family background, can predict youth's FSA needs (Ilmakunnas, 2018; Ilmakunnas & Moisio, 2019; Kauppinen et al., 2014). Parental financial difficulties, for example, can hinder parents' abilities to support their child financially; thus FSA may be needed to secure the transition to adult independence.

OHC also showed significant associations with financial difficulties, and OHC also mediated a significant proportion of the association between prenatal substance exposure and financial difficulties. Children and youth often leave OHC at the age of emancipation. This typically occurs at the age of 18, when the youth has not reached the full capacity to support themselves. Thus, financial difficulties among youth with an OHC history can reflect the difficulties that youth who leave OHC can encounter when transitioning from OHC to independent adulthood. Prior research has also indicated that youth with a history of OHC experience challenges in many areas of life, including mental health and behaviour, education, and financial self-supporting (Bronsard et al., 2016; Kääriälä et al., 2018, 2019; Vinnerljung & Sallnäs, 2008), which can further increase challenges during the transition period.

The association between OHC and youth's financial difficulties may not only reflect youth's potential difficulties and lack of financial and social support during the transition from OHC to independent adulthood, but also the aftercare services provided during the transition from OHC to independence. In Finland, aftercare services aim to support youth in achieving adult independence after OHC. Aftercare services include supportive measures such as assistance in arranging accommodation or education, financial support, and psychosocial support. During the study period, aftercare services were provided until the age of 21 but were extended to the age of 25 in 2020. The need for financial social assistance among youth with a history of OHC during the transition to adulthood can be reflected in the aftercare services and provision of financial social assistance. However, it is important to note that FSA is only granted to individuals whose income and assets do not cover their basic needs. Thus, financial social assistance among these youth reflects a true need for support when transitioning from OHC to independence and might also reflect a lack of family support (e.g. financial support).

The characteristics of OHC (including the type of care, age at placement, and placement stability) can also influence youth outcomes (Jones et al., 2011). Although the influence of these OHC characteristics was not studied in this dissertation, these observations have been made in other studies conducted among prenatally substance-exposed children placed in OHC (Bada et al., 2008; Fagerlund et al., 2011; Koponen et al., 2009, 2013). These studies indicate that early placement in a stable care environment can ameliorate the risk of further developmental or behavioural problems, whereas instability of the child's living situation, including moves and changes in caretaker, can predict developmental challenges in the areas of behaviour and adaptive functioning (Bada et al., 2008). It can be common that when children are being placed in OHC, they

experience transitions between multiple placements before the final placement decision has been made. Although the different characteristics of OHC were not studied in detail in this dissertation, the descriptive results showed that the exposed youth experienced a median of 3 separate OHC placements compared to 2 among the unexposed. These multiple placements can indicate not only instability in the care provision but also disruptions in the attachment relationship between the child and the caregiver −and thus a potential risk to later developmental trajectories (Fearon et al., 2010; Groh et al., 2017; Pallini et al., 2019). However, strong conclusions should be avoided, as the associations between the characteristics of OHC and youth's financial difficulties were not studied in this dissertation.

The results of Study III, in which mood and neurotic disorders among youth were studied, showed that the direct effect of prenatal substance exposure on disorders was subtle, and in addition to female sex, exposure to a cumulative number of maternal adversities and OHC were important predictors of mood and neurotic disorders. These findings are in accordance with prior research that has shown associations between exposure to adversities in the postnatal caregiving environment and an increased likelihood of various mental/behavioural disorders including disorders on the internalising continuum (Coles et al., 2022; Koponen et al., 2020b; O'Connor & Paley, 2006; Walthall et al., 2008), in prenatally substance-exposed populations. Similar associations have also been observed in studies conducted in the general youth population (Björkenstam et al., 2016; McKay et al., 2022; Raitasalo et al., 2019; Raitasalo & Holmila, 2017). Interestingly, the likelihood of mood and neurotic disorders in Study III was similar across a number of adversities, i.e. the likelihood of these disorders did not increase with an increasing number of adversities. In addition, exposure to one adversity did not show statistically significant association with mood and neurotic disorders.

Although associations between prenatal substance exposure, adverse experiences, and specific mood and neurotic disorders were not studied in this dissertation, particularly interesting was the observed higher occurrence of specialised healthcare episodes for reaction to severe stress and adjustment disorders and dissociative disorders in the exposed cohort, although the number of specialised healthcare episodes for this specific disorder category was low. These disorders could reflect exposure to serious adverse or traumatic experiences or disruptions in attachment and caregiving (Bailey & Brand, 2017; Boyer et al., 2022). However, strong conclusions should be avoided since these associations were not studied here. These findings reflect the need

for research to further explore the effects of adverse experiences on various mental health outcomes in children and youth with prenatal substance exposure.

The mechanisms that can underlie the associations between exposures to adverse experiences during childhood and mental health disorders (including internalising disorders) can be viewed from different perspectives. From a neurobiological perspective, the plasticity of the brain in the early years of life and the maturation of different brain regions until adolescence make the brain vulnerable to the influence of exposure to early life adversities (Bick & Nelson, 2016; Hart & Rubia, 2012; Lupien et al., 2009). Exposure to repeated and prolonged stress during the early years of life, in particular, can lead to structural and functional abnormalities in a child's brain, particularly in the stress-sensitive brain areas that include the prefrontal cortex, amygdala, and hippocampus. Dysfunction in these brain regions can manifest as deficits in cognitive, behavioural, and socio-emotional functioning and increased vulnerability to internalising disorders (Bick & Nelson, 2016; Shonkoff & Garner, 2012).

Another perspective relates to the association between exposure to early life stress and alterations in the body's biological stress response systems. Exposure to prolonged stress has also been associated with HPA axis dysfunction, which has an important role in the body's responses to stressors. HPA axis dysfunction can increase the body's sensitivity to stressors and maladaptive responses to stress. Furthermore, HPA axis dysfunction can increase the risk of poor health outcomes, including mental health disorders (Weinberg et al., 2008), and HPA axis dysfunction has been identified as an underlying factor in mood and neurotic disorders (Hellemans et al., 2010).

Prenatally substance-exposed children can be especially vulnerable to the effects of exposure to stressors. The associations between prenatal substance exposure, neurobiological alterations in a child's brain (Etemadi-Aleagha & Akhgari, 2022; Martin et al., 2016; Moore et al., 2014; Nuñez et al., 2011), and impairments in the body's stress response systems, including the dysregulation of the HPA axis, can make them vulnerable to early life adversities and stress (McLachlan et al., 2020; Weinberg et al., 2008). In addition, the accumulation of adversities in these populations, as also shown by the results of this dissertation, can further increase their vulnerability to inferior developmental outcomes in different developmental domains. Prior research evidence supports these notions, and studies have indicated that children with prenatal exposure to substances and early life adversities are at a high risk of poor outcomes in various developmental domains (Chu et al., 2020; Henry et al., 2007; Kambeitz et al., 2019; Karpova et al., 2021).

Another important aspect is caregiving and the caregiver-child attachment. A caregiver-child attachment relationship established in infancy is crucial for the survival of the child (Bowlby, 1969) and their later socio-emotional development (Groh et al., 2017). Maternal substance abuse and co-occurring life difficulties can negatively influence the mother's ability to take care of the child and respond to their cues for care in a sensitive, responsive, and predictable way (Frigerio et al., 2019; Pajulo et al., 2001; Salo et al., 2009) and thus negatively affect the attachment relationship between the mother and child (O'Connor et al., 2002). An insecure attachment relationship between the caregiver and the child, typically seen in mothers with substance abuse and their children (Frigerio et al., 2019; O'Connor et al., 2002; Pajulo et al., 2001; Salo et al., 2009), has been associated with long-term developmental concerns in children. An insecure attachment relationship in childhood can increase the risk of externalising disorders as well as peer relationship difficulties (Fearon et al., 2010; Groh et al., 2012; Pallini et al., 2019). Also, the association between an insecure attachment relationship and a child's impaired capability for emotion regulation and coping with stress and internalising disorders have been reported in prior studies (Cooke et al., 2019; Groh et al., 2012; Schore, 2001).

Overall, the findings of this dissertation showed that children and youth with prenatal substance exposure are a vulnerable group with exposure to an accumulation of adversities during childhood, which can predispose them to an increased susceptibility to secondary disabilities. The findings also indicated that the secondary disabilities in these populations are multifaceted, as also illustrated in Figure 1. In addition to the effects of prenatal substance exposure, the postnatal caregiving environment and caregiving instability also have a significant role in predicting the likelihood of secondary disabilities.

7.2 Strengths and limitations

The strengths of the studies of this dissertation include the use of data from several national administrative registers with high completeness and validity (Gissler & Haukka, 2004; Sund, 2012). The use of register data excludes limitations related to the risk of recall bias, underreporting of adverse events, and data collection inaccuracies related to retrospectively collected information. In addition, the strengths include a long follow-up time and a matched unexposed control group.

There are also limitations that warrant attention when interpreting the results of this dissertation. One of the limitations relates to the assessment of maternal prenatal substance use among mothers of exposed youth. The information on maternal prenatal substance use collected at the HAL clinics − including the type of substances the mother has used and the severity of substance use − is inevitably inaccurate. Thus, the data precluded any meaningful substance-specific or dose-response-specific analyses. The data also precludes any meaningful analyses of the potential changes in maternal substance use behaviours during pregnancy. However, referral criteria for the HAL clinics provide firm evidence that the exposed cohort represents a high-risk population, i.e. children born to women with significant substance abuse and/or polysubstance use during pregnancy. Thus, the results for the exposed cohort are not representative of children born to mothers with occasional or low levels of prenatal substance use.

In addition, the characteristics of the mothers of the exposed offspring indicate that the mothers of the exposed offspring likely represent a high-risk population as also found in other studies (e.g. Esper & Furtado, 2014; Flannigan et al., 2021). The high prevalence of various adverse maternal characteristics likely reflects a mother's difficult life situation linked to substance abuse. These findings need to be considered when interpreting or generalizing the findings to other populations.

One unexposed cohort-related limitation relates to the risk of misclassification and the possibility that the unexposed cohort includes offspring with exposure to low levels of maternal substance use during pregnancy not being identified by the public health nurses at antenatal care or from the register data. To reduce the risk of misclassification, maternal care episodes in inpatient and outpatient hospital care were reviewed to identify any maternal substance-use-related primary or secondary diagnoses or external causes one year before or at the time of birth of the offspring. In addition, the Register of Malformation, the Hospital Discharge Register, and the Care Register for Health Care were reviewed to confirm that the unexposed cohort did not have any evidence of diagnosis within the FASD spectrum or Neonatal Abstinence Syndrome. Despite these efforts, we cannot rule out that the unexposed cohort still include offspring exposed to substances during pregnancy, especially in unexposed children with gestational exposure to maternal tobacco smoking, which could be a marker of alcohol and/other substance use (Esper & Furtado, 2014; Flannigan et al., 2021). Excluding unexposed offspring with gestational exposure to tobacco smoking could be considered in future studies to further reduce the potential risk of misclassification.

Another limitation worth discussing relates to the potential selection bias in the unexposed cohort and the representatives. The unexposed cohort was obtained from the Medical Birth Register including all births with a birth weight of at least 500g and gestational age of at least 22 weeks that have occurred in Finland. Furthermore, matching an unexposed cohort was based on five maternal characteristics, and no additional inclusion/exclusion criteria were applied. In addition, the results for the unexposed cohort (e.g. completed secondary education at the age of 23 years, occurrence of mood and neurotic disorders, FSA needs, OHC) are in line with national estimates (Forsell & Kuoppala, 2022; Haula & Vaalavuo, 2021; Suomen virallinen tilasto, 2019). Therefore, the risk of selection bias is expected to low and the unexposed cohort is likely to be a representative sample of the general population.

Another study population related limitation relates to the relatively small sample size in studies I, II, and III. The small sample size can result in low statistical power and wider confidence intervals, increasing the uncertainty in the estimates. Thus, the estimates and findings of this dissertation should be interpreted in the light of these limitations.

There are data limitations that warrant attention. One limitation is that the register data likely includes the most severe cases of the studied phenomenon and only reaches 'the tip of the iceberg' (Gissler & Haukka, 2004; Pirkola et al., 2006). This can especially be the case with youth and maternal mental/behavioural disorders and maternal pre- or postnatal substance use. The assessment of the studied forms of mental/behavioural disorders among the youth and their mothers was based on registered diagnoses in the specialised healthcare data. Therefore, the data likely include the most severe cases requiring specialised healthcare and individuals with access to such care. Milder forms of mental/behavioural disorders not requiring specialised healthcare, disorders treated in primary healthcare, and individuals not seeking or accessing healthcare, are not likely to have been captured by the register data used in this dissertation.

Similarly, maternal postnatal substance use was based on substance-use-related primary or secondary diagnoses, or external causes registered in the specialised healthcare data. By relying on register data, only maternal severe pre- or postnatal substance use requiring specialised healthcare and individuals seeking and accessing such care may have been identified, thus excluding maternal low-level or occasional substance use.

Furthermore, another limitation relates to the identification of mental/behavioural disorders or substance use disorders by using diagnosis codes. The medical diagnoses

in the healthcare registers are based on similar criteria used by the medical professionals, and the diagnosis is expected to reflect the medical conditions. Although the validity of diagnosis codes in Finnish register data is expected to be high (Sund, 2012), the possibility of coding errors by medical professionals or invalid diagnosis codes cannot be ruled out. Furthermore, although the completeness of primary diagnoses recorded in the healthcare register is expected to be high, missingness in secondary diagnoses or external causes registered in the data source cannot be completely avoided.

Additional limitations also exist related to the data. Although data linkages between several national registers were made to have a comprehensive data set, limitations also exist related to missing information on specific indicators of the studied phenomenon and uncontrolled or unmeasured confounders not being identified by the register data. In Study I, information was missed on educational outcomes, school performance, and special education in comprehensive education, which could have offered a more detailed picture of the youth's educational performance and outcomes prior to attaining secondary education. Furthermore, in Study III, the data on reimbursements for prescription medicines used for the treatment of mood and neurotic disorders did not include detailed reimbursement information, including the date of the prescription and indication for medication use (i.e. diagnosis) hence, the data were not used in the analysis. Data on the medication used for the treatment of the disorders would have offered an alternative way to confirm the presence of mood and neurotic disorders in combination with the diagnosis code. In addition, such data would have provided additional information on the severity of the disorders.

Another data-related limitation relates to the lack of assessment of the severity of the effects of prenatal substance exposure. To the best of my knowledge, validated algorithms were not available using register data to assess the severity of the effects of prenatal substance on child development. Future studies could consider assessing the severity as it may be associated with the studied secondary disabilities and provide a better understanding of the findings.

In addition, the limitations related to the indicators of specific adverse childhood experiences should be acknowledged. Out-of-home care generally indicates significant issues in the postnatal caregiving environment or parenting domains that endanger the child's health, safety, and development. However, by using only register data, information on specific indicators of adverse experiences (including physical and emotional abuse, peer conflicts or bullying, or witnessing domestic violence) may have been missed. In addition, the register data does not include information on caregiver-

child interaction or attachment relationships crucial for child development, which is potentially one of the most important mediating mechanisms between prenatal substance exposure and youth outcomes.

Furthermore, the data included information only on the biological mother; thus data covering paternal information or information on foster parents was not available. A father or foster parent can have a significant role equal to the mother's in a child's life. The foster parent can have a significant role especially if the child has been placed outside the home in the early years of life. Therefore, information on the foster parent(s) would have allowed for studying the influence of foster parent characteristics on the studied outcomes. Lastly, as this is an observational study, causal links are difficult to prove.

7.3 Implications for future research

The results of this dissertation give directions and suggestions for future studies. To begin with the secondary disabilities, studies extending into later adulthood are needed to better understand in which areas of adult life the prenatally substance-exposed individuals experience or continue to experience challenges. This can also help in understanding how individuals exposed to substances during pregnancy can be supported in adult life.

Considering the significant influence of mental/behavioural disorders on secondary disabilities found in this dissertation, future studies on secondary disabilities could include information on cognitive, behavioural, and adaptive functioning to draw a broader picture of how impairments in these developmental domains contribute to the susceptibility to secondary disabilities, and how impairments in these areas of functioning potentially mediate the association between prenatal substance exposure and secondary disabilities. Such research could provide directions for prevention.

Another suggestion for future studies is to consider using the above-described youth characteristics (e.g. IQ, cognitive, behavioural, and adaptive functioning) as matching criteria for exposed and unexposed groups to study youth with comparable functional abilities. Here, the register data did not allow for matching exposed and unexposed cohorts by these youth characteristics. However, offspring with intellectual disabilities were excluded, thus youth with similar premises for achieving adult independence were included in the exposed and unexposed cohorts. Future studies could also consider the

use of additional or alternative matching criteria, such as maternal socioeconomic status or OHC status, or matching methods such as propensity scores to ensure comparable exposed and unexposed cohorts.

As shown by the results of this dissertation, the adverse characteristics of the postnatal caregiving environment can increase the likelihood of secondary disabilities. Although it is challenging to distinguish the influence of prenatal substance exposure and postnatal adversities on long-term outcomes, it is important to consider the influence of these risk factors in the analysis of future studies (e.g. the mediating effect of stressful events on the development of physical and mental/behavioural conditions). Another important perspective of this is the caregiver-child attachment relationship. Future studies could consider including information on the quality of care and the caregiver-child attachment relationship, thus allowing the influence of the quality of caregiving to be studied, as this quality could be a strong mediating factor for developmental concerns and secondary disabilities in these populations. In addition, the data used in this dissertation included information only on biological mothers; hence, future studies should include information on other caregivers who can have an equally important role in a child's life (e.g. father and foster parent).

Furthermore, the OHC data used in this dissertation did not include detailed information on the reasons for OHC or the characteristics of aftercare services. Therefore, future studies could consider including more detailed information on the characteristics of OHC that may influence developmental outcomes. However, this calls for ensuring that register data includes detailed characteristics of OHC and preferably also aftercare services.

Another area in which research is needed is the prevalence of maternal substance use during pregnancy and the prevalence of children born with prenatal substance use-related impairments and FASD. The results of the dissertation showed that only 7.5% of the youth with prenatal substance exposure in the total study population (Table 7) were diagnosed with a condition within the FASD spectrum. The low percentage of diagnosed individuals in the exposed cohort could reflect the fact that diagnosing FASD is a difficult clinical procedure requiring a trained multiprofessional team. It could also reflect the lack of diagnose in these populations or difficulties identifying the exposed individuals. The prevalence estimates of alcohol and/or illicit drug use among pregnant women and the number of children born with prenatal exposure to these substances also have a public health importance. Without a clear understanding of the size of the

problem, it is difficult to gain the attention the topic would require and enough resources for prevention.

Finally, future studies could consider the use of national register data, and a linkage of register data to primary data, when studying the secondary disabilities in individuals exposed to substances during pregnancy. Register data provides a rich source of information for this type of research, including accessible population-level data and a source for obtaining a comparison group. Register data also enables a long follow-up of individuals. Future register-based studies could consider how to assess the severity of the effects of prenatal substance exposure reliably from register data sources. No consensus presently exists on this matter. This dissertation may provide directions for severity assessment as well as for the assessment of secondary disabilities in prenatally substance-exposed populations in register-based studies.

7.4 Implications for public health and prevention

Prenatal substance use and its long-term effects on child development is a public health, policy, and economic issue that warrants preventative measures. The effects of prenatal exposure to substances extend the prenatal period and childhood. And, as shown by the results of this dissertation, youth with prenatal substance exposure can encounter various secondary disabilities in the sensitive youth period that lays the groundwork for adult life.

Considering the results of this dissertation, youth with prenatal substance exposure can be considered as a vulnerable group at high risk of unfavourable developmental trajectories or social exclusion in need of support from various sources and sectors throughout their life. Thus, prenatal substance exposure and its consequences can also create a significant economic burden due to the costs stemming from the need for social, healthcare, and educational services and child welfare services, in addition to the productivity losses of caregivers and the costs of socially excluded youth (Greenmyer et al., 2018, 2020; Hilli et al., 2017). Consequently, as a lifelong disability, prenatal substance use not only concerns the exposed individual, but also their family and society (Popova et al., 2023).

As shown in Figure 1, secondary disabilities in youth with prenatal substance exposure are multifaceted, and several factors during the life course influence the susceptibility to these disorders. Therefore, prevention of secondary disabilities in these

youth requires preventative measures at different levels and involves different professionals and service providers (Autti-Rämö, 2022; Jacobsen et al., 2022; Petrenko et al., 2014). Figure 9 summarises the preventative actions discussed in this section.

Prevention is preferably started in early childhood. An initial step is the early identification of children and youth with prenatal substance exposure and the identification of the challenges they may encounter. Prenatal substance exposure can be especially prevalent in children placed in OHC in early childhood, and therefore these children may require special attention (Chasnoff et al., 2015; Tenenbaum et al., 2020). Early identification can help in diagnosing conditions and providing early interventions, specialised health and social care services and the follow-up to prevent further difficulties. However, often the challenge is that children and youth with prenatal substance exposure are identified and diagnosed later in life when the challenges start to occur or have already occurred or are not identified and diagnosed at all (Chudley et al., 2007). A lack of information on prenatal substance exposure, symptom overlap, and lack of physiological indicators can challenge the identification of prenatally substance-exposed children. Furthermore, the lack of confirmation of prenatal substance exposure can make it challenging to differentiate diagnoses, and conditions such as FASD and ADHD can have many overlapping features and co-occur in individuals with prenatal alcohol exposure. However, the aetiology of these may differ and there may be differences in the patterns of deficits and thus in the treatment of these disorders (National Center on Birth Defects and Developmental Disabilities et al., 2004; Peadon et al., 2010; Rasmussen et al., 2010).

The challenges in identifying prenatally substance-exposed children and youth early on can also reflect the lack of knowledge of prenatal substance exposure and its effects on child and youth development across different sectors, for example, in healthcare, social care, and education, including early childhood education (Howlett et al., 2019; Mukherjee et al., 2015; Payne et al., 2005). More comprehensive knowledge among professionals working with these individuals could help in the identification of signs of difficulties and the interpretation of the child's or youth's behaviours. Together, these could also improve diagnostic capabilities and early referral to appropriate services targeting the individual needs of these children and youth. Improved knowledge could also lead to better recognition of FASD and the effects of prenatal substance exposure (National Center on Birth Defects and Developmental Disabilities et al., 2004; Petrenko et al., 2014).

The school environment, including early childhood education, is a significant developmental setting during childhood and youth. Professionals in the school environment meet the children and youth almost daily and therefore have an important role in identifying signs of wellbeing issues, reduced abilities to carry out educational activities, and signs of absence from school or withdrawal from social contacts that can indicate potential concerns that require attention. If such concerns arise, the professionals have an important role in referring a child or youth to further services (Marttunen & Karlsson, 2021). However, this requires that professionals working with children and youth have the appropriate training, feel comfortable and confident in taking action if concerns arise, and are aware of the availability of services.

In Finland, the welfare services provided at school, including school health services and annual health check-ups, have a particular role in monitoring children's wellbeing and development. The aim of the welfare services is to promote, maintain, and secure conditions that support the child's or youth's learning, mental and physical health, and social wellbeing. These services also have an important role in co-operation with parents or caregivers and identifying any concerns in the home environment. In Finland, by law, three comprehensive health check-ups, including examination by a nurse and doctor, are carried out in grades 1, 5, and 8 (typically at age 7, 11, and 14). Parents are invited to participate in these health check-ups to discuss the overall wellbeing of the family. Topics discussed with the parents typically include the child's or youth's wellbeing, parental health, relationships, communication, and interaction within the family, parenting behaviours, the child's health, and the livelihood and safety network (Aalto-Setälä et al., 2020).

However, despite efforts to invite parents to participate in these health check-ups, participation can vary. Kivimäki et al. (2021), for example, showed that less than half of parents participated in the health check-ups carried out in the 8th grade. Factors associated with non-participation included maternal low education, the student not living with both the mother and father, and the student having an immigrant background. Students who had daily health complaints, alcohol use issues, or communication difficulties with parents also reported parents' non-participation more frequently (Kivimäki et al., 2021).

Considering the findings by Kivimäki et al. (2021), support for parental participation in the health check-ups and other welfare services provided at school should be emphasised. Parental participation should be emphasised especially in children and youth with prenatal substance exposure and among other vulnerable groups,

considering their susceptibility to various concerns endangering school participation, overall wellbeing, and the potential risk factors and stressors in the home environment (e.g. parental mental health disorders, substance use or financial difficulties). Parent or caregiver also have a crucial role in promoting child or youth development and wellbeing. Therefore, hearing about the child's or youth's wellbeing and family environment from the parent's or caregiver's perspective can help in understanding the family's overall wellbeing and any risks that may exist in the home environment. This can also help in providing services and support for the family and parenting to prevent further concerns.

In addition to the efforts to identify children and youth with developmental concerns, the availability and accessibility of timely services for children and youth with prenatal substance exposure, and youth in general, should also be secured. This is particularly important for the prevention of mental/behavioural disorders, considering the prevalence of and onset of these disorders in childhood and youth (Kessler et al., 2007; Patel et al., 2007). The plasticity of development in childhood and youth can create an optimal window of opportunity to impact later development and mental health outcomes (Fusar-Poli, 2019). Therefore, support in the childhood and youth period is crucial to prevent the persistence of these disorders in adulthood. Prevention of these disorders is also crucial to prevent the secondary disabilities considering the associations as shown by the results of this dissertation.

In relation to service provision, another critical aspect of the prevention of secondary disabilities in youth with prenatal substance exposure relates to OHC. OHC services and the characteristics of such services have an important role in supporting the development of children and youth with prenatal substance exposure. Regarding the characteristics of OHC, studies have shown that early placement and longer duration in stable, nurturant, and good-quality home care can protect children and youth with prenatal substance exposure from later developmental concerns (e.g. Bada et al., 2008; Fagerlund et al., 2011; Koponen et al., 2013; Streissguth et al., 2004). Emphasis on the known protective factors and securing a safe and stable environment for these vulnerable children and youth, based on individual needs, could help in preventing developmental or health concerns. Moreover, the highly prevalent health concerns stress the importance of investing in the overall wellbeing and development of children and youth in OHC. This also requires cooperation between different professionals and service providers, including the caregiver, as well as resources for the providers of OHC services.

Services provided for youth leaving OHC are also critically important, as these youth may lack support or safety nets. The law requires the provision of aftercare services for children and youth until the age of 25 (Lastensuojelulaki 417/2007). These services aim to support the transition from OHC to independent adulthood. Based on individual needs, this may require the inclusion of various services and multiprofessional support, including housing, education, financial support, psychosocial support, and healthcare services. The provision of aftercare services is particularly crucial for children and youth with prenatal substance exposure because of health concerns, including mental/behavioural disorders, the level of maturation, and potential developmental delays (e.g. Crocker et al., 2009; Fagerlund et al., 2012), potentially hindering the ability to support themselves independently at the time of leaving OHC when they are legally considered adults. The potential risk factors in the family environment and lack of support from biological parent may add to this. Thus, the service provision following OHC needs investment, as it can offer comprehensive support for these youth to secure the transition to independent adulthood.

The prevention of secondary disabilities in youth with prenatal substance exposure also calls for preventative measures aiming to prevent prenatal substance use. This requires measures at different levels, i.e. primary, secondary, and tertiary prevention (Autti-Rämö, 2022, Popova et al., 2023). Primary prevention focuses on preventing prenatal substance use; thus, preventative efforts are needed before pregnancy (Autti-Rämö, 2022). These includes measures such as informing people of all ages about the harms of substance use (also during pregnancy), and about birth control. Another important part of primary prevention is a clear message recommending abstinence during pregnancy and when planning for pregnancy. This not only concerns women of childbearing age, women who plan to become pregnant, or expecting mothers, but also society as a whole (Popova et al., 2023). Survey studies conducted outside of Finland indicate that there is still room for improvement when it comes to informing people about the risks associated with the use of substances during pregnancy (e.g. Peadon et al., 2010).

Secondary prevention focuses on the expectant mother (and her partner). Measures of secondary prevention focus on preventing substance use or continuation of substance use during pregnancy and fetal harm (Autti-Rämö, 2022). A discussion about substance use during pregnancy and the potential risks associated with it should be held with every expectant mother and her partner sensitively as early as possible as a part of routine discussion of life style habits during pregnancy (Popova et al., 2023). This

discussion should be held at every antenatal care meeting, as life situations and substance use behaviours may change (Autti-Rämö, 2022). This discussion requires that healthcare professionals are trained to deliver such a sensitive discussion (Popova et al., 2023). Studies indicate that healthcare professionals may not feel comfortable discussing substance use among expectant mothers because it is a sensitive topic with a stigma attached to it (Howlett et al., 2019; Payne et al., 2005). This calls for the training of healthcare professionals so that they feel comfortable discussing substance use in a supportive, sensitive, and non-judgmental way.

A discussion on substance use with the expectant mother may be sufficient to identify substance use. However, self-reported information on substance use during pregnancy often has challenges regarding the reliability and true estimates of the substance use. Therefore, validated tools for screening alcohol use (e.g. the AUDIT test) or use of illicit drugs (e.g. the Drug Use Disorders Identification Test, DUDIT) can be used in identifying substance use, especially problematic use. In addition, the use of laboratory screening measures can be considered as an alternative method to identify substance use objectively (National Center on Birth Defects and Developmental Disabilities et al., 2004).

Screening tools can also help healthcare professionals to discuss substance use before and during pregnancy. Screening with every expectant mother can also reduce the stigma attached to the topic as screening would not rely solely on a healthcare professional's subjective evaluation of mothers who might be at risk of using substances. If a partner is included, substance use should also be discussed with the partner. The partner's awareness of the harms related to substance use during pregnancy can help them to support the expectant mother in abstaining from substances throughout the pregnancy.

If such screening tools are used to identify alcohol and/or illicit drug use among expectant mothers, the results of the screening could be recorded in the maternal pregnancy record. The information recorded in the journal could help to confirm potential prenatal exposure to substances later, which could help in diagnosing potential difficulties the child may encounter. In addition, recorded information on potential maternal prenatal substance use could help in establishing prevalence estimates on the use of substances during pregnancy and how many children are affected by prenatal substance use.

The support of abstinence or the discontinuation of substance use during pregnancy may require different approaches and methods (e.g. motivational interviewing, brief

intervention, or referral to a special antenatal clinic), considering the expecting mother's substance-using behaviours (National Center on Birth Defects and Developmental Disabilities et al., 2004). If further services are deemed necessary, for example in the case of serious substance use problems, these services for the expectant mother should be available, preferably free of charge. The services should also consider other potential co-occurring psychosocial difficulties, including financial difficulties and health concerns such as mental health disorders and trauma experiences, that may not only influence the wellbeing of the mother but also her ability to take care of the child. Thus, a holistic and multiprofessional approach to care provision for the mother is essential (Autti-Rämö, 2022; National Center on Birth Defects and Developmental Disabilities et al., 2004). If substance use occurs during pregnancy, this also calls for the involvement of child welfare services. In Finland, the Child Welfare Act obligates professionals to do a child welfare notification as early as during the pregnancy if there is any reason to suspect that the child will need child welfare services immediately after birth (Lastensuojelulaki 417/2007). Reasons for this can include the mother's or partner's substance use problems or significant mental health disorders. The child welfare notification allows for the planning of support and services together with the expectant mother (and her partner) already during the pregnancy (Lastensuojelulaki 417/2007).

Services provided for pregnant women with substance use can also include interventions targeted at the mother-child interaction and attachment relationship (Belt et al., 2012; Salo et al., 2020). These services can be provided as early as during pregnancy. One example of such services is the Holding Tight Treatment® system (Pidä kiinni® -hoitojärjestelmä in Finnish) provided by the Federation of Mother and Child Homes and Shelters (Ensi- ja turvakotien liitto in Finnish) in Finland (Ensi- ja turvakotien liitto, 2016). The purpose of the treatment is to guarantee physical and psychosocial safety for the newborn and to support parents in sobriety and parenting. The treatment recognises pregnancy as a special opportunity for a woman with substance-use problems to change her lifestyle habits and substance-using behaviours and build a relationship with the newborn that does not include substances (Ensi- ja turvakotien liitto, 2016). Nonetheless, parenting, caregiving, and prevention of postnatal caregiving adversities should not be the focus only during the pregnancy or the first years of a child's life but should continue throughout childhood. This is particularly important in families where prenatal substance use has occurred, considering the existence of other risk factors and stressors potentially affecting parental abilities to take

care of the child and the influence this can have on the caregiver-child attachment (Autti-Rämö, 2022; Belt et al., 2012).

Strengthening parenting is also part of tertiary prevention that focuses on securing a safe and stable postnatal caregiving environment for the child, which is a basic right of every child (Autti-Rämö, 2022). Preventative measures aiming to secure such an environment and investing in parental wellbeing are crucial, especially in the context of prenatal substance use (Autti-Rämö, 2022). Child health centres have an important role in building trustworthy relationships between the parent or caregiver and supporting them in securing a safe and nurturing environment for the child. Child health centres also have an important role in acting if concerns for child safety exist in families.

It is crucial that professionals working with children across different sectors understand how early life adversities − in addition to poor parenting behaviours and attachment difficulties between the caregiver and child − can affect a child's health and long-term development. This is especially important in the context of prenatal substance exposure, as it commonly co-occurs with exposure to various early life adversities and caregiving instability. The interaction between neurological impairments caused by prenatal substance exposure and environmental adversities can contribute to inferior developmental outcomes. Understanding these interplays has a significant role in prevention (e.g. Morgart et al., 2021).

To conclude, the prevention of secondary disabilities among youth with prenatal substance exposure calls for preventative measures at different levels and a multiprofessional approach and co-operation of services in different sectors, as summarised in Figure 9. It also calls for better understanding and awareness of the harms associated with prenatal substance use, not only among pregnant women or women of childbearing age but also among other individuals and especially among various professionals (Popova et al., 2023). The prevention of prenatal substance use and the lifelong consequences it has for the exposed child also requires political measures considering the role alcohol and/or other substances have in people's lifestyles, culture, and society. Alcohol, the most used substance in Finnish society, is not an ordinary commodity, and it plays a significant role in a wide range of health conditions and social problems (Babor et al., 2022). The harms associated with alcohol use extend beyond the drinker, and unfortunately, the most detrimental effects concern the unborn child. Considering the suggested estimates of the prevalence of alcohol use among pregnant women in Finland (Mårdby et al., 2017; Popova et al., 2017; Voutilainen et al., 2022), the estimated number of children born annually in Finland

with prenatal substance use related impairments (Fagerlund, 2013), the increase in the use of alcohol (especially harmful use), and the use of illicit drugs among women of childbearing age and women in general (Karjalainen, 2020; Mäkelä, 2018), the prevention of prenatal substance use also calls for political measures, including effective alcohol and drug policy measures.

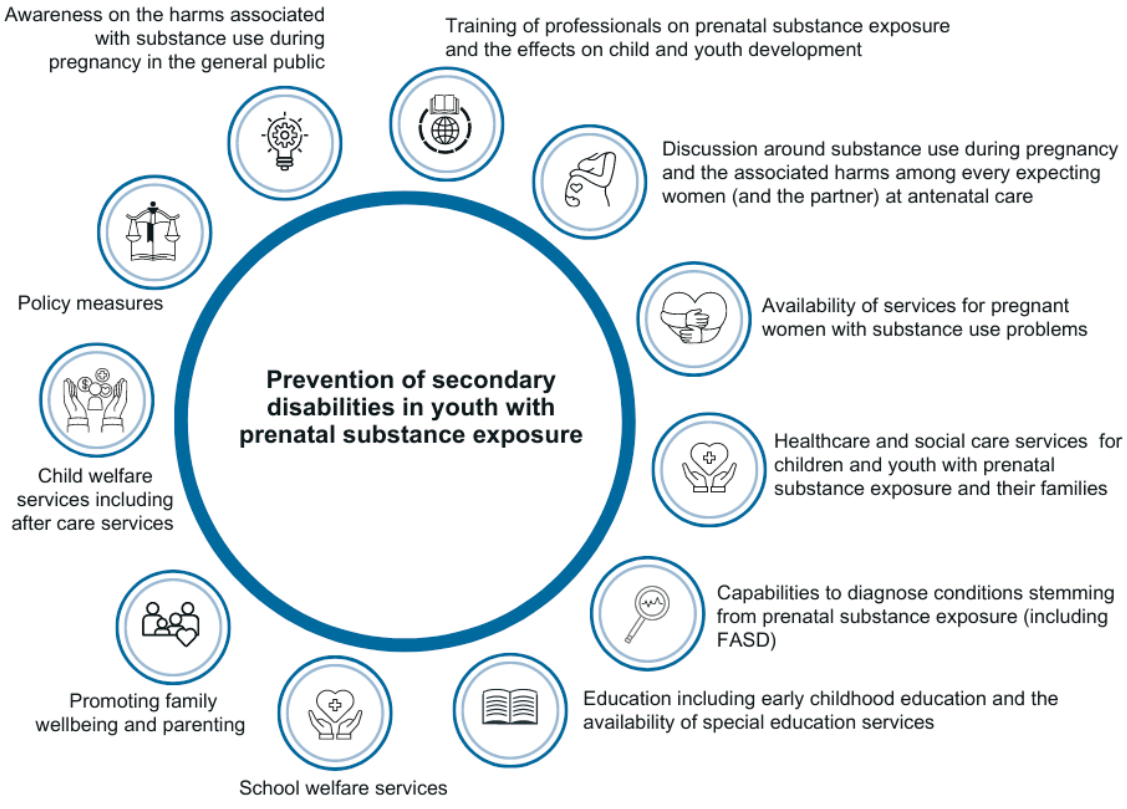


Figure 9. Summary of measures and actions to prevent secondary disabilities in youth with prenatal substance exposure

8 CONCLUSIONS

The findings of this dissertation add to the current literature by showing that youth with a history of exposure to maternal substance abuse during pregnancy are at heightened risk of experiencing avoidable secondary disabilities, measured as the lack of secondary education, financial difficulties, and mood and neurotic disorders. The findings also add to the literature by showing that exposure to maternal prenatal substance abuse was not an independent risk factor for the secondary disabilities. The secondary disabilities are multifaceted in the prenatally substance-exposed populations. And over time, risk factors associated with maternal prenatal substance abuse (including postnatal caregiving adversities) predispose these youth to an increased likelihood of secondary disabilities. In addition, the results of this dissertation indicated that youth's mental/behavioural disorders, commonly observed among youth with prenatal substance exposure, were an important factor in increasing their susceptibility to secondary disabilities.

Secondary disabilities in youth can predispose individuals with prenatal substance exposure to poor developmental trajectories and challenges later in adult life, leaving them at risk of social exclusion. These disabilities are avoidable, but their prevention requires preventative measures at different levels and sectors.

To conclude, every child or youth with prenatal substance exposure has their own set of strengths and abilities. Unfortunately, we often tend to see only the problematic behaviours or disabilities of these children and youth and the risk factors in their lives. It is important to understand the disabilities and areas of challenges these children and youth may encounter, and the risk factors that predispose them to challenges so that we can better tackle the risk factors and support them in performing in daily life and reduce the risk of further challenges. However, by focusing on their strengths and abilities and protective factors, we may foster and encourage positive child and youth development and enable their fulfilling life and active participation in society despite the disabilities and other life experiences they have encountered.

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PUBLICATIONS

PUBLICATION I

Completed secondary education among youth with prenatal substance exposure: A longitudinal register-based matched cohort study

Nissinen, N.M., Gissler, M., Sarkola, T., Kahila, H., Autti-Rämö, I. & Koponen A.M.

Journal of Adolescence (2020), *86*(1), 15-27
DOI: 10.1016/j.adolescence.2020.11.006

Journal of Adolescence 86 (2021) 15–27

Contents lists available at ScienceDirect

Journal of Adolescence

journal homepage: www.elsevier.com/locate/adolescence

Completed secondary education among youth with prenatal substance exposure: A longitudinal register-based matched cohort study

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ARTICLE INFO

Keywords:
Prenatal substance exposure
Secondary education
Youth
Childhood adversities
Out-of-home care
Mental disorders
Behavioral disorders

ABSTRACT

Introduction: The dual impact of prenatal substance exposure (i.e. alcohol/drugs) and adverse postnatal caregiving environment on offspring secondary education completion is an understudied research area. The aim was to investigate the influence of childhood adversities, out-of-home care, and offspring's mental and/or behavioural disorders on secondary education completion among prenatally exposed offspring in comparison to matched unexposed offspring.
Methods: This is a longitudinal register-based matched cohort study in Finland including offspring with a history of prenatal substance exposure and a matched unexposed cohort. The study sample included 283 exposed and 820 unexposed offspring aged 18–23 years.
Results: The results showed a time lag in secondary education completion and lower educational attainment overall among exposed compared with unexposed (37.8% vs. 51.0%, respectively). The results from the multivariate logistic regression models showed that the differences in the secondary education completion between exposed and unexposed were diminished in the presence of covariates. A cumulative childhood adversity score and out-of-home care were not associated with secondary education completion in the multivariate models, whereas the different domains of offspring's mental and/or behavioural disorders including psychiatric disorders (AOR 0.65, 95% CI 0.45–0.96), neuropsychological disorders (AOR 0.35, 95% CI 0.23–0.54) and dual psychiatric and neuropsychological disorder (AOR 0.29, 95% CI 0.18–0.48) showed an independent negative effect on secondary education completion.

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https://doi.org/10.1016/j.adolescence.2020.11.006
Received 2 April 2020; Received in revised form 10 November 2020; Accepted 11 November 2020
Available online 29 November 2020

Conclusions: Inferior educational outcomes may not be directly linked with prenatal substance exposure but may rather reflect the extent of evolving offspring's mental and/or behavioural disorders over time influenced by childhood adversities.

1. Introduction

Substance use (i.e. alcohol and/or drugs) during pregnancy represents a major public health concern and a risk for the fetus (Irner, 2012; Riley, Infante, & Warren, 2011). Recent data from Finland indicate that alcohol use during pregnancy is still a major problem (Mårdby, Lupattelli, Hensing, & Nordeng, 2017; Popova, Lange, Probst, Gmel, & Rehm, 2017) and drug use (e.g. marijuana, amphetamine, ecstasy) has been increasing among women of childbearing age since the 1990s (Karjalainen, Pekkanen, & Hakkarainen, 2020). Considering that approximately four out of ten pregnancies are unplanned in Finland among women <30 years old and nearly one in five among women aged ≥30 years (Klemetti, Gissler, Lammi-Taskula, & Miettinen, 2014), there is a risk that the fetus is exposed to substances before pregnancy recognition.

Prenatal alcohol exposure has been associated with impairments in neurocognitive and neurobehavioral functioning, which can appear as deficits in executive functioning (Connor, Sampson, Bookstein, Barr, & Streissguth, 2000; Irner, 2012; Mattson, Crocker, & Nguyen, 2011), and in adaptive behaviour (Dalen, Bruarøy, Wentzel-Larsen, & Laegreid, 2009; Fagerlund et al., 2012). The detrimental effects of prenatal alcohol exposure can manifest as poor academic progress in school and inferior educational outcomes (Olson et al., 1997; Streissguth, 1996; Streissguth et al., 2004). However, only a few studies have investigated educational outcomes among young adults with prenatal alcohol exposure in terms of completed secondary education. These studies show that young adults completely or partly meeting Fetal Alcohol Syndrome (FAS) criteria including a combination of growth retardation, central nervous system dysfunction and typical facial features (Hoyme et al., 2016), have less often completed secondary education (Freunscht & Feldmann, 2011; Rangmar et al., 2015; Spohr, Willms, & Steinhausen, 2007) or post-secondary education (Rangmar et al., 2015).

Studies on prenatal exposure to drugs (e.g. cocaine, marijuana, methamphetamine, opiates) describe deficits in cognitive abilities, and problems with internalizing and externalizing behaviour among children (Ackerman, Riggins, & Black, 2010; Behnke, Smith, Committee on Substance Abuse, & Committee on fetus and newborn, 2013; Lambert & Bauer, 2012; Nygaard, Moe, Slinning, & Walhovd, 2015; Richardson, Willford & Goldschmidt, 2002) potentially contributing to poorer educational outcomes (Goldschmidt, Richardson, Cornelius, & Day, 2004). However, long-term effects of prenatal drug exposure, in terms of completed secondary education, remain an understudied research area.

Offspring with prenatal substance exposure are often exposed to a double burden in life. The negative consequences of prenatal substance exposure are often accompanied by a postnatal caregiving environment challenged by adverse family events and out-of-home care (OHC) (Koponen, Kalland, & Autti-Rämö, 2009; Lambert & Bauer, 2012; Minnes, Lang, & Singer, 2011; Price, Cook, Norgate, & Mukherjee, 2017). Childhood adversities (e.g. neglect, abuse, parental substance abuse, parental mental health disorders, family stress and poverty) can influence child's health, behaviour, and social functioning long-term (Anda et al., 2006; Hughes et al., 2017; Koponen et al., 2020; Norman et al., 2012). Childhood adversities have also been associated with poorer educational outcomes (Berg, Bäck, Vinnerljung, & Hjern, 2016; Erola, Jalonen, & Lehti, 2016; Kääriälä, Berlin, Lausten, Hiilamo, & Ristikari, 2018; Sirin, 2016; Vinnerljung, Bo, Öman, & Gunnarson, 2005).

Secondary education plays a crucial role in the transition to independent adulthood by affecting opportunities to seek higher education and finding employment. Lack of secondary education can increase the likelihood of unemployment and the risk of further social problems in adulthood (Ilmakunnas & Moisio, 2019; McMahon & Oketch, 2013; Sipilä, Kestilä, & Martikainen, 2011). To date, only a few studies have addressed the dual impact of prenatal substance exposure and childhood adversities with inferior educational outcomes among youth (e.g. Howell, Lynch, Platzman, Smith, & Coles, 2006). The aim was, then, to study the prevalence of completed upper secondary education (secondary education hereafter) among offspring aged 18–23 years with a history of prenatal substance exposure (i.e. exposed cohort) in comparison to a matched unexposed offspring (i.e. unexposed cohort). Furthermore, the association of childhood adversities (defined as maternal low socioeconomic status, single parenthood, mental and/or behavioural disorders, substance misuse, criminality, recipiency of long-term social assistance, death) and offspring OHC, and offspring's mental and/or behavioural disorders with completed secondary education among exposed and unexposed offspring was investigated. Considering the direct and indirect effects of prenatal substance exposure on neurocognitive and neurobehavioural functioning (e.g. Behnke, Smith, & Committee on Substance Abuse, & Committee on Fetus and Newborn, 2013; Irner, 2012) and its potential impacts on educational outcomes (Goldschmidt et al., 2004; Streissguth, 2007), the study had three hypotheses: 1) exposed offspring are less likely to have completed secondary education, 2) childhood adversities and OHC are negatively associated with secondary education completion among both exposed and unexposed offspring, and 3) offspring's mental and/or behavioural disorders reduce the likelihood of having completed secondary education among both exposed and unexposed offspring.

2. Methods

2.1. Study population

The present study is part of a ADEF Helsinki (alcohol and/or drug exposure during fetal life) research project, which is a longitudinal register-based matched cohort study. In the present study, we investigate offspring who were exposed to substances during

pregnancy (i.e exposed cohort) and their matched unexposed cohort at the age of 18–23 years (median follow up 20.1 years, IQR 18.8–21.1).

The exposed cohort consisted of offspring born in 1992–2001 to mothers with a history of gestational follow-up due to substance use. Assessment of substance use among pregnant women was done by public health nurses at the maternity clinics in the Helsinki metropolitan area. The identification of substance use was based on Alcohol Use Disorders Identification Test (AUDIT) (score $\geq$ 8 points), identified use of drugs, nonmedical use of central nervous system medications or opioid therapy, and on the general evaluation of the mother's life situation. The public health nurses were advised to refer pregnant women with identified substance use to the three special antenatal clinics (i.e. HAL clinics) at the Helsinki University Hospital (HUS) for pregnancy follow-up. The HAL (abbreviation for illicit drugs, alcohol, and medications for the central nervous system with misuse potential) clinics at Helsinki University Central Hospital, The Midwifery Hospital, and Jorvi Hospital are special outpatient clinics for pregnant women with substance misuse problems. The pregnant women with identified substance misuse were followed up at the HAL clinics in multidisciplinary service settings every 2–4 weeks and intensified support and easy access to addiction treatment and psychiatric care were offered. Information on the exposed offspring mother's substances used and the type of substances used (i.e. alcohol, cannabis, amphetamine, heroin, buprenorphine, other drugs) were collected by self-reported information and voluntary urine toxicology screening at each visit at the HAL clinic and documented in the hospital medical records. Information on exposure to tobacco smoking during pregnancy was obtained from the Medical Birth Register.

In 1992–2001, 524 pregnant women with identified substance misuse were followed-up at the HAL clinics and gave birth to 640 offspring (i.e. exposed cohort). During 1992–2001 the total number of live-born children in the catchment area was 172 600, and the exposed cohort represented 0.4% of the total population (Sarkola, Kahila, Gissler, & Halmesmäki, 2007). Two exposed offspring could not be linked later due to an incorrect maternal identification number.

A matched unexposed cohort was obtained from the Medical Birth Register. Three non-misuse mother-offspring pairs were obtained for each misuse mother-offspring pair. The unexposed group consisted of offspring (n = 1914) born in 1992–2001 to women (n = 1792) with no registered evidence of alcohol or other substance use one year prior or at the time of delivery. Mother-offspring pairs were matched for five maternal characteristics including maternal age, parity, number of fetuses, a month of birth, and delivery hospital of the index offspring.

Register data were collected identically for exposed and unexposed matched mother-offspring pairs. Information was obtained from Medical Birth Register, Digital and Population Data Services Agency, Hospital Discharge Register (until 1993) or the Care Register for Health Care (since 1994), National Child Welfare Register, Register of Congenital Malformations, Register on Social Assistance, and Criminal Records. Data linkages were done by using the personal identification number assigned to each Finnish citizen at birth or migration. Data collection and anonymization of the data were done by the register keepers. A detailed description of the data collection has been published by Koponen et al., (2020).

The follow-up of the study extends from birth until the end of 2016 or death. The results of the follow-up from birth until the end of 2007 (median 9 years, range 6–15 years) have been published by Sarkola et al. (2007; 2011; 2012) and Kahila, Gissler, Sarkola, Autti-Rämö, and Halmesmäki (2010).

The present study focuses on secondary education, with a focus on offspring aged 18–23 years (i.e. individuals born 1992–1997) in 2015 (i.e. the year from which the latest information of the education is available). Individuals who died before the age of 18 (5 of the exposed, 8 of the unexposed) and individuals who had ever received a diagnosis for intellectual disability (International Classification of Diseases ICD-9 code 317–319, ICD-10 code F70–F79; 5 of the exposed, 6 of the unexposed) were excluded from the analyses. The sample of the present study then includes 283 exposed and 820 unexposed offspring with similar premises to complete secondary education and represents 45.9% of the total study population.

Permission to use the data has been obtained from all authorities maintaining the registers. The Finnish Institute for Health and Welfare performed all the register linkages as the statistical authority and pseudonymized the data. Study subjects were not contacted. The study has been approved by the local ethical committee of The Hospital District of Helsinki and Uusimaa.

2.2. Measures

2.2.1. Outcome

2.2.1.1. Completed secondary education. The Finnish educational system consists of a comprehensive nine-year education period commonly starting during the year of turning seven years old. The non-mandatory secondary education is a post-comprehensive education, and the most common options are general upper secondary school and vocational education. The 2–4 year general upper secondary education leads to matriculation examination and qualifies for further higher education. The 3-years vocational education is more practice-oriented education and provides general eligibility for further higher education as well.

The annually collected information on secondary education was obtained from the Education Register maintained by Statistics Finland. The information included data on completion of secondary education (no, yes) and the level of completed education (i.e. vocational education, general upper secondary school, and bachelor's degree from University or University of Applied Sciences). These data were available from 2010 until the end of 2015, and the highest completed secondary education level for each offspring was used in the analyses.

2.2.2. Covariates

2.2.2.1. Offspring's demographic variables. Data on sex were obtained from the Medical Birth Register (female, male), mortality data were obtained from the Cause of Death Register, and information on the offspring's mother language (Finnish, Swedish, other) were obtained from the Digital and Population Data Services Agency.

2.2.2.2. Offspring's health status at birth. Birth weight (<2500 g, ≥2500 g), gestational age (<37 weeks, ≥ 37 weeks), Apgar score at 1 min (0–6 points, 7–10 points), and exposure to smoking during pregnancy (no, yes) was obtained from the Medical Birth Register. Data on diagnosis within the Fetal Alcohol Spectrum Disorders (FASD) continuum (no, yes) were obtained from the Register of Congenital Malformations and from the Hospital Discharge Register or the Care Register for Health Care including both inpatient and outpatient hospital visits (ICD-9 code 760.71, ICD-10 code Q86.0). Information on diagnosed Neonatal Abstinence Syndrome (NAS) (no, yes) was obtained from the Medical Birth Register, Hospital Discharge Register or the Care Register for Health Care including both inpatient and outpatient hospital care (ICD-9 code 779.5, ICD-10 code P96.1), and from the hospital chart of HAL clinics.

2.2.2.3. Out-of-home care. Taking a child into care (OHC hereafter) is considered an urgent municipal child protective service in the setting of 1) child's biological home environment or child's own behaviour seriously threatens a child's development or health, and 2) non-residential services are considered inadequate. OHC can be voluntary or involuntary (Ministry of Social Affairs and Health, 2013). Data on OHC between 1992 and 2016 were obtained from the Child Welfare Register. This included the OHC episode (no, yes), age at first OHC episode, cumulative length of OHC episodes, and the number of separate OHC episodes.

2.2.2.4. Offspring's mental and/or behavioural disorders. Data on the offspring's mental and/or behavioural disorders were received from Hospital Discharge Register or the Care Register for Health Care. A study variable of offspring's primary diagnosis for mental and/or behavioural disorders from inpatient or outpatient hospital care during 1992–2016 was created. This included the following ICD codes: ICD-9 (1992–1995) codes 290–319 (317–319 excluded), and ICD-10 (1996–2016) codes F00-F99 (F17, F70–F79 excluded). Mental and/or behavioural disorders were categorized into four subgroups: no psychiatric (F10–F60 and/or the corresponding ICD-9 codes) or neuropsychological disorders (F80–F99 and/or the corresponding ICD-9 codes), psychiatric disorders only (F10–F60 and/or the corresponding ICD-9 codes), neuropsychological disorders only (F80–F99 and/or the corresponding ICD-9 codes), and dual psychiatric and neuropsychological disorder (both F10–F60 and F80–F99 and/or the corresponding ICD-9 codes).

2.2.2.5. Maternal characteristics. Mother's age at offspring's birth (<25 years, ≥25 years) was obtained from the Medical Birth Register. Information on mother's socioeconomic status (low status indicated by manual workers/students/pensioners/others, high status indicated by lower-/upper-level employees/self-employed) was based on maternal occupation during pregnancy, and marital status (married, unmarried) at the time of offspring's birth was obtained from the Medical Birth Register.

2.2.2.6. Offspring's childhood adversities. A variable of childhood adversities was computed by including five indicators that describe adverse maternal characteristics that can negatively impact on parenting and caregiving during childhood and thus be associated with inferior educational outcomes (Berg et al., 2016; Erola et al., 2016; Sirin, 2016). These five indicators have occurred before the birth of the offspring or when the offspring has been less than 18 years old; death of a mother, maternal mental and/or behavioural disorder, maternal substance misuse, maternal recipiency of long-term social assistance, and maternal criminality.

Mortality data (no, yes) were obtained from the Cause of Death Register. Mental and/or behavioural disorder (no, yes) was defined as at least one primary diagnoses from inpatient or outpatient hospital care for ICD-9 codes (1987–1995) 290 and 293–319 (303–305 excluded), and ICD-10 codes (1996–2016) F00-F09 and F20-F99 and data were obtained from Hospital Discharge Register or the Care Register for Health Care. Substance misuse (no, yes) was defined as at least one primary diagnosis from inpatient or outpatient hospital care for alcohol and/or drug-related misuse using the following diagnostic codes: ICD-9 codes (1987–1995): 291–292, 303–305, 3570, 4255, 5353, 5710, 5711–5713, 6483, 6555, 9650, and 9696–9697 and ICD-10 codes (1996–2016) E24.4, F10-F16, F18-F19, G31.2, G40.5, G40.51, G40.52, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, K86.08, O35.4-O35.5, P04.4, R78.0-R78.5, T40, T43.6, T50.2-T50.3, T51, Z71.4, Z72.1–Z72.2. Information on substance misuse was obtained from Hospital Discharge Register or Care Register for Health Care. Data on the maternal criminality (i.e. sentenced to unconditional or conditional imprisonment) (no, yes) between 1985 and 2018 was obtained from Criminal Records.

Social assistance information was obtained from the Register of Social Assistance. Social assistance is defined as the last-resort of financial assistance for individuals and families, and it is intended to be a short-term source of financial aid. Individuals and families living or residing in Finland can apply for social assistance if their necessary expenses are not covered by income and assets. Short-term social assistance was defined as received social assistance at least once 1–9 months during a one year period. Long-term social assistance was defined as received social assistance at least once 10–12 months during a one year period. The information on the use of social assistance covered the years of 2002–2016.

As childhood adversities occur in clusters (e.g. Björkenstam et al., 2015; Björkenstam, Vinnerljung, & Hjern, 2017), we analyzed the cumulative exposure of adversities in four groups including the presence of 0, 1, 2, or 3–5 adverse maternal characteristics (cumulative childhood adversity score hereafter).

2.3. Statistical analyses

Chi-squared (χ^2) test was used to compare the categorical variables, whereas The Mann-Whitney *U* test was used to compare nonparametric continuous variables between unexposed and exposed, as appropriate. Univariate logistic regression analyses were used to explore associations between completed secondary education and each covariate separately for exposed and unexposed.

Table 1
Descriptive statistics and comparison of the exposed and unexposed cohorts [a].

	Exposed (n = 283)	Unexposed (n = 820)	p-value
Follow-up time (until the end of 2015) (median, IQR)	20.2 (18.8–22.2)	20.1 (18.8–22.1)	0.769
Offspring's demographic variables, n (%)			
Sex			0.626
Male	144 (50.9)	431 (52.6)	
Female	139 (49.1)	389 (47.4)	
Language			<0.001
Finnish	273 (96.5)	705 (86.0)	
Swedish	8 (2.8)	55 (6.7)	
Other	2 (0.7)	60 (7.3)	
Offspring's health status			
Birth weight			<0.001
<2500 g	42 (14.8)	55 (6.7)	
≥2500 g	241 (85.2)	765 (93.9)	
Gestational age			0.705
<37 weeks	29 (10.3)	91 (11.1)	
≥37 weeks	253 (89.7)	729 (88.9)	
Missing	1 (0.4)	0 (0.0)	
Apgar score at 1 min			0.296
0-6	11 (3.9)	22 (2.7)	
7-10	270 (96.1)	798 (97.3)	
Exposure to smoking during pregnancy	224 (79.2)	163 (19.9)	<0.001
Fetal Alcohol Spectrum Disorder	31 (11.0)	0 (0.0)	<0.001
Neonatal Abstinence Syndrome	14 (4.9)	0 (0.0)	<0.001
Out-of-home care			
At least one OHC episode	181 (64.0)	51 (6.2)	<0.001
Age at the first OHC episode in years (median, IQR)	3.0 (1.0–7.0)	12.0 (7.0–14.0)	<0.001
The cumulative lifetime duration of OHC episodes in years (median, IQR)	10.8 (2.7–16.1)	1.9 (0.3–5.0)	<0.001
Number of separate OHC episodes (median, IQR)	3.0 (3.0–2.0)	2.0 (1.0–2.0)	<0.001
Offspring's mental and/or behavioral disorders			
Categorized mental and/or behavioral disorders			<0.001
No psychiatric or neuropsychological disorders	118 (41.7)	589 (71.8)	
Psychiatric disorders	54 (19.1)	87 (10.6)	
Neuropsychological disorders	57 (20.1)	80 (9.8)	
Dual psychiatric and neuropsychological disorder	54 (19.1)	64 (7.8)	
Maternal characteristics at offspring's birth, n (%)			
Age			0.745
<25 years	100 (35.3)	281 (34.3)	
≥25 years	183 (64.7)	539 (65.7)	
Marital status			<0.001
Unmarried	217 (76.7)	288 (35.1)	
Married	66 (23.3)	532 (64.9)	
Socioeconomic status			<0.001
Low	173 (66.0)	320 (40.0)	
High	89 (34.0)	481 (60.0)	
Adverse maternal characteristics			
Death	32 (11.3)	5 (0.6)	<0.001
Mental and/or behavioural disorders	122 (43.1)	127 (15.5)	<0.001
Substance misuse	144 (50.9)	25 (3.0)	<0.001
Social assistance			<0.001
No social assistance	34 (12.0)	596 (72.7)	
Short-term social assistance	54 (19.1)	126 (15.4)	
Long-term social assistance	195 (68.9)	98 (12.0)	
Criminal record	29 (10.2)	2 (0.2)	<0.001
Cumulative childhood adversity score			<0.001
0	38 (13.4)	627 (76.5)	
1	82 (20.9)	144 (17.6)	
2	70 (24.7)	34 (4.1)	
3-5	23 (8.1)	15 (1.8)	

[a] Comparison of categorical variables between exposed and unexposed cohorts based on χ^2 test, comparison of continuous variables based on Mann-Whitney *U* test, Abbreviation: IQR, interquartile range, Cumulative childhood adversity score includes maternal death, maternal mental and/or behavioural disorder, maternal substance misuse, maternal recipiency of long-term social assistance, maternal criminality.

Spearman correlations were used to explore correlations between the study variables and measure potential multicollinearity (not reported). Due to moderate correlations between the adverse maternal characteristics and the prenatal substance exposure status, a sum variable of the adverse maternal characteristics (i.e. childhood adversity score) was used in the multivariate models to reduce the problems of multicollinearity. Six multivariate logistic regression models were constructed to study associations between completed secondary education and different covariates. The selection of covariates was based on previous research (e.g. Behnke et al. 2013; Berg et al., 2016; Brännlund, Strandh, & Nilsson, 2017; Erola et al., 2016; Kääriälä et al., 2018; Sirin, 2016), data availability, and the statistically significant results from the univariate analyses ($p < 0.05$). The first model evaluated the crude differences in completed secondary education between exposed and unexposed. The second model investigated the differences after adjusting for sex and exposure to smoking during pregnancy. In models 3 and 4, additional adjustments were made for maternal characteristics including socioeconomic status and the cumulative childhood adversity score. Adjustments were made for OHC in model 5 and offspring's mental and/or behavioural disorders in model 6. Odds ratios (OR), and adjusted odds ratios (AOR) with 95% confidence intervals (CI) are reported. The statistically significant level was set to p-value < 0.05. IBM SPSS Statistics version 25 was used in the analyses.

3. Results

Table 1 describes the characteristics of the study population and differences between the exposed and unexposed cohorts. In the sample of 283 exposed and 820 unexposed offspring, 50.9% of the exposed and 52.6% of the unexposed were males. The median follow-up from birth was 20.2 years for exposed and 20.1 years for unexposed. Of the exposed, 14.8% were categorized as having birth weight less than 2500 g compared to 6.7% of the unexposed. There were no differences in gestational age, and Apgar score at 1 min between exposed and unexposed.

The exposed cohort is a heterogeneous group of exposure to alcohol and multiple substances. Nearly four out of five (79.2%) of the exposed were exposed to maternal smoking during pregnancy compared with less than one in five (19.9%) among unexposed. Only a minority (11.0%) of the exposed had a registered diagnosis within the Fetal Alcohol Spectrum Disorder continuum, and 4.9% were diagnosed with Neonatal Abstinence Syndrome during the neonatal period (Table 1).

A majority of the exposed (64.0%) had a history of at least one OHC episode prior to 18 years of age compared with 6.2% among unexposed. The exposed were of younger age at first OHC episode, the number of separate OHC episodes was higher, and the cumulative lifetime duration of OHC was longer compared with unexposed. Differences were also observed between the exposed and unexposed in the domains of mental and/or behavioural disorders including psychiatric disorders, neuropsychological disorders, and dual psychiatric and neuropsychological disorder, which were more common among exposed compared with unexposed offspring (Table 1).

Regarding the maternal characteristics, being unmarried (76.7% vs. 35.1%, respectively) and from the lower socioeconomic status group (66.0% vs. 40.0%, respectively) were more common among the exposed compared with the unexposed. Regarding offspring childhood adversities, maternal mental and/or behavioural disorders, substance misuse, recipiency of long-term social assistance, and

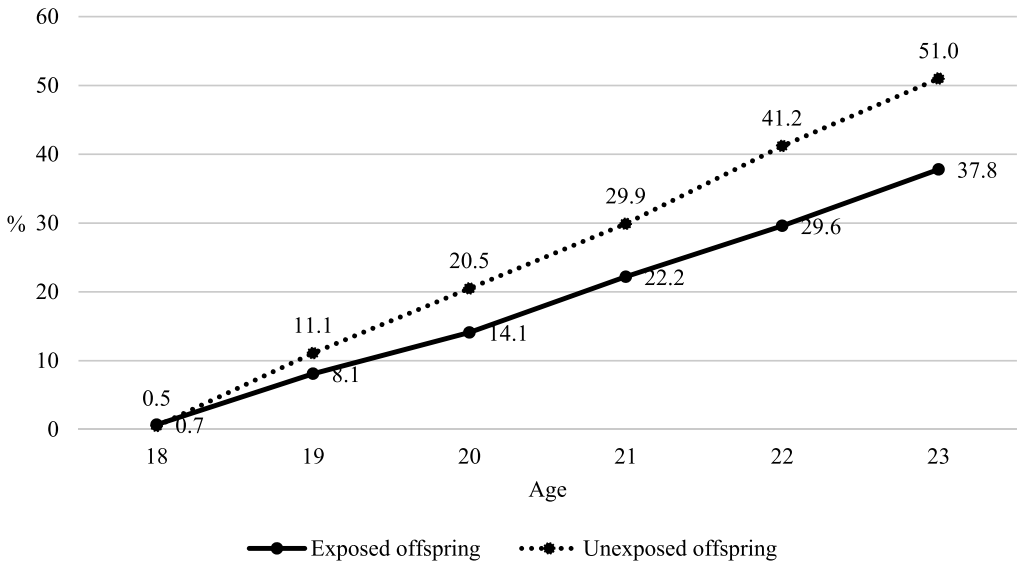

Fig. 1. Cumulative proportions of exposed and unexposed offspring with completed secondary education at the age of 18–23 years.

criminality were all more common among the exposed compared with unexposed. In the cumulative offspring's childhood adversity score, the difference between the exposed and unexposed scored increased with an increasing cumulative amount of adverse maternal characteristics (Table 1).

Fewer exposed had completed secondary education compared with the unexposed offspring and the difference in the cumulative proportions of exposed and unexposed offspring with completed secondary education increased linearly with age as presented in Fig. 1. Differences in the level of completed secondary education were also observed with exposed showing a higher level of completed vocational education and a lower level of completed general upper secondary school compared with unexposed (Table 2). Among the 31 exposed offspring with a diagnosis within the FASD continuum, 16 had completed secondary education, 13 of them had completed vocational education and 3 had completed general upper secondary school.

OHC was related to less often completed secondary education and with the level of completed secondary education among unexposed but not among exposed (Table 3a). Offspring's mental and/or behavioural disorders were negatively related both with secondary education completion and level of completed secondary education among both the exposed and unexposed (Table 3b).

The univariate logistic regression analyses were performed for the exposed and unexposed offspring separately to explore associations between completed secondary education and different offspring and maternal covariates. For exposed offspring, of the offspring's mental and/or behavioural disorders, neuropsychological disorders (OR 0.25, 95% CI 0.12–0.52) and dual psychiatric and neuropsychological disorder (OR 0.36, 95% CI 0.18–0.74) reduced the likelihood of completing secondary education. None of the other covariates showed statistically significant associations with secondary education completion (Table 4).

For unexposed, the offspring-related covariates that reduced the likelihood of completing secondary education were exposure to smoking during pregnancy (OR 0.69, 95% CI 0.49–0.97), at least one OHC episode (OR 0.34, 95% CI 0.18–0.64), and the different domains of mental and/or behavioural disorders including psychiatric disorders (OR 0.54, 95% CI 0.34–0.85), neuropsychological disorders (OR 0.51, 95% CI 0.32–0.82) and dual psychiatric and neuropsychological disorder (OR 0.25, 95% CI 0.14–0.46). Of the maternal factors, a mother being <25 years old (OR 0.73, 95% CI 0.55–0.98), having low socioeconomic status (OR 0.65, 95% CI 0.49–0.87) and being a recipient of long-term social assistance (OR 0.47, 95% CI 0.30–0.73) all reduced the likelihood of secondary education completion. None of the other covariates showed statistically significant associations with secondary education completion (Table 4).

Six multivariate models were constructed to study associations between secondary education completion and different covariates (Table 5). The selection of variables for the multivariate models was based on the statistically significant results from the univariate analyses or prior knowledge of the factors associated with educational outcomes. Maternal age at offspring's birth was not included in the multivariate analyses as it was one of the matching criteria.

The crude OR from model 1 showed that the exposed were less likely to have completed secondary education compared with unexposed offspring (OR 0.59, 95% CI 0.44–0.77). The difference in the completion of secondary education between the exposed and

Table 2
Comparison of completed secondary education and the level of completed secondary education among exposed and unexposed offspring [a].

	Exposed (n = 283)	Unexposed (n = 820)	p-value
Secondary education, n (%)			<0.001
No completed secondary education	176 (62.2)	402 (49.0)	
Completed secondary education	107 (37.8)	418 (51.0)	
Level of completed secondary education, n (%)			<0.001
Vocational education	76 (26.9)	184 (22.4)	
General upper secondary school	30 (10.6)	225 (27.4)	
Bachelor's degree	1 (0.4)	9 (1.1)	

[a] Comparison between exposed and unexposed cohorts based on χ^2 test.

Table 3a
Comparison of completed secondary education and the level of completed secondary education by out-of-home care (OHC) for exposed and unexposed separately [1].

	Exposed			Unexposed		
	No OHC episodes (n = 102)	At least one OHC episode (n = 181)	p-value	No OHC episodes (n = 769)	At least one OHC episode (n = 51)	p-value
Secondary education, n (%)			0.912			0.001
No completed secondary education	63 (61.8)	113 (62.4)		365 (47.5)	37 (72.5)	
Completed secondary education	39 (38.2)	68 (37.6)		404 (52.5)	14 (27.5)	
Level of completed secondary education, n (%)			0.898			0.002
Vocational education	28 (18.8)	48 (26.5)		174 (15.2)	10 (11.2)	
General upper secondary school	11 (7.4)	19 (10.5)		221 (19.2)	4 (4.5)	
Bachelor's degree	0 (0.0)	1 (0.6)		9 (0.8)	0 (0.0)	

[1] Group comparison based on χ^2 test.

Table 3b
Comparison of completed secondary education and the level of completed secondary education by offspring's mental and/or behavioural disorders for exposed and unexposed separately [1].

	Exposed				
	No psychiatric or neuropsychological disorders (n = 118)	Psychiatric disorders (n = 54)	Neuropsychological disorders (n = 57)	Dual psychiatric and neuropsychological disorder (n = 54)	p-value
Secondary education, n (%)					<0.001
No completed secondary education	60 (50.8)	30 (55.6)	46 (80.7)	40 (74.1)	
Completed secondary education	58 (49.2)	24 (44.4)	11 (19.3)	14 (25.9)	
Level of completed secondary education, n (%)					0.003
Vocational education	40 (33.9)	15 (27.8)	9 (15.8)	12 (22.2)	
General upper secondary school	18 (15.3)	8 (14.8)	2 (3.5)	2 (3.7)	
Bachelor's degree	0 (0.0)	1 (1.9)	0 (0.0)	0 (0.0)	
	Unexposed				
	No psychiatric or neuropsychological disorders (n = 589)	Psychiatric disorders (n = 87)	Neuropsychological disorders (n = 80)	Dual psychiatric and neuropsychological disorder (n = 64)	p-value
Secondary education, n (%)					<0.001
No completed secondary education	255 (43.3)	51 (58.6)	48 (60.0)	48 (75.0)	
Completed secondary education	334 (56.7)	36 (41.4)	32 (40.0)	16 (25.0)	
Level of completed secondary education, n (%)					<0.001
Vocational education	137 (23.3)	16 (18.4)	20 (25.0)	11 (17.2)	
General upper secondary school	190 (32.3)	19 (21.8)	11 (13.8)	5 (7.8)	
Bachelor's degree	7 (1.2)	1 (1.1)	1 (1.3)	0 (0.0)	

[1] Group comparison based on χ^2 test.

unexposed remained after adjusting for sex and exposure to smoking during pregnancy in model 2 (AOR 0.70, 95% CI 0.51–0.97). In model 3, differences between the exposed and unexposed were not statistically significant after the effect of maternal socioeconomic status was added to the model. Further adjustments for the cumulative childhood adversity score in model 4 and at least one OHC episode in model 5 did not make any change. In the final model, the offspring's mental and/or behavioural disorders were added to the model. Statistically significant differences in the completed secondary education between the exposed and unexposed were not observed. The results indicated that of the offspring's mental and/or behavioral disorders, psychiatric disorders (AOR 0.65, 95% CI 0.45–0.96), neuropsychological disorders (AOR 0.35, 95% CI 0.23–0.54) and dual psychiatric and neuropsychological disorder (AOR 0.29, 95% CI 0.18–0.48) showed an independent negative effect on the secondary education completion compared with offspring without mental and/or behavioural disorders.

4. Discussion

In this register-based matched cohort study, we investigated the prevalence of completed secondary education among offspring with a history of prenatal exposure to substances (i.e. alcohol and/or drugs), and whether childhood adversities, OHC and offspring's mental and/or behavioural disorders were associated with secondary education completion in comparison to matched unexposed offspring aged 18-23 years. From the analyses, we excluded offspring with intellectual disabilities, and therefore, the exposed and unexposed cohorts included offspring with similar premises to complete secondary education.

The study shows a time lag in education completion and lower educational attainment overall among offspring with prenatal substance exposure compared with unexposed. This difference was diminished when adjusting for potential confounders, and in the final analyses, the different domains of offspring's mental and/or behavioural disorders appeared as the only independent variable associated with secondary education completion. Thus, the results indicate that offspring's mental and/or behavioural disorders importantly postpone secondary education completion among both exposed and unexposed, and prenatal substance exposure is not independently related with this.

The findings are in agreement with earlier studies indicating that individuals who completely or partly meet Fetal Alcohol Syndrome (FAS) criteria are less likely to complete secondary education (Freunscht & Feldmann, 2011; Rangmar et al., 2015; Spohr et al.,

Table 4
Odds ratios (OR) for completed secondary education in relation to covariates for exposed and unexposed offspring separately.

	Exposed (n = 283)		Unexposed (n = 820)	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Offspring's demographic variables				
Sex				
Male (ref)	1		1	
Female	1.48 (0.91–2.39)	0.115	0.98 (0.74–1.28)	0.856
Offspring's health status				
Birth weight				
<2500 g (ref)	1		1	
≥2500 g	1.11 (0.56–2.20)	0.762	1.00 (0.58–1.73)	0.992
Exposure to smoking during pregnancy				
No (ref)	1		1	
Yes	0.86 (0.48–1.54)	0.610	0.69 (0.49–0.97)	0.035
Out-of-home care				
At least one OHC episode				
No (ref)	1		1	
Yes	0.97 (0.59–1.60)	0.912	0.34 (0.18–0.64)	0.001
Offspring's mental and/or behavioural disorders				
Categorized mental and/or behavioural disorders				
No psychiatric or neuropsychological disorders (ref)	1		1	
Psychiatric disorders	0.83 (0.43–1.58)	0.566	0.54 (0.34–0.85)	0.008
Neuropsychological disorders	0.25 (0.12–0.52)	<0.001	0.51 (0.32–0.82)	0.005
Dual psychiatric and neuropsychological disorder	0.36 (0.18–0.74)	0.005	0.25 (0.14–0.46)	<0.001
Maternal characteristics at offspring's birth				
Age				
≥25 years (ref)	1		1	
<25 years	0.73 (0.44–1.21)	0.218	0.73 (0.55–0.98)	0.036
Marital status				
Married (ref)	1		1	
Unmarried	0.61 (0.35–1.06)	0.081	0.85 (0.64–1.13)	0.253
Socioeconomic status				
High (ref)	1		1	
Low	1.51 (0.88–2.58)	0.132	0.65 (0.49–0.87)	0.003
Adverse maternal characteristics				
Death				
No (ref)	1		1	
Yes	2.03 (0.97–4.25)	0.061	0.64 (0.11–3.85)	0.625
Mental and/or behavioural disorders				
No (ref)	1		1	
Yes	0.99 (0.61–1.61)	0.975	0.81 (0.55–1.18)	0.268
Substance misuse				
No (ref)	1		1	
Yes	0.97 (0.60–1.57)	0.913	0.75 (0.34–1.67)	0.480
Social assistance				
No social assistance (ref)	1		1	
Short-term social assistance	0.90 (0.38–2.13)	0.810	0.74 (0.50–1.09)	0.124
Long-term social assistance	0.59 (0.28–1.23)	0.158	0.47 (0.30–0.73)	0.001
Criminality				
No (ref)	1		1	
Yes	0.40 (0.16–1.01)	0.051	NA	NA
Cumulative childhood adversity score				
0 (ref)	1		1	
1	0.79 (0.36–1.74)	0.563	0.74 (0.52–1.07)	0.107
2	0.92 (0.41–2.04)	0.832	0.54 (0.27–1.10)	0.092
3-5	0.76 (0.35–1.64)	0.478	0.44 (0.15–1.30)	0.137

2007). A major strength of our study in comparison to previous studies is that we were able to adjust for several known confounders associated with inferior educational outcomes including exposure to smoking during pregnancy, childhood adversities, OHC, and the different domains of offspring's mental and/or behavioural disorders. Thus, we were able to show that the association between prenatal substance exposure and secondary education completion was largely related to other maternal substance misuse and offspring-related factors. This stresses the importance of childhood adversities and offspring mental and/or behavioural disorders influencing the time lag in offspring secondary education completion as also indicated by others (e.g. Carta et al., 2001).

Previous research has shown a negative association between childhood caregiving adversities, OHC and offspring's educational outcomes (Berg, Bäck, Vinnerljung, & Hjern, 2016; Erola, Jalonen, & Lehti, 2016; Kääriälä, Berlin, Lausten, Hiilamo, & Ristikari, 2018). In the present study, OHC reduced secondary education completion among unexposed in the univariate analyses. However, either OHC or childhood caregiving adversities were not significantly associated with secondary education completion in multivariate models. OHC provided early and long-term could be protective factor for exposed offspring as their childhood environment is often

Table 5
Odds ratios (OR) and adjusted odds ratios (AOR) of completing secondary education in six multivariate logistic regression models.

	Crude model	Model 2	Model 3	Model 4	Model 5	Model 6
	OR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)	AOR (95% CI)
Prenatal substance exposure						
Unexposed (ref)	1	1	1	1	1	1
Exposed	0.59 (0.44–0.77)***	0.70 (0.51–0.97)*	0.72 (0.51–1.02)	0.85 (0.57–1.27)	0.91 (0.60–1.38)	0.93 (0.61–1.43)
Offspring's sex						
Male (ref)		1	1	1	1	1
Female		1.07 (0.85–1.36)	1.05 (0.82–1.34)	1.05 (0.82–1.34)	1.05 (0.82–1.34)	0.95 (0.74–1.23)
Exposure to smoking during pregnancy						
No (ref)		1	1	1	1	1
Yes		0.73 (0.54–0.98)*	0.79 (0.59–1.08)	0.83 (0.611.13)	0.84 (0.62–1.15)	0.80 (0.58–1.11)
Maternal socioeconomic status						
High (ref)			1	1	1	1
Low			0.80 (0.62–1.03)	0.83- 0.64–1.07)	0.83 (0.64–1.07)	0.83 (0.64–1.08)
Cumulative childhood adversity score						
0 (ref)				1	1	1
1				0.80 (0.57–1.12)	0.83 (0.59–1.16)	0.94 (0.66–1.33)
2				0.73 (0.44–1.19)	0.81 (0.48–1.38)	0.92 (0.53–1.59)
3-5				0.70 (0.41–1.19)	0.79 (0.45–1.40)	0.79 (0.44– 1.41)
At least one OHC episode						
No (ref)					1	1
Yes					0.78 (0.51–1.20)	1.17 (0.73–1.86)
Offspring's mental and/or behavioural disorders						
No psychiatric or neuropsychological disorders						1
Psychiatric disorders						0.65 (0.45–0.96)*
Neuropsychological disorders						0.35 (0.23–0.54)***
Dual psychiatric and neuropsychological disorder						0.29 (0.18–0.48)***

Significance indicated at *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

challenged by caregiving adversities as also shown previously (e.g. Streissguth et al., 2004). Among unexposed, older age at the first OHC episode and shorter OHC lifetime duration could potentially be explained by child's behavioural problems that per se may be associated with inferior educational outcomes (e.g. Vinnerljung, & Sallnäs, 2008). However, strong conclusions should be avoided due to the lack of data on specific OHC indications and limited study power in subgroup analyses.

In the present study, the different domains of offspring's mental and/or behavioural disorders were more common among the exposed offspring compared with the unexposed. The common mental and/or behavioural disorders, deficits in neuropsychological functioning, in particular, and the association between prenatal substance exposure have been previously reported (Irner, 2012; Koponen et al., 2020 Sandtorv, Hysing, Rognlid, Nilsen, & Elgen, 2017). The negative association between offspring's mental and/or behavioural disorders and secondary education completion among both exposed and unexposed are supported by previous research indicating that mental and/or behavioural disorders can impair educational performance and be associated with inferior educational outcomes, due to difficulties with behaviour, self-regulation, concentration, attention, and executive functioning and cognitive abilities (Brännlund et al., 2017; Howell et al., 2006; Jangmo et al., 2019; Polderman, Boomsma, Bartels, Verhulst, & Huizink, 2010). We have recently shown that childhood adversities and low birth weight are linked with offspring's mental and/or behavioural disorders (Koponen et al., 2020) similar to other studies (Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, & Oosteriaan, 2009; Björkenstam et al., 2017; Kambeitz, Klug, Greenmyer, Popova, & Burd, 2019). The results of the present study and prior research suggest then that the time lag in completed secondary education may not be a direct cause of prenatal substance exposure but rather reflect the impact of evolving offspring's mental and/or behavioural disorders influenced by adverse experiences during childhood.

Secondary education is important during the transition to adulthood. Low educational attainment can impact several life domains and increase the risk of further social problems, as well as limit occupational opportunities long-term (McMahon & Oketch, 2013; Sipilä et al., 2011). Significant disabilities and limitations in adolescent skills and abilities may challenge the increased demands of independent decision making and responsibility encountered during the transition to adulthood. Consequently, developmental deficits may together with low educational attainment comprise independent living and future employment in adulthood (Moore & Riley, 2015; Spohr & Steinhausen, 2008; Streissguth, 1996). Therefore, substance use identification and counselling during gestation,

offspring development and health follow-up, sufficient social support and addressing special needs in school and education seem important for educational attainment optimization.

4.1. Strengths and limitations

Previous research in the field has been criticized for moderate sample size, lack of a control group and variables reflecting postnatal caregiving environment and potential childhood adversities. This study was able to avoid these weaknesses by including a matched unexposed comparison group and accounting for potential confounders (e.g. OHC, offspring's mental and/or behavioural disorders, childhood adversities) known to influence educational outcomes. In addition, our prospective hospital medical record and comprehensive mandatory national register-based study design provided us with the opportunity to avoid data collection inaccuracies related to retrospective self-reported information, low response rates, or recall bias (e.g. under-reporting of adverse events), and problems related to loss to follow-up of study subjects. However, register data only reflects health care utilization, not health care needs, and therefore we may have missed information on less severe health issues not requiring hospital care. Good quality of Finnish register data has, nevertheless, been ascertained previously (Aro, Koskinen, & Keskimäki, 1990; Gissler & Haukka, 2004).

We also lack detailed information on the type, timing and amount of maternal substance use during pregnancy precluding substance-specific analyses. In addition, the study does not include offspring paternal information. We also lack direct information on childhood adversities related to abuse and neglect, domestic violence, peer and school-related adverse events, and child-caregiving interactions. However, OHC as a child welfare intervention generally indicates substantial and significant documentation of child maltreatment, neglect, and/or severe problems in the caregiving environment or in a child's behaviour. Lastly, as this is an observational study, causal links with completed secondary education are challenging to prove.

5. Conclusion

In conclusion, the results indicate that offspring exposed to substances during pregnancy and with a normal cognitive level have less often completed secondary education. Furthermore, childhood adversities, out-of-home care, and mental and/or behavioural disorders are more common among exposed offspring compared with unexposed. The results suggest that the time lag in completed secondary education may not be a direct cause of prenatal substance exposure but rather reflect the impact of evolving offspring's mental and/or behavioural disorders influenced by adverse experiences during childhood. A lower final educational attainment level may predispose these offspring to other challenges later in adulthood, and therefore, identification of individuals at risk and early support is important for educational attainment optimization.

Role of funding source

This work was supported by Samfundet Folkhälsan i svenska Finland, Finland; Juho Vainio Foundation, Finland; Signe and Ane Gyllenberg Foundation, Finland; Medicinska Understödsföreningen Liv och Hälsa, Finland, and the Finnish Foundation for Alcohol Studies, Finland. The funding sources had no involvement in the study.

Declaration of competing interest

No conflicts of interest to declare.

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PUBLICATION II

Financial difficulties among youth prenatally exposed to substances: a longitudinal register-based cohort study

Nissinen, N.M., Rangmar, J., Autti-Rämö, I., Gissler, M., Kahila, H., Raitasalo, K. & Sarkola, T.

Drugs: Education, Prevention and Policy (2023)
DOI: 10.1080/09687637.2023.2176285

DRUGS: EDUCATION, PREVENTION AND POLICY
https://doi.org/10.1080/09687637.2023.2176285

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Financial difficulties among youth prenatally exposed to substances: a longitudinal register-based cohort study

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ABSTRACT

Aim: The receipt of long-term financial social assistance (FSA) as an indicator of financial difficulties among Finnish youth with prenatal substance exposure (PSE) was investigated in comparison with unexposed youth.

Methods: Data from national health and social welfare registers were collected for 18–24-year-old exposed ($n = 355$) and unexposed ($n = 1011$) youth. The influence of youth and maternal characteristics and out-of-home care (OHC) on the association between PSE and youth's long-term FSA receipt was studied by generalized linear models and mediation analyses.

Results: Exposed youth had an increased likelihood of long-term FSA receipt (OR 4.89, 95% CI 3.76, 6.37) but the difference with unexposed was attenuated following adjustments for youth and maternal characteristics and OHC (AOR 1.33, 95% CI 0.89, 1.98). Maternal long-term FSA receipt (0.48, 95% CI 0.35, 0.64) and OHC (0.63, 95% CI 0.47, 0.83) mediated a large proportion of the association between PSE and youth's long-term FSA receipt. Youth's mental or behavioral disorders partly mediated the association (0.21, 95% CI 0.14, 0.30), but the mediating effect of lack of secondary education was minor (0.03, 95% CI 0.01, 0.07).

Conclusion: Receipt of long-term FSA among youth with PSE likely reflects maternal substance abuse linked with maternal financial situation and care instability in childhood.

ARTICLE HISTORY
Received 16 June 2022
Revised 24 January 2023
Accepted 26 January 2023

KEYWORDS
Youth; prenatal substance exposure; financial social assistance; childhood adversities; out-of-home care

1. Introduction

Transition to adulthood is a critical period of life characterized by several significant parallel developmental phases and life-course events. These include the psychological transition from parental care and social safety nets, to increased demands on adult role taking including financial independence (Arnett, 2000; Scales et al., 2016).

During transition phases, temporary financial difficulties can be common among youth (Ilmakunnas & Moisio, 2019). In Finland, one important indicator of financial difficulties is the receipt of financial social assistance (FSA) (Haula & Vaalavuo, 2021; Ristikari et al., 2018). FSA is a means-tested (i.e. only accessible to individuals with insufficient income or resources) last-resort financial benefit for individuals and families living or residing in Finland whose income and assets do not cover the necessary expenses. FSA is intended to help the recipient to overcome temporary financial difficulties. Prior research indicates that receipt of FSA is relatively common among youth, but its duration is often short (Ilmakunnas & Moisio, 2019; Raittila et al., 2018). Studies in Finland have shown that long-term FSA needs among youth can indicate financial difficulties during the transition to adult independence, and other health and social concerns or disadvantaged family background (Haula & Vaalavuo, 2021; Ilmakunnas & Moisio, 2019; Vauhkonen et al., 2017). These studies also show that youth with long-term FSA needs can be in a socially disadvantaged position during the transition to adult independence and have an increased risk of further problems in being an active member of society (Ilmakunnas & Moisio, 2019; Ristikari et al., 2018).

Financial difficulties in youth can be especially common in the setting of prenatal substance exposure (PSE) (i.e. alcohol and/or illicit drugs) and are potentially explained by the direct effects of PSE on cognitive and behavioral functioning and health overall (Behnke & Smith, 2013; Gunn et al., 2016; Mattson et al., 2019). Impairments in cognitive and behavioral

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functioning associated with PSE can contribute to challenges with adaptive functioning, mental health, educational attainment, and independent living (Fagerlund et al., 2012; McLachlan et al., 2020; Oei, 2018; Weyrauch et al., 2017). Impairments and challenges in these areas can increase the risk of financial difficulties among exposed youth.

Financial difficulties among youth with PSE can also be linked to adverse childhood caregiving factors (e.g. parental socioeconomic and psychological adversities) and childhood caregiving instability commonly co-occurring with PSE (Flannigan et al., 2021; Price et al., 2017; Sarkola et al., 2007). Interrelated risk factors in the childhood caregiving environment including parental financial difficulties, substance abuse and mental health disorders can negatively influence youth's developmental outcomes including mental health and educational attainment (Pitkänen et al., 2021; Raitasalo et al., 2021; Weitoft et al., 2008), and thus, directly or indirectly, increase youth's vulnerability to financial difficulties (Haula & Vaalavuo, 2021; Ilmakunnas & Moisio, 2019; Kauppinen et al., 2014; Ristikari et al., 2018).

Furthermore, children with PSE are often placed in out-of-home care (OHC) in early childhood (Flannigan et al., 2021; Sarkola et al., 2007). In the Finnish child welfare system, OHC is considered the last-resort measure of municipal child protective services. A child can be taken into OHC if the home environment or child's behavior seriously endangers their health or development, and non-residential services are insufficient. The reasons for OHC among small children typically include neglect due to parental mental health problems, parental substance abuse, and family violence. Reasons for OHC among older children and youth typically relate to offspring factors such as major mental health disorders or behavioral problems (e.g. violence, substance abuse, criminality) or severe problems endangering school participation (Heino et al., 2016). In a Finnish cohort study including children born in 1997 ($n = 57\ 174$), 5.7% of the children had experienced placement in OHC prior to the 18th birthday (Kääriälä et al., 2021). Prior studies show troubling outcomes including mental and behavioral disorders, lower educational attainment, and financial difficulties among youth with OHC history (Gypen et al., 2017; Kääriälä et al., 2019; Vinnerljung & Sallnäs, 2008). Therefore, financial difficulties among youth with PSE can also reflect care instability in their childhood environment and difficulties during the transition from OHC to financial independence.

Research on financial difficulties among youth with PSE and the influence of youth and maternal characteristics and OHC on financial difficulties in young adulthood is lacking. Financial difficulties in youth with PSE during the transition to adulthood can indicate other health and social concerns and predispose the youth to further social problems. Studying financial difficulties in these populations is important to prevent further challenges in life. Therefore, the aim was to compare the receipt of long-term FSA as an indicator of financial difficulties among 18–24-year-old youth with PSE with a matched unexposed cohort. The second aim was to investigate associations between youth's long-term FSA receipt and youth and maternal postnatal characteristics, and OHC. The third aim was to investigate how these characteristics mediate the association between PSE and youth's long-term FSA receipt.

2. Materials and methods

2.1. Study population

ADEF Helsinki (Alcohol/Drugs Exposure during Fetal life) is a longitudinal register-based cohort study including data for 615 youth with PSE (i.e. exposed cohorts) and 1787 unexposed youth aged 15–24 years (Koponen et al., 2020). In the present study, we focused on the receipt of long-term FSA after the age of 18. Therefore, the data comprised individuals from the ADEF cohort aged 18–24 years at the end of follow-up in 2016 (i.e. individuals born in 1992–1998) including 368 exposed and 1060 unexposed youth. The following cases were excluded: (1) individuals with intellectual disability (primary diagnosis from specialized healthcare, i.e. inpatient or outpatient hospital care following the International Statistical Classification of Diseases and Related Health Problems ICD-9 codes 317–319, ICD-10 codes F70–F79) (6 exposed, 10 unexposed), and (2) individuals who died or were lost during the follow-up (7 exposed, 39 unexposed). The final study population included 355 exposed and 1011 unexposed youth aged 18–24 years.

The exposed cohort consisted of children born to women with a history of intensified pregnancy follow-up and counseling provided every 2–4 weeks at special multidisciplinary HAL clinics (abbreviation for illicit drugs, alcohol, and central nervous system medicines with abuse potential) at the Helsinki University Maternity Hospital (Helsinki, Finland) serving the Helsinki metropolitan area. HAL clinics are outpatient clinics established in 1983. These clinics have extensive experience in the antenatal follow-up of pregnant women with substance abuse including intensified frequent follow-ups and counselling during antenatal follow-up, and screening of substance use (i.e. alcohol, cannabis, amphetamine, heroin, buprenorphine, and other drugs) based on self-report, voluntary urine toxicology screenings, and conventional blood tests reflecting alcohol consumption (Sarkola et al., 2000). HAL clinics also offer referrals for the treatment of opioid dependence. Indications for a referral from primary healthcare maternity clinics to the HAL clinics included an Alcohol Use Disorder Identification Test (AUDIT) score $\geq$8 points, ongoing maternal opioid maintenance treatment, drug abuse, or nonmedical use of central nervous system medication.

In ADEF, three unexposed mother-child dyads with no evidence of maternal substance abuse in national registers within one year prior to or at the time of the child's birth were obtained from the Medical Birth Register for each exposed mother-child dyad. The population-based exposed and unexposed cohorts were matched for five characteristics, including maternal age, parity, number of fetuses, the month of birth, and delivery hospital of the index child. Register data (Table 1) were collected identically for exposed and unexposed mother-child dyads and linked using unique personal identification numbers.

The study was approved by the local ethical committee of the Hospital District of Helsinki and Uusimaa. The authorities maintaining the registers approved the use of data. The register linkages and pseudonymization of the data were conducted by the Finnish Institute of Health and Welfare

Table 1. Summary of the main outcome variable, mediators and covariates, and data sources.

Variables	Definition and classification	Data Source (maintained by)	Years covered
Main outcome variable			
Youth's long-term financial social assistance receipt	Receipt of financial social assistance for at least four months during a calendar year at least once between the ages of 18 to 24 years (no, yes)	Register of Social Assistance (THL)	2010–2016
Other characteristics of youth financial social assistance receipt			
Age at the first long-term financial social assistance receipt	Age in years at the first long-term financial social assistance receipt	Register of Social Assistance (THL)	2010–2016
The cumulative number of years for which long-term financial social assistance was granted	The cumulative number of years for which long-term financial social assistance was granted	Register of Social Assistance (THL)	2010–2016
Mediator variables			
Youth characteristics			
Mental or behavioral disorders	Primary or secondary diagnosis from specialized healthcare (i.e. inpatient or outpatient hospital care) following the ICD-9 codes 290–316 (292 excluded) and ICD-10 codes F00–F99 (F17, F70–F79 excluded) during the follow-up (no, yes)	Hospital Discharge Register or Care Register for Health Care (THL)	1992–2016
Secondary education completion	Completed upper secondary education by the end of the follow-up (no, yes)	Education Register (Statistics Finland)	2010–2015
Maternal postnatal characteristics (occurred between child's birth and 18th birthday)			
Maternal mental or behavioral disorders	Primary or secondary diagnosis from specialized healthcare (i.e. inpatient or outpatient hospital care) care following the ICD-9 codes 290 and 293–319 (303–305 excluded), and ICD-10 codes F00–F09 and F20–F99 (no, yes)	Hospital Discharge Register or Care Register for Health Care (THL)	ICD–9 1987–1995 ICD–10 1996–2016
Maternal substance abuse	Primary diagnosis from specialized healthcare (i.e. inpatient or outpatient hospital care) following ICD-9 codes 291–292, 303–305, 3570, 4255, 5353, 5710, 5711–5713, 6483, 6555, 9650, and 9696–9697, and ICD-10 codes E24.4, F10–F16, F18–F19, G31.2, G40.5, G40.51, G40.52, G62.1, G72.1, I42.6, K29.2, K70, K85.2, K86.0, K86.08, O35.4–O35.5, P04.4, R78.0–R78.5, T40, T43.6, T50.2–T50.3, T51, Z71.4 and Z72.1–Z72.2 (no, yes)	Hospital Discharge Register or Care Register for Health Care (THL)	ICD–9 1987–1995 ICD–10 1996–2016
Maternal long-term financial social assistance receipt	Receipt of financial social assistance for at least four months during a calendar year at least once (no, yes)	Register of Social Assistance (THL)	2002–2016
Out-of-home care	At least one out-of-home care (OHC) episode prior to the youth's 18th birthday (no, yes), age in years at the first OHC episode, cumulative lengths of OHC episodes in years	Child Welfare Register (THL)	1992–2016
Covariates			
Sex	Female, male	Medical Birth Register (THL)	1992–2016

(THL) as the statistical authority. Study subjects were not contacted, and thus informed consent was not required.

2.2. Main outcome variable

Youth's financial difficulties were measured by the receipt of long-term financial social assistance (FSA). Information on the receipt of FSA in 2010–2016 was obtained from the Register of Social Assistance maintained by THL (Table 1). The study focused on primary FSA, including basic FSA and supplementary FSA. Basic FSA is intended to cover expenses for daily necessities (e.g. food, clothing, and transportation), whereas supplementary FSA is intended to cover other expenses or necessary expenses arising from special needs (e.g. pharmaceuticals) or circumstances.

Long-term FSA receipt has been defined in various ways in prior research. According to the Finnish Law (Act of Rehabilitative Work) (Laki kuntouttavasta työtoiminnasta 189/2001, 2001), a youth less than 25 years can be referred to rehabilitate work if she/he has been recipient of FSA for more than four months during a calendar year. Following the law, FSA receipt was considered prolonged among the youth if received for at least four months during a calendar year. Therefore, long-term FSA was defined as receipt of FSA for four months or longer during a calendar year at least once during the follow-up, to exclude brief 1–3-month FSA provided during educational summer breaks (Ristikari et al., 2018).

2.2.1. Other characteristics of youth's financial social assistance receipt

We also included other characteristics of youth financial social assistance receipt in the descriptive analyses, including age at the first long-term FSA receipt and the number of years for which it was granted (Table 1).

2.3. Mediator variables

The selection of mediators was based on prior research showing associations between maternal substance abuse during pregnancy, and financial difficulties among youth (Flannigan et al., 2021; Haula & Vaalavuo, 2021; Kauppinen et al., 2014) as well as data availability within the ADEF Helsinki study. Detailed information on mediators and data sources are outlined in Table 1.

Youth characteristics included the presence of mental or behavioral disorders and information on secondary education completion. Mental or behavioral disorders were defined by at least one specialized healthcare episode due to primary or secondary ICD-9 or ICD-10 diagnosis. Secondary education completion by the end of follow-up was coded as present or not present.

Maternal postnatal characteristics included mental or behavioral disorders, maternal substance abuse, and maternal financial difficulties measured by the receipt of long-term FSA. Maternal mental or behavioral disorders were defined as at least one specialized healthcare care episode due to primary or secondary ICD-9 or ICD-10 diagnoses. Maternal substance abuse was defined by primary ICD-9 and ICD-10 substance abuse-related diagnoses from specialized healthcare care. Maternal receipt of long-term FSA was defined similarly to youth long-term FSA receipt. These maternal characteristics were derived from the registers from the child's birth until 18th birthday.

Out-of-home care (OHC) was defined as at least one OHC episode between the child's birth and 18th birthday. We also included additional characteristics of OHC (age at the first OHC episode, cumulative length of OHC episodes) in the descriptive analysis.

2.4. Data analyses

First, we compared (1) the characteristics of youth and their mothers between the exposed and unexposed cohorts, and (2) the same characteristics between the exposed and unexposed recipients of long-term FSA, using the Chi-Squared test (χ^2) and Mann-Whitney U-test. The long-term FSA needs between the cohorts were analyzed using the χ^2-test and Independent-Samples t-Test. We present results from the descriptive analyses as counts and percentages, medians and Interquartile Range (IQR), as well as means and standard deviations (SD).

Second, we defined unadjusted and adjusted associations between PSE, youth (i.e. sex, mental or behavioral disorders, lack of secondary education) and maternal characteristics (i.e. mental or behavioral disorders, substance abuse, receipt of long-term FSA), OHC, and youth's receipt of long-term FSA with generalized linear models. First, we regressed bivariate associations between PSE, the youth and maternal characteristics, and OHC and the youth's receipt of long-term FSA. Second, in the adjusted model, we included all the youth and maternal characteristics and OHC simultaneously to account for the potential effect of these predictors on the association between PSE and youth's receipt of long-term FSA. The model was also adjusted for the follow-up time to account for differences in the follow-up time between birth years, and thus, for the likelihood of FSA receipt. The results of the unadjusted and adjusted models are reported as parameter estimates (*b*) with standard error (SE), odds ratios (OR), and *p*-values.

Mediation analyses were applied to investigate how the association between PSE and youth's receipt of long-term FSA is mediated by the selected mediators. The selection of the variables for the mediation analyses in a combined exposed and unexposed dataset was based on the results from the adjusted generalized linear models and included variables showing independent associations with youth's long-term FSA receipt (i.e. youth's mental or behavioral disorders, lack of secondary education, maternal receipt of long-term FSA, and OHC).

We first defined the direct association (c') between PSE (X) and the youth's receipt of long-term FSA (Y). Second, we defined path a, which indicates the association between PSE (X) and mediator (M). Third, we defined path b, indicating the association between mediator (M) and youth's receipt of long-term FSA (Y) while controlling for the effect of PSE (X). Fourth, the indirect (ab) association and total effect (c) were defined. Indirect association indicates the mediation effect (i.e. the effect of PSE on youth's receipt of long-term FSA that goes through a mediator), whereas total effect (c) sums the direct and indirect effects. Lastly, the proportion mediated describes the proportion of the effect of X on Y that goes through the mediator (M). The results of mediation analyses are reported as parameter estimates (*b*) with standard errors (SE), 95% Confidence Intervals (95% CI), and *p*-values.

Statistical significance was set to $p < 0.05$. The descriptive analyses were conducted using IBM SPSS version 28, and the bivariate and multivariable generalized linear models with R. The mediation analyses were performed with a bootstrapping method including 1000 simulations and conducted with the mediation package for R (Tingley et al., 2014).

3. Results

Characteristics of and differences between exposed and unexposed cohorts are presented in Table 2. The median follow-up time in years in the exposed and unexposed cohorts was 20.5 (IQR 19.2, 22.7) and 20.4 (IQR 19.2, 22.5) ($p = 0.770$), respectively. Exposed and unexposed cohorts differed in all characteristics except for sex. Mental or behavioral disorders were more common in the exposed youth compared with the unexposed youth (57.2% vs. 28.5%, $p < 0.001$), and a lower proportion of the exposed youth had completed secondary education at follow-up (30.1% vs. 41.3%, $p < 0.001$) compared with the unexposed youth. Mothers of exposed children were more likely to have been in specialized healthcare for mental or behavioral disorders and substance abuse and were more often recipients of long-term FSA compared with mothers of unexposed children. A majority of the exposed had at least one OHC episode compared with the unexposed (64.5% vs. 7.0%, $p < 0.001$). The exposed had been placed in OHC at a younger age (3.2 vs. 12.9 years,

Table 2. Descriptive characteristics and comparison of 18–24-year-old exposed and unexposed youth and recipients of long-term financial social assistance.

	Total study population			Recipients of long-term financial social assistance		
	Exposed $n = 355$	Unexposed $n = 1011$	p-value	Exposed $n = 179$	Unexposed $n = 174$	p-value
Youth characteristics						
Sex			0.411			0.692
Female	175 (49.3)	524 (51.8)		84 (46.9)	78 (44.8)	
Male	180 (50.7)	487 (48.2)		95 (53.1)	96 (55.2)	
Mental or behavioral disorders			<0.001			0.006
No	152 (42.8)	723 (71.5)		56 (31.3)	79 (45.4)	
Yes	203 (57.2)	288 (28.5)		123 (68.7)	95 (54.6)	
Secondary education completion			<0.001			0.521
No	248 (69.9)	592 (58.7)		133 (74.3)	124 (71.3)	
Yes	107 (30.1)	418 (41.3)		46 (25.7)	50 (28.7)	
Maternal postnatal characteristics						
Maternal mental or behavioral disorder			<0.001			0.017
No	204 (57.5)	840 (83.1)		107 (59.8)	125 (71.8)	
Yes	152 (42.5)	171 (16.9)		72 (40.2)	49 (28.2)	
Maternal substance abuse			<0.001			<0.001
No	202 (56.9)	979 (96.8)		96 (53.6)	161 (92.5)	
Yes	153 (43.1)	32 (3.2)		84 (46.4)	13 (7.5)	
Maternal long-term financial social assistance receipt			<0.001			<0.001
No	97 (27.3)	858 (84.9)		37 (20.7)	106 (60.9)	
Yes	258 (72.7)	153 (15.1)		142 (79.3)	68 (39.1)	
Out-of-home care (OHC)			<0.001			<0.001
No	126 (35.5)	940 (93.0)		44 (24.6)	127 (73.0)	
At least one OHC episode	229 (64.5)	71 (7.0)		135 (75.4)	47 (27.0)	
Age in years at the first OHC episode (median, IQR)	3.2 (1.2, 7.5)	12.9 (6.8, 14.7)	<0.001	4.6 (1.9, 9.9)	13.1 (7.9, 14.8)	<0.001
Cumulative length of OHC episodes in years (median, IQR)	10.6 (2.6, 16.0)	1.6 (0.2, 5.0)	<0.001	6.8 (1.8, 15.0)	1.9 (0.3, 5.0)	<0.001

IQR: Interquartile Range; p-values based on χ^2 test for categorical variables and Mann-Whitney U-test for continuous variables.

Table 3. Comparison of receipt of financial social assistance among 18–24-year-old exposed and unexposed youth.

	Exposed $n = 355$	Unexposed $n = 1011$	p-value
Main outcome variable			
Receipt of long-term financial social assistance, n (%)	179 (50.4)	174 (17.2)	<0.001
Other characteristics of youth's receipt of financial social assistance			
Age at first long-term financial social assistance receipt (mean, SD)	18.8 (0.97)	19.3 (1.39)	<0.001
Cumulative number of years for which long-term financial social assistance was granted (mean, SD)	2.5 (1.6)	2.1 (1.4)	0.039

Long-term financial social assistance is defined as received financial social assistance for 4–12 months during a calendar year at least once during the follow-up, SD: Standard Deviation, p-values based on χ^2 test for categorical variables and Independent-Samples t-Test for continuous variables.

$p < 0.001$) and for a longer time period (10.6 vs. 1.6 years, $p < 0.001$) compared with the unexposed (Table 2).

The comparison of characteristics of the exposed and unexposed recipients of long-term FSA indicated no sex or educational differences between the cohorts. The exposed and unexposed recipients of long-term FSA differed significantly with respect to the other youth and maternal characteristics and OHC (Table 2).

The comparison of long-term FSA receipt between the cohorts indicated that the receipt of long-term FSA was significantly more common among the exposed compared with the unexposed youth (50.4% vs. 17.2%, $p < 0.001$). The comparison of other characteristics between the cohorts indicated that the exposed were slightly younger at first long-term FSA receipt (18.8 years vs. 19.3 years, $p < 0.001$) and received long-term FSA for a longer period on average (2.5. years vs. 2.1 years, $p = 0.039$) compared with the unexposed youth (Table 3).

Table 4 presents the unadjusted and adjusted predictors of youth's receipt of long-term FSA. Results of the unadjusted analyses indicated that exposed youth had a nearly five-fold increased likelihood of long-term FSA receipt compared with the unexposed youth (OR 4.89, 95% CI 3.76, 6.37). The results also indicated that youth characteristics including mental or behavioral disorders and lack of secondary education, maternal postnatal characteristics including maternal mental or behavioral disorders, substance abuse and receipt of long-term FSA, and OHC were positively associated with youth's receipt of long-term FSA. After adjusting the analysis for all the variables simultaneously, the difference in the likelihood of long-term FSA receipt between the exposed and unexposed cohorts was attenuated to nonsignificant levels (AOR 1.33, 95% CI 0.89, 1.98), and the youth's mental or behavioral disorders (AOR 2.28, 95% CI 1.68, 3.10), lack of secondary education (AOR 5.39, 95% CI 3.55, 8.17), maternal receipt of long-term FSA (AOR 3.09, 95% CI 2.13, 4.48), and OHC (AOR 3.39, 95% CI 2.20, 5.23) were independently associated with youth's receipt of long-term FSA.

Next, mediation analyses were conducted to investigate whether these independent predictors of youth's long-term FSA receipt mediate the association between PSE and youth's long-term FSA receipt (Table 5 and Figure 1). A positive association was found between PSE and youth's mental or behavioral disorders ($b = 1.21$, $p < 0.001$), and the association

Table 4. Unadjusted and adjusted predictors of long-term financial social assistance receipt among 18–24-years old youth.

	Unadjusted				Adjusted*			
	b	SE	OR (95% CI)	p-value	*b*	SE	AOR (95% CI)	*p*-value
Prenatal substance exposure	1.59	0.14	4.89 (3.76, 6.37)	<0.001	0.28	0.21	1.33 (0.89, 1.98)	0.167
Youth characteristics								
Male sex	0.16	0.12	1.17 (0.92, 1.49)	0.200	0.15	0.15	1.17 (0.87. 1.57)	0.312
Mental or behavioral disorders	1.48	0.13	4.38 (3.39, 5.65)	<0.001	0.82	0.16	2.28 (1.68, 3.10)	<0.001
Lack of secondary education	0.68	0.14	1.97 (1.51, 2.57)	<0.001	1.68	0.21	5.39 (3.55, 8.17)	<0.001
Maternal postnatal characteristics								
Maternal mental or behavioral disorders	0.75	0.14	2.11 (1.61, 2.76)	<0.001	0.01	0.18	1.01 (0.70, 1.44)	0.979
Maternal substance abuse	1.36	0.16	3.88 (2.82, 5.34)	<0.001	–0.27	0.25	0.76 (0.47, 1.24)	0.274
Maternal long-term financial social assistance receipt	1.78	0.13	5.93 (4.56, 7.72)	<0.001	1.13	0.19	3.09 (2.13, 4.48)	<0.001
Out-of-home care (OHC)								
At least one OHC episode	2.09	0.15	8.07 (6.08, 10.72)	<0.001	1.22	0.22	3.39 (2.20, 5.23)	<0.001

Unadjusted and adjusted parameter estimates (*b*) with standard error (SE), odds ratios (OR), adjusted odds ratios (AOR), 95% Confidence Intervals (CI) and *p*-values are reported for bivariate and multivariable generalized linear models.
*Adjusted for prenatal substance exposure, youth characteristics, maternal postnatal characteristics, OHC, and follow-up time.

between PSE and youth's receipt of long-term FSA was partly mediated by these disorders (0.21, 95% CI 0.14, 0.30). PSE was also positively associated with the lack of secondary education ($b = 0.49$, $p < 0.001$), but only 3% (95% CI 0.01, 0.07) of the association between PSE and youth's long-term FSA receipt was mediated by the lack of secondary education. The results also indicated that PSE was strongly associated with maternal long-term FSA receipt ($b = 2.70$, $p < 0.001$) and OHC ($b = 3.18$, $p < 0.001$). A large proportion of the association between PSE and youth's long-term FSA receipt was mediated by maternal long-term FSA receipt (0.48, 95% CI 0.35, 0.64) and OHC (0.63, 95% CI 0.47, 0.83) (Table 5, Figure 1).

4. Discussion

In this study, financial difficulties measured by the receipt of long-term financial social assistance (FSA) were significantly more common among 18–24-year-old youth with a history of prenatal substance exposure (PSE) compared with a matched prenatally unexposed cohort. However, this study found that the difference in long-term FSA receipt between exposed and unexposed cohorts was largely explained by maternal financial difficulties, also measured by the receipt of long-term FSA, child's out-of-home care (OHC), and to some degree also by youth mental or behavioral disorders. Youth's lack of secondary education explained only a small proportion of the association between PSE and youth's long-term FSA needs. Overall, it seems that financial difficulties among exposed youth are largely predicted by maternal substance abuse and dependence linked with maternal financial situation and care instability in childhood (OHC), and to some extent also by youths mental or behavioral disorders possibly influencing cognitive and behavioral functioning and overall wellbeing during the transition to adult independence.

This study expands previous research on financial difficulties among the general youth population by investigating long-term FSA needs among a vulnerable youth population with PSE. We were unable to find similar studies on financial difficulties among youth born to mothers followed up prenatally for substance abuse. Studies from the general youth population show that temporary financial difficulties are common among youth during transition phases (Ilmakunnas & Moisio, 2019). It has been reported that 18.9% of 18–24-year-old Finnish youth received FSA for at least one month in 2017, and for a majority, the receipt of FSA was short-term (Raittila et al., 2018). In another Finnish study, 29.8% of youth aged 18–24-years received FSA for at least one month during the study period (Haula & Vaalavuo, 2021). Although these estimates are not fully comparable due to differences in the studied duration and form of FSA and changes in the administration of FSA in Finland in 2017, receipt of long-term FSA among exposed youth (50.4%) is significantly higher than the estimates in the general Finnish youth population (Haula & Vaalavuo, 2021; Raittila et al., 2018).

The financial difficulties among the exposed youth could be linked to the direct effect of PSE on children's cognitive and behavioral functioning and health (Behnke & Smith, 2013; Gunn et al., 2016; Mattson et al., 2019), which, can contribute to challenges with adaptive functioning, mental health, educational attainment and independent living (Fagerlund et al., 2012; McLachlan et al., 2020; Weyrauch et al., 2017). Problems in these areas can be reflected as financial difficulties during the transition to adulthood among exposed youth. Lower educational attainment and other psychosocial outcomes among exposed youth may add to this (Howell et al., 2006; Nissinen et al., 2021; Rangmar et al., 2015). However, our findings indicated no difference in secondary education completion between exposed and unexposed recipients of long-term FSA, and this is consistent with only a marginal prediction of long-term FSA needs in our mediation analyses. We speculate that the small mediating effect of lack of secondary education in the mediation analysis could be due to the relatively young age of our study cohort, low proportion of completed secondary education overall, but also the mitigating support from the population-based mandatory comprehensive Finnish education system. The previously reported time lag in secondary education completion in our prenatally exposed cohort might, however, predict long-term FSA needs later in adulthood (Nissinen et al., 2021).

Our findings linking youth's mental or behavioral disorders with financial difficulties are consistent with previous studies (Haula & Vaalavuo, 2021; Ringbom et al., 2021). The results of

Table 5. The mediating effect of youth's characteristics (i.e. mental or behavioral disorders, lack of secondary education), maternal long-term financial social assistance receipt and child out-of-home care on the association between prenatal substance exposure and youth's long-term financial social assistance (FSA) receipt.

	Mediators															
	Youth characteristics								Maternal characteristics				Out-of-home care			
	Mental or behavioral disorder				Lack of secondary education				Long-term financial social assistance receipt				Child out-of-home care			
	b	SE	95% CI	*p*-value	*b*	SE	95% CI	*p*-value	*b*	SE	95% CI	*p*-value	*b*	SE	95% CI	*p*-value
Prenatal substance exposure and mediator (a)	1.21	0.13		<0.001	0.49	0.13		<0.001	2.70	0.15		<0.001	3.18	0.17		<0.001
Mediator and youth's long-term FSA receipt (b)	1.23	0.14		<0.001	0.58	0.14		<0.001	1.35	0.16		<0.001	1.69	0.18		<0.001
Indirect effect (ab)	0.07		0.05, 0.10	<0.001	0.01		0.004, 0.02	<0.001	0.16		0.12, 0.20	<0.001	0.20		0.16, 0.26	<0.001
Direct effect (c')	0.26		0.20, 0.32	<0.001	0.32		0.26, 0.38	<0.001	0.17		0.10, 0.24	<0.001	0.12		0.05, 0.20	<0.001
Proportion mediated (ab/(ab + c'))	0.21		0.14, 0.30	<0.001	0.03		0.01, 0.07	0.004	0.48		0.35, 0.64	<0.001	0.63		0.47, 0.83	0.002
Total effect (c)	0.33		0.28, 0.39	<0.001	0.33		0.28, 0.39	<0.001	0.33		0.28, 0.39	<0.001	0.32		0.27, 0.39	<0.001

Parameter estimates (*b*) with standard error (SE), 95% Confidence Interval (CI) and p-values.

the mediation analyses also showed that youth's mental or behavioral disorders partly mediate the association between PSE and long-term FSA needs.

Our results also show that youth with PSE face the accumulation of several interrelated risk factors and care instability in childhood that can predispose them to financial difficulties, as also reported in prior studies from the general youth population (Gypen et al., 2017; Ilmakunnas & Moisio, 2019; Kauppinen et al., 2014). Children and youth exposed to substances prenatally often face double jeopardy (Carta et al., 2001; Flannigan et al., 2018). Not only are their developmental outcomes influenced by PSE, but they are also often exposed to an accumulation of risk factors in their postnatal caregiving environment, including socioeconomic and psychological adversities (Carta et al., 2001; Flannigan et al., 2018). Due to this, youth exposed to substances prenatally can be more vulnerable to risks and stress during the transition to adulthood, potentially predisposing them to other challenges then, including financial difficulties.

Our findings showed that maternal financial difficulties were common among mothers of exposed children, that is, mothers with potential substance abuse during pregnancy. In addition, maternal financial difficulties mediated a large proportion of PSE-related long-term FSA needs. Studies from the general youth population show that family socioeconomic factors including financial difficulties can predict youth's long-term FSA needs (Kauppinen et al., 2014; Ristikari et al., 2018). Parents with financial difficulties may not have the resources to support the youth during their transition to independent adulthood, and thus, FSA is needed to ensure this process. Parental financial difficulties can also reflect the accumulation of adversities including parental mental health disorders or substance abuse (Jääskeläinen et al., 2016), which can directly or indirectly increase youth's vulnerability to poor developmental outcomes (Pitkänen et al., 2021; Raitasalo et al., 2021; Rodwell et al., 2018), and influence their transition to financial self-support (Haula & Vaalavuo, 2021; Ilmakunnas, 2018; Kauppinen et al., 2014; Ristikari et al., 2018).

Moreover, the results indicated that a significant proportion of the exposed youth had been placed in OHC during early childhood. Long-term outcomes in various life areas including financial self-support difficulties tend to be common among youth with OHC history (Gypen et al., 2017; Kääriälä et al., 2019; Vinnerljung & Sallnäs, 2008). In Finland, the receipt of FSA among youth with OHC history can reflect the aftercare services provided following OHC. However, the receipt of FSA can also reflect a lack of social and financial support or other factors including mental or behavioral disorders or educational challenges which can predispose former OHC youth to a challenging transition to financial self-support. Our results also showed that OHC was associated with the youth's financial difficulties, and the results of the mediation analyses indicated that OHC mediated a large proportion of the association between PSE and the youth's receipt of long-term FSA. However, studies extending into later adulthood are needed to investigate the transition from OHC to financial independence.

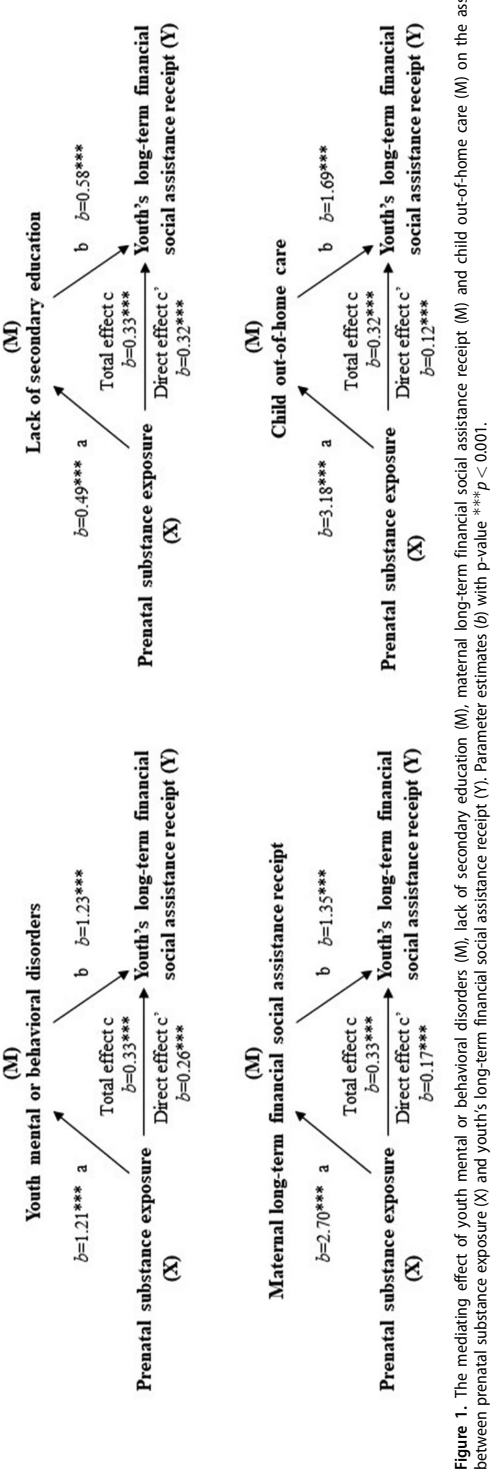

Figure 1. The mediating effect of youth mental or behavioral disorders (M), lack of secondary education (M), maternal long-term financial social assistance receipt (M) and child out-of-home care (M) on the association between prenatal substance exposure (X) and youth's long-term financial social assistance receipt (Y). Parameter estimates (*b*) with p-value $^{***}p < 0.001$.

Studies extending into adulthood are also needed to investigate whether the financial difficulties among youth with PSE reflect challenges in establishing financial independence during young adulthood or long-term challenges in being an active member of society.

4.1. Strengths and limitations

Strengths of the study include a matched unexposed cohort and the availability of data on factors known to be associated with financial difficulties among youth. By using a prospective hospital medical record and comprehensive mandatory national register-based study design, we were able to avoid data collection inaccuracies related to retrospective self-reported information, low response rate, recall bias (e.g. under-reporting of adverse events), or losses in the follow-up. We also consider the mediation analyses exploring the role of different predictors explaining the variance of the association between prenatal substance exposure and youth's long-term financial social assistance receipt in our combined exposed and unexposed dataset as a strength.

We acknowledge limitations related to the lack of data on the type, timing, and severity of maternal substance use during pregnancy. Self-reported information on substance use is inevitably inaccurate, precluding analyses on independent associations with a specific type of substance, and hence, the exposed vs. unexposed categorization was used in the analysis. Our exposed cohort includes children born to mothers with significant substance abuse identified at maternity clinics and therefore excludes children born to mothers with low or occasional substance use during pregnancy. We acknowledge that the unexposed cohort may include women with minor substance use during pregnancy not identified by screening the registers for maternal substance abuse-related primary and secondary diagnosis and external causes of injuries from outpatient and inpatient hospital care one year prior or at the time of child's birth among the mothers of the unexposed children. Another limitation is the lack of information on another caregiver that may have an equal and significant role in the youth's life including the father or foster parent(s).

By using register data, we may not have captured all potential characteristics of the childhood caregiving environment that may influence financial difficulties in youth. However, OHC, as the last-resort measure of municipal child protective services, generally indicates significant challenges in the caregiving environment endangering a child's health and development. Another limitation related to the register data relates to data on secondary education that was only available until 2015. Thus, the number of exposed and unexposed who have completed secondary education by the end of 2015, especially among the youngest study participants, may be underestimated. Lastly, considering the study's observational nature, causal links cannot be proved.

5. Conclusions

This study finds financial difficulties to be more common among 18–24-year-old youth with prenatal substance exposure (PSE) compared with unexposed youth. However, the increased likelihood of long-term FSA among exposed youth was attenuated to nonsignificant levels when adjusting for youth and maternal postnatal characteristics and child OHC. The results from the mediation analysis indicated that the association between PSE and youth's financial difficulties were mainly mediated by maternal financial difficulties and child OHC, and partly by youth mental or behavioral disorders. Lack of secondary education was related to financial difficulties only to a minor extent, and this likely reflects the mitigating support from the population-based mandatory comprehensive Finnish education system. It seems that FSA among youth with PSE to ensure the transition to adult independence likely reflects maternal substance abuse and dependence linked with maternal financial situation and care instability in childhood. Early identification and support of youth at risk seem important for optimizing the transition to financial independence.

Acknowledgments

We would like to thank Aku-Ville Lehtimäki for advice on statistical analyses.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Alli Paasikiven Säätiö, Juho Vainion Säätiö, Medicinska Understödsföreningen Liv och Hälsa, Alkoholitutkimussäätiö, Samfundet Folkhälsan, Signe ja Ane Gyllenbergin Säätiö.

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Data availability statement

The data are not publicly available due to data confidentiality and the authors do not have permission to share the data. Similar data can be applied from Findata, the Finnish Social and Health Data Permit Authority: (https://findata.fi/en/).

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PUBLICATION III

Mood and neurotic disorders among youth with prenatal substance exposure: A longitudinal register-based cohort study

Nissinen, N.M., Sarkola, T., Autti-Rämö, I., Gissler, M., Kahila, H. & Koponen, A.M.

Journal of Affective Disorders (2022), *1*(308), 328–336
DOI: 10.1016/j.jad.2022.04.039

Journal of Affective Disorders 308 (2022) 328–336

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Mood and neurotic disorders among youth with prenatal substance exposure: A longitudinal register-based cohort study

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ARTICLE INFO

Keywords:
Mood disorders
Neurotic disorders
Prenatal substance exposure
FASD
Childhood adversities

ABSTRACT

Background: Prenatal substance exposure is associated with mood and neurotic disorders but this association is complex and understudied. This study investigated the recorded use of specialised healthcare services for mood and neurotic disorders among youth with prenatal substance exposure in comparison with an unexposed matched cohort. Furthermore, the influence of adverse maternal characteristics and out-of-home care (OHC) is investigated.

Methods: This longitudinal register-based matched cohort study included 594 exposed and 1735 unexposed youth. Cox proportional hazard regression models were applied to study the first episode of mood and neurotic disorders in specialised healthcare from 13 years of age, and the influence of adverse maternal characteristics and OHC. Mediation analysis was applied to study the mediating effect of OHC on the association between prenatal substance exposure and the disorders.

Results: The exposed cohort had a two-fold higher likelihood of being treated at specialised healthcare for mood and neurotic disorders compared with the unexposed cohort (HR 2.34, 95% CI 1.86–2.95), but this difference was attenuated to non-significant levels (AHR 1.29, 95% CI 0.92–1.81) following adjustments with adverse maternal characteristics and OHC. OHC mediated 61% (95% CI 0.41–0.94) of the association between prenatal substance exposure and youth's mood and neurotic disorders.

Limitations: Register data likely include more severe cases of disorders, and as an observational study, causality cannot be assessed.

Conclusion: Mood and neurotic disorders are more common following prenatal exposure to substances and interlinked with significant adversities in the postnatal caregiving environment and OHC.

1. Introduction

Mood disorders (e.g. depressive disorders) and neurotic disorders (e.g. anxiety), often referred to as internalizing disorders, are common and often comorbid mental health disorders occurring throughout the life-course. Often these disorders become evident in childhood or adolescence and can persist into adulthood (Kessler et al., 2007; Patel et al., 2007). These disorders contribute to functional impairments, and health and developmental concerns which may influence educational achievements, peer relationships and substance abuse behaviours (Patel

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https://doi.org/10.1016/j.jad.2022.04.039
Received 22 September 2021; Received in revised form 16 March 2022; Accepted 9 April 2022
Available online 16 April 2022

et al., 2007).

Several factors can increase the risk of mood and neurotic disorders over time, and often these disorders are more common among females (Kuehner, 2003; Rapee et al., 2009). Other factors include problems in the prenatal period (e.g. alcohol exposure) and early life adversities (e.g. financial difficulties in the family, parental psychiatric morbidity, parental substance abuse, death of a family member) (Basu and Banerjee, 2020; Essex et al., 2006; Rapee et al., 2009; Su et al., 2021). These risk factors can negatively influence parenting behavior and parent-child interaction, and subsequent mental health outcomes in children (Brumariu and Kerns, 2010; Rapee et al., 2009; Reising et al., 2013; Staton-Tindall et al., 2013). Furthermore, often these factors are indications for child protective services during early childhood (Kestilä et al., 2012; Sarkola et al., 2007). Mental health disorders, including mood and neurotic disorders, are highly overrepresented among children in out-of-home care or foster care in many studies (Bronsard et al., 2016; Egelund and Lausten, 2009; Lehmann et al., 2013).

Prenatal alcohol exposure is linked with neurodevelopmental disorders in children (Stein and Donald, 2018). Associations with mood and neurotic disorders seem more complex and less studied (Carta et al., 2001; O'Connor, 2014). Prior research has typically included small or clinically referred samples and parental assessment of a child's symptomatology. These studies have investigated depression and anxiety symptoms among exposed children or children with Foetal Alcohol Spectrum Disorders (FASD), and show an increased prevalence of symptoms among the exposed children compared with healthy controls (Fryer et al., 2007; Roebuck et al., 1999; Walthall et al., 2008; Weyrauch et al., 2017). To date, few studies have shown elevated rates of depressive or anxiety disorders (Famy et al., 1998) among youth or young adults with FASD (Famy et al., 1998; Streissguth, 1996). Prior studies, however, indicate that the mood and neurotic disorders in childhood have been likely influenced by factors within the postnatal caregiving environment and parenting domains (O'Connor and Paley, 2006; Walthall et al., 2008; Weyrauch et al., 2017).

Prenatal exposure to other substances (e.g. marijuana, cocaine, opiates, amphetamine) may also disrupt foetal neurodevelopment and can influence subsequent cognitive processing and behavior (Behnke et al., 2013; Morie et al., 2019; Nygaard et al., 2016). Research on mood and neurotic disorders among children and youth is, however, scarce and suggests an association between prenatal marijuana, opioid or polysubstance exposure and depressive symptoms in children (Gray et al., 2005) and youth (Nygaard et al., 2020).

Prenatal exposure to alcohol and/or other substances (prenatal substance exposure hereafter) is often linked with early life stressors such as maternal socioeconomic factors (e.g. low educational level, financial difficulties), maternal mental health problems and polysubstance use (Esper and Furtado, 2014; Flannigan et al., 2021; Jääskeläinen et al., 2016). A high proportion of these children need child protective services after birth, and they are placed in out-of-home care in early childhood due to significant risks in the caregiving environment (Lange et al., 2013; Sarkola et al., 2007). The increased likelihood of mood and neurotic disorders among individuals with prenatal substance exposure can, therefore, reflect this instability in care and exposure to early life adversities (Basu and Banerjee, 2020; Bronsard et al., 2016; Essex et al., 2006).

This study uses longitudinal comprehensive register data to study recorded use of specialised health care services covering inpatient and outpatient hospital care for mood and neurotic disorders among youth prenatally exposed to substances compared with a matched unexposed cohort. In addition, the study investigates the influence of offspring and maternal characteristics as well as out-of-home care on these disorders. The specific objectives were:

1. To study the specialised healthcare utilisation for mood and neurotic disorders among youth prenatally exposed to substances from 13 years of age in comparison to a matched unexposed cohort.
2. To study the influence of offspring and maternal characteristics and OHC on specialised healthcare utilisation for mood or neurotic disorders in relation to prenatal exposure.
3. To study the mediating effect of OHC on the association between prenatal substance exposure and mood and neurotic disorders.

2. Methods

2.1. Study design and population

The data used in this study are from a longitudinal register-based matched cohort study which has been described earlier (Koponen et al., 2020; Sarkola et al., 2007). The study population consisted of 615 youth with prenatal substance exposure (i.e. the exposed cohort) and a matched unexposed cohort ($n = 1787$). Offspring who died before the age of 13 (7 of the exposed, 15 of the unexposed) or were lost to follow-up before the age of 13 (1 of the exposed, 22 of the unexposed) were excluded from the final study population. In addition, offspring who had received a diagnosis for an intellectual disability following the International Classification of Diseases ICD-9 code 317–319 and ICD-10 code F70-F79 (13 of the exposed, 15 of the unexposed) were excluded due to the complexity of mood and neurotic disorders and the diagnosis of these disorders in this group (Rojahn and Meier, 2009). Therefore, the final study population comprised 594 exposed and 1735 unexposed youth (Fig. 1). None of those who died or were lost to follow-up before the age of 13 years was diagnosed with mood and neurotic disorders.

The exposed cohort represents offspring born in 1992–2001 to women with an antenatal follow-up at special outpatient clinics for women with substance use during pregnancy. The mothers were followed up every 2 to 4 weeks with information on substance use (i.e. alcohol, amphetamine, heroin, buprenorphine, non-medical use of central nervous system medication and other drugs) documented by self-reported use, voluntary urine toxicology screenings and conventional blood tests reflecting alcohol consumption at each follow-up visit and documented in hospital medical records (Sarkola et al., 2000). Information on tobacco smoking during pregnancy was collected from the Medical Birth Register.

The unexposed cohort was obtained from the Medical Birth Register and represent offspring born in 1992–2001 to women with no registered evidence of substance use one year prior to or at the time of the offspring's birth. The cohorts were matched for five maternal characteristics: maternal age, parity, number of foetuses, the month of birth, and delivery hospital of the index child. Register data were collected identically for the matched exposed and unexposed mother-offspring pairs (Supplementary material 1).

The local ethical committee of The Hospital District of Helsinki and Uusimaa has approved the study, and permission for data linkages was obtained from all the authorities maintaining the registers. The Finnish Institute for Health and Welfare performed the register linkages and pseudonymised the data prior to analyses. No study subjects were contacted and the data are considered highly confidential.

2.2. Study variables

2.2.1. Outcome variables

Data on all the offspring's mood disorder (ICD-10 codes F30-F39) and neurotic disorder (ICD-10 codes F40-F48) diagnoses were collected from birth, but as these disorders typically evolve in adolescence (Kessler et al., 2007), we focused on episodes from 13 years of age until the end of 2016 when participants were 15–24 years old. The onset age of mood and neurotic disorders was based on the first diagnoses in specialised healthcare (i.e. outpatient or inpatient hospital care) after the 13th birthday in the Care Register for Health Care maintained by the Finnish Institute for Health and Welfare. Data on all inpatient care episodes are available from 1992 to 2016 and outpatient care episodes in public hospitals from 1998 to 2016.

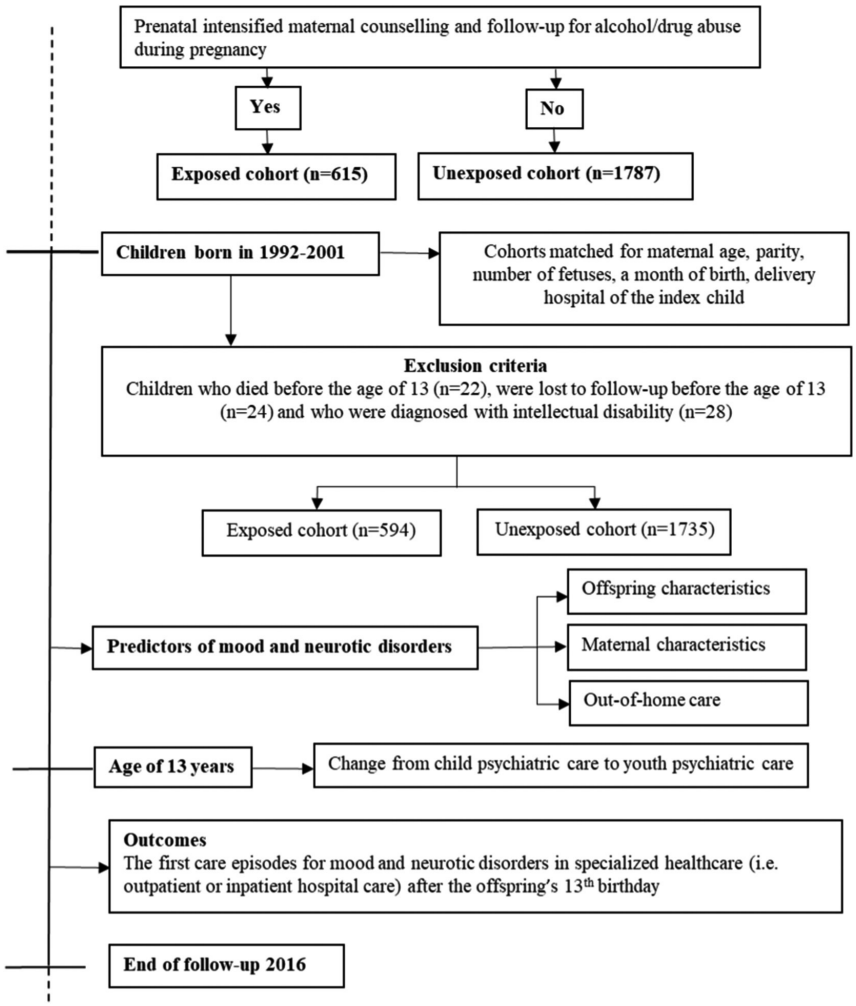

Fig. 1. Study outline.

2.2.2. Covariates

The selection of covariates was based on data availability and prior research demonstrating associations with mood and neurotic disorders (Basu and Banerjee, 2020; Bronsard et al., 2016; Essex et al., 2006). The selected covariates are described in detail in Supplementary material 1.

The studied offspring characteristics included sex, gestational age at birth, birth weight, prenatal exposure to tobacco smoking, and diagnosis within the FASD spectrum for exposed offspring. The variables describing adversities in the postnatal caregiving environment and potential confounders linked with offspring's mood and neurotic disorders were based on maternal characteristics. These included maternal age at the time of offspring's birth, maternal socioeconomic status, measured as maternal occupation during pregnancy, and marital status at the time of offspring's birth. Often childhood adversities co-occur (Carta et al., 2001), and therefore, a cumulative childhood adversity score including 0, 1, 2, or 3 to 5 adversities was constructed based on data before offspring's 13th birthday. This score included maternal mental or behavioural disorder, maternal substance misuse, maternal long-term financial social assistance, maternal criminality and death of the mother (Supplementary material 1).

Taking a child into care is considered as the last resort of child protective service in the Finnish child welfare system. Out-of-home care (OHC) generally refers to significant neglect in a child's care due to parental mental health problems, substance misuse or family violence. A child can be taken into care also if the child's behavior endangers the child's health or development. In this study, OHC was analysed in three categories: no OHC episodes, first OHC episode prior to offspring's 13th birthday, and first OHC episode at 13 years of age or later. We also included information on the median age at the first OHC episode and the cumulative number of years in OHC (Supplementary material 1).

2.2.3. Data analysis

The characteristics of the exposed and unexposed cohorts were compared using the Chi-squared test (χ^2) for categorical variables and the Mann-Whitney *U* test or independent samples *t*-test for continuous variables, as appropriate. Univariate Cox proportional hazard regression analyses were performed to investigate the associations between the covariates and specialised healthcare for mood and neurotic disorders separately for the exposed and unexposed.

Five multivariable Cox regression models were computed to study the association between prenatal substance exposure and mood and neurotic disorders and the influence of selected covariates. The selection of covariates for multivariable models was based on the results from the univariate analyses, prior research evidence indicating associations with youth's mood and neurotic disorders (Basu and Banerjee, 2020; Su et al., 2021), and data availability. Adjustments were not made for maternal marital status and gestational exposure to tobacco smoking due to substantial statistical multicollinearity with prenatal substance exposure. Maternal age at the time of offspring's birth was not included in the analyses as it was one of the matching criteria for the cohorts.

The crude association between prenatal substance exposure and mood and neurotic disorders was studied in the first multivariable Cox regression model. In model 2, adjustments were made for offspring's sex. In model 3, the influence of maternal characteristics was analysed, and adjustments were made for offspring's sex and cumulative childhood adversity score. The influence of OHC was studied in model 4, and adjustments were made for offspring's sex and OHC. In model 5, all covariates were included simultaneously. In the multivariable Cox regression models, the follow-up started at the offspring's 13th birthday and continued until the first record of diagnoses for mood and neurotic disorders in specialised healthcare, death or end of follow-up in 2016. Hazard ratios (HR) and adjusted hazard ratios (AHR) with a 95% Confidence Interval (CI) are reported.

Mediation analysis was applied to estimate the total effect of prenatal substance exposure on mood and neurotic disorders and the mediating effect of OHC. We begin by defining the direct association (c′) between prenatal substance exposure (X) and youth's mood and neurotic disorders (Y). Second, the association (a) between prenatal substance exposure (X) and the mediator (M) was defined. Next, we defined the association (b) between mediator (M) and youth's mood and neurotic disorders (Y) while controlling for the effect of prenatal substance exposure (X). Fourth, the indirect association (ab) indicating the path from prenatal substance exposure (X) to youth's mood and neurotic disorders (Y) through the mediator (M) was defined, following the definition of the total effect (c), which indicates the sum of the direct effect and indirect effect. Lastly, we defined the proportion mediated, which indicates the proportion of the effect of prenatal substance exposure (X) on youth's mood and neurotic disorders (Y) that is explained by the mediator (M). Parameter estimates (*b*) with standard errors (SE), 95% CIs and *p*-values are reported.

The statistical significance was set to $p < 0.05$. The descriptive analyses and Cox regression analyses were performed using IBM SPSS Statistics 28. The mediation analyses were done following a bootstrapping method including thousand simulations and performed with the mediation package for R (Tingley et al., 2014).

3. Results

Characteristics of the study population and a comparison between the cohorts are presented in Table 1. Significant differences between the exposed and unexposed cohorts were found in all of the offspring characteristics, except for sex and gestational age at birth (Table 1). Significant differences between the cohorts were also found for all maternal characteristics, except for maternal age at the time of offspring's birth, which was a matching criterion for the cohorts. Exposed youths' mothers were more often unmarried, from the lower socioeconomic status, and more likely to have mental or behavioural disorders, substance misuse, financial social assistance needs and criminal convictions. Also, a higher proportion of the exposed youth's mothers had died during the follow-up compared with unexposed. The cumulative childhood adversity score indicated that a higher proportion of the exposed youth had been exposed to multiple adversities compared with unexposed. The exposed and unexposed cohorts differed also with respect to OHC, and a higher percentage of the exposed had been placed in OHC during childhood and youth, at a younger age and for a longer cumulative period compared with the unexposed (Table 1).

Outpatient and inpatient hospital care for mood and neurotic disorders was more common among the exposed youth than the unexposed (Table 2). The number of outpatient care episodes (210.4 vs. 95.1 per 1000 people, $p < 0.001$) and the number of inpatient care episodes (60.6 vs. 16.7 per 1000 people, $p < 0.001$) were significantly higher among the exposed compared with the unexposed during the follow-up period. Statistically significant differences in the median age at the first care episode for the disorders in outpatient (14.5 vs. 15.1, $p = 0.112$) or inpatient hospital care (15.6 vs. 16.5, $p = 0.173$) were not found between the exposed and unexposed cohorts. Neither was the cumulative number of care episodes at outpatient or inpatient hospital care statistically significantly different (Table 2). Due to the low number of inpatient hospital care episodes for mood and neurotic disorders from 13 years of age, the outcome variable in the Cox regression analyses was the first record of the diagnoses for mood and neurotic disorders either in inpatient or outpatient hospital care (i.e. specialised healthcare). Of the exposed, 20.9% had been in specialised healthcare for the disorders ≥13 years of age compared with 9.6% among unexposed. The number of care episodes in specialised healthcare for the disorders was significantly higher among exposed compared with unexposed during the follow-up period (208.8 vs. 95.7 per 1000 people, $p < 0.001$) (Table 2).

The results from the univariate Cox regression analysis for the covariates in relation to mood and neurotic disorders are presented in Fig. 2 for the exposed and in Fig. 3 for the unexposed. Among the exposed, only female sex and first OHC episode ≥13 years of age were associated with youth's mood and neurotic disorders (Fig. 2). Among the unexposed, all the studied covariates except for low birth weight were associated with youth's mood and neurotic disorders (Fig. 3).

Table 3 present the results from the multivariable Cox regression analysis. The crude model (model 1) indicated that the exposed were twice more likely to have been in specialised healthcare for mood and neurotic disorders compared with the unexposed (HR 2.34, 95% CI 1.86–2.95). The further adjustments made for offspring's sex in model 2 yielded similar significant results on the association between the exposure and mood and neurotic disorders (AHR 2.34, 95% CI 1.85–2.95). In model 3, the association between the exposure and specialised healthcare for mood or neurotic disorders was diminished and statistically insignificant (AHR 1.30, 95% CI 0.96–1.77) following adjustments for cumulative childhood adversity score. In model 4, the influence of OHC was studied, and the association between the exposure and mood and neurotic disorders remained insignificant (AHR 1.36, 95% CI 0.99–1.85) after adjusting the model for offspring's sex and OHC. The results of model 5 in which all covariates were included simultaneously yielded insignificant results on the association between the exposure and specialised healthcare for mood and neurotic disorders (AHR 1.08, 95% CI 0.78–1.49). The results of model 5 indicated that female sex (AHR 2.44, 95% CI 1.90–3.12), cumulative childhood adversity score and OHC were

Table 1
Descriptive statistics and comparison between the exposed and unexposed cohorts.

	Exposed $n = 594$	Unexposed $n = 1735$	p-value
Follow-up time in years (median, IQR)	18.8 (16.7; 21.0)	18.6 (16.7; 20.9)	0.713
Offspring characteristics, *n* (%)			
Sex			0.475
Male	296 (49.8)	894 (51.5)	
Female	298 (50.2)	841 (48.5)	
Gestational age at birth			0.790
<37 weeks	48 (8.1)	148 (8.5)	
≥37 weeks	538 (90.6)	1584 (91.3)	
Missing data	8 (1.3)	3 (0.2)	
Gestational exposure to tobacco smoking			<0.001
No	138 (23.2)	1400 (80.7)	
Yes	456 (76.8)	335 (19.3)	
Birth weight			<0.001
<2500 g	70 (11.8)	109 (6.3)	
≥2500 g	524 (88.2)	1624 (93.6)	
Missing data	- (0.0)	2 (0.1)	
A diagnosis within the FASD spectrum			<0.001
No	553 (93.1)	- (0.0)	
Yes	41 (6.9)	- (0.0)	
Maternal characteristics, *n* (%)			
Maternal age at the time of offspring's birth			0.612
<25 years	225 (37.9)	637 (36.7)	
≥25 years	369 (62.1)	1098 (63.3)	
Maternal age at the time of offspring's birth (mean, SD)	27.3 (6.5)	27.6 (6.5)	0.449
Maternal marital status			<0.001
Unmarried (single/widowed/divorced)	474 (79.8)	705 (40.6)	
Married	120 (20.2)	1030 (59.4)	
Maternal socioeconomic status			<0.001
Low (manual workers/students/pensioners/others)	409 (68.9)	789 (45.5)	
High	185 (31.1)	946 (54.5)	
Maternal mental or behavioural disorder*			<0.001
No	318 (53.5)	1491 (85.9)	
Yes	276 (46.5)	244 (14.1)	
Maternal substance misuse*			<0.001
No	300 (50.5)	1701 (98.0)	
Yes	294 (49.5)	34 (2.0)	
Maternal recipiency of financial social assistance*			<0.001
No	65 (10.9)	1207 (69.6)	
Short-term (1–9 months during a calendar year)	140 (23.6)	322 (18.6)	
Long-term (10–12 months during a calendar year)	389 (65.5)	206 (11.9)	
Maternal criminality*			<0.001
No	549 (92.4)	1727 (99.5)	
Yes	45 (7.6)	8 (0.5)	
Death of mother*			<0.001
No	542 (91.2)	1729 (99.7)	
Yes	52 (8.8)	6 (0.3)	
Childhood adversity score*			<0.001
0	90 (15.2)	1353 (78.0)	
1 adversity	161 (27.1)	289 (16.7)	
2 adversities	173 (29.1)	73 (4.2)	
3 to 5 adversities	170 (28.6)	20 (1.2)	
Out-of-home care			
First OHC episode, n (%)			<0.001
No OHC episodes	213 (35.9)	1594 (91.9)	
Yes, <13 years of age	344 (57.9)	86 (5.0)	
Yes, ≥13 years of age	37 (6.2)	55 (3.2)	
Age in years at the first OHC episode (median, IQR)	2.9 (1.0; 6.9)	10.8 (5.3; 14.3)	<0.001
Cumulative length of OHC episodes in years (median, IQR)	9.2 (2.1; 15.0)	1.1 (0.2; 4.1)	<0.001

Note: p-values based on χ^2 test for categorical variables and Mann-Whitney U test or independent samples t-test for continuous variables, SD: Standard Deviation, IQR: Interquartile Range, FASD: Fetal Alcohol Spectrum Disorders, *occurred prior to the offspring's 13th birthday, Childhood adversity score includes the occurrence of maternal mental and/or behavioural disorder, maternal substance misuse, maternal long-term financial social assistance, maternal criminality, and death of the mother.

increasingly associated with mood and neurotic disorders. Regarding the cumulative childhood adversity score, the likelihood of mood and neurotic disorders was nearly similar across the categories and AHR spanned from 1.83 (1.33–2.51) for 1 adversity, AHR 1.90 (1.25–2.87) for 2 adversities to AHR 2.00 (1.24–3.22) for 3 to five adversities. With respect to OHC, the likelihood of the disorders differed between the categories, AHR spanning from 1.77 (95% CI 1.22–2.55) for first OHC episode <13 years of age to AHR 5.12 (95% CI 3.53–7.43) for first OHC episode ≥13 years of age (Table 3).

In the mediation analyses, we studied the mediating effect of OHC on the association between prenatal substance exposure and mood and neurotic disorders during youth. Although prenatal substance exposure showed a minor direct effect on mood and neurotic disorders ($b = 0.04$, 95% CI 0.01–0.08), the mediating effect of OHC was strong (indirect effect $b = 0.07$, 95% CI 0.05–0.08). The results indicated that OHC mediated 61% (95% CI 0.41–0.94) of the association between prenatal substance exposure and mood and neurotic disorders (Table 4, Fig. 4).

Table 2
Specialised healthcare for mood and neurotic disorders among the exposed and unexposed.

	Exposed ($n = 594$)	Unexposed ($n = 1735$)	p-value
Outpatient hospital care			
Care episodes (≥13 years of age) per 1000 people	210.4	95.1	<0.001
First care episode by age, n (%)			<0.001
No care episodes	431 (72.6)	1529 (88.1)	
<13 years of age	38 (6.4)	41 (2.4)	
≥13 years of age	125 (21.0)	165 (9.5)	
Age at the first care episode (median, IQR)	14.5 (13.3; 16.7)	15.1 (13.5; 16.8)	0.112
Cumulative number of care episodes ≥13 years of age (median, IQR)	14.0 (5.0; 32.0)	13.0 (2.0; 35.0)	0.386
Inpatient hospital care			
Care episodes (≥13 years of age) per 1000 people	60.6	16.7	<0.001
First care episode by age, n (%)			<0.001
No care episodes	548 (92.3)	1700 (98.0)	
<13 years of age	10 (1.7)	6 (0.3)	
≥13 years of age	36 (6.1)	29 (1.7)	
Age at the first care episode (median, IQR)	15.6 (13.2; 17.1)	16.5 (14.6; 17.9)	0.173
Cumulative number of days spent in inpatient hospital care ≥13 years of age (median, IQR)	12.0 (3.0; 28.0)	12.0 (3.5; 22.5)	0.861
Outpatient or inpatient hospital care			
Care episodes (≥13 years of age) per 1000 people	208.8	95.7	<0.001
First care episode by age, n (%)			<0.001
No care episodes	429 (72.2)	1525 (87.9)	
<13 years of age	41 (6.9)	44 (2.5)	
≥13 years of age	124 (20.9)	166 (9.6)	

Note: Mood and neurotic disorders based on ICD-10 categories F30-F39 and F40-F48; Comparison between exposed and unexposed based on χ^2 test for categorical variables and Mann-Whitney *U* test for continuous variables, IQR; Interquartile Range.

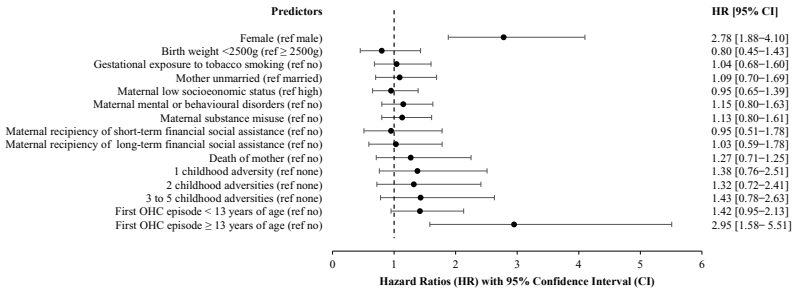

Fig. 2. Hazard ratios (HR) with 95% Confidence Intervals (CI) for predictors in relation to mood and neurotic disorders for exposed offspring. Follow-up starts from the 13th birthday and continues until the first episode in specialised healthcare (≥13 years of age), death or end of follow-up 2016 ($n = 594$).

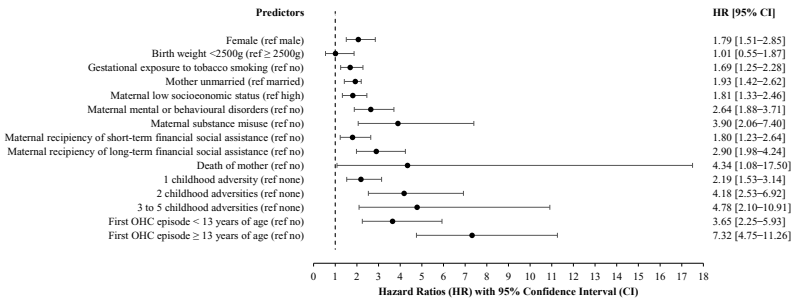

Fig. 3. Hazard ratios (HR) with 95% Confidence Intervals (CI) for predictors in relation to mood and neurotic disorders for unexposed offspring. Follow-up starts from the 13th birthday and continues until the first episode in specialised healthcare (≥13 years of age), death or end of follow-up 2016 ($n = 1735$).

Table 3
Cox proportional hazard regression analysis with crude Hazard Ratio (HR) and adjusted Hazard Ratios (AHR) with 95% Confidence Intervals (CI) for specialised healthcare for mood or neurotic disorders. Follow-up starts from the 13th birthday and continues until the first episode in specialised healthcare, death or end of follow-up 2016 ($N = 2329$).

	Model 1		Model 2		Model 3		Model 4		Model 5	
	HR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value	AHR (95% CI)	p-value
Offspring characteristics										
Prenatal substance exposure										
Unexposed (ref)	1		1		1		1		1	
Exposed	2.34 (1.86–2.95)	<0.001	2.34 (1.85–2.95)	<0.001	1.30 (0.96–1.77)	0.095	1.36 (0.99–1.85)	0.055	1.08 (0.78–1.49)	0.648
Sex										
Male (ref)			1		1		1		1	
Female			2.35 (1.83–3.00)	<0.001	2.34 (1.83–2.99)	<0.001	2.44 (1.91–3.13)	<0.001	2.44 (1.90–3.12)	<0.001
Maternal characteristics										
Cumulative childhood adversity score*										
No (ref)					1				1	
1 adversity					2.17 (1.60–2.96)	<0.001			1.83 (1.33–2.51)	0.067
2 adversities					2.60 (1.76–3.83)	<0.001			1.90 (1.25–2.87)	0.002
3 to 5 adversities					2.66 (1.71–4.15)	<0.001			2.00 (1.24–3.22)	0.005
Out-of-home care										
First OHC episode										
No OHC episodes							1		1	
Yes, <13 years of age							2.34 (1.66–3.29)	<0.001	1.77 (1.22–2.55)	0.002
Yes, ≥13 years of age							5.97 (4.14–8.60)	<0.001	5.12 (3.53–7.43)	<0.001

Note: Childhood adversity score includes the occurrence of maternal mental or behavioural disorder, maternal substance misuse, maternal recipiency of long-term financial social assistance, maternal criminality, and death of the mother prior to offspring's 13th birthday.

Table 4
The effect of out-of-home care (OHC) on the association between prenatal substance exposure and youth's mood and neurotic disorders. Parameter estimates (*b*) with standard error (SE), 95% Confidence Interval (CI) and *p*-value.

	Out-of-home care			
	b	SE	95% CI	p-Value
Prenatal substance exposure and mediator (a)	0.59	0.02		<0.001
Mediator and youth's mood and neurotic disorder (b)	0.94	0.11		<0.001
Indirect effect (ab)	0.07		0.05–0.08	<0.001
Direct effect (c')	0.04		0.01–0.08	0.028
Proportion mediated (ab / (ab + c'))	0.61		0.41–0.94	<0.001
Total effect (c)	0.11		0.07–0.14	<0.001

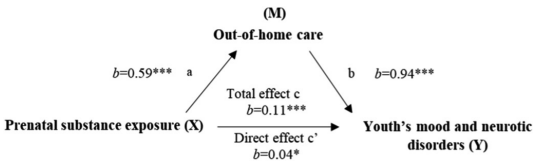

Fig. 4. The mediating effect of out-of-home care (M) on the association between prenatal substance exposure (X) and youth's mood and neurotic disorders (Y). Parameter estimates (*b*) with *p*-value ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$.

4. Discussion

This study shows a two-fold higher likelihood of specialised healthcare episode for mood and neurotic disorder among youth with prenatal substance exposure compared with matched unexposed youth. The study shows that mood and neurotic disorders are influenced by female sex, adversities in the postnatal caregiving environment and out-of-home care (OHC), and the association between prenatal substance exposure and mood and neurotic disorders is mediated by OHC.

Prior research has mainly studied specific mood or neurotic disorders among small samples of children and youth exposed to alcohol or other substances during pregnancy, and the information on symptomatology has mainly been based on parental assessment (Fryer et al., 2007; Gray et al., 2005; Nygaard et al., 2020; Roebuck et al., 1999; Walthall et al., 2008; Weyrauch et al., 2017). Despite these methodological differences, our results are in line with prior evidence indicating a higher prevalence of mood and neurotic disorders among prenatally exposed youth.

Earlier studies among children with FASD (Famy et al., 1998; Fryer et al., 2007; Walthall et al., 2008; Weyrauch et al., 2017), and children and youth with prenatal exposure to other substances (Gray et al., 2005; Nygaard et al., 2020) show, similar to the present study, the association between mood and neurotic disorders and caregiving adversities. Mood and neurotic disorders are, thus, multifaceted in these populations, and involve both adverse prenatal and postnatal conditions. In line with prior studies (Kuehner, 2003; Rapee et al., 2009), the study also shows that mood and neurotic disorders are more common among female youth.

A strength of our study was the ability to address the influence of multiple types of postnatal risk factors in our analyses. Our results are in line with earlier studies showing that maternal substance use during pregnancy is associated with other, often co-occurring risk factors in the postnatal caregiving environment including single parenthood, maternal mental health disorders, substance misuse, financial difficulties and challenges in the parenting domain (Esper and Furtado, 2014; Jääskeläinen et al., 2016). Our results showed that the exposure to a cumulative number of adversities in the postnatal caregiving environment was associated with an increased likelihood of mood and neurotic disorders. The significant influence of early life adversities on youth's mental health outcomes has been identified also in earlier studies (Basu and Banerjee, 2020; Essex et al., 2006). Exposure to adversities in the postnatal caregiving environment can be associated with the stress of the child and this can cause physiological and anatomical

alternations in the brain (Danese and McEwen, 2012; Shonkoff and Garner, 2012; Su et al., 2021), potentially affecting child's mental health outcomes. Adversities in childhood can also negatively influence parenting behaviours and parent-child interaction, and thus, indirectly increase the likelihood of a child's symptomatology of mood and neurotic disorders (Brumariu and Kerns, 2010; Rapee et al., 2009; Reising et al., 2013; Staton-Tindall et al., 2013).

The adversities in the postnatal caregiving environment and instability in care are also common indications for child protection services and a high proportion of prenatally exposed children need OHC during early childhood (Flannigan et al., 2021; Sarkola et al., 2007). Also, our results show that a high proportion of the exposed youth had been placed in OHC in childhood. Previous studies also show that multiple types of childhood adversities (Basu and Banerjee, 2020; Björkenstam et al., 2017; Essex et al., 2006) and OHC predict mood and neurotic disorders in childhood (Bronsard et al., 2016; Sarkola et al., 2011). In line with prior studies, also the mediation analyses indicated a significant influence of OHC on mood and neurotic disorders and showed that 61% of the association between prenatal substance exposure and youth's mood and neurotic disorders was explained by the influence of OHC. OHC typically refers to significant problems in the postnatal caregiving environment and parenting domains, which can negatively influence a child's mental health. However, it was not in the scope of this study to investigate the role of OHC in more detail, and therefore, more studies investigating the influence of OHC are needed. The influence of OHC likely differs between the cohorts considering the timing of the first OHC episode and the duration, potentially reflecting different reasons for OHC placement among the exposed and unexposed. However, having to be separated from biological parents is a traumatic experience as such and underlying capacity and resilience to cope with this experience may also differ between the exposed and unexposed children.

Youth is a period for education completion, finding a job and establishing relationships. Mood and neurotic disorders commonly evolve in youth, and the high prevalence of these disorders among exposed youth may contribute to functional impairments and challenge the accomplishment of these activities (Patel et al., 2007). The disorders may, therefore, have a substantial impact on economic and social outcomes extending into adulthood. With a view to the prevention of these disorders and related problems, the optimisation of postnatal parenting and caregiving among prenatally exposed children and youth seems important. Early preventative interventions aiming to reduce the long-term consequences of prenatal substance exposure should focus on reducing postnatal childhood adversities and potential adverse effects of OHC.

4.1. Strengths and limitations

A strength of this study is the use of national health and social care registers with high completeness and validity (Aro et al., 1990; Gissler and Haukka, 2004). By using national mandatory health and social care register data on specific types of childhood adversities, we were able to avoid the risk of recall bias or under-reporting of adverse events. In addition, we included data on specialised healthcare episodes for mood and neurotic disorders and thus were able to avoid data collection inaccuracies related to retrospectively reported information on youth symptomatology only. However, specialised healthcare data likely include more severe cases of youth with mood and neurotic disorders, and we may have missed milder forms of the studied psychiatric disorders.

Although the delivery of out-of-home care generally indicates significant problems in the caregiving environment or the parenting domain, we acknowledge the limitations related to the indicators of childhood adversities and the possibility of missed information on specific indicators (e.g. neglect, abuse, witnessing domestic violence, parent-child interaction, and paternal influences) that could be linked with mood and neurotic disorders.

In addition, we acknowledge the lack of specific information on the type, timing and severity of maternal alcohol and/or other substance use during the pregnancy. Self-reported information on substance use in the clinic setting is inevitably inaccurate and the data precludes meaningful analyses on independent associations with a specific type of substance. Therefore, exposed vs. unexposed categorisation was applied in the analyses. Our exposed cohort, however, represent children born to women with significant substance misuse during pregnancy, and thus excludes children born to mothers with low or moderate substance use. Furthermore, the unexposed cohort may also include cases with low prenatal substance exposure. All efforts were made to exclude from the unexposed group youth with registered information on maternal substance misuse related primary or secondary diagnoses or external causes in specialised healthcare one year before delivery or at the time of delivery. Substance use is also commonly linked with significant psychiatric comorbidity as shown among mothers in our exposed cohort. Our data did not, however, allow us to separately delineate contributions of maternal postnatal substance use and psychiatric comorbidities on youth outcomes. Lastly, as this is an observational study, causal links are difficult to prove.

5. Conclusions

Mood and neurotic disorders are more common following prenatal substance exposure and are interlinked with significant postnatal caregiving adversities and OHC. These disorders could potentially be prevented with efforts focused not only on preventing prenatal substance exposure but also on improving the postnatal caregiving environment and optimising child protection services.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.04.039.

Author contributions

NMN merged the data, conducted the statistical analyses and drafted the manuscript and revised the later versions. MG participated in data collection design, anonymised the original data, advised with statistical analyses and reviewed and revised the manuscript. TS, IAR, and HK participated in data collection design and reviewed and revised the manuscript. AK acquired funding for the research, designed the data collection and reviewed and revised the manuscript. All the authors approved the final version and consented to its publication.

Data availability

The data are not publicly available due to data confidentiality. The authors do not have permission to share the data, but similar data can be applied for from Findata, the Finnish Social and Health Data Permit Authority: (https://findata.fi/en/).

Role of funding source

The work was supported by Samfundet Folkhälsan i svenska Finland rf; the Juho Vainio foundation; the Signe and Ane Gyllenberg Foundation; Medicinska Understödsföreningen Liv och Hälsa rf.; the Alli Paasikivi Foundation. The funding sources had no role in this study.

Conflict of interest

The authors have no conflicts of interest to declare.

Acknowledgement

We would like to thank Aku-Ville Lehtimäki for advice on statistical analyses.

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