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PRENATAL PSYCHOLOGICAL DISTRESS AND PARENTING IN THE CONTEXT OF TOBACCO AND SUBSTANCE USE DISORDERS: HOW TO BREAK THE CHAIN OF ADVERSITY?

Heidi Jussila

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University of Turku

Faculty of Medicine
Department of Child Psychiatry
Department of Obstetrics and Gynecology
Doctoral Programme in Clinical Research

Supervised by

Professor Hasse Karlsson,
Faculty of Medicine
Department of Clinical Medicine
Psychiatry
University of Turku, Finland

Adjunct Professor Eeva Ekholm,
Faculty of Medicine
Department of Clinical Medicine
Obstetrics and Gynaecology
University of Turku, Finland

Adjunct Professor Marjukka Pajulo,
Faculty of Medicine
Department of Clinical Medicine
Child Psychiatry
University of Turku, Finland

Reviewed by

Professor Inger Sundström Poromaa
Department of Women's and Children's Health
Obstetrics and Gynecology
Uppsala University, Sweden

Adjunct Professor Mirjami Mäntymaa
Faculty of Medicine
Child Psychiatry
University of Oulu, Finland

Opponent

Professor Ilona Luoma
Faculty of Health Sciences
Institute of Clinical Medicine
Child Psychiatry
University of Eastern Finland, Finland

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To my family: Ville, Onni, Vilja and Valo
To my childhood family: Mother, Father, Antti, Noora and Anna
To all of my teachers

UNIVERSITY OF TURKU
Faculty of Medicine
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ABSTRACT

This dissertation aimed at investigating momentums to break the chain of adverse outcomes in the context of tobacco and substance use disorders in pregnancy. First, we evaluated the efficacy of the new parental mentalization focused ultrasound intervention on maternal prenatal parenting, psychological distress, participation in obstetric care, fetal drug exposure and perinatal outcomes using a randomized and controlled research design in a sample of 90 pregnant women with substance use problems. The beneficial effects of the intervention could not be confirmed with the methodology and design used. However, it is of note that high study retention and adherence were observed, especially in the intervention group and regarding the parenting focused interactive ultrasound sessions. Second, we investigated the role of maternal-fetal attachment and pregnancy-related anxiety in determining smoking in pregnancy and smoking cessation during pregnancy in the FinnBrain Birth Cohort Study of over 3700 pregnant women. Our findings did not substantiate associations of the total level of maternal-fetal attachment and pregnancy-related anxiety with prenatal smoking behavior. However, the results revealed that experiencing stronger altruistic maternal-fetal attachment associated with an increased probability of smoking cessation among pregnant smokers. Further, those women who smoked and suffered from more intense fear of childbirth were less likely to quit smoking in early pregnancy than those women experiencing low or moderate fear of childbirth. In conclusion, the parental mentalization focused ultrasound intervention constitutes a promising method of encountering pregnant women with harmful substance use as the approach seemed to be well-accepted by these high-risk women who often perceive barriers to treatment and are at risk of inadequately attending prenatal care. The studies conducted in the pregnancy cohort suggest that the experience of a stronger maternal-fetal attachment by the women who smoked associated with a greater likelyhood of quitting smoking during pregnancy, and severe fear of childbirth seems to represent a barrier to smoking cessation. Thus, stregthening altruistic maternal-fetal attachment and alleviating fear of childbirth constitute interesting novel focuses for interventions promoting prenatal smoking cessation.

KEYWORDS: substance use disorder, smoking, pregnancy, prenatal, prenatal parenting, prenatal psychological distress, maternal-fetal attachment, paretal mentalization, pregnancy-related anxiety, fear of childbirth, intervention

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen laitos
Lastenpsykiatria
Synnytys- ja naistentautioppi
HEIDI JUSSILA: Tutkimus mahdollisuuksista katkaista raskausajan tupakka- ja päihdehäiriöihin liittyvää ylisukupolvista vastoinkäymisten ketjua. Huomion kohteena äidin raskausajan vanhemmuus ja stressi
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TIIVISTELMÄ

Väitöstutkimuksessa selvitettiin mahdollisuuksia vaikuttaa odottavan äidin raskausajan tupakka- ja päihdehäiriöihin liittyvään ylisukupolviseen kielteisten päätetapahtumien ketjuun. Tutkimuksen ensimmäisessä osassa tarkasteltiin 90 päihdeongelmaisen raskaana olevan naisen otoksessa vanhemmuutta vahvistavan ultraääni-intervention vaikuttavuutta satunnaistetussa ja kontrolloidussa asetelmassa. Tutkimuksella ei voitu käytetyin menetelmin todentaa intervention myönteistä vaikutusta odottavan äidin raskausajan vanhemmuuteen, stressitasoon, obstetrisen hoidon käyttöön, sikiön päihdealtistukseen tai lapsen terveyteen syntymähetkellä. Huomionarvoista kuitenkin oli, että interventioryhmään kuuluneiden odottavien äitien keskuudessa tutkimuksen keskeyttäminen oli harvinaisempaa kuin kontrollisryhmässä, ja heidän osallistumisasteensa vanhemmuutta vahvistaviin hoidollisiin ultraäänitutkimuksiin oli korkea. Toisessa osassa tarkasteltiin raskaudenaikaisen kiintymyksen ja raskauteen liittyvän ahdistuneisuuden yhteyttä raskausajan tupakointiin ja tupakoinnin lopettamiseen yli 3700 naisen FinnBrain–raskauskohorttiaineistossa. Raskaudenaikaisen kiintymyksen tai raskauteen liittyvän ahdistuneisuuden kokonaistason ei havaittu olevan yhteydessä raskausajan tupakointikäyttäytymiseen, mutta voimakkaampi altruistinen kiintymys sikiöön liittyi suurempaan tupakoinnin lopettamisen todennäköisyyteen. Tutkimus osoitti myös, että tupakoivat naiset, jotka kokivat voimakasta synnytyspelkoa, kykenivät harvemmin lopettamaan tupakoinnin kuin naiset, jotka kokivat vähäistä tai kohtalaista synnytyspelkoa. Yhteenvetona todetaan, etttä vanhemmuutta vahvistava ultraääni-interventio on lupaava hoitomuoto erityisesti sen vuoksi, että päihdeongelmaiset naiset, jotka usein kokevat esteitä raskaudenaikaiselle hoidolle ja osallistuvat siihen riittämättömästi, näyttivät hyväksyvän uuden hoitomuodon ja sitoutuvan siihen hyvin. Tutkimukset raskauskohorttiaineistossa osoittivat, että voimakkaampi altruistinen kiintymys sikiöön liittyy korkeampaan ja voimakas synnytyspelko matalampaan tupakoinnin lopettamisen todennäköisyyteen raskausaikana. Täten altruistisen kiintymyksen vahvistaminen ja synnytyspelon lievittäminen muodostavatkin kiinnostavia fokuksia tupakoinnin lopettamista tukeville interventioille.

AVAINSANAT: päihdehäiriö, tupakointi, raskaus, raskausaika, raskausajan vanhemmuus, raskausajan stressi, kiintymys sikiöön, mentalisatiokyky, raskauteen liittyvä ahdistuneisuus, synnytyspelko, interventio

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Abbreviations

DSM-5	Diagnostic and Statistical Manual of Mental Disorders, fifth edition
ICD-10	International Classification of Diseases, tenth revision
ICD-11	International Classification of Diseases, eleventh revision
NIDA	The National Institute of Drug Abuse in the USA
FASD	Fetal alcohol spectrum disorders
NAS	Neonatal abstinence syndrome
MFAS	Maternal-fetal Attachment Scale
P-PRFQ	Prenatal Parental Reflective Functioning Questionnaire
RF	Reflective Functioning
ASAM	The American Society of Addiction Medicine
HAL clinic	The abbreviation HAL refers to the acronym generated from the Finnish words for: illicit drugs, alcohol and prescription medication. The HAL clinic is a specialized obstetric outpatient unit offering multidisciplinary prenatal care for women with substance use problems.
4D	Four-dimensional ultrasound
2D	Two-dimensional ultrasound
3D/4D	Three or four-dimensional ultrasound
RCT	Randomized and controlled clinical trial
TAU	Treatment-as-usual
gwks	gestational weeks
TWEAK	A brief screening questionnaire for prenal alcohol use. The acronym TWEAK refers to the warnings signs of alcohol use disorder: an increased alcohol *tolerance*, friends and relatives being *worried* about one's alcohol use, a need for *eye-openers*, having *amnesia* related to alcohol use or feelings that drinking needs to be *(k)cut down*.
EuropASI	European Addiction Severity Index–questionnaire
UHPLC-QTOF/MS	Ultra-high performace liquid chromatography-quadrupole time-of-flight mass spectrometry
LC-MS/MS	Liquid chromatography-tandem mass spectrometry

THC-COOH	Tetrahydrocannabinol carboxylic acid
SGA	Small for gestational age
M	Mean
SD	Standard deviation
OR	Odds ratio
aOR	Adjusted odds ratio
CI	Confidence interval
SE	Standard error
P-value	Probability value
ANCOVA	Analysis of covariance
BF	Bayes Factor
ANOVA	Analysis of variance
EPDS	Edinburgh Pre/Postnatal Depression Scale
SCL-90	Symptom Checklist-90
PRAQ-R2	Pregnancy-Related Anxiety Questionnaire, revised version 2
STAI	State-Trait Anxiety Inventory

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Jussila, H., Ekholm, E., & Pajulo, M. (2020). A New Parental Mentalization Focused Ultrasound Intervention for Substance Using Pregnant Women. Effect on Self-reported Prenatal Mental Health, Attachment and Mentalization in a Randomized and Controlled Trial. International Journal of Mental Health and Addiction, 1–24. https://doi.org/10.1007/s11469-019-00205-y

II Jussila, H., Pajulo, M., & Ekholm, E. (2020). A Novel 4D Ultrasound Parenting Intervention for Substance Using Pregnant Women in Finland: Participation in Obstetric Care, Fetal Drug Exposure, and Perinatal Outcomes in a Randomized Controlled Trial. Maternal and Child Health Journal, 24(1), 90–100. https://doi.org/10.1007/s10995-019-02773-w

III Jussila, H., Pelto, J., Korja, R., Ekholm, E., Pajulo, M., Karlsson, L., Karlsson, H. (2020). The Association of Maternal-Fetal Attachment with Smoking and Smoking Cessation during Pregnancy in The FinnBrain Birth Cohort Study. BMC Pregnancy and Childbirth, 20(741), 1–13. https://doi.org/10.1186/s12884-020-03393-x

IV Jussila, H., Pelto, J., Korja, R., Ekholm, E., Pajulo, M., Karlsson, L., Karlsson, H. The Role of Pregnancy-Related Anxiety in Smoking in Pregnancy and Smoking Cessation during Pregnancy in The FinnBrain Birth Cohort Study. *Manuscript.*

1 Introduction

Pregnancy is a very unique period in the course of life. Becoming a parent has been considered one of the most profound psychological, social and neurobiological transitions in adult life (Ammaniti & Gallese, 2014; Hoekzema et al., 2017; Mayes, Rutherford, Suchman, & Close, 2012; Rilling & Young, 2014; Stern, Bruschweiler-Stern, & Freeland, 1998). Further, the fetus grows and develops very rapidly during pregnancy, and the first 1000 days from conception has been considered an extremely important phase for brain development and the period that shapes the whole future of an individual (Britto et al., 2017; Lo, Das, & Horton, 2016). It is a great public health concern that the opportunities are not equal for all newborns as their health at the moment of birth has been found to determine their wellbeing, attainments and wealth in the course of life (Aizer & Currie, 2014; Behnke, Smith, Committee on Substance Abuse, & Committee on Fetus and Newborn, 2013; Bilgin, Mendonca, & Wolke, 2018). Health related inequalities, all too often, stem from the intergenerational chain linking maternal prenatal adversities to vulnerabilities in the fetus/child (Aizer & Currie, 2014; Behnke et al., 2013; Stein et al., 2014). Maternal tobacco and substance use disorders in pregnancy constitute a significant burden for the health and well-being of both individuals: the expectant mother and the unborn child (Behnke et al., 2013; Kahila, Gissler, Sarkola, Autti-Ramo, & Halmesmaki, 2010). Fetal exposure to maternal smoking or substance use has several detrimental effects on fetal brain development and neonatal health (Behnke et al., 2013; Ekblad, Korkeila, & Lehtonen, 2015; O'Leary et al., 2013; Roozen et al., 2016). Research to date has established that prenatal exposure to tobacco or substances predicts impairment in many outcomes, such as the offspring's neurocognitive development, growth, learning, educational attainment, income and subjective wellbeing in both short term and long term (Behnke et al., 2013; Bilgin et al., 2018; Forray & Foster, 2015). Further, maternal tobacco and substance use disorders often indicate an accumulation of prenatal adversity. Pregnant women with tobacco or substance use disorders are particularly prone to experience a high level of prenatal psychological distress (Biaggi, Conroy, Pawlby, & Pariante, 2015; Goodwin, Cheslack Postava, Nelson, Smith, Hasin et al., 2017; Holbrook & Kaltenbach, 2012; Ordean, Kahan, Graves, Abrahams, & Boyajian, 2013; Strengell, Väisänen, Joukamaa, Luukkaala,

& Seppä, 2014) which has been found to associate with a wide spectrum of independent adverse effects on the offspring and the quality of postnatal parenting (Earls, Yogman, Mattson, & Rafferty, 2019; Stein et al., 2014). The potential mechanisms underlying the detrimental effect of prenatal psychological distress on child outcomes may be mediated by maternal prenatal health practices (Dunkel Schetter, 2011; Huizink & de Rooij, 2018; Staneva, Bogossian, Pritchard, & Wittkowski, 2015). Unfortunately, prenatal psychological distress has been found to compromise the abstinence practices of pregnant women who want to cease substance use or smoking (Alhusen, Jeanne, Ayres, & DePriest, 2016; Cannella, Yarcheski, & Mahon, 2018; Riaz, Lewis, Naughton, & Ussher, 2018). Further, maternal tobacco and substance use disorders, together with comorbid mental health problems and psychosocial stressors, often severely compromise the quality of postnatal nurturing care for the child (Earls et al., 2019; Romanowicz et al., 2019; Smith, Wilson, & Comittee on Substance Use and Prevention, 2016; Suchman, & DeCoste, 2018; Tandon et al., 2013) thereby posing a serious threat to healthy child development (Britto et al., 2017; Smith et al., 2016).

Research to date has established that parenting begins in pregnancy and, especially in populations at high risk, stronger prenatal parenting constitutes a counterforce to adversities by promoting maternal prenatal health practices (Cannella et al., 2018; Magee et al., 2014; Massey et al., 2015), neonatal/child outcomes (Branjerdporn, Meredith, Strong, & Garcia, 2017) and a resilience-building nurturing environment for the child (Dubber, Reck, Muller, & Gawlik, 2015; Foley, 2018; Tichelman et al., 2019). Prenatal exposures to drugs, alcohol or tobacco are preventable risks for fetal/child development, and maternal-fetal attachment has been suggested as the most important predictor of the expectant mother's positive health practices (Cannella et al., 2018). Research to date has established that becoming a caregiver constitutes a strong motivational drive for abstinence and recovery from substance use disorders (Jessup et al., 2014; Kendler, Ohlsson, Svikis, Sundquist, & Sundquist, 2017; Massey & Wisner, 2018). Further, the expectant mother's stronger prenatal attachment towards the fetus predicts a better quality of nurturing care for the child (Foley, 2018); this has been demontrated to be especially protective as regards the child's development in families affected by parental substance use (Bada et al., 2012; Milligan et al., 2019; Niccols, Milligan, Sword et al., 2012; Wlodarczyk, Schwarze, Rumpf, Metzner, & Pawils, 2017).

This dissertation research project aimed at investigating potential momentums for intervening in the intergenerational chain of adversity in the context of maternal tobacco and substance use disorders in pregnancy. First, we investigated the efficacy of the new prenatal parental mentalization focused ultrasound intervention for treatment of high-risk pregnant women with recent or current harmful substance use in a randomized and controlled clinical trial. Second, we evaluated the role of

maternal-fetal attachment and pregnancy-related anxiety in determining smoking in pregnancy and smoking cessation during pregnancy in the large population-based FinnBrain Birth Cohort Study; the primary interest being to investigate these specific psychological phenomena related to the transition to parenthood, and hence, to find potential new points for prenatal interventions. Two very different approaches and samples were used to gain a more profound understanding of the potential ways to overcome intergenerational adversity connected to prenatal tobacco and substance use disorders.

2 Review of the Literature

2.1 Prenatal tobacco and substance use disorders

2.1.1 Prenatal tobacco use disorder

2.1.1.1 Conceptualization

Tobacco use disorder has been defined in the fifth and most recent edition of Diagnostic and Statistical Manual (DSM-5) of The American Psychiatric Association. Based on DSM-5, tobacco use disorder is determined by three main criteria: loss of control over smoking, tolerance to the effects of tobacco smoking, and withdrawal symptoms associated with attempts to reduce or quit smoking. Difficulties in controlling the use of tobacco are manifested in the following ways: inability to reduce or quit smoking despite efforts to do so, craving for tobacco, excessive time spent in smoking, neglect of responsibilities due to smoking and, continuation of smoking despite potential harms to health and social relationships. Tolerance to nicotine refers to an adaptation to repeated nicotine administration and hence reduced subjective effects of tobacco and a tendency to increase the amount of smoking in order to gain the same effects as before. Typical nicotine withdrawal symptoms consist of depressive and anxiety symptoms, agitation, headaches, weight gain due to increased appetite, slower heart rate, and sleep and concentration difficulties. Furthermore, the DSM-5 offers a tool for the assessment of the severity of tobacco use disorder. Based on the number of symptoms, the severity of tobacco use disorder is classified into three levels – mild, moderate or severe (American Psychiatric Association, 2013). The tenth revision of International Classification of Diseases (ICD-10) by the World Health Organization presents the criteria defining two main diagnostic classifications of tobacco use disorder: harmful tobacco use and tobacco dependence. The criteria for tobacco dependence consist of six attributes, and at least three of them have to be present together at some time during the previous year. At the level of dependence, a person has a strong desire or compulsion to smoke, difficulties in controlling smoking, tolerance to the effects of tobacco, nicotine-specific withdrawal symptoms when smoking use has reduced or stopped,

a progressive tendency to neglect other interests or sources of pleasure because of tobacco smoking use and to continue smoking despite its harmful consequences and awareness of the harmful effects (World Health Organization, 1992).

The nomenclature regarding tobacco use disorder is changing in the upcoming eleventh version of the International Classification of Diseases (ICD-11) and the next revision will address *disorders due to use of nicotine* (World Health Organization, 2020). Indeed, nicotine addiction constitutes the core problem in prenatal smoking behavior (Crume, 2019; Riaz et al., 2018). Nicotine addiction often develops during adolescence, and heavier smoking as well as more severe nicotine addiction prior to pregnancy have been demonstrated to predict smoking in pregnancy and persistent smoking during pregnancy (Crume, 2019; Riaz et al., 2018). In general, tobacco products are considered to exert the strongest dependence potential among substances, constituted by the abuse liability and product appeal (Henningfield, Hatsukami, Zeller, & Peters, 2011). Unfortunately, previous research has suggested that women are more prone to nicotine addiction and to experience greater difficulties in smoking cessation than males due to more efficient nicotine metabolism, stronger conditioning to the rewarding effects of smoking and avoidance of negative affective states during tobacco withdrawal (Benowitz, 2010). Further, at the same level of nicotine exposure women have been found to display more severe dependence on tobacco and to experience more frequently the health related harm of smoking, such as pulmonary diseases (Baraona, Lovelace, Daniels, & McDaniel, 2017). Nicotine metabolism has been found to accelerate during pregnancy which may lead to increased smoking in early pregnancy, continuation of smoking during pregnancy and decreased effectiveness of prenatal nicotine replacement therapy (Arger et al., 2019; Bowker, Lewis, Coleman, & Cooper, 2015). The neurobiology of nicotine addiction involves positive reinforcement of smoking behavior due to pleasure and increased arousal induced by nicotine administration (Benowitz, 2010). On the other hand, a tendency to avoid and relieve nicotine withdrawal symptoms by continued smoking leads to negative reinforcement, the process referring to persistence and increase in smoking that an individual can avoid negative consequences of reducing or quitting smoking (Benowitz, 2010). Moreover, the development of nicotine addiction is also related to conditioning in which the association between the cues and anticipated effects of nicotine administration contributes to cravings for tobacco (Benowitz, 2010).

2.1.1.2 Aetiology and risk factors

Smoking in pregnancy has been considered to reflect an adverse developmental cascade which has its roots in the expectant mother's childhood / adolescence or even beyond, in the intergenerational burden of familial risks and disadvantage

leading to health related inequality (Aizer & Currie, 2014; Bay, Morton, & Vickers, 2016; Benowitz, 2010; Brumana, Arroyo, Schwalbe, Lehtimaki, & Hipgrave, 2017; Catalano et al., 2012; Gray & Squeglia, 2018). The majority of those women who smoke before pregnancy have been found to continue smoking during pregnancy (Schoenaker, Ploubidis, Goodman, & Mishra, 2017). Tobacco smoking begins usually in adolescence, and around 80% of smokers start smoking by the age of 18 years (Benowitz, 2010). The risk factors for starting smoking in childhood / adolescence consist of genetic predisposition, parental and peer influences and the child's own developmental trajectory, especially externalizing and behavioral problems (Benowitz, 2010). The heritability of nicotine addiction, including its severity, has been found to be around 50% or even higher (Benowitz, 2010). Family environmental factors, such as parental substance use and childhood adverse experiences, have been found to associate with an increased risk for tobacco use disorder (Hughes et al., 2017; Stone, Becker, Huber, & Catalano, 2012). Externalizing behavioral problems and depression (Benowitz, 2010; Groenman, Janssen, & Oosterlaan, 2017) as well as a tendency to risk taking, rebelliousness and poor performance at school have been linked with smoking initiation in childhood / adolescence (Benowitz, 2010). An intergenerational continuity has been established as externalizing problems in childhood have been demonstrated to associate with smoking during pregnancy (Sutin, Flynn, & Terracciano, 2017) and maternal prenatal smoking has been found to associate independently with the offspring's increased risk for externalizing behavior (Ekblad, Mikael, Lehtonen, Korkeila, & Gissler, 2017). Further, the intergenerational transmission of health risks is supported by the observation that there is a detrimental association between maternal prenatal smoking and the offspring's lifetime smoking (Kandel, Griesler, & Schaffran, 2009). Tobacco use and mental disorders have been shown to be highly comorbid, and the mechanisms underlying the co-occurrence of tobacco smoking and mental disorders are likely to involve a shared genetic predisposition and a tendency of nicotine to alleviate psychiatric symptoms (Benowitz, 2010). Extensive literature has established a detrimental association between prenatal psychological distress and smoking behavior during pregnancy (Biaggi et al., 2015; Lancaster et al., 2010; Räisänen et al., 2014; Riaz et al., 2018; Smedberg, Lupattelli, Mardby, Overland, & Nordeng, 2015).

Unfortunately, smoking in pregnancy is also strongly predicted by socioeconomic factors and environmental influences (Brumana et al., 2017; Catalano et al., 2012; Härkönen, Lindberg, Karlsson, Karlsson, & Scheinin, 2018; Kandel et al., 2009; Patton et al., 2018). Prenatal smoking accumulates in more disadvantaged and vulnerable populations in our society (Aizer & Currie, 2014; Biaggi et al., 2015; Ekblad, Gissler, Korkeila, & Lehtonen, 2014; Härkönen et al., 2018). In Finland, smoking in pregnancy has shown to be robustly predicted by

socio-economic factors, such as a low level of maternal education, younger maternal age and single parenthood (Ekblad et al., 2014). Several prior studies have addressed the adverse association between educational disadvantage and maternal prenatal smoking habits (Aizer & Currie, 2014; Kandel et al., 2009; Smedberg, Lupattelli, Mårdby, & Nordeng, 2014). One large population-based study from the USA has shown that women with lower education start smoking earlier in adolescence, are more likely to smoke and continue smoking during pregnancy, smoke a greater number of cigarettes per day, display more severe nicotine addiction and higher urine/blood cotinine levels than women with higher education (Kandel et al., 2009). In Finland, maternal low education has been found to constitute the strongest predictor for smoking in pregnancy (Härkönen et al., 2018). Even though the level of maternal education is a robust and well-established predictor for smoking behavior during pregnancy, the mechanisms underlying the detrimental association between educational disadvantage and prenatal smoking habits are not so well-elucidated (Kandel et al., 2009). The association may be explained by disparities between well-educated and poorly educated pregnant women in genetic profiles and associative personality characteristics (Belsky et al., 2016; Hampson, Goldberg, Vogt, & Dubanoski, 2007; Massey et al., 2016), familial risks (Belsky et al., 2016; Kandel et al., 2009), social roles, the distribution of psychosocial stressors and personal attitudes as regards health behavior and lifestyle (Kandel et al., 2009). Childhood adverse experiences have been found to impact negatively on educational outcomes and to increase the risk for unhealthy adult lifestyle, such as smoking (Shonkoff & Garner, 2012). Further, the intergenerational chain of adversity is addressed by the observation that women with lower education are more likely to smoke during pregnancy and their children are more likely to manifest behavioral problems during their development and smoke in adulthood (Kandel et al., 2009).

2.1.1.3 Prevalence

The estimated global prevalence of smoking in pregnancy has been reported to be around 1.7% (Lange, Probst, Rehm, & Popova, 2018). However, the prevalence rates of smoking in pregnancy are considerably higher in Western countries where around 6–8% of pregnant women smoke (Lange et al., 2018). In Finland, the prevalence of smoking in pregnancy has persisted for a long time at around 15% (Ekblad et al., 2014). Smoking in pregnancy is remarkably more common in Finland than in many other European regions where the average estimated prevalence of smoking in pregnancy has been reported to be around 8% (Lange et al., 2018). From a global perspective, the proportion pregnant smokers who quit smoking during pregnancy has been demonstrated to be approximately 47% (Lange et al., 2018). Based on the Finnish Perinatal Statistics, the percentage of pregnant smokers who quit smoking

during pregnancy varied between 39% and 49% during the data collection period of these studies: from 2011 to 2015 (Vuori & Gissler, 2016). There has been a decreasing trend in prenatal smoking and, in addition, the percentage of smokers who quit smoking during pregnancy has also recently increased among Finnish women (Vuori & Gissler, 2016) .

2.1.2 Prenatal substance use disorders

2.1.2.1 Conceptualization

Substance use disorders have been defined in both the leading diagnostic manuals for mental disorders, in the fifth edition of the Diagnostic and Statistical Manual (DSM-5) by the American Psychiatric Association (American Psychiatric Association, 2013) and in the tenth revision of the International Classification of Diseases (ICD-10) by the World Health Organization (World Health Organization, 1992). According to ICD-10, the harmful use of substances refers to the pattern of substance use that causes individual level harm to mental or physical health. The diagnosis of dependence syndrome requires that three or more of the following criteria have been present together at some time within one year: 1) a strong desire or compulsion to use the substance, 2) difficulty in controlling substance use as regards the onset, termination, or intake of substance use, 3) substance-specific withdrawal symptoms when trying to reduce or quit substance consumption, 4) tolerance to substance observed in an increase of substance consumption to achieve the same effect as earlier, 5) neglect of other pleasures or interests due to substance use and a substantial amount of time being spent in obtaining the substance, using it or recovering from the effects of use, or 6) continuation of substance use despite its harmful consequences and awareness of harmful effects of substance use (World Health Organization, 1992).

Extensive literature has established that substance use disorders are chronically relapsing and multistage neurobiological brain diseases manifesting in the dysregulation of three major neuronal circuits related to pleasure and reward, stress, and self-control (Koob & Volkow, 2016). The following processes have been found to represent the key neurobiological disturbances in substance addictions: 1) In the stages of binge drinking and intoxication, the reward from substance use induces the development of exaggerated incentive salience and drug-seeking and involves the neuroplastic changes especially in the dopamine and opioid neurotransmission in the basal ganglia; 2) In the stage of withdrawal symptoms and negative affect, the dysphoric stress and anxiety-like responses involve a decrease in dopaminergic neurotransmission within the reward system and an increase in the level of stress-related corticotropin-releasing hormone; 3) In the stage of anticipation of substance

effect and preoccupation with substance use, craving and deficits in executive functions take place due to dysregulation of the afferent circuities from the prefrontal cortex and insula (Koob & Volkow, 2016). The dysregulation of brain reward circuitries is considered to constitute the core of pathogenesis in addictions (Koob & Volkow, 2016; National Institute on Drug Abuse, 2018), but long-term changes in the brain systems and circuits regulating stress, judgment, decision-making, memory and behavior are also involved (National Institute on Drug Abuse, 2018). Particularly the dysregulation of reward-stress neurocircuitries by substance addiction has been considered to constitute a neurobiological pathway through which the quality of caregiving behavior may often be compromised in parents suffering from substance dependence (Rutherford & Mayes, 2017). The dysregulation of neural reward-stress circuitries in substance addictions has been implicated in a decreased salience to infant signals, reward deficits in parent-child interactions and increased stress when caregiving (Rutherford & Mayes, 2017).

Currently, the widely spread conceptualization of addictions is the brain disease model (National Institute on Drug Abuse, 2018). Even though this conceptualization has been widely supported, there has also been debate around the brain disease model of addictions and a call for a wider perspective to conceptualize addictions (Hall, Carter, & Forlini, 2015; Lewis, 2018; Nathan, Conrad, & Skinstad, 2016). *The developmental model of addictions* proposes that "addiction may be better understood as a developmental disorder, in which genetic, epigenetic, and neurobiological factors interact with adverse caregiving experiences during key developmental stages, increasing the risk of future substance use disorders" (Alvarez-Monjaras, Mayes, Potenza, & Rutherford, 2018). Ultimately, vulnerability to addictions is transmitted to the next generation by mechanisms involving an unfavorable genotype, perinatal environment, parent-infant interactions and parental mentalization (Alvarez-Monjaras et al., 2018). The developmental perspective on addictions is supported by observations suggesting that an accumulation of adverse childhood experiences associates with an increased risk for substance use disorders. Individuals with multiple adverse childhood experiences have a two- to three-fold risk for tobacco smoking and heavy alcohol use, a three- to six-fold risk for problematic alcohol use and illicit drug use and up to a ten-fold risk for problematic drug use when compared with individuals who have not faced childhood adversity (Hughes et al., 2017). Extensive literature have addressed the fact that the development of addictions is substantially determined by childhood relational experiences (Alvarez-Monjaras et al., 2018; Eiden et al., 2016; Otten, Mun, Shaw, Wilson, & Dishion, 2019; Rutherford & Mayes, 2017; Strathearn et al., 2019). Promoting early secure attachment bonds through psychosocial interventions has estimated to contain the potential to break the developmental cascade of addictions and associative adversity (Alvarez-Monjaras et al., 2018). Pregnancy, including the

psychological and neurobiological processes implicated to the emerging caregiving relationship with the unborn child, has been considered to be able to interrupt pregnant women's ongoing addictive processes (Alvarez-Monjaras et al., 2018; Kendler et al., 2017; Massey & Wisner, 2018; Strathearn et al., 2019) . In addition, greater maternal sensitivity has been found to protect the child from the trajectory leading to substance use problems in adolescence (Eiden et al., 2016). The developmental model of addictions suggests that especially pregnancy and early childhood constitute a window of opportunity to influence the fundamental risk factors for substance use disorders and, therefore, to prevent the burden of disease and intergenerational continuity in substance use disorders (Alvarez-Monjaras et al., 2018; Brumana et al., 2017).

2.1.2.2 Aetiology and risk factors

As is the case with to tobacco use disorders, the development of substance use disorders is largely rooted in the intergenerational and developmental processes. For example, heritability of alcohol and opioid use disorders have been reported to be up to 50% (Crist, Reiner, & Berrettini, 2019; Hart & Kranzler, 2015). Substance use disorders have been demonstrated to be polygenic in nature (Crist et al., 2019; Hart & Kranzler, 2015), and also gene × environment interaction effects, gene × gene interactions and epigenetics mechanisms are involved in the risk of developing substance use disorders (Crist et al., 2019; Stone et al., 2012). For example, fetal exposure to substances has been found to cause epigenetic alterations which, unfortunately, seem to lead to heightened vulnerability to addictions (Wanner, Colwell, & Faulk, 2019).

The prevalence of substance use disorders peaks during emerging adulthood (Stone et al., 2012), that is to say, when young women reach their reproductive years. Maternal health and expectant mothers' health practices during pregnancy are very closely linked to preconception health (Brumana et al., 2017; Catalano et al., 2012; Stephenson et al., 2018; Toivonen, Oinonen, & Duchene, 2017). From the global perspective, the promotion of a healthy lifestyle in the preconception period among girls and young women has been emphasized as an important means to improve maternal and child health and reduce prenatal substance use (Brumana et al., 2017; Catalano et al., 2012; Stephenson et al., 2018; Toivonen et al., 2017). However, very early environmental factors, especially early attachment and relational experiences, have been found to play a significant role in determining the risk of developing substance use disorders (Alvarez-Monjaras et al., 2018; Eiden et al., 2016; Hughes et al., 2017; Strathearn et al., 2019). Prenatal exposure to substances, parental substance use, parental mental disorders, neglect or maltreatment in childhood, family conflicts and parent-child relationships problems have been demonstrated to

increase the risk of substance use disorders in young adults (Stone et al., 2012) . Ineffective parenting, such as poor parental supervision and a very aloof or harsh parenting styles, has been demonstrated to associate with an offspring's substance use problems in emerging adulthood (Meque, Salom, Betts, & Alati, 2019; Stone et al., 2012). However, relational experiences can also be protective. Parental warmth and sensitivity in early parent-infant interactions and better parental monitoring of the child in pre-adolescent years constitute protective factors in the developmental cascade model of addictions (Eiden et al., 2016).

One important and robust predictor for substance use disorders has demonstrated to be a childhood developmental trajectory (Groenman et al., 2017; Meque et al., 2019; Stone et al., 2012). Prenatal substance exposure increases the risk for childhood behavioral problems, for example, fetal exposure to alcohol has been found to predict externalizing behavioral problems with a large effect (Khoury, Jamieson, & Milligan, 2018). According to the recent large-scale meta-analysis, childhood psychopathology substantially increases the risk of substance use disorders, and the greatest risk for subsequent substance use problems has been linked to oppositional defiant and conduct disorders in childhood (Groenman et al., 2017). This finding supports the work of other studies especially linking childhood externalizing problems with substance use disorders in adulthood (Meque et al., 2019; Stone et al., 2012). Further, early relational experiences play a crucial role in determining a child's developmental trajectory regarding behavior and self-regulation (Eiden et al., 2016; Otten et al., 2019; Stone et al., 2012). Early life stress and negative parent-child interactions characterized by coercive parental engagement have been shown to detrimentally associate with the development of inhibitory control and self-regulation in childhood, which predisposes the child to behavioral and social problems and increases the child's risk for substance use problems in adolescence (Otten et al., 2019). However, high quality nurturing care and supportive family relationhips in childhood have a protective moderation effect on the association between behavioral problems in childhood and the subsequent risk for substance use disorders (Stone et al., 2012).

An accumulation of adverse childhood experiences has been found to increase the risk of tobacco smoking and substance use problems (Hughes et al., 2017). In line with this, maternal adverse childhood experiences have been linked with substance use problems in pregnancy (Smith, Gotman, & Yonkers, 2016). Maternal early life adversity predicts poor pregnancy outcomes, such as preterm birth and the neonate's low birth weight (Smith et al., 2016). The association between maternal adverse childhood experiences and poor pregnancy outcomes has been found to be largely mediated by maternal substance use in pregnancy, especially by tobacco smoking and illicit drug use (Smith et al., 2016). These observations call for a life-cycle approach and early interventions to reduce the risk of substance use disorders

and, ultimately, prenatal substance use and fetal substance exposure (Brumana et al., 2017).

More proximate predictive factors for prenatal use of prescription opioid pain killers and neonatal abstinence syndrome have been evaluated in a large population based study in the USA (Patrick et al., 2015). This study demonstrated that pregnant women who had used prescription opioids during pregnancy were more likely to be depressed, suffer from anxiety disorders and smoke than the pregnant women who had not used opioid pain killers during pregnancy (Patrick et al., 2015). Additionally, one study from Australia has shown that low socio-economic status, mental disorders, smoking, living in the urban area and single marital status associate with an increased risk of substance use in pregnancy (Kennare, Heard, & Chan, 2005).

2.1.2.3 Prevalence

In Finland, recent population-based estimates on substance use in pregnancy are not available. One population-based study utilizing health care and social service registers between 1998 and 2009 in Finland found that the prevalence of substance use problems was approximately 2% among Finnish mothers before their child reached the age of 7 years (Raitasalo, Holmila, Autti-Ramo, Notkola, & Tapanainen, 2014). According to the findings from the population-based survey from the USA, pregnant women reported a current use of alcohol in around 9% of the cases and the use of illicit drugs in 5% of the cases (Substance Abuse and Mental Health Services Administration, 2014). Globally, the use of prescription opioids has increased in a way that has been described as "epidemic" among women of childbearing age or pregnant (Desai et al., 2015; Ollgren et al., 2014; Patrick et al., 2015). In Finland, the latest national estimates indicate that both the number of problem drug users and the proportion of reproductive age women among them have also increased (Ollgren et al., 2014). In the recent large-scale meta-analysis, the prevalence of fetal alcohol spectrum disorders (FASD) was estimated to be 2.3% on a global scale (Roozen et al., 2016). However, the prevalence estimates on prenatal substance which are based on registers or even self-reports are likely to represent only a small proportion of the maternal prenatal substance use problems (Dietz et al., 2010; Kotelchuck et al., 2017; Raitasalo et al., 2014).

2.1.3 Consequences of maternal prenatal tobacco and substance use disorders

Tobacco and substance use disorders in pregnancy constitute a significant source of health inequality and a major public health concern (Aizer & Currie, 2014; Behnke et al., 2013; Brumana et al., 2017; Reddy, Davis, Ren, & Greene, 2017; Roozen et

al., 2016). Fetal exposure to substances has several deleterious effects on fetal development, especially on brain architecture and neural connections (Behnke et al., 2013; Ekblad et al., 2015; Forray & Foster, 2015; O'Leary et al., 2013). Particularly prenatal alcohol exposure has detrimental effects on the developing fetus (Forray & Foster, 2015; O'Leary et al., 2013; Roozen et al., 2016). Prenatal alcohol exposure constitutes the leading cause for intellectual disability in the cases where genetic reasons for disability have not been demonstrated (O'Leary et al., 2013). Fetal alcohol spectrum disorders (FASDs) are categorized into four distinct categories: fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (PFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) (Hoyme et al., 2016). Hoyme and colleagues (2016) have presented the updated diagnostic criteria and algorithm for the diagnosis of FASDs; during the diagnostic process maternal prenatal alcohol consumption is assessed and the child's facial dysmorphology, pre- and postnatal growth, head circumference, structural brain anomalies, birth defects and major malformations, the manifestation of recurrent nonfebrile seizures, cognitive and behavioral impairments and developmental delays are examined. Short palpebral fissures, the thin vermilion border of the upper lip and a smooth philtrum are the characterisctic dysmorphic features of the FASDs. However, ARND and ARBD can be present without facial anomalies or other dysmorphic features (Hoyme et al. 2016). The updated clinical guidelines for diagnosing fetal alcohol spectrum disorders by Hoyme and colleagues (2016) present the consensus definition for significant prenatal alcohol exposure, that is to say, six or more drinks per week for at least two weeks during pregnancy (≥ 6 drinks per week for ≥ 2 weeks during pregnancy), or three or more drinks per an occasion at least twice during pregnancy (≥ 3 drinks per an occasion on ≥ 2 occasions during pregnancy). However, the guidance given by The American Academy of Pediatrics emphasizes that: "*During pregnancy, no amount of alcohol intake should be considered safe; there is no safe trimester to drink alcohol; all forms of alcohol, such as beer, wine, and liquor, pose similar risk; and binge drinking poses dose-related risk to the developing fetus*." (Williams & Smith, 2015; Hoyme et al., 2016). In Nordic countries, national guidelines advise pregnant women to abstain from any substance use and smoking during pregnancy (Nissinen & Frederiksen, 2020). Smoking in pregnancy also harmfully affects fetal brain development (Ekblad et al., 2015). Substance use and smoking during pregnancy predict poor perinatal outcomes, especially preterm birth and low birth weight for gestational age (Behnke et al., 2013; Forray & Foster, 2015; Kotelchuck et al., 2017; Ludlow, Evans, & Hulse, 2004) which, in turn, predict impaired health and socio-economic situation in long term (Aizer & Currie, 2014; Bilgin et al., 2018). In summary, prenatal exposure to tobacco or substances severely compromises the offspring's neurobehavioral and cognitive development, growth and attainments from the long-term perspective

(Behnke et al., 2013; Forray & Foster, 2015). Table 1 presents a summary of the effects of fetal substance exposure on the fetus/child.

Recently, opioid use during pregnancy has been reported to be a major public health concern in many countries (Behnke et al., 2013; Forray & Foster, 2015; Reddy et al., 2017). Fetal opioid exposure causes serious perinatal complications of which the most significant one is the neonatal abstinence syndrome (NAS) (Behnke et al., 2013; McQueen & Murphy-Oikonen, 2016; Reddy et al., 2017; Wachman, Schiff, & Silverstein, 2018). According to the comprehensive review by McQueen and Murphy-Oikonen (2016), the NAS refers to the postnatal opiod withdrawal syndrome of a newborn – a complex bundle of symptoms involving primarily central and autonomous nervous systems and a gastrointestinal tract. The symptoms typically manifest within the first few days after birth and consist of tremors, high-pitched crying, sleep disturbances, increased muscle tone, myoclonic jerks, irritability, seizures, regurgitation, vomiting, loose stools, weight loss, poor feeding, excessive sucking, frequent yawning, sneezing, sweating, increased respiratory rate, tachypnea and fever. The Finnegan Neonatal Abstinence Scoring tool is the most widely used instrument for the assessment of the severity of the NAS and for guidance of treatment which is consisted of non-pharmacological approaches (swaddling, comfort, frequent feeding and support for breastfeeding) and opiod replacement therapy followed by protocol-specified weaning. The NAS often leads to an admission to a neonatal intensive care unit and prolonged hospitalization (on average, 17 days) of the newborn. In addition to the NAS, prenal opiod exposure associates with other adverse outcomes, such as an increased risk for fetal growth restriction, placental abruption, preterm birth, cardiac abnormalities and neonatal death (McQueen & Murphy-Oikonen, 2016).

Table 1. The effects of prenatal exposure to tobacco or substances on the fetus/child (Behnke et al., 2013).

	Nicotine	Alcohol	Marijuana	Opiates	Cocaine	Metamphetamine
Short-term effecets/Birth outcome						
Fetal growth	Effect	Strong effect	No effect	Effect	Effect	Effect
Anomalies	No consensus on effect	Strong effect	No effect	No effect	No effect	No effect
Withdrawal symptoms	No effect	No effect	No effect	Strong effect	No effect	*
Neurobehavior	Effect	Effect	Effect	Effect	Effect	Effect
Long-term effects						
Growth	No consensus on effect	Strong effect	No effect	No effect	No consensus on effect	*
Behavior	Effect	Strong effect	Effect	Effect	Effect	*
Cognition	Effect	Strong effect	Effect	No consensus on effect	Effect	*
Language	Effect	Effect	No effect	*	Effect	*
Achievement	Effect	Strong effect	Effect	*	No consensus on effect	*

*Note. * refers to limited or no data available.*

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In addition to the effects of prenatal substance exposure presented in Table 1, the following aspects should be considered. First, public discussions often focus on the harmful effects of illegal drug use in pregnancy. Evidence to date suggests, however, that prenatal use of legal substances, tobacco and alcohol, is especially detrimental from the perspective of the fetal/child development (Forray & Foster, 2015) and affects unborn children on a considerably large scale (Ekblad et al., 2014; Roozen et al., 2016). Second, the very typical pattern of problematic substance use is polysubstance abuse, often combined with smoking (Basnet, Onyeka, Tiihonen, Föhr, & Kauhanen, 2015; Forray & Foster, 2015; Strengell et al., 2014). For example, 88–95% of pregnant women receiving medication-assisted treatment for an opioid use disorder smoke during pregnancy (Akerman et al., 2015). Third, tobacco and maternal substance use disorders identified in pregnancy often indicate an accumulation of adversity. Therefore, it is essential to simultaneously consider *the cumulative effects of substance use disorders and associative problems*, such as comorbid maternal mental disorders (Kennare et al., 2005; Strengell et al., 2014) ,

psychological distress (Woods, Melville, Guo, Fan, & Gavin, 2010), socio-economic disadvantage (Ekblad et al., 2014; Holmila, Raitasalo, & Kosola, 2013; Kahila et al., 2010), substantial psychosocial stressors, such as inter-parental conflict or intimate partner violence (Strengell et al., 2014), and the expectant mother's adverse childhood experiences (Håkansson, Watten, Söderström, Skårderud, & Øie, 2018; Isosävi et al., 2016; Strengell et al., 2014) on maternal and fetal/child health (Vesterinen, Morello Frosch, Sen, Zeise, & Woodruff, 2017). One population-based study from Australia has suggested that only a small amount of variance in obstetric and perinatal outcomes is explained by pregnant women's substance use alone and, the detrimental effects of prenatal substance use on perinatal outcomes are difficult to separate from the harmful effects of other risk factors which associate with substance use problems (Kennare et al., 2005) . In addition, one systematic review on human and animal studies has revealed that fetal exposure to substances and maternal stress associates with an increased risk for low birth weight, and the poorest perinatal outcome was linked with simultaneous exposure to both, maternal prenatal distress and substance use (Vesterinen et al., 2017). Further, a recent population-based cohort study has shown that the newborns of pregnant women with poly-drug / illicit drug use and comorbid mental disorders demonstrate the poorest neonatal outcomes (Zhao, McCauley, & Sheeran, 2017).

Tobacco and substance use disorders identified in pregnancy constitute *a significant burden for health and wellbeing of two individuals*, both the expectant mother and her unborn child (Reitsma et al, 2017; Basnet et al., 2015; Kahila et al., 2010; Schoenaker et al., 2017). One survey with a long follow-up period of over three decades has revealed that more than half of the women who have smoked before their first pregnancy are current smokers in midlife, and of the smoking women who have been able quit smoking during pregnancy around 40% smoke at the age of 55 years (Schoenaker et al., 2017). In general, smoking constitutes one of the leading risk factors for early death and disability accounting for nearly 12% of global deaths and 6% of global disability-adjusted life years in 2015 (Reitsma et al., 2017). Smoking and substance related problems cause a considerable burden of diseases for women as tobacco smoking has been found to be the ninth and substance use the twelfth leading risk factor for disability-adjusted life years in women in 2015 (Forouzanfar et al., 2016). Moreover, one study from Finland has established that the prognosis of pregnant women referred to specialized obstetric outpatient care due to substance use problems is strikingly poor in the long term (Kahila et al., 2010). The study by Kahila et al. (2010) which had a follow-up of a median of nine years revealed that the adjusted odds of mortality were 38 times higher, and the odds of morbidity to mental disorders nearly nine times, viral infections 23 times and bacterial infections six times higher when compared with mortality and morbidity among matched controls without substance related problems. Almost 8% of the

women with identified prenatal substance abuse died during the follow-up period whereas only 0.2% of the matched controls died during the same time frame (Kahila et al., 2010).

2.2 Prenatal psychological distress

2.2.1 Conceptualizations

Several conceptualizations for prenatal psychological distress have been presented (Nast, Bolten, Meinlschmidt, & Hellhammer, 2013). The most widely used definitions within quantitative research have been reported to be anxiety or depressive symptoms, irritations related to daily hassles, a wider spectrum of psychological symptoms, stressful life experiences, specific socio-environmental stressors, and stress related to pregnancy or parenting (Nast et al., 2013). In addition, severe prenatal psychological distress can also be related to perinatal mental disorders, such as anxiety and major depressive disorders (Howard et al., 2014). The assessment of prenatal psychological distress relies mainly on clinical structured or semi-structured interviews or patient-reported outcome measures, and altogether more than forty measures for the assessment of prenatal psychological distress have been introduced (Nast et al., 2013). For just the assessment of prenatal anxiety, the number of measures introduced has been reported to be around seventeen (Brunton, Dryer, Saliba, & Kohlhoff, 2015). The specific threshold scores have been presented for some of the self-report measures to screen large populations and identify those pregnant women who may suffer from a clinically significant level of prenatal psychological distress and need a referral to treatment (The American College of Obstetricians and Gynecologists, Committee on Obstetric Practice, 2015; Gibson, McKenzie McHarg, Shakespeare, Price, & Gray, 2009; Howard et al., 2014; Stein et al., 2014). In addition, many studies have focused on evaluating biological or neurobiological correlates of prenatal psychological distress and investigated their associations with maternal and child outcomes (Van den Bergh et al., 2017). Due to variety of conceptualizations and assessment methods, the interpretation and comparability of research findings regarding prenatal psychological distress can sometimes be complex. For example, intervention studies addressing prenatal psychological distress have reported inconclusive findings depending on the conceptualizations of distress (Matvienko-Sikar et al., 2020).

Pregnancy-related anxiety refers to fears, worries and concerns specifically related to pregnancy (Bayrampour et al., 2016; Huizink, Mulder, Robles de Medina, Visser, & Buitelaar, 2004). In replicated studies, this specific type of pregnancy anxiety has been shown to constitute a distinct clinical entity in which the variance is not largely explained by symptoms of general anxiety or depression (Blackmore,

Gustafsson, Gilchrist, Wyman, & G O'Connor, 2016; Brunton et al., 2015; Brunton, Robyn, Dryer, Saliba, & Kohlhoff, 2019; Huizink et al., 2004). In the concept analysis, nine causes of pregnancy-related anxiety has been established: fetal health, loss of fetus, childbirth, mother's own wellbeing, body image, parenting capacities, concerns related to encounters in health care, financial issues and social/family support (Bayrampour et al., 2016). The pregnant women's tendency to excessive cognitive processing, perceived real or imagined threats to pregnancy or the fetus, and a low sense of control have been reported to precede pregnancy-related anxiety which manifests itself in the pregnant women's emotional responses, cognitions and somatic complaints (Bayrampour et al., 2016). The severity of pregnancy-related anxiety has been found to be reflected to its behavioral consequences consisted of negative attitudes, problems with patience and concentration, a tendency to seek reassurance in an excessive manner or exhibit avoidant behaviors (Bayrampour et al., 2016). Interestingly, some studies have suggested that pregnancy-related anxiety may predict impaired pregnancy and neonatal outcomes to an even greater extent than the other forms of prenatal psychological distress (Bayrampour et al., 2016). It is important to note that merely assessing general anxiety during pregnancy does not seem to capture pregnancy-related anxiety (Brunton, Robyn et al., 2019; Huizink et al., 2004).

2.2.2 Aetiology and risk factors

The aetiology of prenatal psychological distress has been demonstrated to be complex and multifactorial (Biaggi et al., 2015; Lancaster et al., 2010). Based on two systematic reviews, the following have been found to increase the risk of prenatal anxiety and depression: low maternal education and income, smoking in pregnancy, single marital status, a lack of partner and social support, a history of maltreatment or mental disorders, prior or current domestic violence, unintended pregnancy, adverse life events, subjective severe stress, prior or current pregnancy complications and a prior pregnancy loss (Biaggi et al., 2015; Lancaster et al., 2010). In one large register-based study conducted between 2002 and 2010 in Finland, a prior history of depression was found to most strongly predict prenatal depression (Räisänen et al., 2014). All things considered, risk factors for prenatal psychological distress often stem from a history of prior psychopathology, an accumulation of adverse life experiences and a lack of resilience building resources, such as social and partner support (Howard et al., 2014). Further, the risk factors for prenatal distress reflect socioeconomic disparities in health as a low socio-economic status associates with an increased risk of prenatal depression and anxiety (Howard et al., 2014).

Pregnancy-related anxiety can be differentiated from the conventional symptoms of generalized anxiety disorder in term of several external correlates (Blackmore et al., 2016). Parity, the expectant mother's age at the first pregnancy, the number of previous miscarriages and maternal age have been found to be more strongly associated with pregnancy-related anxiety than with symptoms of general anxiety in pregnancy (Blackmore et al., 2016). Nulliparity was found to correlate positively with pregnancy-related anxiety and advanced maternal age at first pregnancy predicted concerns about the birth (Blackmore et al., 2016). The number of miscarriages and maternal age associated negatively with specific concerns about the birth (Blackmore et al., 2016). In addition, one study from Netherlands has shown that nulliparity, maternal anxious or depressed mood and minority status associate with an elevated level of pregnancy-related anxiety (Westerneng et al., 2017). One large-scale population-based study from Canada has revealed that an unintended pregnancy, nulliparity, the presence of higher obstetric risk and the expectant mother's perceived risks of pregnancy complications independently associate with a higher risk of feeling anxious, concerned, afraid or panicky about being pregnant (Dunkel Schetter, Niles, Guardino, Khaled, & Kramer, 2016). In addition, the expectant mother's sense of low self-esteem and low control over the pregnancy, weaker commitment to pregnancy, experiences of stress and work-related stress, stressful life events and disadvantage in their early years were found to associate with a higher level of pregnancy-related anxiety (Dunkel Schetter et al., 2016).

2.2.3 Prevalence

Psychological distress and perinatal mental disorders, such as anxiety and major depressive disorders, have been demonstrated to be relatively common during pregnancy (Fawcett, Fairbrother, Cox, White, & Fawcett, 2019; Gavin et al., 2005; Howard et al., 2014; Woods et al., 2010). Gavin et al. (2005) have estimated that the point prevalence of prenatal depression is around 11% in the first trimester and 9% in the second and third trimesters, and the period prevalence of depressive disorders during pregnancy is around 18% including minor and major depressive disorders. Furthermore, 13% of pregnant women suffer from a major depressive disorder during pregnancy and the incidence of major depression, in other words the percentage of pregnant women with a new episode of a major depressive disorder during pregnancy, has been reported to be 8% (Gavin et al., 2005). The existing body of literature suggests that around 21–25% of pregnant women suffer from anxiety during pregnancy (Field, 2017). A recent meta-analysis has shown that every fifth woman fulfills the diagnostic criteria for at least one anxiety disorder during perinatal period (Fawcett et al., 2019). One population-based study from the USA has reported that around 6% of expectant mothers report a high level of prenatal

stress (Woods et al., 2010). Prenatal psychological distress has been found to comprise distinct trajectories during pregnancy: pregnant women may experience an increasing or decreasing level of distress and for some pregnant women the level of distress is constantly low or high (Korja et al., 2018). In the recent study from the Finnish Birth Cohort, lower maternal education, multiparity, selective serotonin reuptake inhibitor medication and prenatal smoking have been found to associate with constantly high levels of depressive and anxiety symptoms during pregnancy (Korja et al., 2018). Persistent prenatal anxiety and depressive symptoms have also been linked with lesser optimism, a stressful life situation, a lack of social support and a prior history of mental health problems (Bayrampour, McDonald, & Tough, 2015). Screening for perinatal depression and anxiety with validated interview methods or/and self-report measures has been recommended, importantly, in combination with effective treatment programs (The American College of Obstetricians and Gynecologists: Committee on Obstetric Practice, 2015; Fawcett et al., 2019).

2.2.4 Consequences of prenatal psychological distress

Prenatal psychological distress, also as a manifestation of maternal perinatal mental disorders, associates with a broad range of adverse maternal and fetal/child outcomes (Stein et al., 2014; Van den Bergh et al., 2017). In 2014, the Lancet carried out a large-scale series of articles about perinatal mental health and consequences of perinatal disorders, predominantly depression and anxiety, on the fetus and child (Howard et al., 2014; Stein et al., 2014). The comprehensive review of Stein and colleagues (2014) concluded that perinatal mental disorders associate with an increased risk of psychological and developmental disturbances in the offspring, but the negative consequences are not inevitable and, in the absence of severe or long-standing adversity, the adverse effects of perinatal mental disorders on the fetus/child are on average small or moderate (Stein et al., 2014). In addition, several other reviews have been published on the effects of prenatal anxiety, depression, distress and pregnancy-related anxiety on the offspring (Adamson, Letourneau, & Lebel, 2018; Ding et al., 2014; Rees, Channon, & Waters, 2019; Stein et al., 2014; Van den Bergh et al., 2017). Some key findings from these reviews are presented in Table 2.

Some studies have suggested that pregnancy-related anxiety may predict impaired pregnancy and perinatal outcomes even to a greater extent than other dimensions of prenatal psychological distress (Blackmore et al., 2016; Kramer et al., 2009; Reck et al., 2013). Blackmore et al. (2016) demonstrated that pregnancy-related anxiety, especially anxiety concerning fetal/child health, associated negatively with the neonate's birth weight and gestational age at birth and predicted low birth weight independently of conventional symptoms of generalized anxiety

(Blackmore et al., 2016). Reck et al. (2012) observed that childbirth-specific anxiety predicted a longer average length of labor whereas symptoms of general anxiety were not found to associate with the duration of delivery (Reck et al., 2013). In a large population-based cohort study, Kramer et al. (2008) showed that pregnancy-related anxiety was the only dimension of prenatal stress that consistently and independently predicted an increased risk of preterm birth (Kramer et al., 2009). Further, in one study from the Netherlands, pregnancy-related anxiety has been found to constitute a more robust predictor of postnatal parenting stress than prenatal depression and state anxiety (Huizink et al., 2017).

The adverse effects of prenatal psychological distress on the offspring have been linked with the construct of allostatic load and the process of fetal programming (Barker, 1998; Huizink & de Rooij, 2018; McEwen, 1998). In the late 80's, the epidemiologist David Barker presented a theory of *developmental origins of health and disease*, later known as *DOHaD* or *Barker's hypothesis*, in which he introduced his findings suggesting the link between prenatal nutritional conditions and the offspring's risk for cardiovascular diseases in adulthood. Barker's novel idea was to consider *fetal origins of diseases* and the process of *fetal programming* referring to permanent changes in the offspring's structures or metabolisms due to adaptation to adverse prenatal conditions and the contribution of these permanent changes to a wide range of diseases in adulthood (Barker, 1998). In 1998, neuroendocrinologist Bruce S. McEwen published a scientific paper entitled "Stress, Adaptation and Disease. Allostasis and Allostatic Load" and introduced the concepts of the allostatic load and *the allostatic load model* (McEwen, 1998). The term *allostasis* refers to the process of adaptation to stress which involves activation of several neurobiological, neuroendocrine and immune system mechanisms. However, the adaptation to stress, allostasis, can be overridden which leads to an increased risk of illness in the course of time. The allostatic load refers to exposure to an excessive and toxic burden of stress and failure to maintain allostasis, which causes alterations in the developing individual that do not serve better adaptation over time. Instead, these alterations lead to vulnerability or maladaptive calibration of several neurobiological systems and proneness to diseases later in the course of life. (McEwen, 1998). It is of note that prenatal stress may also have some beneficial effects on the fetus/child, even if this has been much less investigated (Hartman & Belsky, 2018). Recent findings suggest that prenatal stress exposure may foster and enhance postnatal developmental plasticity and lead to heightened susceptibility to environmental effects, "for better and for worse" (Hartman & Belsky, 2018). According to Hartman and Belsky (2018), prenatal stress exposure is associated with elevated negative emotionality and physiological reactivity both of which are considered as indicators of enhanced developmental plasticity and to represent either developmental risk factors or "opportunity" factors, depending on the quality of

postnatal environment (Hartman & Belsky, 2018). On the one hand, children exposed to prenatal stress may display enhanced developmental plasticity postnatally and thus gain the greatest benefits from favorable and highly nurturing environment – and potentially from early parenting interventions. On the other hand, children exposed to maternal prenatal distress may be especially vulnerable to the effects of environmental adversity that persist beyond pregnancy. Therefore, the adverse consequences of prenatal stress exposure may substantially reflect the negative influence of unsupportive postnatal environment on a highly susceptible individual (Hartman & Belsky, 2018). Several mechanisms through which maternal prenatal psychological distress affects childhood and adult health and well-being have been proposed (Beijers, Buitelaar, & de Weerth, 2014; Huizink & de Rooij, 2018; Stein et al., 2014; Talge, Neal, & Glover, 2007; Waters, Hay, Simmonds, & van Goozen, 2014). Recent literature has presented evidence for the following mechanisms underlying the adverse association between prenatal psychological distress and child outcomes: the contributions of genetics and epigenetics, dysregulation of maternal hypothalamic-pituitary-adrenal axis and cortisol secretion, compromised placental functioning, increased levels of maternal catecholamines, compromised maternal immune system and intestinal microbiota, and negative effects of maternal distress on prenatal health practices, such as smoking, substance use, sleeping and nutrition (Beijers et al., 2014). In addition, prenatal psychological distress may disrupt the neurocognitive process concerned with sensitive caregiving for the child, the cascade referred in maternal programming (Stein et al., 2014).

Unfortunately, *psychological distress and mental disorders, such as anxiety and depression, during pregnancy often constitute a continuum in postnatal mental disorders and distress* (Blackmore et al., 2016; Huizink et al., 2017; Underwood, Waldie, D'Souza, Peterson, & Morton, 2016). Almost 7 % of pregnant women have been found to suffer from significant depressive symptoms during pregnancy that then persist after childbirth (Underwood et al., 2016). A review of longitudinal studies on prenatal depression has established that around 40% of those pregnant women who suffer from prenatal depression continue to suffer from postnatal depression (Underwood et al., 2016). Prenatal anxiety has been shown to associate with an increased risk of postnatal depression, also when prenatal depression has been controlled for (Grigoriadis et al., 2019). In addition, pregnancy-related anxiety, especially anxiety concerning fetal/child health, has been found to independently predict maternal postnatal mood disturbances (Blackmore et al., 2016) and parenting stress (Huizink et al., 2017).

One important mechanism demonstrating how perinatal mental disorders affect child development, health, safety and well-being is *the quality of postnatal nurturing care* (Earls, 2019). Maternal perinatal mental disorders and distress have been shown to predict impaired caregiving for the child and a greater risk for the child's insecure

attachment (Earls et al., 2019; Stein et al., 2014). A recent review and policy statement by The American Academy of Pediatrics addressed the fact that maternal perinatal depression associates with early life adversity, such as an increased risk for inadequate breastfeeding, poor family functioning, compromised parent-infant interactions and child attachment security and, in the most serious cases, with an increased risk for child abuse and neglect. Furthermore, adversities related to maternal perinatal depression affect fetal/chilhood brain development during an especially critical developmental period (Earls et al., 2019). However, the negative consequences of perinatal mental disorders are not inevitable (Stein et al., 2014). In the *Series about perinatal mental health* published in the Lancet in 2014, Stein et al. (2014) emphasize that parenting is a key mediator of association between maternal prenatal distress and adverse child outcomes and should be specifically focused in early interventions for treatment of perinatal mental disorders, especially in disadvantaged populations where risks for child development have been found to be highest (Stein et al., 2014).

Table 2. Summary of some key effects of prenatal psychological distress and pregnancy-related anxiety on the fetus/child.

Effects of prenatal mental disorders (anxiety and depression) and prenatal psychological distress on the fetus/child
Perinatal outcomes Prenatal depression has been found to associate with premature delivery and decrease in breastfeeding initiation (Grigoriadis et al., 2013). Prenatal anxiety has been found to associate with an increased risk for the neonate's prematurity and low birth weight (Ding et al., 2014). Pregnancy-related anxiety has been found to associate negatively with the neonate's birth weight and gestational age at birth (Blackmore et al., 2016), to increase a risk for spontaneous preterm birth (Kramer et al., 2009) and longer total duration of labor (Reck et al., 2013) .
Newborn / infant outcomes The negative effect of prenatal psychological distress has been demonstrated on the newborn's state regulation, sleeping, autonomic stability and neurobehavioral maturity. The adverse effect on motor skills have been observed especially in boys. (Van den Bergh et al., 2017). A majority of studies have suggested that prenatal psychological distress associates with the infant's negative affectivity (sadness, distress to limitations, fear, discomfort and anger) and "difficult temperament" constituted of negative affectivity, and a tendency towards intense reactions and difficulties in adaptation to novel situations or changes in daily routines (Van den Bergh et al., 2017). Even highly comorbid, some specificity in the effects of prenatal anxiety and depression on child outcomes has been demonstrated as prenatal depression has been found to predict impairment in the infant's fear regulation while maternal antenatal anxiety has been found to predict the infant's behavioral inhibition in the presence of distress caused by a novel stimulus (Stein et al., 2014). Among disadvantaged pregnant women, impaired perinatal mental health has been linked to poor infant growth whereas in high income countries maternal perinatal chronic depression has been found to associate with the offspring's overweight (Stein et al., 2014). Prenatal depression has been found to associate with impairment the mother's capacities for responsive caregiving for the child and infant/child insecure/disorganized attachment (Earls et al., 2019; Stein et al., 2014).
Childhood / Adolescence outcomes In several studies, prenatal psychological distress has been found to associate with the offspring's emotional problems and impaired mental health later in life, such as internalizing symptoms, externalizing symptoms, aggressive behavior, social behavioral problems, autistic traits, attention deficits, total conduct and psychiatric problems. Longitudinal studies have suggested that the negative effect of prenatal psychological distress on the offspring's mental health may last until adulthood. Prenatal psychological distress has been found to associate with the offspring's increased risk for behavioral problems, internalizing and externalizing symptoms, anxiety and depression in adolescence/young adulthood. (Rees et al., 2019; Stein et al., 2014; Van den Bergh et al., 2017) Prenatal depression (both symptoms and clinical disorder) has been demonstrated to associate with an impairment in the offspring's cognitive development, including an intelligence quotient in childhood. However, the effect sizes have been found small and all studies have not demonstrated a significant association between prenatal depression and child cognitive development. (Stein et al., 2014; Van den Bergh et al., 2017) Exposure to prenatal anxiety has been found to associate with alterations in the offspring's brain structure and functions in frontal, temporal, and limbic areas during childhood and adolescence (Adamson et al., 2018) . Both in infancy and childhood, perinatal mental disorders predict an increased risk for child maltreatment (Ayers, Bond, Webb, Miller, & Bateson, 2019; Plant, Pariante, Sharp, & Pawlby, 2015).

2.2.5 Prenatal psychological distress in the context of prenatal tobacco and substance use disorders

Tobacco and substance use disorders in pregnancy often indicate an accumulation of adversity. In general, substance use disorders have been shown to be highly comorbid with mental disorders, such as mood and anxiety disorders (Gómez-Coronado et al., 2018; Hunt, Malhi, Lai, & Cleary, 2020; Lai, Cleary, Sitharthan, & Hunt, 2015; Mathew, Hogarth, Leventhal, Cook, & Hitsman, 2017). The mechanisms underlying the comorbidity of substance use and mood disorders have not yet been fully understood (Gómez-Coronado et al., 2018; Stoychev, 2019; Yang et al., 2018). The comorbidity may involve the pathway from a mental disorder to a dual diagnosis when psychiatric symptoms lead to increase in substance consumption and thus, repetitive exposure to substance and an exacerbation of addictive process especially in individuals with genetic or early risk factors for substance use disorders (Yang et al., 2018). Recent studies provide evidence for the self-medication hypothesis in patients with mood or anxiety disorders and trauma-related symptoms and suggest that of the individuals suffering from these disorders at least 21–24% use substances to cope with their psychiatric symptoms (Hawn, Cusack, & Amstadter, 2020; Turner, Mota, Bolton, & Sareen, 2018). Among the psychiatric symptoms, especially impaired memory processing and associative vulnerability to select maladaptive behavioral patterns, reduced cognitive control, negative emotions and impulsivity may increase the risk for developing a comorbid mental and substance use disorder (Yang et al., 2018). On the other hand, the comorbidity of substance use and mental disorders may involve the trajectory from substance misuse to the comorbidity when substance abuse induces psychiatric symptoms and the development of mental disorders (Yang et al., 2018). A recent review has supported both cascades leading to the comorbidity of alcohol use and major depressive disorders (Yang et al., 2018). The neurobiological mechanisms involved in the comorbidity substance use and mental health problems have been found to be related to the dysregulation of several neurotransmission systems and hypothalamic–pituitary–adrenal axis as well as negative effects of oxidative stress and excessive inflammatory responses (Gómez-Coronado et al., 2018). Preliminary neuroimaging studies have suggested that the comorbidity of substance use and mental disorders associate with more salient structural brain changes than in mental disorders alone, and the comorbidity of anxiety and substance use disorders seems especially to associate with the reduced brain volume of limbic structures, i.e. nucleus accumbens, hippocampus, amygdala (Stoychev, 2019). In addition, substance use and mental disorders are likely to have a shared genetic background to some extent, but the role of genetic factors in comorbid substance use and mood disorders is still somewhat inconclusive (Gómez-Coronado et al., 2018). Early life adversity has been found to increase the risk of both, substance use and mental

disorders in adulthood (Hughes et al., 2017). Childhood neglect and maltreatment cause neurocognitive alteration in four important neurocognitive domains: threat processing, reward processing, emotion regulation and executive control (McCrory, Gerin, & Viding, 2017). Initially, these alterations have probably contributed to better adaptation to adversity (McCrory et al., 2017). However, these specific alterations engender the "latent vulnerability" or "maladaptive calibrations" of higher order systems essential in socioemotional and cognitive functioning; the process which has been found to increase the risk of poor mental health later in the course of life (McCrory et al., 2017). Dysregulation in the same neurocognitive domains, that is to say reward and stress processing, self-control and executive functions, have been demonstrated to constitute the core of pathogenesis in substance addictions (Koob & Volkow, 2016).

The prevalence of comorbid perinatal mental disorders has also been reported to be considerably high in pregnant women with substance use disorders (Holbrook & Kaltenbach, 2012; Strengell et al., 2014). In Finland, 57% of pregnant women with substance use problems have been found to fulfill diagnostic criteria for at least one mental disorder, most commonly for mood or anxiety disorders (Strengell et al., 2014). Both women who smoke and pregnant women with recent or current alcohol use have been found to be at an increased risk for prenatal depression (Biaggi et al., 2015). Among pregnant women with substance use disorders, the prevalence of prenatal depression has been demonstrated to be around 40–50% (Holbrook & Kaltenbach, 2012; Ordean et al., 2013; Pajulo et al., 2011b) which is considerably higher than the estimated prevalence of major depressive disorder of 13% in a general population of pregnant women (Gavin et al., 2005). Drug use during pregnancy has been found to associate with an elevated level of prenatal psychological distress with a strong effect (Woods et al., 2010). Extensive research to date has established a detrimental association between prenatal psychological distress and smoking behavior during pregnancy (Biaggi et al., 2015; Goodwin et al., 2017; Lancaster et al., 2010; Räisänen et al., 2014; Riaz et al., 2018; Smedberg et al., 2015). One large population-based study from the USA has revealed that women suffering from depression or anxiety are 1.5 times more likely to smoke prior to conception and 1.7 times more likely to smoke during pregnancy and, unfortunately, less likely to cease smoking during pregnancy (Tong et al., 2016). One large population-based study from the USA has shown that nearly 40% of pregnant women who experience current severe psychological distress smoke (Goodwin et al., 2017).

The high prevalence of comorbidity between prenatal substance use and mental disorders including severe prenatal psychological distress has been found to influence in an adverse manner on maternal and fetal health through multiple pathways. First, perinatal mental disorders and psychological distress have a wide

spectrum of independent detrimental effects on the developing fetus (Stein et al., 2014; Waters et al., 2014). Second, prenatal psychological distress, especially with symptoms of depression, has been shown to have a negative impact on maternal prenatal lifestyle and health practices (Alhusen et al., 2016; Cannella et al., 2018) and to increase the risk of substance use in pregnancy (Alhusen et al., 2016; Hyer et al., 2019; Shmulewitz & Hasin, 2019). Maternal prenatal health practices have been considered one important potential mediating mechanism underlying the negative effects of prenatal psychological distress on the offspring's health (Dunkel Schetter, 2011; Huizink, Anja & de Rooij, 2018; Staneva et al., 2015). In general, a higher level of psychological distress associates with more intense substance cravings (MacLean, Armstrong, & Sofuoglu, 2019). In line with this, prenatal psychological distress has been found to increase the consumption of marijuana and alcohol during pregnancy (Hyer et al., 2019). Further, pregnant women suffering from symptoms of depression are at an increased risk for binge drinking (Shmulewitz & Hasin, 2019). Psychological distress has been found to constitute a significant barrier to engagement in a healthy lifestyle during pregnancy (Alhusen et al., 2016; Cannella et al., 2018; Dunkel Schetter, 2011; Riaz et al., 2018). For example, pregnant women suffering from psychological distress are more often incapable of reducing or quitting smoking (Riaz et al., 2018). Third, the concurrence of substance use problems and psychological distress during pregnancy is likely to have an additive detrimental effect on fetal/child outcomes (Zhao et al., 2017) and important resilience-building factors, such as the quality of pre- and postnatal parenting (Rutherford & Mayes, 2019). One recent population-based cohort study has demonstrated that the interaction effect of maternal prenatal substance use and mental disorders predicts a substantially increased risk of low birth weight in newborns, and the poorest neonatal outcome observed was among pregnant women with illicit drug use and a comorbid mental disorder (Zhao et al., 2017). Further, co-occurrence of smoking, maternal distress and socioeconomic disadvantage in pregnancy has been found to indicate an accumulative burden for maternal and child health (Aizer & Currie, 2014; Vesterinen et al., 2017).

Only a few studies have investigated the association between pregnancy-related anxiety and maternal prenatal smoking behavior (Goedhart, van der Wal, Cuijpers, & Bonsel, 2009; Lobel et al., 2008; Westerneng et al., 2017). One study has addressed an adverse relationship of pregnancy-related anxiety with smoking during pregnancy in a sample of women attending prenatal care in the USA (Lobel et al., 2008). Westerneng et al. (2017) investigated the association of pregnancy-related anxiety with prenatal health practices in a low-risk sample of over 4500 pregnant women and demonstrated that both low and high levels of pregnancy-related anxiety associate with a higher risk of smoking in pregnancy (Westerneng et al., 2017). In

addition, one population-based cohort study from the Netherlands has found that both low and high levels of pregnancy-related anxiety associate with persistent smoking during pregnancy in the sample of women who smoke (Goedhart et al., 2009). The authors of these two studies discussed the possible explanations for this non-linear association, and suggested that a low level of pregnancy-related anxiety may reflect the expectant mother's indifference about her own and her unborn child's health and therefore associate with poor maternal health practices (Goedhart et al., 2009; Westerneng et al., 2017). On the other hand, smoking may constitute a coping mechanism to deal with a high level of pregnancy-related anxiety which may contribute to an increased risk of smoking in pregnancy and continuation of smoking during pregnancy (Goedhart et al., 2009; Westerneng et al., 2017).

2.3 Prenatal parenting

2.3.1 Conceptualizations

The transition to parenthood begins during pregnancy and becoming a parent can be considered the greatest neurobiological, psychological and social transition in adult life (Mayes et al., 2012). The transition to parenthood has been referred to as a birth of the mother and intersubjectivity (Ammaniti & Gallese, 2014; Stern, Buschweiler-Stern, & Freeland, 1998), which especially address the expectant mother's new identity as a caregiver and the awakening of the unique relationship between the mother and her child. In 2017, the scientists Vivette Glover and Lauren Capron published an article entitled *Prenatal parenting* (Glover & Capron, 2017) which can be considered a very important statement in the field of perinatal psychiatry. The first key message of this scientific communication was that parenting begins in pregnancy and parents already affect their offspring's development before birth. Second, prenatal parenting was addressed as an effective focus for very early interventions to improve fetal/child developmental outcomes, especially in populations at risk. Both psychological factors, such as maternal prenatal psychological distress and early trauma, and environmental factors including fetal exposure to maternal substance use, were recognized as important risk factors for fetal/child development. Prenatal parenting was conceptualized as the effects of prenatal attachment and biological environment on fetal development. (Glover & Capron, 2017).

In addition to social and psychological processes, the transition to prenatal parenthood involves an enormous neurobiological shift to caregiving – a complex process which substantially and permanently transforms human brain and drives the mother's motivational salience to infant stimuli and her behavior towards caring for her offspring (Duarte-Guterman, Leuner, & Galea, 2019; Hoekzema et al., 2017). In

human experiments, maternal oxytocin levels during pregnancy and the postpartum period have been found to associate with more responsive caregiving and, interestingly, with more balanced and rewarding maternal mental representations regarding attachment. Several neuroanatomical areas are involved in the neurobiological process of becoming a mother. The medial preoptic areas (MPOAs) play a crucial role in the development of parental responses and attitudes as these areas are connected with the mesolimbic dopamine system which is largely responsible for reward processing, also in the context of parent-child relationship. Therefore, the neurobiological transition to parenthood during pregnancy is connected with the experience of psychological attachment, caring for the offspring and rewards of parenting (Ammaniti & Gallese, 2014). This process may protectively interfere with the neurobiological dysfunctions and vulnerabilities present in maternal prenatal substance addictions (Kendler et al., 2017; Massey & Wisner, 2018).

During the last decades many scientists have contributed to the theory of prenatal attachment (Brandon, Pitts, Denton, Stringer, & Evans, 2009). In the early 80s, Mecca Cranley created the first theoretical definition for maternal-fetal attachment and referred to "the extent to which women engage in behaviors that represent an affiliation and interaction with their unborn child". In addition, she designed the first measure entitled the Maternal-fetal Attachment Scale (*MFAS*) for quantitative evaluation of the maternal-fetal attachment (Cranley, 1981). However, Mecca Cranley's conceptualization of maternal-fetal attachment was criticized due to its focus on only behavioral aspects of maternal-fetal attachment whereas the expectant mothers' internal representations of attachment were not captured (Brandon et al., 2009; Muller, 1993). Consequently, alternative conceptualizations for maternal-fetal attachment and measures for its assessment were introduced. Researcher Mary E. Muller presented the Prenatal Attachment Inventory (*PAI*) in 1993. This measure was built on the developmental model of attachment and focused especially on the expectant mother's internal representations of the attachment and relationship with the unborn child (Muller, 1993). Also in the 1990s, Condon and Corkindale presented a new conceptualization for maternal-fetal attachment and referred to "the emotional tie or bond which normally develops between the pregnant woman and her unborn infant" (Condon, 1993; Condon & Corkindale, 1997). In addition, they introduced a novel questionnaire measure, the Maternal Antenatal Attachment Scale (*MAAS*), which was primarily designed to capture the expectant mother's thoughts, feelings and affective experiences regarding the unborn child (Condon, 1993; Condon & Corkindale, 1997). At the beginning of the 2000s, Doan and Zimerman created a multidimensional view to prenatal attachment (Brandon et al., 2009; Doan, 2003) and somewhat later with a developmental model of maternal-fetal attachment (Doan & Zimerman, 2008). They suggested that "prenatal attachment is an abstract

concept, representing the affiliative relationship between the parent and fetus, which is potentially present before pregnancy, is related to cognitive and emotional abilities to conceptualize to another human being, and develops within an ecological system" (Doan, 2003). Therefore, several different conceptualizations of maternal-fetal attachment have been presented during the last decades. Nevertheless, the relationship between the expectant mother and her unborn child constitutes the essence of the concept, and the different conceptualizations of maternal-fetal attachment emphasize the different dimensions of this unique emotional bond and caregiving relationship (Brandon et al., 2009; Condon, 1993; Condon & Corkindale, 1997; Cranley, 1981; Doan, 2003; Muller, 1993).

Prenatal parenting has also been found to imply the expectant mother's capacity to conceptualize the unborn child as an separate individual and reflect her own experiences and her unborn child's perspective during pregnancy (Pajulo et al., 2015; Zeanah, 2019). In 2005, the concept of parental mentalization was introduced for the first time and defined as a "parent's capacity to reflect upon her own and her child's internal mental experience" by the scientist and clinical psychologist Arietta Slade (Slade, 2005). The construct of parental mentalization was based on the theory of mentalization and the concept of reflective functioning (RF) (Fonagy, 1991; Fonagy, 2004). In 1991, Peter Fonagy and his colleagues had started to investigate the concordance between parental attachment security and the infant's attachment security (Fonagy, 1991). In the context of the London Parent-Child Project, the construct of reflective functioning, or initially reflective-self functioning, was operationalized – referring to the measurable dimensions of the human capacity to understanding mental states (Fonagy, 1991). Fonagy et al. (1991) framed:

> "A prereflective self, which is the immediate – that is to say unmediated – experiencer of life and the reflective self, the internal observer of mental life, the dialectical complement of the experiencing self. The reflective self knows that the self feels, perceives, reacts, and so on. The reflective self reflects upon mental experience of feelings and thoughts, desires and beliefes. Most important, it is aware that its representations of its behaviour and action are shaped by the content of others' mentation." (Fonagy, 1991).

Subsequently, *parental reflective functioning* was referred to as a mother's ability to mentalize in relation to her child (Slade, 2005). This parental capacity has been demonstrated to play an important role in the transmission of attachment patterns between the generations (Katznelson, 2014). Parental mentalization has been considered the element that "makes parenting work" as the parent's capacity to understand and reflect the child's mental states underlying the child's behavior has

been found to associate with a better quality of caregiving, such as more favorable maternal affective communication, sensitivity and more responsive behavior in mother-infant interactions, better support for the child's emotional regulation and importantly, a child secure attachment (Camoirano, 2017; Katznelson, 2014; Zeegers, Colonnesi, Stams, & Meins, 2017). Parental mentalization capacity has been considered to promote and protect child healthy development by ensuring better nurturing care for the child (Camoirano, 2017; Katznelson, 2014). One recent meta-analysis has established that parental mentalization capacity positively correlates with maternal sensitivity and infant attachment security (Zeegers et al., 2017). In addition, preliminary findings from one experimental study have suggested that a stronger capacity for parental mentalization contributes to the mother's better tolerance to emotional and parenting distress (Rutherford, Booth, Luyten, Bridgett, & Mayes, 2015). A parent's better capacity to parental mentalization has been found to foster the development of the child's own reflective functioning (Camoirano, 2017). In the context of maternal substance use disorders, this developmental cascade has been considered potentially modifiable and target for interventions in the intergenerational chain of adversity as the children of mothers with substance use disorders and weak reflective functioning are especially at risk for developing addictions in adulthood (Alvarez-Monjaras et al., 2018). Maternal low parental mentalization capacity has been found to associate with the child's emotional problems, such as anxiety, impaired emotional regulation and externalizing behaviors (Camoirano, 2017) which, in turn, increase the risk of substance use disorders later in life (Alvarez-Monjaras et al., 2018; Meque et al., 2019; Stone et al., 2012).

More recently, there has been an increasing interest in the prenatal awakening of reflective functioning in relation to the unborn child and expectant parent's own experiences during the transition to parenthood (Pajulo et al., 2015; Slade & Sadler, 2019). According to Slade and Sadler, *prenatal parental mentalization* has been defined as "the mother's capacity to reflect on her own internal states, and on those of the people closest to her, and to imagine that the child will have a mind and feelings of his or her own, in that sense be separate from her" (Slade & Sadler, 2019). Recently, a novel measure titled Prenatal Parental Reflective Functioning Questionnaire (P-PRFQ) has been introduced for the assessment of prenatal parental mentalization and tested in the general population of Finnish pregnant women (Pajulo et al., 2015). So far, prenatal parental mentalization has been investigated in a general population (Smaling, Huijbregts, van der Heijden, van Goozen, & Swaab, 2016), in a sample of adolescent pregnant women (Sadler, Novick, & Meadows-Oliver, 2016) and in a sample of pregnant women considered to be at high risk due to substance use or mental disorders, low socioeconomic status or inadequate social support, single parenthood or teenage pregnancy (Smaling et al., 2015). The findings

from these studies have shown that pregnant women considered to be at high risk due to young age, socioeconomic disadvantage or substance use and mental disorders demonstrate on average a low capacity for prenatal parental reflective functioning (Sadler et al., 2016; Smaling et al., 2015). Further, a low level of prenatal parental mentalization has been found to associate with poorer child developmental outcome manifested in an increased risk for infant physical aggression at the age of 20 months (Smaling et al., 2016). The expectant mother's capacity to reflect her own and her unborn child's mental experience as well as hold the child in her mind are considered important prerequisites for adequate parental mentalization which profoundly promotes protective, responsive and nurturing caregiving for the child and healthy child development (Berthelot, Lemieux, Garon Bissonnette, Lacharité, & Muzik, 2019; Camoirano, 2017; Slade & Sadler, 2019; Zeegers et al., 2017). Engaging the mother in the process of mentalizing her own mental states and the mind of her own child as early as possible has been considered to offer a great intervention potential especially in vulnerable populations (Camoirano, 2017; Suchman & DeCoste, 2018). A higher capacity for mentalization has been found to protect pregnant women with a history of childhood adversity from prenatal distress (Berthelot et al., 2019) and, in general, to associate with better distress tolerance (Rutherford et al., 2015). Further, early interventions which aim at improving parental mentalization potentially prepare the expectant mother for more sensitive parenthood and promote child development. Stronger parental mentalization has been demonstrated to predict more sensitive and responsive caregiving for the child (Zeegers et al., 2017) and more favorable child developmental trajectory in terms of secure attachment (Zeegers et al., 2017), reflective functioning (Camoirano, 2017) and self-regulation (Camoirano, 2017; Smaling et al., 2016). In Finland, a new parental mentalization-based group intervention for depressed pregnant mothers has been designed lately and, the effectiveness of the intervention has been demonstrated in improved maternal sensitivity, parental mentalization capacity and reduced depressive symptoms (Salo et al., 2019).

2.3.2 Predictive factors

Parenting behavior strongly stems from the intergenerational continuum as the quality of nurturing care which the expectant mother has received in her early years begets her prerequisites for her own parenting capacities and behavior (Lomanowska, Boivin, Hertzman, & Fleming, 2017). Both parental reflective functioning and capacity for maternal-fetal attachment have been considered developmental achievements which can be endangered due to adverse relational experiences (Camoirano, 2017; Doan & Zimerman, 2008; Katznelson, 2014). In

general, the expectant mother's own childhood experiences are important determinants for her parenting capacity (Lomanowska et al., 2017). Women with substance use disorders have often faced childhood neglect or maltreatment (Håkansson, Watten, Söderström, Skårderud, & Øie, 2018; Isosävi et al., 2016) and parenthood after a history of childhood adversity is often compromised (Berthelot et al., 2019; Chamberlain et al., 2019; Lomanowska et al., 2017). Motherhood requires the appropriate functioning of neural systems that regulate perception, sensation, emotional state, reward processing, executive functions, learning and caregiving behavior (Barrett & Fleming, 2011). Childhood adverse experiences compromise the mother's parenting behavior, such as her capacities to consider the child as a separate individual and to understand the child's mind, rewards of caregiving, affect regulation, executive functions and her responsiveness, parenting practices and mothering style (Barrett & Fleming, 2011). For example, experiences of childhood emotional abuse have been demonstrated to associate with a lower parental mentalization capacity in mothers with substance use disorders (Håkansson et al., 2018b). Further, substance using mothers with a low parental reflective functioning self-report significantly more often adverse experiences in childhood than substance using mothers with a moderate to high capacity for parental mentalization (Håkansson et al., 2018b). A higher prenatal mentalization capacity has been demonstrated to play a protective role after a history of childhood maltreatment as higher prenatal reflective functioning has been shown to protect the expectant parent from psychological distress during pregnancy by mitigating the detrimental association between the expectant parent's own childhood maltreatment experiences and prenatal psychological distress (Berthelot et al., 2019).

During the last decades, several reviews have collected and synthetized data from a large number of individual studies investigating the determinants of prenatal parenting. In the original study from the 1980s, Mecca Cranley introduced and defined the concept of maternal-fetal attachment and demonstrated that social support contributed to stronger prenatal attachment while psychological distress inhibited maternal-fetal attachment to evolve. Further, maternal age, parity, socioeconomic status or self-esteem were not found to correlate with the awakening of maternal-fetal attachment (Cranley, 1981). John T. Condon investigated the correlates of antenatal attachment in the late 90s and showed that pregnant women with prenatal depression and anxiety, low social support and a high degree of control, domination and criticism in their intimate relationship displayed weaker attachment towards the fetus (Condon & Corkindale, 1997). However, maternal age, socioeconomic situation and obstetric risks were not found to correlate with the level of prenatal attachment (Condon & Corkindale, 1997). A large-scale integrative review by Cannella et al. (2005) aimed at estimating the role of psychosocial variables (the expectant mother's social support, relationships with others, self-

esteem, sense of mastery, anxiety, depression, stress, coping skills, health and well-being), demographic variables (maternal age, number of children, education, socioeconomic situation, marital status, race/ethnicity), pregnancy related variables, longitudinal variables (the change in maternal-fetal attachment during pregnancy and its capacity to predict longitudinal outcomes) and interventions focused on improving maternal-fetal attachment (Cannella, 2005). Unfortunately, the results were inconclusive to a high degree. Only the progress in pregnancy was consistently found to correlate with stronger maternal-fetal attachment (Cannella, 2005). A few years later, Yarcheski et al. (2009) reviewed 72 studies altogether and identified 14 predictors for maternal-fetal attachment (Yarcheski, Mahon, Yarcheski, Hanks, & Cannella, 2009). The duration of gestation, prenatal ultrasound consultations and social support were found to associate with stronger prenatal attachment with a moderate effect. Intendedness of pregnancy, maternal prenatal psychological distress, self-esteem, age, parity, ethnic background and socioeconomic situation had only a relatively weak relationship with maternal-fetal attachment and obstetric risks played a diminutive role in awakening of maternal-fetal attachment (Yarcheski et al., 2009). Very recently, Tichelman et al. (2019) identified over 130 studies which had evaluated the role of more than one hundred factors potentially influencing in the awakening of maternal-fetal attachment and mother-to-infant bonding. The findings from this systematic review were largely inconclusive again, and only three factors were found to consistently associate with maternal-fetal attachment and postnatal bonding. First, advancing gestational age had a positive association with maternal-fetal attachment. Second, maternal depressive symptoms associated negatively with postnatal bonding. Third, stronger attachment towards the fetus/child at an earlier time point associated with stronger attachment at later time points. In addition, planned pregnancy and social support were observed to correlate positively with prenatal attachment in the most of the studies (Tichelman et al., 2019).

Research on prenatal parental mentalization is still emerging and thus only a few studies have been published on the topic so far. One study from the Netherlands has shown that a higher level of maternal education and an adequate social support predict the expectant mother's higher capacity for prenatal parental mentalization (Smaling et al., 2015). In contrast, substance use during pregnancy was found to the significant predictor for a weak prenatal parental mentalization capacity among disadvantaged pregnant women (Smaling et al., 2015). The study validating the Prenatal Parental Reflective Functioning Questionnaire (P-PRFQ) among Finnish parents showed that primiparous pregnant women self-reported a stronger capacity for reflecting the fetus-child than multiparous women, and that mothers in general showed stronger parental RF than fathers during pregnancy. Women with a higher level of educational achievements self-reported a lower capacity to understand the opacity of mental states (Pajulo et al., 2015).

2.3.3 Consequences of prenatal parenting

Nurturing care, provided especially by the parents, is considered to be the most important factor promoting healthy child development (Britto et al., 2017). Every child has an unique developmental potential which can be reached in conditions ensuring adequate nurturing care and protection from adverse childhood experiences (Britto et al., 2017; Hughes et al., 2017). Extensive research has established that high-quality nurturing care is a powerful resilience-building factor whose beneficial effects can be seen in health, subjective wellbeing, learning and wealth even in adulthood (Britto et al., 2017). In 2017, the Lancet published a series of articles titled *Advancing early childhood development: From Science to Scale* in which nurturing care was defined as "a stable environment that is sensitive to children's health and nutritional needs, with protection from threats, opportunities for early learning, and interactions that are responsive, emotionally supportive, and developmentally stimulating" (Britto et al., 2017). A recent meta-analysis has contributed to the prior knowledge by establishing that expectant parents' prenatal representations of the unborn child and parental-fetal attachment predict postnatal nurturing care and mother-infant interaction quality (Foley, 2018). Therefore, the process implicated to sensitive parenting has been shown to emerge during pregnancy. The promotion of child development and the quality of nurturing care already begins during pregancy and interventions focusing especially on maternal mental health and early parenting play a pivotal role in supporting children in adversity to reach their optimal developmental potential (Britto et al., 2017; Glover & Capron, 2017).

High-quality prenatal parenting is considered protective for fetal/child development as recent evidence suggests that stronger maternal-fetal attachment associates with more favorable maternal health practices during pregnancy (Alhusen, Gross, Hayat, Woods, & Sharps, 2012; Cannella et al., 2018; Lindgren, 2001) and contributes to better neonatal (Alhusen et al., 2012) and child developmental outcomes (Branjerdporn et al., 2017). In addition, stronger maternal-fetal attachment has been found to associate with the better quality of postnatal nurturing care as regards the mother's responsiveness in early mother-infant interactions (Foley, 2018; Siddiqui & Hagglof, 2000) and capacities to enable secure child attachment (Dubber et al., 2015). In addition, a preliminary result from one study by Goecke et al. (2012) has suggested that stronger maternal-fetal attachment associates with a lower level of prenatal symptoms of depression and therefore prenatal parenting can be considered a potential protective counterforce against prenatal psychological distress (Goecke et al., 2012). The parental mentalization has also been reported to be protective for child development (Camoirano, 2017). For example, parental reflective functioning has been found to predict favorable parent-infant relationship and child attachment security even to a greater extent than

maternal sensitivity during mother-infant interactions (Zeegers et al., 2017). Parenting is considered to be the key modifiable factor mediating the effects of perinatal mental disorders on child development (Stein et al., 2014) and, importantly, a modifiable factor through which resilience in vulnerable children can be fostered (Traub & Boynton Jarrett, 2017). Some of the most important protective effects of prenatal parenting are presented in Table 3.

Table 3. Some of the key protective effects of prenatal parenting on maternal and fetal health.

Some of the key protective effects of prenatal parenting on maternal and fetal health.
In the recent meta-analysis, maternal-fetal attachment has been found to constitute the strongest predictor for positive prenatal health practices (Cannella et al., 2018).
Among pregnant smokers, stronger maternal-fetal attachment has been shown to associate with lower salivary cotinine levels and a tendency to smoke smaller maximum number of cigarettes per day. Especially, stronger altruistic maternal-fetal attachment has been found to associate with a greater likelihood of smoking cessation during pregnancy (Magee et al., 2014; Massey et al., 2015).
Stronger maternal-fetal attachment has been shown to associate with better neonatal outcomes in the sample of disadvantaged pregnant women (Alhusen et al., 2012).
A recent systematic review has revealed that stronger maternal-fetal attachment associates with more favorable child developmental outcomes, such as less difficult infant temperament, more adaptive behaviours including better sleep and lesser infantile colic, and increased milestone attainment, for children under 2 years old (Branjerdporn et al., 2017).
Prenatal attachment towards the fetus has been shown to predict the quality of postnatal nurturing care in terms of parent-infant interactions. A recent meta-analytic review has established that parental-fetal attachment and expectant parents' representations of their fetus-child have a modest but robust positive association with observed parent-child interaction quality (Foley, 2018).
Stronger maternal-fetal attachment has been demonstrated to associate with better postnatal bonding, and a lower level of postnatal maternal anxiety (Doster et al., 2018).
Stronger maternal-fetal attachment has been demonstrated to predict the better quality of maternal mind-mindedness at 7 and 19 months after birth. Mind-mindedness is considered as one dimension of parental mentalization, and it has been shown to correlate positively with maternal sensitivity and infant attachment security (McMahon, Camberis, Berry, & Gibson, 2016; Zeegers et al., 2017).
Stronger maternal-fetal attachment has been found to predict better maternal sensitivity in caregiving and free play situations with their 6-months old infant. A higher level of maternal sensitivity has been found to predict child attachment security, also among pregnant women with substance use disorders (Maas, de Cock, Vreeswijk, Vingerhoets, & van Bakel, 2016; Suchman, Nancy, DeCoste, Borelli, & McMahon, 2018).
Stronger prenatal parental mentalization has been found to constitute a protective factor in mothers with a history of adverse childhood experiences as it contributes to a lower level on prenatal psychological symptoms, stronger antenatal attachment and parental confidence (Berthelot et al., 2019).

2.3.4 Prenatal parenting in the context of tobacco and substance use disorders in pregnancy

In this paper, studies addressing the parenting in the context of maternal tobacco and substance use disorders are briefly reviewed in order to understand why prenatal parenting can be considered a particularly important focus in prenatal care for women with tobacco and substance use disorders. In pregnant women with severe substance use disorders, the transition to parenthood and awakening of maternal-fetal attachment is often burdened by struggles with cravings, concerns for fetal health and contradictory feelings, such as guilt, discomfort and uncertainty (Shieh & Kravitz, 2002). Extensive research has shown that mothers with substance use disorders are likely to be at higher risk of displaying impaired parenting (Parolin & Simonelli, 2016; Romanowicz et al., 2019; Rutherford & Mayes, 2017; Strathearn et al., 2019). For example, Romanowicz et al. (2019) evaluated the effects of parental opioid use disorder on the early parent-infant relationship in the recent systematic review which recognized 12 studies assessing the parent-child relationship as a primary outcome. The mothers with an opioid use disorder were found to be more irritated, ambivalent and disengaged in parent-child interactions. These mothers also displayed considerable difficulties in interpreting the child's signals and cues correctly. Unfortunately, the children of mothers with an opioid use disorder were found to demonstrate avoidant and disorganized attachment behavior in parent-child interactions and to be at increased risk of maltreatment and neglect (Romanowicz et al., 2019). It is of note that tobacco smoking in pregnancy has also been found to associate with considerably impaired parenting style and behaviors, such as verbal and physical child maltreatment and rejecting parenting style (Tandon et al., 2013). In the context of maternal tobacco and substance use disorders, impaired parenting is reflected in the child's physical and psychological safety (Raitasalo, Holmila, Autti-Ramo, Notkola, & Tapanainen, 2014; Tandon et al., 2013; Zeegers et al., 2017). The mechanisms linking maternal substance use disorders with an increased risk of child maltreatment involve deficits in the mother's emotional regulation and knowledge of favorable parenting practices and child development, an accumulation of psychosocial stress, imbalance between resources and requirements, preoccupation with substance-seeking and decreased pleasure from rearing of the child (Neger & Prinz, 2015). Previous studies concerning mothers with substance use problems have demonstrated that their capacity for parental mentalization is often weak (Camoirano, 2017; Håkansson, Söderström, Watten, Skårderud, & Øie, 2018; Håkansson et al., 2018; Katznelson, 2014; Pajulo et al., 2008; Pajulo et al., 2012; Suchman, DeCoste, Leigh, & Borelli, 2010) which, in turn, has been found to be negatively related to infant attachment security (Zeegers et al., 2017). Among mothers with substance use disorders, mental health problems have been found to compromise parental reflective functioning further (Håkansson et al., 2018). A low

level of prenatal parental reflective functioning has been reported to associate with more severe manifestations of substance use disorders and difficulties in executive functioning in mothers with substance use disorders (Håkansson et al., 2018). However, the stronger capacity for parental mentalization have been found to associate with more responsive caregiving, also in mothers with substance use disorders (Pajulo et al., 2012; Suchman et al., 2018; Suchman, Decoste, McMahon, Rounsaville, Mayes 2011; Suchman et al., 2010).

Maternal substance use disorders in pregnancy pose risks for health and safety of the child. One Finnish register-based study has revealed that the children of mothers with substance use disorders need hospital treatment more often (aOR = 1.2–2.0), are more likely to have infections (aOR = 1.2–2.0) and injuries (OR = 1.4–1.7) than the children born to mothers without substance related problems (Raitasalo et al., 2014). In addition, the risk for losing a custody of the child was found to be considerably high (aOR = 5.4–8.6) among mothers with substance related problems (Raitasalo et al., 2014). Both maternal alcohol and drug related problems were found to associate with an increased risk for the child's hospitalizations, infections, injuries and out-of-home placements, but the worst outcomes were observed in the children of mothers with both alcohol and drug abuse (Raitasalo et al., 2014). Within mothers with substance use disorders, the risk of a child being placed in foster care has been found to be predicted by maternal characteristics, such as low socioeconomic status, younger age, criminality, mental disorders, intravenous drug use, adverse childhood experiences and inadequate formal and informal support including prenatal care, treatment for substance use disorders and social support (Canfield, Radcliffe, Marlow, Boreham, & Gilchrist, 2017).

A recent review has introduced a biopsychosocial approach for modelling the multilevel risks for parenting in the context of maternal substance use disorders (Cataldo, Azhari, Coppola, Bornstein, & Esposito, 2019). This model suggests that suboptimal parenting style and behavior reflect a complex dynamic socio-relational process which involves several levels, such as specific physiological and biological mechanisms leading to impaired parenting, the influence of substance use on maternal psychological state (attitudes and mindset regarding parenting practices, the parent's own capacities for emotional regulation), social environment and the manifestation of triggers that moderate parent-child interactions moment by moment. The biopsychosocial approach to parenting in the context of parental substance use disorders addresses that parenting is a complex multidimensional concept involving the mother's (neuro)biology, beliefs, attitudes, practices, emotional regulation and, is rooted in social and cultural environment (Cataldo et al., 2019). This multilevel model of risks for parenting is likely to apply to the prenatal transition to parenthood in the presence of maternal tobacco and substance use

disorders. Indeed, research to date suggests that substance use disorders challenge the transition to parenthood at biological, psychological, social and practical levels (Alhusen, 2008; Cannella, 2005; Isosävi et al., 2016; Roberts & Pies, 2011; Rutherford & Mayes, 2017; Shieh & Kravitz, 2002).

Substance addictions constitute a specific neurobiological risk factor for the complicated transition to parenthood during pregnancy (Strathearn et al., 2019) and impair parenting (Parolin & Simonelli, 2016; Rutherford & Mayes, 2017; Rutherford & Mayes, 2019; Strathearn et al., 2019). Rutherford and Mayes (2017) have presented the reward-stress dysregulation model which proposes that "the dysregulation of stress and reward neural circuits by addiction represents a neurobiological pathway through which to understand how caregiving may be compromised in addicted parents" (Rutherford & Mayes, 2017). Substance use disorders compromise the essential neurobiology of parenting as the neural circuitries regulating reward from parenting, motivational salience to infant cues and parenting distress have been found to be dysregulated in substance addictions (Rutherford & Mayes, 2017; Rutherford & Mayes, 2019; Strathearn et al., 2019). These specific neurobiological vulnerabilities lead to decreased salience to infant stimuli, reduced engagement in caregiving, and passive or disengaged parenting behaviors (Rutherford & Mayes, 2017). Tobacco smoking has also been found to associate with mothers' dysregulated neural processing of infant cues, such as delayed responses to infant faces (Rutherford & Mayes, 2017). Mothers with substance dependence have been found to be especially prone to parenting distress, which may lead to increased craving and relapse in substance use (Rutherford & Mayes, 2017; Rutherford & Mayes, 2019). In addition, prenatal substance use has been demonstrated to affect the oxytocin-related affiliation system (Strathearn et al., 2019). For example, maternal cocaine use during pregnancy has been shown to associate with a decreased oxytocin level in the postnatal period (Strathearn et al., 2019). The brain oxytocin system has been found to play an important role in the transition to parenthood, caregiving behaviors and in the formation of attachment bond (Ammaniti & Gallese, 2014).

The children born to mothers with either tobacco or substance use disorders often need especially high quality nurturing care because they potentially suffer from neonatal withdrawal symptoms and/or other short and long term negative consequences of fetal substance exposure (Behnke et al., 2013; Forray & Foster, 2015). A secure attachment bond seems to be one of the most important protective factors for child mental health and the main factor contributing to resilience of children whose families are affected by parental alcohol or drug use (Smith et al., 2016; Traub & Boynton Jarrett, 2017; Wlodarczyk et al., 2017). An accumulation of protective resources, such as better family functioning, high quality of nurturing care and positive family relationships, have been found to be able to mitigate the

detrimental consequences of fetal substance exposure (Bada et al., 2012). Awakening of maternal-fetal attachment and concerns about fetal health have been found to constitute strong motivational drives for seeking prenatal care (Frazer, McConnell, & Jansson, 2019) and reducing substance use (Shieh & Kravitz, 2002). Maternal-fetal attachment constitutes the strongest predictor for the expectant mother's positive health practices (Cannella et al., 2018) and previous research has established that expectant mothers experiencing stronger maternal-fetal attachment are less likely to smoke during pregnancy (Alhusen et al., 2012; Lindgren, 2001). Among pregnant women who smoke, stronger prenatal attachment towards the fetus has been reported to associate with a tendency to smoke a lower maximum number of cigarettes per day and lower salivary cotinine concentrations (Magee et al., 2014). Interestingly, the women who smoke and consider smoking cessation have been found to display stronger maternal-fetal attachment than the pregnant women who smoke in the pre-contemplation stage of change (Slade, Laxton-Kane, & Spiby, 2006). The stronger altruistic dimension of maternal-fetal attachment, that is the one subscale titled "*Giving of self*" in the Maternal-Fetal Attachment Scale, has been found to especially predict a higher likelihood of smoking cessation among pregnant women who smoke (Massey et al., 2015). This altruistic dimension of maternal-fetal attachment reflects the expectant mother's feelings that all the difficulties of being pregnant are worth it, her positive self-perceptions during pregnancy, her willingness to make favorable changes in lifestyle, and the commitment to follow a healthy diet and give up unhealthy practices, essentially for the sake of the unborn child (Cranley, 1981; Massey et al., 2015).

All things considered, evidence to date addresses the association between maternal tobacco and substance use disorders and impaired parenting (Romanowicz et al., 2019; Smith et al., 2016; Tandon et al., 2013). Children whose families are affected by parental substance use are at risk of not reaching their full developmental potential due to possible prenatal exposure to substances, compromised nurturing care and an accumulation of adverse childhood experiences, all of which pose serious threats to the child's development and wellbeing (Britto et al., 2017; Hughes et al., 2017; Romanowicz et al., 2019; Smith et al., 2016). An intergenerational continuity in parenting behaviors has been established (Lomanowska et al., 2017). For these reasons, supporting prenatal parenting seems to contain the potential to intervene in the intergenerational transmission of adversity in the context of maternal prenatal tobacco and substance use disorders.

2.4 Breaking the chain of adversity in the context of tobacco and substance use disorders in pregnancy

2.4.1 Special issues in encountering pregnant women with tobacco and substance use disorders

Despite multiple treatment needs, pregnant women with either tobacco or substance use disorder are at an increased risk of inadequately attending prenatal care (Feijen-de Jong et al., 2012; Kahila et al., 2010; Kotelchuck et al., 2017; Roberts & Pies, 2011), which has also demonstrated to be true in Finland (Kahila et al., 2010; Raatikainen, Heiskanen & Heinonen, 2007). Pregnant women with substance use disorders have been shown to excessively utilize prenatal emergency and hospital care, but less preventive prenatal care (Kotelchuck et al., 2017). Unfortunately, they experience several barriers to prenatal treatment which are constituted of the pregnant woman's emotional experiences, manifestations and symptoms of substance use disorders, inadequate social support and a lack of life management and practical resources (Roberts & Pies, 2011). Further, the expectant mother's fear of losing the custody of the child, reluctance to leave other children or a partner, fear of stigma and practical issues, such as a lack of childcare and transportation have been shown to constitute obstacles to treatment (Frazer et al., 2019). Pregnant women with either tobacco or substance use disorder are especially reluctant to disclose their substance use to health care providers, experience fear of detection and may adopt detrimental strategies, such as isolation and missing prenatal appointments, in order to prevent detection (Dietz et al., 2010; Stone, 2015). It has been found that around 23% of pregnant women who smoke do not admit their tobacco smoking to health care professionals compared with the non-disclosure rate of 9% among women who are not pregnant and smoke (Dietz et al., 2010). Public policies, practices and ways of encountering pregnant women with substance-related problems within the health care system may also constitute barriers to prenatal care of women with substance use disorders (Davis & Yonkers, 2012; Frazer et al., 2019; Terplan, Kennedy-Hendricks, & Chisolm, 2015). Judgemental punitative attitudes and stigmatization especially prevent them from seeking treatment (Frazer et al., 2019; Terplan et al., 2015) as encounters which they find threatening have been found to discourage them from seeking prenatal care (Stone, 2015). In 2017, the American Academy of Pediatrics, in cooperation with the American College of Obstetricians and Gynecologists, published a recommendation that:

> "A public health response, rather than a punitive approach to the opioid epidemic and substance use during pregnancy, is critical, including the following: a focus on preventing unintended pregnancies and improving access to contraception; universal screening for alcohol and other drug use in women of childbearing age; knowledge and informed consent of maternal drug testing and reporting practices; improved access to comprehensive obstetric care, including opioid replacement therapy; gender-specific substance use treatment programs; and improved funding for social services and child welfare systems." (Patrick, Schiff & Comittee on Substance Use and Prevention, 2017).

Indeed, promotion of easy access to treatment, support for the expectant mother's self-efficacy and self-worth and positive alliance with these high-risk patients, are likely to increase the treatment retention of pregnant women with substance use disorders (Davis & Yonkers, 2012). Contemplations of reducing or quitting substance use, concerns related to fetal health, a fear of losing the custody of the baby or other children, the drive to escape a violent home environment or homelessness and a wish to have a better life management have been found to motivate them to seek treatment (Frazer et al., 2019). The expectant mother's concerns about fetal health and wellbeing constitute important motivators for seeking treatment and remaining in treatment programs, unless guilt overrides this motivation (Frazer et al., 2019; Roberts & Pies, 2011). For these reasons, public health response which acknowledges the expectant mother's emerging caregiving relationship with the child, aims at collaborative and compassionate encounters with these high-risk patients and providing optimal multidisciplinary care to these women and their children is considered essential (Frazer et al., 2019; Roberts & Pies, 2011; Smith et al., 2016; Terplan et al., 2015).

2.4.2 Focus on substance use and tobacco use disorders in pregnancy

The American Society of Addiction Medicine (ASAM) has recommended that pregnant women with substance use disorders should be given priority access to treatment, and the addiction treatment services should be able to meet the specific needs of pregnant and parenting women and their families by providing optimal treatment for substance use disorders and, in addition, at least medical care of co-occurring disorders and support for childcare, transportation, reproductive health, nutrition and parenting (American Society of Addiction Medicine, 2017). The specific framework consisting of *screening, a brief intervention and a referral to treatment* (SBIRT) has been considered a corner stone in the identification and treatment of pregnant women with substance use disorders in primary health care

facilities (American Society of Addiction Medicine, 2017; Haug, Duffy, & McCaul, 2014; Wright et al., 2016). A comprehensive medical assessment has been recommended so that complex and unmet treatment needs of pregnant women with substance use disorders can be identified (Haug et al., 2014). For pregnant women with substance use disorders, diverse medical, psychosocial and behavioral treatment options should be provided at different intensity levels ranging from outpatient services to medically managed intensive inpatient services, depending on the severity of the substance use disorder(s), comorbid condition and resources, such as housing, employment, partner and social support (Haug et al., 2014). Opioid assisted treatment, combined with psychosocial interventions, is considered standard care for pregnant women with an opioid use disorder (American Society of Addiction Medicine, 2017; Reddy et al., 2017). The Nordic Welfare Centre, an institution under the Nordic Council of Ministers, has recently published an overview on prenatal substance use problems and their treatment in Nordic countries (Nissinen & Frederiksen, 2020). In Nordic countries, maternity care is principally based on publicly funded primary health care and national guidelines which contain recommendations for screening of substance use with valid instruments or interview methods in early pregnancy. Prenatal treatment for women with substance use problems is provided at different levels of the healthcare system depending on the severity of substance use disorders and includes antenatal follow-up visits, psychoeducation, brief interventions and specialized maternal healthcare services which often involve a multidisciplinary and integrated approach. There are also specialized rehabilitation options for pregnant women with substance use problems, for example a residential care program called Holding Tight® organized by the Federaration of Mother and Child Homes and Shelters in Finland. Treatments rely on collaborative care and an alliance between pregnant woman and health care professionals – with an exeption of Norway which is the only European country also allowing compulsory inpatient treatment of pregnant women with substance use disorders (Nissinen & Frederiksen, 2020).

In Cochrane's systematic review, Terplan et al. (2015) have evaluated the efficacy of psychosocial interventions for the treatment of pregnant women with illicit drug use (Terplan, Ramanadhan, Locke, Longinaker, & Lui, 2015). The review included 14 studies with over 1200 patients and merely identified trials investigating the efficacy of two different kinds of psychosocial interventions, i.e. motivational interviewing and a contingency management. The control conditions constituted of very heterogeneous intervention methods, such as pharmacological treatment including opioid maintenance, different psychosocial interventions, standard counselling, prenatal care, testing, transportation, or childcare. The expectant mother's drug toxicology, self-reported drug use and treatment retention were assessed. In addition, the efficacy of the psychosocial intervention on neonatal

outcomes, such as preterm birth, low birth weight, neonatal toxicology screening and a duration of child hospital stay, were evaluated. This systematic review revealed that psychosocial interventions alone, when comprehensive treatment-as-usual was also available, were not more effective than the control conditions as regards the following outcomes: the pregnant women's treatment retention, substance use or the perinatal child outcomes. The only exception to this was that the duration of the neonate's hospital stay was found to be shorter in the newborns whose mothers had received contingency management treatment during pregnancy (Terplan et al., 2015).

Even though randomized and controlled trials have not been able to provide evidence of the efficacy of psychosocial interventions for treatment of pregnant women with substance use disorders (Terplan et al., 2015), the whole picture regarding effectiveness of treatment programs for these high-risk pregnant women does not seem to be so pessimistic. Integrated treatment programs combining maternity care and substance use treatment have been shown to improve pregnancy and neonatal outcomes and to be cost-effective (Armstrong et al., 2003; Goler et al., 2012). Further, Kotelchuck et al. (2017) conducted a large population based study investigating the effectiveness of substance use treatment during pregnancy. The study sample consisted of nearly 375 000 pregnant women and their children born in Massachusetts in the USA between 2003 and 2007. The data regarding maternal substance use during pregnancy was obtained from health care registers. The results revealed that 5.5% of the pregnant women had substance use problems during pregnancy. The neonatal outcomes of the newborns born to substance using mothers were found to be significantly poorer than the outcomes of the neonates born to mothers who had not abused substances during pregnancy. However, the newborns of substance using mothers who had received substance use treatment during pregnancy displayed significantly better neonatal outcomes than the newborns of whose mothers who had not attended substance use treatment during pregnancy. However, the alarming finding was that only 66% of pregnant women with substance use problem had received medical treatment for their condition (Kotelchuck et al., 2017).

The efficacy of psychosocial and pharmacotherapeutic interventions to promote smoking cessation in pregnancy has been estimated in the two updated Cochrane's systematic reviews (Chamberlain et al., 2017; Claire et al., 2020). The first review evaluating the efficacy of the psychosocial interventions to promote smoking cessation during pregnancy included 120 studies and involved over 28 000 pregnant women. The intervention methods were primarily consisted of counselling, health education, feedback, incentives, social support and physical exercise. The results suggested that psychosocial interventions were effective in increasing the proportion of women who were able quit smoking during pregnancy. Further, the beneficial

effect of the psychosocial interventions was observed on the newborn's birth weight and need for neonatal intensive care after birth (Chamberlain et al., 2017). The efficacy of pharmacotherapies for treatment of nicotine addiction during pregnancy has been evaluated in the second recent systematic review which included 11 studies involving around 2400 pregnant women who smoked. Nine of these studies investigated the efficacy of nicotine replacement therapy and two of the studies assessed the efficacy of bupropion combined with psychosocial treatment. There were no studies evaluating the efficacy of varenicline or electronic cigarettes to promote smoking cessation during pregnancy. The authors of the review concluded that those pregnant women who smoke and receive nicotine replacement therapy may be more likely to quit smoking during pregnancy, however, the efficacy of bupropion was not substantiated (Claire et al., 2020). Nevertheless, there is still a considerably more to be done to improve the smoking cessation rate among pregnant women who smoke as only less than a half of these women are able to quit smoking during pregnancy (Lange et al., 2018) and of those women who receive smoking cessation interventions during pregnancy only about 13% are permanently committed to abstinence from smoking (Jones, Lewis, Parrott, Wormall, & Coleman, 2016).

2.4.3 Focus on prenatal parenting

To our knowledge, psychosocial interventions supporting prenatal parenting have not previously been investigated with a randomized and controlled research design among pregnant women with tobacco and substance use disorders (Glover & Capron, 2017; Howard et al., 2014; Neger & Prinz, 2015; Terplan et al., 2015). As far as we can acertain, prenatal parenting has not yet explicitly been focused on psychosocial interventions designed to promote smoking cessation (Chamberlain et al., 2017). Therefore, we mainly review previous studies investigating parenting focused interventions and treatment programs for women with substance use disorders and their children. Multidisciplinary and integrated treatment programs have widely been recommended for treatment of mother's with substance use problems and their children in order to break the intergenerational chain of poor maternal and child health outcomes, dysfunctional family environment and accumulative adversity (Milligan et al., 2010; Niccols, Milligan, Smith et al., 2012a; Niccols et al., 2012b; Smith et al., 2016). Integrated care for pregnant or parenting women with substance use disorders has typically consisted of treatment for maternal substance use disorders combined with mental health support, prenatal care and/or parenting support, child focused practices and social services (Niccols et al., 2012a; Niccols et al., 2012b). The meta-analysis of Milligan et al. (2010) evaluated the efficacy/effectiveness of integrated treatment programs for

pregnant or parenting women with substance abuse issues (Milligan et al., 2010). In this review and meta-analysis, the main interest was focused on the effects of the integrated treatment programs on maternal substance use outcomes (Milligan et al., 2010). The study group identified altogether 21 studies conducted between 1990 and 2007. Only two of the studies were randomized and controlled trials, and the remainder of the studies utilized quasi-experimental or observational research designs. All the integrated programs had specifically been developed to meet the needs of pregnant or parenting women with substance use problems, but the content of programs varied greatly from residential programs to integrated outpatient care, such as enhanced methadone-assisted treatment or standard outpatient addiction services combined with maternal psychotherapy or parenting interventions. The findings demonstrated that the integrated treatment programs were effective in improving maternal substance use outcomes, such as urine toxicology, severity of drug and alcohol use and preoccupation with substance use. Four of the studies compared the integrated treatment programs with non-integrated treatment approaches in terms of maternal urine toxicology and self-reported substance use, but statistically significant differences in these outcomes were not observed between the integrated and non-integrated treatment programs. In addition, the same research group evaluated the efficacy/effectiveness of integrated treatment programs on parenting (Niccols et al., 2012b) and child outcomes (Niccols et al., 2012a). Niccols et al. (2012) recognized altogether 31 studies which had estimated the effects of the integrated treatment programs on parenting outcomes (Niccols et al., 2012b). Only four of these studies were randomized and controlled trials. The findings from this systematic review suggested that the integrated treatment programs associated with improvements in the quality of parenting. Further, the findings revealed that integrated residential treatment programs and integrated programs augmented with mental health services were found to have the largest positive effect on parenting outcomes (Niccols et al., 2012b). Niccols et al. (2012) estimated the effect of integrated treatment programs on child outcomes and identified altogether 13 studies of which only two were randomized and controlled trials (Niccols et al., 2012a). The majority of the studies reported the beneficial effect of integrated care on child development and socioemotional functioning. The infants of mothers in integrated care were more likely to develop and grow better than the infants of women who were not attending treatment programs. In addition, the findings regarding the children's emotional and behavioral functioning favored the integrated treatment programs over non-integrated care with a small effect (Niccols et al., 2012a).

More recently, the review of Neger and Prinz (2015) recognized altogether 21 intervention studies addressing both parenting and parental substance use (Neger & Prinz, 2015). Nine of these studies were randomized and controlled trials. In the

randomized studies, the control condition constituted of addiction treatment combined with different kinds of psychosocial support, such as case management, couple's behavioral therapy and parent education brochures. The studies estimated the efficacy/effectiveness of 17 parenting intervention programs which aimed at increasing the mother's resources (employment, housing, social support), her knowledge of child development and beneficial parenting practices, her emotional self-regulation, parental mentalization, and engagement in child care instead of preoccupation with substance abuse. The most common intervention mechanisms were to improve the mother's psychosocial functioning, parenting knowledge and emotional regulation. Only a few interventions were found to focus on reinforcing the parent's engagement in nurturing caregiving for the child instead of drug seeking, and none of the studies directly focused on increasing the pleasure of parenting role even though mothers with substance addictions often experience reduced reward from parent-child interactions. The authors of the review concluded that treatment for substance use disorders augmented with parenting interventions has benefits over and above non-integrated care as regards parental substance use, parenting practices and even child adjustment outcomes. Nonetheless, this review did not address prenatal parenting as a therapeutic focus in treatment for pregnant women with substance use disorders (Neger & Prinz, 2015) .

Parental mentalization has been considered an efficient focus for parenting intervention as it fosters the mother's capacity for responsive caregiving and secure attachment bond with the child, which also has been found true among mothers with substance use disorders (Camoirano, 2017; Katznelson, 2014; Parolin & Simonelli, 2016; Suchman & DeCoste, 2018). In Finland, parental mentalization focus has explicitly been utilized in residential treatment program for pregnant and parenting women with substance use problems (Pajulo, Suchman, Kalland, & Mayes, 2006; Pajulo et al., 2012). The results from a study reporting the effectiveness of this residential treatment program suggested that parental mentalization capacity strengthened in response to mentalization focused work during residential care and, the mothers with a stronger capacity for parental mentalization relapsed less frequently to substance use and were more likely to maintain the custody of child (Pajulo et al., 2012). In the USA and global perspective, psychologist and researcher Nancy Suchman is recognized as a world leader and pioneer in developing and testing attachment based intervention programs for mothers with substance use disorders (Suchman et al., 2017; Suchman et al., 2018; Suchman, Mayes, Conti, Slade, & Rounsaville, 2004; Suchman et al., 2010a; Suchman et al., 2010b). Suchman and her colleagues have designed and tested the intervention method called "*The Mothers and Toddlers Program*" / "*Mothering from Inside Out*" for treatment of parenting women with substance addictions (Suchman et al., 2017; Suchman et al., 2010a; Suchman &

DeCoste, 2018). *The Mothers and Toddlers Program* is a manualized 12-weeks attachment-based individual parenting therapy which is combined with outpatient addiction treatment (Suchman et al., 2010a). In *The Mothers and Toddlers Program*, the therapist can assist the mother with her basic needs (food, housing, child care, health care needs) but the core of the intervention method is to invite and engage the mother in the process mentalizing her child and her own experiences regarding parenting (Suchman et al., 2010a). In addition, the mother is encouraged to explore, reflect and understand mental states underlying her own behavior and her infant behavior by watching video recordings of mother-infant interactions. The efficacy of *The Mothers and Toddlers Program* has been investigated in a randomized and controlled study which showed that the mothers in the intervention group demonstrated stronger parental mentalization capacity, more coherent representations of the child, better sensitivity and caregiving behaviors in mother-infant interactions in comparison with the mothers in the control group receiving parent education (Suchman et al., 2010a). The second testing of *The Mothers and Toddlers Program* showed that the positive effects of the intervention on maternal parental mentalization and caregiving behavior was sustained in a follow-up period of 6 weeks (Suchman, Decoste, McMahon, Rounsaville, Mayes, 2011). In addition, the findings revealed that particularly the improvement in the mother's self-focused component of parental mentalization, which reflects the mother's capacity to mentalize her own emotional experiences and the impact of her own emotions on the infant's experience, was linked with better maternal sensitivity and capacity to foster the child's socio-emotional and cognitive growth (Suchman et al., 2010b). Further, the mother's enhanced capacity for self-mentalization was especially found to contribute to the sustained beneficial effect of the intervention on parental mentalization (Suchman et al., 2010b). *The Mothering from Inside Out* – program followed in the footsteps of *The Mothers and Toddlers Program* and represents the second randomized and controlled trial testing of the efficacy of the manualized individual therapy with 12 sessions aiming at enhancing the mother's capacity for parental mentalization (Suchman et al., 2017; Suchman & DeCoste, 2018). This second trial established that maternal parental mentalization, the quality of maternal caregiving representations and mother-infant interactions improved in response to *The Mothering from Inside Out* – intervention in comparison with the mothers in the control group receiving parent education (Suchman et al., 2017). Moreover, the protective effect of the intervention on the parenting outcomes was found to be greater as the severity of the mother's substance use disorder increased (Suchman et al., 2017). After a one year follow-up period, the mothers who have received the mentalization focused parenting intervention demonstrated greater sensitivity and their children were found to be more involved in mother-child interactions (Suchman et al., 2017).

Furthermore, the parent-child interactions of dyads in the intervention group were found to be more reciprocal (Suchman et al., 2017). Suchman et al. (2018) demonstrated that the therapist's fidelity to parental mentalization focus was the key efficient component in the intervention and the mother's improved parental mentalization and representations of caregiving especially contributed to her caregiving sensitivity after controlling for competitive interventive mechanisms, such as alleviation of psychological distress or decreased severity of substance use problems. However, only maternal caregiving sensitivity was found to promote child attachment security. Unfortunately, the study was not able to demonstrate that improvements in parental mentalization and caregiving representations would have lead to a decreased risk of relapse in substance use (Suchman et al., 2018).

Strengthening maternal-fetal attachment has also been suggested as an intervention strategy with considerable potential to have positive effects on maternal and fetal health (Glover & Capron, 2017). A recent narrative review identified several interventions methods designed to enhance the parental-fetal relationship (Borg Cunen, Jomeen, Borg Xuereb, & Poat, 2017). These prenatal interventions were aimed at promoting the pregnant woman's mental wellbeing, her capacity to be aware of the fetus and conceptualize the unborn child as an individual person (Borg Cunen et al., 2017). Further, the interventions to strengthen maternal-fetal attachment have provided prenatal education and psychosocial support for the expectant parent (Borg Cunen et al., 2017). From the perspective of prenatal interventions, fetal ultrasound has been considered the most promising intervention method to enhance maternal-fetal attachment (Borg Cunen et al., 2017). Indeed, several prior studies have established the positive association between the visualization of the fetus with ultrasound imaging and maternal-fetal attachment (Borg Cunen et al., 2017; Boukydis et al., 2006a; de Jong-Pleij et al., 2013; Sedgmen, McMahon, Cairns, Benzie, & Woodfield, 2006; Yarcheski et al., 2009). The review by de Jong-Pleij et al. (2013) suggested that both two-dimensional (2D) and three/four-dimensional (3D/4D) ultrasound imaging are effective in improving maternal-fetal-attachment, but 4D ultrasound imaging offers better and more accurate visualization of the fetus and therefore may contribute to a more intensive and positive experience of maternal-fetal attachment (de Jong-Pleij et al., 2013). A researcher and developmental / clinical psychologist Zack Boukydis devoted his career to working with parents in the perinatal period and development of perinatal interventions, for example the intervention method called "ultrasound consultation" (Boukydis & Stockman, 2012; Boukydis et al., 2006a; Boukydis, 2006b). The ultrasound consultation is a manualized intervention method which aims at supporting the maternal-fetal relationship during pregnancy through interventive use of ultrasound imaging and enhanced collaboration with expectant mothers while looking at the fetus via ultrasound

(Boukydis & Stockman, 2012; Boukydis et al., 2006a; Boukydis, 2006b). Ultrasound consultation has been demonstrated to strengthen maternal-fetal attachment and alleviate maternal anxiety, and to increase positive attitudes as regards maintaining good prenatal health (Boukydis et al., 2006a; Boukydis, 2006b). Obstetric ultrasound has provided considerable benefits for maternal and fetal health and is considered to be relatively safe, however, the use of prenatal ultrasound imaging always requires a medical indication, risk-benefit analysis and good clinical practices as ultrasound in pregnancy may contain potential risks, for example diagnostic errors (over diagnosis, under diagnosis, reporting errors) and bio effects, i.e. potential deleterious thermal and mechanical effects on fetal tissues which has been demonstrated in animal studies but not in human studies, except for the over-representation of non-right handedness in males (Abramowicz, 2013; Van den Hof, 2018). The ultrasound consultation has been conducted during the second trimester (Boukydis et al., 2006a; Boukydis, 2006b) when the potential risks of ultrasound imaging are considered smaller in comparison with the potential risks of early pregnancy ultrasound (Abramowicz, 2013; Van den Hof, 2018).

2.4.4 Focus on prenatal psychological distress

There is a paucity of studies evaluating prenatal interventions to alleviate psychological distress among pregnant women with substance abuse or addictions. Therefore, this literature review relies on studies from diverse populations. The Lancet published a large-scale series of articles regarding perinatal mental disorders in 2014 (Howard et al., 2014; Stein et al., 2014). In general, these comprehensive reviews recognized the paucity of studies evaluating interventions for treatment of maternal perinatal mental disorder, with the exception of postnatal depression (Howard et al., 2014; Stein et al., 2014). Primarily, non-pharmacological treatment options are recommended for treatment of non-psychotic mental disorders during the perinatal period (Howard et al., 2014). Unfortunately, evidence of psychosocial interventions for treatment of prenatal depression has been limited to findings from relatively small trials evaluating the efficacy of interpersonal and cognitive behavioral therapy (Howard et al., 2014). Further, no pharmacological intervention studies have been conducted except for treatment of postnatal depression (Howard et al., 2014). The efficacy of interventions for treatment of maternal prenatal mental disorders and psychological distress involves two perspectives, maternal and child health. It is important to note that improved maternal outcomes in response to prenatal interventions do not necessarily lead to improvement in child outcomes with the similar effect (Goodman, Cullum, Dimidjian, River, & Kim, 2018). A recent systematic review by Goodman et al. (2018) has addressed the fact that interventions for prevention or treatment of prenatal depression, constituted of very heterogenous

treatment approaches such as cognitive behaviour therapy, couple therapy, yoga/massage, counselling, psychoeducation, parent training or enhanced maternal nutrition, associate with improved child outcomes with a small effect (Goodman et al., 2018). Therefore, the children of expectant mothers with prenatal psychological distress have been demonstrated to benefit from prenatal interventions, even though the effect of the prenatal interventions on maternal mood was found to be larger, that is a medium size effect (Goodman et al., 2018). In 2017, van Ravesteyn et al. evaluated the efficacy of interventions for treatment of prenatal mental disorders in a systematic review and meta-analysis (van Ravesteyn, Lambregtse-van den Berg, Mijke P, Hoogendijk, & Kamperman, 2017). Only interventions for treatment of major depressive and anxiety disorders were identified, and none of the studies estimated the efficacy of pharmacological interventions for treatment of prenatal mental disorders. This meta-analysis revealed that cognitive behavioral therapy had a moderate beneficial effect for pregnant women with a major depressive disorder. Moreover, interpersonal psychotherapy was also found to be effective, even though with a smaller effect size (van Ravesteyn et al., 2017). In addition, one Cochrane's systematic review has been conducted to evaluate the efficacy of other types of non-pharmacological interventions, such as massage, acupuncture, bright light and omega-3 supplementation, for treatment of prenatal depression (Dennis & Dowswell, 2013). The findings from these studies have largely been inconclusive (Dennis & Dowswell, 2013).

Fontein-Kuipers et al. (2013) evaluated the efficacy of the prenatal interventions to alleviate maternal psychological distress and recognized ten high-quality randomized trials conducted between 2001 and 2008. This systematic review and meta-analysis did not provide evidence of the efficacy of the preventive interventions (prenatal education, mentoring, music therapy, group prenatal care) whereas treatment interventions, such as relaxation, acupuncture, a self-help workbook and mindfulness, were found to be effective in reducing maternal prenatal distress with a small effect (Fontein-Kuipers, Nieuwenhuijze, Ausems, Bude, & de Vries, 2014). A very recent systematic review has evaluated the efficacy of interventions for women and their partners to prevent or alleviate psychological distress and anxiety during the first 1000 days from conception (Matvienko-Sikar et al., 2020). Matvienko-Sikar et al. (2020) recognized 15 different kinds of interventions to alleviate parental perinatal stress/anxiety and the intervention studies involved nearly two thousand participants (Matvienko-Sikar et al., 2020). The intervention methods were consisted of cognitive behavioral approaches, mindfulness, psychoeducation, stress management techniques, heart rate variability biofeedback combined with breathing exercises, and peer-mentoring. The findings from this review suggested that the interventions contributed to the improvement in some of the measures used to assess prenatal stress and anxiety, but did not improve all the

pre-defined outcomes which were used to quantify stress and anxiety. Only one prenatal cognitive behavioral online intervention was unequivocally effective in reducing symptoms of generalized anxiety and psychological distress in the third trimester. In the majority of studies, the findings were inconsistent or did not provide evidence for the efficacy of the interventions on prenatal stress and anxiety. Two of the studies estimated the efficacy of interventions which took place both pre- and postnatal period. One study evaluated the effect of pre/postnatal home-visiting intervention which was found to reduce stress only among women with low psychosocial resources. Another pre/postnatal intervention utilized cognitive behavioral stress management which was found to reduce subjective distress, but neither the beneficial effect on cortisol measurements nor sustained positive effects on distress was substantiated. Matvienko-Sikar et al. (2020) concluded that the findings regarding the efficacy of interventions to alleviate prenatal psychological distress are inconsistent. In addition, the risk of bias in the studies included in the systematic review was estimated to be rather high and the interventions were found to be highly heterogeneous regarding the aspects of type, timing, target populations and outcome measures (Matvienko-Sikar et al., 2020). All things considered, thus far there have been no well-elucidated optimal mechanism to alleviate prenatal psychological distress.

2.5 Summary of the literature review

Maternal tobacco and substance use disorders in pregnancy indicate an cumulative adversity and risks for both maternal and fetal/child health (Behnke et al., 2013; Kahila et al., 2010). Fetal exposure to tobacco and substances has a wide spectrum of adverse effects on the offspring's development and well-being in the short and long term (Behnke et al., 2013). In addition, maternal tobacco and substance use disorders identified during pregnancy often associate with an excessive burden of other environmental risk factors for fetal/child development, such as prenatal psychological distress and impaired parenting which amplify the adversity of children affected by prenatal substance exposure (Goodwin et al., 2017; Romanowicz et al., 2019; Smith et al., 2016; Strengell et al., 2014; Tandon et al., 2013). Extensive research has established an intergenerational transmission of risks from maternal prenatal tobacco and substance use disorders and associative problems to the offspring's vulnerabilities (Aizer & Currie, 2014; Alvarez-Monjaras et al., 2018; Behnke et al., 2013; Patrick & Schiff, 2017; Strathearn et al., 2019). However, pregnancy offers a window of opportunities to break the intergenerational processes linking maternal substance use disorders to vulnerabilities in the child (Kendler et al., 2017; Massey & Wisner, 2018). Focusing on supporting parenting and alleviating maternal psychological distress during pregnancy may offer potential

momentums through which it could be possible to intervene in the intergenerational chain of adversity in the context of tobacco and substance use disorders in pregnancy (Alvarez-Monjaras et al., 2018; Cannella et al., 2018; Glover & Capron, 2017; Goodman et al., 2018; Stein et al., 2014).

3 Aims

The primary aim of this dissertation was to investigate the specific psychological phenomena related to the transition to parenthood, that is to say prenatal parenting and prenatal psychological distress, and hence, to establish potential new early focuses to intervene in the intergenerational adversity in the context of prenatal tobacco and substance use disorders. Two very different samples and research designs were used to gain a more profound understanding of these phenomena. First, we evaluated with a randomized and controlled research design the efficacy of the recently developed prenatal parental mentalization focused 4D ultrasound intervention in a sample of pregnant women with recent or current harmful substance use. Second, we investigated the role of prenatal parenting and psychological distress in maternal smoking behavior during pregnancy in the large population-based FinnBrain Birth Cohort Study.

Specifically, the aims were:

1. To investigate the efficacy of the prenatal parental mentalization focused 4D ultrasound intervention on maternal prenatal parenting and psychological distress (Study I)
2. To investigate the efficacy of the prenatal parental mentalization focused 4D ultrasound intervention on the pregnant woman's participation in prental follow-up and care, fetal drug exposure and perinatal child outcomes (Study II)
3. To explore the role of maternal-fetal attachment in the smoking behavior of pregnant women, i.e. smoking in pregnancy and smoking cessation in early pregnancy, and the modifying effect of maternal-fetal attachment on the expected associations between maternal education/prenatal psychological distress and prenatal smoking behavior (Study III)
4. To explore the role of second trimester pregnancy-related anxiety in the smoking behavior of pregnant women, i.e. smoking in pregnancy and smoking cessation in early pregnancy (Study IV)

4 Materials and Methods

4.1 Study designs and participants

4.1.1 The parental mentalization focused 4D ultrasound intervention study (Studies I and II)

4.1.1.1 Study design

The parental mentalization focused 4D ultrasound intervention study was a randomized and controlled clinical trial (RCT) for pregnant women with recent or current substance use problems, carried out at the HAL obstetric outpatient clinic at Turku University Hospital between October 2011 and November 2014. The abbreviation HAL refers to the acronym generated from the Finnish words for: illicit drugs, alcohol and prescription medication. The HAL clinic is a specialized obstetric outpatient unit offering multidisciplinary prenatal care for women with substance use problems. The intervention group received the parental mentalization focused 4D ultrasound intervention and the control condition comprised of treatment as usual (TAU) at this special obstetric outpatient clinic. The participants were randomized into the intervention and control groups using a computer-generated block randomization with a block size of four. Separate blocks for the participants in opioid maintenance treatment were used to ensure their equal allocation into the study groups. The study was retrospectively registered in the database of ClinicalTrials.gov with the reference number of NCT03413631. The study and intervention protocol were implemented in clinical routine practice at this special obstetric outpatient clinic (Table 4).

4.1.1.2 Participants

The participants were pregnant women referred from primary health care to the special obstetric outpatient clinic for pregnant women with substance use problems at Turku University Hospital between October 2011 and November 2014. The eligibility criteria for the study were a singleton pregnancy and a pregnancy duration

of less than 22 gestational weeks (gwks) at referral. The criteria for the referral were: 1) documented or self-reported illicit drug use, abuse of prescription medication or alcohol within three years prior to or during the present pregnancy, 2) and/or a sum score of ≥ 3 points on TWEAK alcohol screening (Russell, 1994). The acronym TWEAK refers to the warnings signs of alcohol use disorder: an increased alcohol *tolerance*, friends and relatives being *worried* about one's alcohol use, a need for *eye-openers*, having *amnesia* related to alcohol use or feelings that drinking needs to be *(k)cut down*. The sensitivity and specifity of TWEAK questionnaire in detecting risky drinking during pregnancy has been reported to be 71–91% and 73–83%, respectively (Burns, Gray, & Smith, 2010). The TWEAK alcohol screening questionnaire, with added questions concerning recent or current use of illicit drugs and misuse of prescription medication, was used in all primary health care units in the geographical area where the intervention study was conducted. Public health nurses carried out a prenatal screening for substance use problems. In Finland, nearly 100% of pregnant women use services provided by public maternity clinics, and thus the coverage of the prenatal screening for substance use problems can be considered excellent during the data collection period of the study (National Institute for Health and Welfare in Finland, 2015). Of all the pregnant women (n = 126) who were referred to specialized obstetric care due to substance use problems, 75 % (n = 95) agreed to participate and gave written informed consent. The participants were randomized into intervention (n = 47) and control groups (n = 48).

4.1.1.3 The parental mentalization focused 4D ultrasound intervention

The parental mentalization focused 4D ultrasound intervention consisted of the following components: three parental mentalization focused interactive 4D ultrasound sessions, a week-by-week pregnancy diary aiming at enhancing parental mentalization and three sessions with an infant mental health professional to work around the reflective pregnancy diary. The important theoretical rationale of the intervention has been presented in the literature review and the detailed description of the intervention has been published in the method article (Pajulo, Pajulo, Jussila, & Ekholm, 2016).

Parental mentalization focused interactive 4D ultrasounds

The parental mentalization focused interactive 4D ultrasound sessions were based on previous work by the researcher and clinical psychologist Zack Boukydis who designed an intervention method titled "ultrasound consultation" for building resilience and reducing risks in the high-risk samples of pregnant women (Boukydis et al., 2006a; Boukydis, 2006b). The objective in the ultrasound consultation is to

observe the fetus together with the expectant mother and focus on exploring the physical features, position and movements of the fetus and providing interpretation of fetal behavior inside the womb (Boukydis et al., 2006a). During the ultrasound consultation, the expectant mother is allowed and encouraged to initiate interaction with her unborn child and to explore the ways in which the unborn child responses to her initiatives for interaction, such as touching her abdomen or speaking/singing to her fetus (Boukydis et al., 2006a). The ultrasound consultation aims at the personification of the fetus, that is to say, to arouse the expectant mother's interest in her unborn child and in thinking more of the child's developing personality (Boukydis et al., 2006a). Ultrasound consultation has been found to promote maternal-fetal attachment, the expectant mother's positive attitudes towards a healthy lifestyle during pregnancy and reduce maternal anxiety (Boukydis et al., 2006a; Boukydis, 2006b).

In the present study, the original idea of the ultrasound consultation was strengthened with the parental mentalization focused approach in which the expectant mother's explicit effort to reflect her own experiences and mental states and her unborn child's perspective was encouraged. The participants in the intervention group were offered three parental mentalization focused 4D ultrasound sessions at 24, 30 and 34 gwks. The interactive ultrasound sessions were designed to take about 30 minutes. The sessions started by asking the expectant mother's personal reflection on her current mental state and wishes for the interactive 4D ultrasound session. During the sessions, an experienced obstetrician and an infant mental health professional worked in collaboration with the primary aim of promoting the expectant mother's active curiosity and interest in the unborn child's development and perspective, her own experiences related to watching the fetus on the screen and becoming a parent to this particular child. The expectant mothers participated in the ultrasound sessions alone, but the father of the unborn child or the mother's close companion was invited to take part to the session after the interventive phase.

Parental mentalization focused week-by-week pregnancy diary and work with an infant mental health professional

A new parental mentalization focused pregnancy diary was designed to promote interest and curiosity in fetal development and to evoke parental mentalization, i.e. to encourage and support the expectant mother's consistent reflective stance regarding the perspective of her unborn baby and her own experiences of this pregnancy, maternal-fetal relationship and the transition to parenthood (Pajulo et al., 2011a). The mentalization focused pregnancy diary contains an spread sheet for each pregnancy week, and offers psychoeducation about pregnancy, fetal development

and positive health practices during pregnancy. The main mentalization-focused interventive elements are the questions and tasks which are supposed to inspire the expectant mother to reflect her experiences about pregnancy and becoming a mother, and her curiosity about the unborn child's developing personality and point of view. The purpose of the diary was to keep the unborn child actively in the expectant mother's mind throughout the pregnancy. The diary was given to the participants in the intervention group after randomization. In addition, three meetings with an infant mental health professional were offered in order to give the participants an opportunity to reflect her experiences and thoughts aroused by the pregnancy diary and to encourage and engage the expectant mother to the process of mentalizing. The reflective pregnancy diary sessions were planned to last approximately 45 minutes, and they were arranged within two weeks after each interactive ultrasound session.

4.1.1.4 Control condition: Treatment as usual

Comprehensive routine care was provided to all the pregnant women referred to this special obstetric care unit due to substance use problems. The pregnant women were scheduled to visits for prenatal care and follow-up which involved multidisciplinary work to support maternal and fetal health, expectant mothers' positive health practices, wellbeing and psychosocial situation. The multidisciplinary treatment team included an obstetrician, a midwife, a social worker and a psychiatric nurse. The systematic assessment of maternal concomitant diseases and psychosocial problems was conducted to recognize treatment needs of these high-risk pregnant women. Pregnancy follow-up consisted of assessments of maternal and fetal health and wellbeing with obstetric ultrasounds and clinical obstetric examinations. Laboratory testing and urine drug screening were used to detect maternal prenatal substance use. The pregnant woman was referred to addiction services or psychiatric care based on her individual needs. In accordance with the Child Welfare Act in Finland, an anticipatory child welfare notification was made in situations where the expectant mother's problematic substance use was identified and the newborn child was estimated to be in need of support from child welfare services immediately after birth. The treatment approach at this special obstetric outpatient clinic aims at integrated care and, therefore a joint meeting with Child Welfare authorities was scheduled for every pregnant woman in the third trimester. In the parental mentalization focused 4D ultrasound intervention study, the control condition was constituted of treatment as usual at the HAL outpatient clinic at Turku University Hospital. In addition, all the participants had access to follow-up and care at local maternity clinics and many of them also attended addiction treatment, opioid maintenance therapy, psychiatric care or prenatal residential care programs.

4.1.1.5 Collection of the data

The background data was derived from maternal self-reports and electronic medical records. Socio-demographic background characteristics were obtained with a ten-item self-report questionnaire at baseline. Further, those pregnant women admitted to specialized obstetric care due to substance use problems were routinely interviewed by the psychiatric nurse and the social worker. The interviews based on the European Addiction Severity Index – questionnaire (EuropASI) in which items regard previous and current maternal physical and mental health, substance use, employment and income, criminality and incarceration, and family/social relationships (Kokkevi & Hartgers, 1995). The pregnant women's responses in the EuropASI interview were saved in the hospital electronic medical records. The information regarding the participants' substance use, psychiatric comorbidity, physical health and different types of treatment modalities utilized during pregnancy was obtained from medical records which based on the EuropASI-interview and clinical documentation. Fetal exposure to substances before and after the positive pregnancy test was determined by the expectant mother's self-reporting and clinical documentation. Medical records about intoxications, positive urine screening results or marks indicating intravenous substance use were considered as clinical documentation referring to prenatal substance use and fetal exposure to substances.

The data regarding the two main outcomes of the study, maternal prenatal psychological distress and prenatal parenting, was collected with standardized self-report measures which were administered to the participants by the social worker at two time points: at baseline before the intervention (<24th gwks) and after the intervention (>34th gwks). The outcome data regarding the pregnant woman's participation in obstetric care and perinatal child outcomes was obtained from the hospital medical records. The outcome data in terms of fetal drug exposure was based on meconium drug screening. One fetal stool sample was routinely collected during the first days after birth. The meconium samples from the newborns were analyzed to detect fetal drug exposure with a more objective measure.

4.1.1.6 Ethical considerations

The parental mentalization focused ultrasound intervention study was approved by the Joint Ethics Committee of the University of Turku and The Hospital District of Southwest Finland on the 14th of June 2011. Written informed consent was obtained from the participants included in the study. The participants were compensated with a 20 euro incentive at 35 gwks, and the gift card was addressed to the child's needs.

Table 4. The study and intervention protocol of the parental mentalization focused 4D ultrasound intervention study for pregnant women with recent or current substance use.

The protocol of the mentalization focused 4D ultrasound intervention study for pregnant women with recent or current harmful substance use							
	< 22 gwks	**< 24 gwks**	**24 gwks**	**30 gwks**	**34 gwks**	**35 gwks**	**After birth**
Standard care for the intervention and control groups at the HAL outpatient clinic	EuropASI interviews by a psychiatric nurse and a social worker Urine drug screening Submission of a Child Welfare Notification	Obstetric assessments including fetal ultrasounds				Joint meeting	Neonatal outcomes: ·Gestational age at birth ·Birth weight ·Apgar scores ·Head circumference ·Meconium toxicology ·Neonatal withdrawal symptoms ·Duration of hospital stay
The study protocol for the intervention and control groups	Information Recruitment Literal consent	Randomization Background data EPDS STAI MFAS P-PRFQ				EPDS STAI MFAS P-PRFQ 20€ gift card	
The intervention protocol for the intervention group		Pregnancy diary	4D US session Diary session	4D US session Diary session	4D US session Diary session		

Note. The table is modified from the tables presented in the original publications (Jussila, Pajulo, & Ekholm, 2020a; Jussila, Ekholm, & Pajulo, 2020b) . *Gwks = gestational weeks; EuropASI = European Addiction Severity Index–questionnaire; EPDS = Edinburgh Pre/Postnatal Depression Scale; STAI = State-Trait Anxiety Inventory; P-PRFQ = Prenatal Parental Reflective Functioning Questionnaire; MFAS = Maternal-Fetal Attachment Scale; 4D US session = four-dimensional ultrasound session*

4.1.2 The FinnBrain Birth Cohort Study (Studies III and IV)

4.1.2.1 Study design

The FinnBrain Birth Cohort Study has primarily been established to investigate the effects of prenatal and early life stress on child development and health (Karlsson et al., 2018). The population-based pregnancy cohort was prospectively collected in the area of Southwest Finland and on the island of Åland in Finland between December 2011 and April 2015 (www.finnbrain.fi). The pregnant women were recruited at the routine nuchal translucency screening visit at approximately the 12 gwk. The pregnant women gave written informed consent on their own and on their child's behalf.

4.1.2.2 Participants

During the collection of the FinnBrain Birth Cohort Study sample between December 2011 and April 2015, 8995 pregnant women attended the early pregnancy ultrasound screening visits in the area of Southwest Finland and on the island of Åland. Sixty-four percent (5790 of 8995) of these women were informed about The FinnBrain Birth Cohort Study. The eligibility criteria for the study were an ability to respond to the questionnaires in Finnish or Swedish, and a normal ultrasound screening result. Of all the women recruited (n = 5790), 65.8 % (n = 3808) were eligible and agreed to participate. Only the women with a singleton pregnancy were included in Studies III and IV, and the total number of pregnant women surveyed in these studies was 3766.

4.1.2.3 Collection of the data

The data for Studies III and IV was collected with survey self-reports and obtained from The Finnish Medical Birth Register administered by the National Institute of Health and Welfare in Finland. The pregnant women responded to the set of self-report questionnaires three times during pregnancy. The survey data was linked with the data derived from The Finnish Medical Birth Register. The Finnish Medical Birth Register contains comprehensive national clinical data on prenatal screening, maternity and obstetric care, perinatal hospital care, pregnancy and neonatal outcomes. The information of maternal education was collected with a self-report questionnaire at 14 gwks, and classified into: low [high school/vocational, < 12 years], middle [polytechnics], and high [university]. Parity (primiparous or multiparous) and maternal age were obtained from The Finnish Medical Birth Register. The data regarding the pregnant women's income and prior history of mental disorders was collected with self-reports. The binary variable describing single parenthood was affirmative in cases

where the pregnant women did not have an intimate relationship based on the survey self-report or she was not cohabiting based on the register data. The research protocol of Studies III and IV is presented in Table 5.

4.1.2.4 Ethical considerations

The Ethics Committee of the Hospital District of Southwest Finland approved the The FinnBrain Cohort Study on the 14th of June 2011. A written informed consent was obtained from all the participants.

Table 5. The research design and protocol of the Studies III and IV conducted in the context of The FinnBrain Birth Cohort Study

Time point 1 (14 gwks)	**Time point 2 (24 gwks)**	**Time point 3 (34 gwks)**
Background data Smoking data	 MFAS PRAQ-R2 EPDS SCL-90 Anxiety Subscale	 Smoking data MFAS PRAQ-R2 EPDS SCL-90 Anxiety Subscale
Medical Birth Register data		
Background data Prenatal smoking data		

Note. gwks = gestational weeks; MFAS = Maternal-Fetal Attachment Scale; PRAQ-R2 = Pregnancy-Related Anxiety Questionnaire, revised version 2; EPDS = Edinburgh Pre/Postnatal Depression Scale; SCL-90 Anxiety Subscale = Symptom Checklist-90 Anxiety Subscale

4.2 Measures and outcomes

4.2.1 Prenatal parenting and psychological distress

4.2.1.1 Edinburgh Pre/Postnatal Depression Scale

The *Edinburgh Pre/Postnatal Depression Scale (EPDS)* was used in the assessment of prenatal depressive symptoms. The EPDS questionnaire is a self-report instrument containing 10 items scored on a 4-point scale from 0 to 3. The total sum score of the EPDS ranges from 0 to 30, and a higher score indicates a higher level of prenatal depressive symptoms. (Cox, Holden, & Sagovsky, 1987).

In the mentalization focused 4D ultrasound intervention study, the EPDS questionnaire was used for the assessment of the primary outcome of the study, that

is to say, the level of of prenatal depressive symptoms. The EPDS was administered to the participants at two time points: before and after the intervention (< 24th and >34th gwks, respectively). In Studies III and IV conducted in the context of the FinnBrain Birth Cohort Study, the EPDS measurements from two time-points at 24 and 34 gwks were utilized as controlled variables. In both studies, the EPDS total scores were used as continuous variables in the statistical analyses.

In addition, the EPDS cut-off scores were used describe the study samples in terms of the proportion of pregnant women reporting a high level of prenatal depressive symptoms. Different cut-off scores of the EPDS has been proposed for screening of pregnant women displaying a high risk for prenatal depression (Gibson et al., 2009; Rubertsson, Borjesson, Berglund, Josefsson, & Sydsjo, 2011). The cut-off score ≥ 13 was used in the intervention study and the cut-off score ≥ 10 was utilized in the FinnBrain Birth Cohort study. The EPDS cut-off score ≥ 13 has been reported to be valid in the screening of prenatal depression, with a sensitivity of 77 % and specificity of 94 % (Rubertsson et al., 2011). Further, the EPDS cut-off score ≥ 10 has also been reported appropriate in the detection of women displaying a high risk for perinatal depression (Gibson et al., 2009). One systematic review on validation studies of the EPDS questionnaire has reported that the sensitivity of the EDPD cut-off score 9/10 ranges from 59% to 100% and the specificity from 44% to 97% in the detection of perinatal depression (Gibson et al., 2009). For the EPDS cut-off 12/13, the sensitivity has been reported to range from 34% to 100% and the specificity from 49% to 100% (Gibson et al., 2009). The lower cut-off score had been chosen for the screening of prenatal depression in the FinnBrain Birth Cohort Study to be able to identify the women at high risk for prenatal depression from the non-clinical and relatively low risk sample pregnant women. Instead, the higher cut-off score ≥ 13 had been chosen for the screening of prenatal depression in the high-risk clinical sample of pregnant women with recent or current harmful substance.

4.2.1.2 Maternal-Fetal Attachment Scale

The *Maternal-fetal Attachment Scale (MFAS)* was used to determine the expectant mother's attachment towards the unborn child and especially behavioral manifestations of this relationship. The MFAS is a 24-item self-report questionnaire in which the items are scored on a five-point scale ranging from 1 to 5. Thus, the total score of the MFAS ranges from 24 to 120 and the higher sum score indicates stronger attachment towards the fetus. The MFAS contains five subscales: "*Role taking*", "*Differentiation of self from fetus*", "*Interacting with the fetus*", "*Attributing characteristics to the fetus*" and "*Giving of self*". (Cranley, 1981).

In the mentalization focused 4D ultrasound intervention study, the MFAS questionnaire constituted a secondary outcome measure and was administered to the

pregnant women before and after the intervention (< 24th and >34th gwks, respectively). At baseline (< 24 gwks), 7 items from the original MFAS questionnaire were selected to be appropriate for use in early pregnancy (the items 2,5,8,11,14,18,23 from the original long 24-item version of MFAS). The whole 24-item measure was used to assess maternal-fetal attachment post intervention (> 34 gwks). In the FinnBrain Birth Cohort Study, maternal-fetal attachment constituted the main independent variable of interest, and the 24-item version of the MFAS questionnaire was administered to the participants twice, at the 24th and 34th gwks. In both studies, the MFAS total sum scores and the subscales scores were used as continuous variables in the statistical analyses.

4.2.1.3 Prenatal Parental Reflective Functioning Questionnaire

The *Prenatal Parental Reflective Functioning Questionnaire (P-PRFQ)* was used to evaluate parental reflective functioning, that is to say, the operationalized concept of prenatal parental mentalization. The P-PRFQ consists of 14 items to which pregnant women respond using a scale from 1 (strongly disagree) to 7 (strongly agree). The P-PRFQ questionnaire includes three types of items: the optimal answer at the high or low end of the scale or in the middle of the scale. After recoding, the higher total sum score and the factor score indicate a stronger prenatal parental mentalization capacity. The P-PRFQ measure contains three subscales: "*Opacity of mental states*", "*Reflecting on the fetus-baby*" and "*Dynamic nature of mental states*" (Pajulo et al., 2015).

In the mentalization focused 4D ultrasound intervention study, eight items which were considered appropriate for use in early pregnancy were selected. This short version of P-PRFQ was administered to the participants at baseline (< 24 gwks). At the beginning of the itervention study, 18 participants also responded to this this shorter version of the measure at the post intervention time point (> 34 gwks). The final construct-validated 14-item version of the P-PRFQ became available during the data collection of the intervention study and was administered to the rest of the sample (n = 51) at the post intervention time point (> 34 gwks). This 14-item version of P-PRFQ constituted a secondary outcome measure in the intervention study. The P-PRFQ total sum score and the three subscale scores of P-PRFQ were used as continous variables in the statistical analyses.

4.2.1.4 The state section in the State-Trait Anxiety Inventory

The state section of the State-Trait Anxiety Inventory (STAI) was used to assess symptoms of general anxiety symptoms during pregnancy . The state section of the STAI questionnaire is a self-report measure containing 20 items scored on a 4-point

scale (1 to 4) and the total sum score ranges from 20 to 80. A higher sum score indicates a higher amount of anxiety symptoms. (Spielberger, Gorsuch, & Lushene, 1970). The STAI questionnaire has been evaluated to be a valid instrument in the assessment of prenatal psychological distress (Grant, McMahon, & Austin, 2008).

In the mentalization focused 4D ultrasound intervention study, the state section of the STAI questionnaire constituted the secondary outcome measure and was administered to the participants at two time points: before and after the intervention (< 24th and >34th gwks, respectively). The total score of the state section of the STAI was used as a continuous variable in the statistical analyses.

4.2.1.5 The anxiety subscale in the Symptom Checklist-90

The anxiety subscale of Symptom Checklist-90 (SCL-90) was used in the assessment of general anxiety symptoms in pregnancy. The anxiety subscale of the SCL-90 measure is a self-report questionnaire containing 10 items scored on a scale ranging from 0 to 4. The total sum score is hence ranging from 0 to 40, and the higher score indicates a higher level of anxiety symptoms. (Derogatis, Lipman, & Covi, 1973; Holi, 2003)

In Studies III and IV, the anxiety measurements with the SCL-90 from two time points at 24 and 34 gwks were utilized as controlled variables. The total score of the anxiety subscale of the SCL-90 measure was used as a continuous variable in the statistical analyses.

4.2.1.6 Pregnancy-Related Anxiety Questionnaire, revised version 2

The Pregnancy-Related Anxiety Questionnaire, revised version 2 (PRAQ-R2) was used in the assessment of fears, worries and concerns related specifically to pregnancy, childbirth and body image issues during pregnancy. PRAQ-R2 is a 10-item self-report questionnaire in which the items are scored on a 5-point scale from 1 (absolutely not relevant) to 5 (very relevant) and the total sum score ranges between 10 and 50. The PRAQ-R2 contains three subscales: "*Fear of Giving Birth",* "*Worries about Bearing a Physically or Mentally Handicapped Child",* and "*Concerns about Own Appearance"*. (Huizink et al., 2016).

In Study IV, the PRAQ-R2 was administered to the participants in the FinnBrain Birth Cohort Study twice, at the 24th and 34th gwks. The total sum scores and the factor scores of PRAQ-R2 at 24 gwks constituted the main independent variables of interest, and were used as continuous variables in the statistical analyses.

4.2.1.7 Reliability of the questionnaire measures

The reliabilities of the questionnaire measures used in Studies I, III and IV are presented in Table 6. The value of Cronbach's α indicates the overall reliability of the questionnaire measures. Several interpretations have been introduced for the Cronbach's α, and according to Field (2013) values around 0.7–0.8 can be considered good (Field, 2013). However, when measuring psychological constructs the Cronbach's α values below 0.7 can be realistically expected due to the diversity of constructs that are measured (Field, 2013).

Table 6. Reliability of the questionnaire measures.

	The high-risk sample of pregnant women with recent or current harmful substance use		**The FinnBrain Birth Cohort Study sample**	
	Cronbach's α < 24 gwks	**Cronbach's α > 34 gwks**	**Cronbach's α 24 gwks**	**Cronbach's α 34 gwks**
EPDS	0.87	0.88	0.84	0.84
MFAS	0.72 [a]	0.83	0.85	0.85
Role taking		0.76	0.81	0.83
Differentiation		0.39	0.53	0.50
Interacting		0.65	0.55	0.55
Attributing		0.56	0.64	0.66
Giving		0.57	0.52	0.51
P-PRFQ	0.70 [b]	0.57		
F1 Opacity		0.71		
F2 Reflecting		0.48		
F3 Dynamic nature of mental states		0.50		
STAI	0.93	0.93		
SCL-90 Anxiety			0.84	0.85
PRAQ-R2			0.83	0.85
F1			0.76	0.75
F2			0.86	0.89
F3			0.81	0.89

Note. gwks = gestational weeks; EPDS = Edinburgh Pre/Postnatal Depression Scale; MFAS = Maternal-Fetal Attachment Scale; the subscales of MFAS: Role taking = Role taking, Differentiation = Differentiation of self from fetus, Interacting = Interacting with the fetus, Attributing = Attributing characteristics to the fetus and Giving = Giving of self; P-PRFQ = Prenatal Parental Reflective Functioning Questionnaire; the factors of P-PRFQ: F1 Opacity = Opacity of mental states, F2 Reflecting = Reflecting on the fetus-baby and F3 Dynamic nature of mental states = The dynamic nature of mental states; STAI = State-Trait Anxiety Inventory; SCL-90 Anxiety = Symptom Checklist-90 Anxiety Subscale; PRAQ-R2 = Pregnancy-Related Anxiety Questionnaire, revised version 2; the PRAQ-R2 factors F1 = Fear of Giving Birth, F2 = Worries about Bearing a Physically or Mentally Handicapped Child, and F3 = Concerns about Own Appearance;

[a] For use in early pregnancy, 7 items were selected from the original 24-item MFAS questionnaire.

[b] In early pregnancy, 8 items from the final construct-validated 14-item P-PRFQ questionnaire were utilized to assess early pregnancy parental mentalization.

4.2.2 Participation in prenatal obstetric care

In Study II, the pregnant woman's participation in prenatal follow-up and care was obtained from the hospital medical records and described in terms of the number of prenatal obstetric consultations, emergency obstetric care consultations, emergency department visits, hospital admissions and the duration of obstetric hospital care. In addition, the number of pregnant women who had withdrawn from scheduled obstetric care visits was assessed in both study groups. Participation in prenatal obstetric care constituted a secondary outcome in the intervention study.

4.2.3 Fetal drug exposure

In Study II, the newborn meconium toxicology testing was conducted as a part of the routine clinical practice, and used for assessment of fetal drug exposure. Fetal drug exposure constituted a secondary outcome in the intervention study. The meconium samples were analyzed in The Hjelt Institute at the University of Helsinki. The samples were screened qualitatively for more than 600 different pharmacological agents and 330 tranquilizers, illicit or designer drugs with ultra-high performace liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-QTOF/MS). Further, the meconium toxicology was analyzed qualitatively with liquid chromatography-tandem mass spectrometry (LC-MS/MS) for tramadol, morphine, 6-monoasethylmorphine, codeine, oxycodone, methadone, buprenorphine, norbuprenorphine, amphetamine, methamphetamine, 3,4-methylenedioxymethamphetamine, 3,4-methylenedioxyamphetamine and a metabolite of tetrahydrocannabinol (THC-COOH). Meconium starts to form after the first trimester of pregnancy. The benefit of the meconium drug screening is the long window of detection due to the accumulation and deposition of drugs and drug metabolites in the meconium matrix. Meconium toxicology testing is able to detect fetal drug exposure which has taken place approximately during the second and the third trimester of pregnancy (Wabuyele, Colby, & McMillin, 2018). However, meconium toxicology testing has been found to be more sensitive for the detection of repeated rather than sporadic drug use (Wabuyele, Colby, & McMillin, 2018).

4.2.4 Neonatal outcomes

In Study II, the data regarding neonatal outcomes was obtained from the hospital medical records, and consisted of information on gestational age, birth weight, small-for-gestational age (SGA) status, prematurity, head circumference, Apgar scores at 5 minutes after birth, neonatal withdrawal symptoms and the length of hospital stay. The neonatal status being small for gestational age (SGA) was defined as a birth weight more than 2 standard deviations (< 2SDs) below the population mean weight

for gestational age, and prematurity (preterm birth) as a birth before 37 gwks. In clinical practice, the Finnegan Neonatal Abstinence Scoring Tool was used for the assessment of neonatal withdrawal symptoms (Finnegan, Connaughton, Kron, & Emich, 1975). The neonatal outcomes constituted secondary outcomes in the intervention study.

4.2.5 Maternal prenatal smoking behavior

In Studies III and IV, the dependent outcome variables describing smoking in pregnancy and cessation of smoking in early pregnancy were constructed by combining the survey data and the register records in The Finnish Medical Birth Register. We created the binary dependent variables *Smoking in pregnancy* and *Cessation of smoking during pregnancy.* In the FinnBrain Birth Cohort Study, the pregnant women's smoking behavior was surveyed twice during pregnancy. At 14 gwks, the participants self-reported whether they had smoked during the index pregnancy. At 34 gwks, the pregnant women responded to whether they had been smoking during the last five months. The survey data was linked with the register data obtained from the Finnish Medical Birth Register which contained information on maternal prenatal smoking behavior in a format: no prenatal smoking, smoking cessation in the first trimester (≤12+0 gwks), continuation of smoking after first trimester (≥12+1 gwks) and no data available. By combining the information regarding prenatal smoking behavior from the survey responses and birth register data, we constructed a binary outcome variable *Smoking in pregnancy* which was affirmative when the pregnant women had self-reported or had a register record of smoking during the index pregnancy. Further, we constructed a binary outcome variable *Cessation of smoking during pregnancy.* The pregnant smoking woman was categorized as a persistent smoker if there was a register record on a continuation of smoking after the first trimester (≥12+1 gwks) or self-reported smoking in late pregnancy.

4.3 Statistical analyses

4.3.1 Studies I and II

The efficacy of the novel mentalization based 4D ultrasound intervention was estimated. We hypothesized that, compared to the control group, 1) the participants in the intervention group would demonstrate stronger prenatal parenting, (prenatal parental mentalization and maternal-fetal attachment) postintervention and greater improvement in prenatal parenting taking into account the baseline levels of maternal-fetal attachmect and prenatal parental mentalization. We also predicted that

2) the participants in the intervention group would experience a lower level of prenatal psychological distress, i.e. depressive and anxiety symptoms, post-intervention and a greater decline in prenatal psychological distress than the participants in the control group. In addition, we hypothesized that 3) the pregnant women in the intervention group would be more likely to participate in obstetric care and 4) the newborns born to the mothers in the intervention group would display better perinatal child outcomes and 5) these newborns would display a lesser degree of fetal drug exposure.

In the intervention study, a priori statistical power analysis was performed to estimate the adequate sample size. The power analysis and sample size estimation were calculated regarding the primary outcome of the study, the symptoms of prenatal depression measured with the EPDS questionnaire. The parameter estimates needed to calculate the sample size were approximated based on previous studies, especially on the FinnBrain Birth Cohort pilot study. The intervention study was designed to detect a clinically meaningful difference of 3 points in the EPDS questionnaire, corresponding to an approximately medium effect size using Cohen's criteria (Cohen, 1988). With an alpha = 0.05 and power = 0.80, the projected sample size needed to detect this effect was approximately N = 80 (40 + 40) for the between group comparison with a t-test. The dropout rate was roughly estimated to be around 15% leading to the adjusted sample size estimation of 95 participants.

In sociodemographic and clinical sample characteristics, comparisons between the intervention and control groups in nominal variables were performed using a Pearson’s chi-square test or a Fisher's exact test, when appropriate. Comparisons between the study groups in normally distributed continuous background variables were conducted using an independent samples t-test and in non-normally distributed continuous variables with a Kruskall-Wallis test.

In testing the efficacy of the intervention, an intention-to-treat analysis method was used. That is, the participants were incorporated in statistical analyses according to the group they were originally allocated, regardless of the degree of participation at the intervention sessions. In the questionnaire data, sporadic missing values were replaced by the mean index item value of each respondent, otherwise only complete cases were analyzed. In Study I, the distribution of the questionnaire data was estimated to allow the use of parametric tests and a two-tailed independent samples t-test was used to analyze the difference between the intervention and control groups in the questionnaire scores regarding prenatal parenting and prenatal psychological distress. The Cohen’s d effect sizes was calculated to indicate the standardized between-groups difference (Cohen, 1988). The reported Cohen’s d effect sizes are positive if the mean difference was in the hypothesized direction with an interpretation 0.2 referring to small, 0.5 to medium and 0.8 to large effect (Cohen, 1988). Analysis of covariance (ANCOVA) was utilized to test the differences

between the intervention and control groups in the questionnaire scores controlling for the baseline scores. Equivalence of the variances was estimated, and significant differences between the groups were not demonstrated. In Study I, the Bayes factors (BF) were calculated using the function lmBF in the BayesFactor R package (Morey, Rouder, & Jamil, 2018). The null hypothesis was that the intervention had zero effect. The prior distribution for the intervention effect (measured in standard deviations of the response variable) under the alternative hypothesis was a Cauchy distribution with the location parameter x0 = 0 and the scale parameter $\gamma = 0.5$ as suggested by Quintana & Williams (Quintana & Williams, 2018). The Bayes factor (BF01) values >1 are interpreted as evidence for the null hypothesis, and BF01 >3 refers to moderate evidence for the zero effect (Quintana & Williams, 2018). In Study II, the between-groups differences in the continuous variables regarding the pregnant women's participation in obstetric care and perinatal child outcomes were tested with a Mann Whitney U test. The effect size *r* for these non-parametric comparisons was calculated using a formula ($r = Z \div \sqrt{N}$) (Field, 2013). The between-groups differences in the nominal outcome variables on perinatal child outcomes and fetal drug exposure were tested with the a Pearson's chi-square test or a Fisher's exact test, as appropriate.

The statistical analyses were performed with SAS for Windows version 9.4, IBM SPSS software version 24 and R software, and probability values below 0.05 were considered as statistically significant.

4.3.2 Studies III and IV

The associations of maternal-fetal attachment and pregnancy-related anxiety with maternal prenatal smoking behavior were investigated in the FinnBrain Birth Cohort sample with a primary focus on finding potential new points for interventions to promote positive health practices in terms of prenatal smoking. In Study III, we hypothesized that a stronger maternal-fetal attachment would associate with 1) a lower risk of smoking in pregnancy and 2) an increase in smoking cessation during pregnancy. In addition, we predicted that 3) a stronger maternal-fetal attachment would modify favorably the expected effect of prenatal psychological distress on prenatal smoking behavior and 4) would also modify beneficially the expected effect of maternal education on prenatal smoking behavior, especially among educationally disadvantaged pregnant women and among women with prenatal mental health related adversity. Prior to the analyses, these hypotheses were defined in the Open Science Framework portal (https://osf.io/v4nd3/). As regards the Study IV, we hypothesized, based on previous studies (Goedhart et al., 2009; Westerneng et al., 2017) that particularly high and low levels of pregnancy-related anxiety would

associate with an increased risk of smoking in pregnancy and with a lower probability of smoking cessation during pregnancy.

The sample size of the FinnBrain Birth Cohort Study was initially determined by the primary outcomes of the main cohort and the outcomes of Studies III and IV were not considered in the original sample size calculation. However, Studies III and IV comprised the whole birth cohort population and the sample size was considered appropriate for testing the hypotheses. As recommended for observational studies, 95% confidence intervals (95% CI) for adjusted odds ratios (aOR) were calculated.

A one-way ANOVA was performed to investigate the level of maternal-fetal attachment and pregnancy-related anxiety by the participants' smoking status (non-smoking, smoking cessation, smoking continuation). In addition, a one-way ANOVA was used to investigate the level of maternal-fetal attachment by the level of maternal education (low, middle, high).

The group differences in descriptive sample characteristics as regards background variables and questionnaire responses were investigated in two sections, that is to say, between the non-smoking and the pregnant women who smoked and, in the sample of women who smoked, between the persistent smokers and those women who ceased smoking during pregnancy. The comparisons between these groups in nominal variables were performed using a Pearson's chi-square test and in normally distributed continuous variables using a two-tailed independent samples t-test. A Mann-Whitney U test was used to analyze the between-group differences in prenatal parenting and psychological distress between the non-smoking and those who smoked, and between the women who quit smoking and those who continued smoking during pregnancy.

Multiple imputation (30 imputed datasets) was used to treat the missing values in the predictor variables. The participants who had responded to the questionnaire measures of maternal-fetal attachment / pregnancy-related anxiety at least once during pregnancy were included in the imputation models. The missing questionnaire responses were imputed by the factors (subscales), and the total sum scores were calculated based on the imputed factors. Separate imputation models were constructed for smoking in pregnancy and smoking cessation during pregnancy. The independent variables included in the analyses models were also included in the imputation models. In Study IV, also the PRAQ-R2 scores in the third trimester were included in the imputation models to improve the accuracy of the estimates.

Binary logistic regression analyses were used to estimate the association of maternal-fetal attachment / pregnancy-related anxiety (the total and subscale scores of MFAS at the 24th and 34th gwks and the total and factor scores of PRAQ-R2 at the 24th gwks) with the binary dependent variables, smoking in pregnancy and smoking cessation during pregnancy. According to previous research (Ekblad et al.,

2014; Goodwin, Cheslack Postava, Nelson, Smith, Wall et al., 2017; Goodwin et al., 2017; Härkönen et al., 2018; Kandel et al., 2009; Riaz et al., 2018; Smedberg et al., 2014; Smedberg et al., 2015), maternal age, education, single parenthood, parity and concurrent symptoms of depression and anxiety were considered as potentially confounding variables and were controlled for in the statistical analyses. The modifying effect of maternal-fetal attachment on the expected associations of both maternal education and prenatal psychological distress with prenatal smoking behavior was explored by adding the interaction effects MFAS × Prenatal Psychological Distress and MFAS × Education in the binary logistic regression models. In Study III, multiple testing corrections were performed. The correlations between the MFAS sum and subscale scores at both trimesters (r = 0.28–0.83) were taken into consideration in the corrections by calculating the effective number of tests (Derringer, 2018) and using that as the correction factor for the p-values. Therefore, the correction factor reduced from 12 to 8.84 in the main effect analyses and from 8 to 5.24 in the interaction analyses. In Study IV, we investigated the role of pregnancy-related anxiety in prenatal smoking behavior also by considering the possible non-linear association between pregnancy-related anxiety and prenatal smoking habits. Therefore, both linear and the quadratic terms of pregnancy-related anxiety were included in the logistic regression models to investigate a possible curved or U-shaped relationship between pregnancy-related anxiety and prenatal smoking behavior.

Descriptive statistical analyses were conducted using IBM SPSS software version 24, and the multiple imputation and the statistical modeling were performed with R software version 3.5.2. P-values < 0.05 were considered statistically significant.

5 Results

5.1.1 An overview on both study samples

We present the characterstics of both the study samples together in Table 7: the clinical sample of high-risk pregnant women with recent or current harmful substance use and the population-based cohort sample of the pregnant women participating in The FinnBrain Birth Cohort Study. Regarding the participants in the FinnBrain Birth Cohort Study, the descriptive sample characteristics are shown by the participants' prenatal smoking status. Both samples were collected approximately at the same time, but it should be noted that the study designs and settings, data collection procedures and the definitions of the socioeconomic variables were significantly different from each other.

First, the overview of the descriptive sample characteristics and the descriptive data suggested that pregnant women with either substance use problems or who continued smoking constitute especially high risk populations in terms of socioeconomic status. Moreover, our findings addressed the vulnerability of these women in terms of the level of prenatal psychological distress and the proportion of women exceeding the EPDS cut-offs utilized for screening of prenatal depression. The majority of pregnant women with substance use problems were educationally and economically more disadvantaged, and the prevalence of prior mental health problems was around 80% compared with the 16–31% prevalence of prior mental health problems among the participants in the FinnBrain Birth Cohort sample. In the high-risk sample of women with substance use problems, the proportion of women exceeding the EPDS cut-off ≥ 13 at the first time point (≈ 24th) and at the second time point (≈34th gwks) were 20% and 9%, respectively. Further, the proportion of women exceeding the lower EPDS cut-off ≥ 10 was was 44% in the second trimester and 28% in the third trimester. A higher proportion of participants exceeded the EPDS cut-offs in early pregnancy. In the population-based FinnBrain Birth Cohort, the proportion of women with a high level of prenatal depressive symptoms depended on the participants' smoking behavior and was 5–11% using the EPDS cut-off ≥ 13, and 13–30% using the lower EPDS cut-off ≥ 10. In the FinnBrain Birth Cohort, the persistent smokers comprised the most vulnerable subpopulation in terms of prenatal psychological distress. The highest level of prenatal depressive

symptoms within the FinnBrain Cohort sample was observed in the pregnant women who continued smoking throughout pregnancy: the proportion of persistent smokers reporting a high level of prenatal depressive symptoms was found to be 11% using the EPDS cut-off ≥ 13, and 24–30% using the lower EPDS cut-off ≥ 10. Moreover, their socioeconomic status was found to be relatively low. The neonatal outcomes were the poorest in the sample of high-risk women with recent or current harmful substance use.

As regards prenatal parenting, the high-risk pregnant women in the intervention study sample displayed a somewhat stronger maternal-fetal attachment and parental mentalization when compared with the pregnant women participating in the population-based FinnBrain Birth Cohort Study. The reasons for this unexpectedly high level of self-reported prenatal parenting are considered in the Discussion section. Interestingly, the pregnant women who ceased smoking during pregnancy self-reported the strongest level of maternal-fetal attachment among the participants in the FinnBrain Birth Cohort Study.

Table 7. An overview on the descriptive sample characteristics and data regarding prenatal parenting, psychological distress and perinatal outcomes in both samples, among the high-risk pregnant women with recent or current substance use and in the population-based sample of the FinnBrain Birth Cohort.

	The pregnant women with recent or current harmful substance use	The non-smoking pregnant women in The FinnBrain Birth Cohort	The smoking pregnant women in The FinnBrain Birth Cohort	The smoking quitters in The FinnBrain Birth Cohort	The smoking continuers in The FinnBrain Birth Cohort
Demographic characteristics					
Age, years (mean (SD))	25 (5.5)	30.7 (4.5)	28.2 (5.2)	28.4 (5.0)	27.8 (5.5)
Nulliparous (%)	71	46	58	65	47
Lowest education (%)	55	32	70	64	83
Lowest income (%)	56	21	29	24	37
Single parent (%)	34	3	11	5	21
Self-reported psychiatric disorder (%)	79[a]	16	27	25	31
Prenatal parenting and psychological distress					
2nd trimester (≈24 gwks)					
EPDS (mean(SD))	8.5 (5.0)	4.8 (4.1)	6.0 (4.3)	5.6 (4.1)	6.8 (4.5)
EPDS ≥ 10 (%)	44	13	18	14	24
EPDS ≥ 13 (%)	20	5	7	5	11
3rd trimester (≈34 gwks)					
EPDS (mean(SD))	6.5 (4.8)	4.7 (4.0)	5.9 (4.5)	5.4 (4.2)	6.8 (4.9)
EPDS ≥ 10 (%)	28	13	23	18	30
EPDS ≥ 13 (%)	9	5	8	6	11
MFAS	98.8 (9.1)	92.0 (10.2)	93.1 (10.2)	93.9 (9.7)	91.8 (10.9)
P-PRFQ index	5.2 (0.6)	3.7 (0.9)	4.0 (0.8)	3.9 (0.8)	4.1 (0.9)
Neonatal outcomes					
Birth weight, g (mean (SD))	3099 (645)	3552 (533)	3469 (548)	3585 (551)	3413 (530)
Low birth weight <2500g (%)	11	2.7	3.5	2.6	4.8
Gestational age, weeks (mean(SD))	38.9 (2.6)	39.3 (1.7)	39.5 (1.8)	39.5 (1.8)	39.4 (1.8)
Preterm birth, <37gwks (%)	13	4.8	4.6	4.2	5.1
SGA (%)	12	2.7	3.3	3.4	3.2

Note. Gwks = gestational weeks; EPDS = Edinburgh Pre/Postnatal Depression Scale; MFAS = Maternal-Fetal Attachment Scale; SGA = small for gestational age, P-PRFQ = Prenatal Parental Reflective Functioning Questionnaire; Lowest income = ≤ 1000 euros; Lowest education = < 9 years (the intervention study) or <12 years (The FinnBrain Birth Cohort Study)

[a] Self-reported or clinically documented psychiatric comorbidity

5.1.2 Efficacy of the parental mentalization focused 4D ultrasound intervention (Studies I and II)

5.1.2.1 Sample characteristics and attrition

Of the 126 pregnant women who were referred to specialized obstetric care due to substance use problems and were informed about the intervention study, 95 (75%) gave written informed consent. After randomization, five participants were excluded due to pregnancy related reasons such as twin pregnancy, miscarriage or induced abortion. The 90 women included in the study were recruited at a median of 13 (range

7–22) gwks. Of all the included participants (n = 90), ten women (11%) discontinued their participation during pregnancy. Eight of these women were allocated to the control group, and they withdrew consent immediately after randomization. The discontinuation rate was significantly higher in the control group than in the intervention group (18% [8/44] vs. 4% [2/46], p = 0.047, respectively). No significant differences were found between the women who discontinued and those women who remained in the intervention study as regards age, parity, marital status, education, substance use history, duration of substance use problems, psychiatric comorbidity, criminality and the number of children taken into custody prior the index pregnancy. During the pregnancy follow-up, three women in the intervention group moved to a location outside the hospital district. At baseline, the questionnaire response rate was 96–98% in the intervention and 80% in the control group. At post-intervention time point, the questionnaire data was available in 89% and 64% of the participants originally included in the study groups, respectively. Regarding the construct validated 14 - item version of P-PRFQ, the post-intervention data was available for 59% of the participants in the intervention group and 55% of the women allocated in the control group.

The demographic sample characteristics are presented in Table 8. The mean age of the patients was 25 (SD 5.5) years. The median length of their substance use history was four years (range 0–28). A vast majority of the pregnant women (81%) reported current or previous use of illicit drugs and nearly half (49%) of the participants had abused both drugs and alcohol. Prenatal clinical assessments and documented maternal self-reports suggested that, within the whole sample, at least 56% of the pregnant women had used alcohol or illicit drugs before the positive pregnancy test and 33% after being aware of the pregnancy. Nearly half (47%) of the pregnant women had a history of intravenous drug abuse and 27% of participants were seropositive for hepatitis C. In addition, 28% of the participants reported somatic comorbidities, most commonly respiratory, neurological, musculoskeletal or thyroid illnesses. Seventy-one percent of the participants were expecting their first child. Pregnancy was unintended in 70% of the cases. The descriptive sample characteristics did not reveal any differences between the study groups at baseline, which indicated a successful randomization procedure.

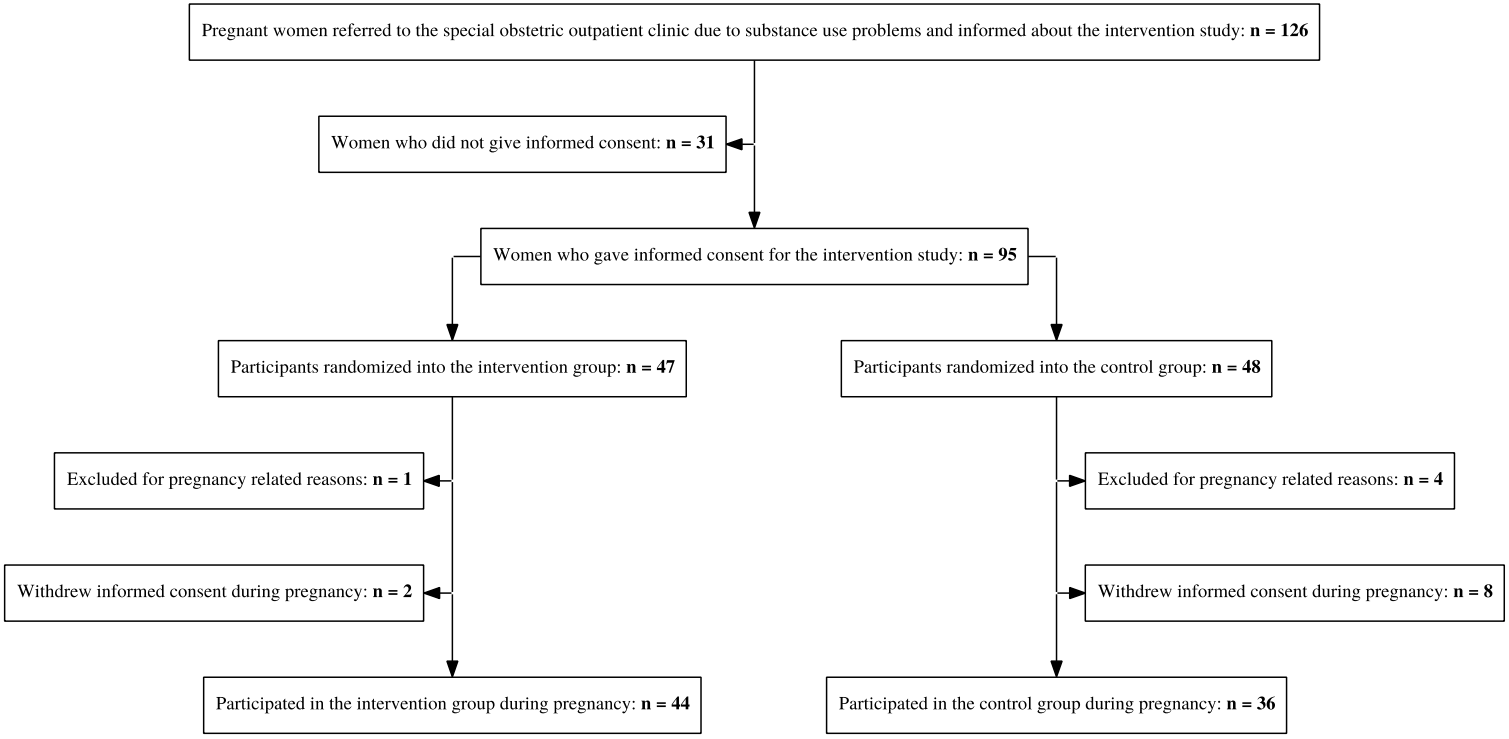

Figure 1. Flow chart of the parental mentalization focused 4D ultrasoudn intervention study for pregnant women with recent or current harmful substance use. Enrollment to the intervention study took place between October 2011 and November 2014.

Table 8. Socio-demographic and clinical characteristics of the pregnant women participating in the parental mentalization focused 4D ultrasound intervention study.

	All (N = 90)	***Intervention (N = 46)***		***Control (N = 44)***	***Between-groups difference***		
	n/N (%)	***n/N (%)***		***n/N (%)***	***df***	***X^2***	***p***
Sociodemographic background							
only basic education (≤ nine years)	44/80 (55)	24/44 (55)		20/36 (56)	2	0.06	0.97
low monthly income (< 1000 euros)	44/78 (56)	25/45 (56)		19/33 (58)	1	0.03	0.86
crimes in background	35/85 (41)	19/45 (42)		16/40 (40)	1	0.04	0.84
children in foster care	14/87 (16)	5/45 (11)		9/42 (21)	1	1.71	0.19
an intimate relationship	60/79 (76)	28/41 (68)		32/38 (84)	1	2.74	0.10
living situation at recruitment					3	2.71	0.44
with the child's father	47/86 (55)	21/45 (47)		26/41 (63)			
alone	29/86 (34)	18/45 (40)		11/41 (27)			
with someone else	4/86 (5)	2/45 (4)		2/41 (5)			
with parents	6/86 (7)	4/45 (9)		2/41 (5)			
father having substance abuse	54/82 (66)	32/43 (74)		22/39 (56)	1	2.95	0.09
Substance use and comorbidity							
most commonly reported substances							
alcohol	62/90 (69)	33/46 (72)		29/44 (66)	1	0.36	0.55
cannabis	48/90 (53)	25/46 (54)		23/44 (52)	1	0.04	0.84
stimulants	42/90 (47)	21/46 (46)		21/44 (48)	1	0.04	0.84
benzodiazepines	34/90 (38)	20/46 (43)		14/44 (32)	1	1.30	0.25
buprenorphine	26/90 (29)	14/46 (30)		12/44 (27)	1	0.12	0.74
history of intravenous substance abuse	40/85 (47)	21/46 (46)		19/39 (49)	1	0.08	0.78
smoking during pregnancy	79/87 (91)	43/46 (93)		36/41 (88)			0.47[a]
cessation of smoking in pregnancy	22/74 (30)	14/40 (35)		8/34 (24)	1	1.15	0.28
fetus exposed to substances before pregnancy test [b]	48/85 (56)	28/46 (61)		20/39 (51)	1	0.79	0.37
fetus exposed to substances after pregnancy test [b]	26/79 (33)	13/44 (30)		13/35 (37)	1	0.51	0.48
psychiatric comorbidity	69/87 (79)	36/46 (78)		33/41 (80)	1	0.07	0.79
depression	40/90 (44)	16/46 (35)		24/44 (55)	1	3.56	0.06
anxiety disorder	27/90 (30)	12/46 (26)		15/44 (34)	1	0.69	0.41
personality disorder	16/90 (18)	8/46 (17)		8/44 (18)	1	0.01	0.92
suicidal tendency	49/82(60)	26/43(60)		23/39(59)	1	0.02	0.89
somatic comorbidity	24/87 (28)	10/46 (22)		14/41 (34)	1	1.67	0.20
psychopharmacological medication	31/77 (40)	15/41 (37)		16/36 (44)	1	0.49	0.48
buprenorphine substitution	16/87 (18)	9/46 (20)		7/41 (17)	1	0.09	0.76
prenatal residential care	14/77 (18)	9/41 (22)		5/36 (14)	1	0.84	0.36
out-patient psychiatric treatment for addiction	52/78 (67)	27/42 (64)		25/36 (69)	1	0.23	0.63
out-patient psychiatric treatment	16/77 (21)	9/41 (22)		7/36 (19)	1	0.07	0.77

Note. N = information available or relevant total *N*; *n* = a number of pregnant women with affirmative responses; [a]Fisher's exact test; [b]Clinically documented or maternal self-reported fetal exposure to alcohol, illicit drugs, or maternal misuse of prescription drugs. Fetal exposure to tobacco smoking is not included. The table is modified from the tables presented in the original publications (Jussila et al., 2020a; Jussila et al., 2020b) .

5.1.2.2 Intervention attendance

The median number of actualized ultrasound sessions per participant in the intervention group was three (range 0 – 3) and of the diary meetings one (range 0–3). Of all the pregnant women in the intervention group, 96% (44/46) attended the 4D ultrasound sessions. Four percent (2/46) of the participants in the intervention group attended one session, 17% (8/46) attended two sessions and 74% (34/46) attended all the three ultrasound sessions. Of those 12 women who did not attend all of the scheduled ultrasound sessions, four delivered prematurely, two withdrew from the intervention study and six did not attend because of logistic reasons (moving to another hospital district or scheduling problems by the research group). Further, sixty-five percent (30/46) of the participants in the intervention group attended the diary meetings: 20% (9/46) of the participants in the intervention group attended one meeting, 26.0% (12/46) attended two meetings and 20% (9/46) attended three meetings.

5.1.2.3 Efficacy of the intervention on prenatal psychological distress (Study I)

Descriptive statistics and the results from the testing of efficacy of the intervention on maternal prenatal psychological distress, conceptualized hereafter as prenatal symptoms of depression and anxiety, are presented in Table 9. We did not demonstrate evidence for the beneficial effect of the intervention on the primary outcome of the intervention study as a between-groups difference in the level of prenatal depressive symptoms ($p = 0.42$, $BF_{01} = 3.11$) was not substantiated. Further, between-groups differences in the level of prenatal anxiety ($p = 1.00$, $BF_{01} = 3.92$) and in the proportion of women exceeding the EPDS cut-off ≥ 13 ($p = 0.21$) were not established at the post-intervention time point. Within the whole sample, the proportion of women exceeding the EPDS cut-off ≥ 13 was 20% in early pregnancy and 9% in late pregnancy.

The level of prenatal psychological distress decreased in both groups during pregnancy. The decline in depressive symptoms was greater in the intervention group, but the between-groups difference did not reach statistical significance and the level of evidence for the alternative hypothesis compared to evidence for the null hypothesis was anecdotal ($p = .07$, Cohen's $d = 0.48$, $BF_{01} = 0.94$). Further, the finding was inconclusive, i.e. BF_{01} within the range of 0.33–3 (Quintana & Williams, 2018), as regards the between-groups difference in prenatal depressive symptoms after adjusting for the baseline EPDS score (*EPDS*: $F[1, 65] = 2.28$, $p = 0.41$, $BF_{01} = 1.54$. A between-groups difference in terms of the level of anxiety symptoms was not substantiated in the analysis of covariance after controlling for the baseline score (*STAI*: $F[1,65] = 0.003$, $p = 0.96$, $BF_{01} = 3.93$).

5.1.2.4 Efficacy of the intervention on prenatal parenting (Study I)

Descriptive statistics and the results from testing the efficacy of the intervention in terms of maternal-fetal attachment and prenatal parental mentalization, are reported in Table 9. At baseline, statistically significant differences were not displayed between the intervention and the control groups in prenatal parenting, which indicated a succesful randomization procedure.

Our hypothesis concerning the beneficial effect of the intervention on prenatal parental mentalization was not substantiated, as the between-groups difference in the total level of late pregnancy parental mentalization was not displayed ($p = 0.73$, $BF_{01} = 3.46$). Further, evidence for the beneficial effect of the intervention on maternal-fetal attachment was not established. The result was inconclusive, that is to say the BF_{01} value within the range of 0.33–3 (Quintana & Williams, 2018), as to whether or not a difference between the groups in the level of maternal-fetal attachment was present post-intervention ($p = 0.10$, $BF_{01} = 0.87$). Unexpectedly, the control group scored higher in the MFAS subscale "*Attributing characteristics to the fetus*" ($p = 0.046$, $BF_{01} = 0.67$) post-intervention. However, the BF_{01} referred to the fact that there was anecdotal evidence for the alternative hypothesis compared to evidence for the null hypothesis (Quintana & Williams, 2018). Analysis of covariance was used to investigate whether there were significant between-groups differences in prenatal parental mentalization and maternal-fetal attachment after controlling for the baseline scores. The findings were inconclusive (the BF_{01} values within the range of 0.33–3) (Quintana & Williams, 2018) as to whether or not a between-groups difference was present in the level of prenatal parental mentalization [$F(1, 46) = 0.54$, $p = 0.47$, $BF_{01} = 2.85$] or in the level maternal-fetal attachment [$F(1, 65) = 2.9$, $p = 0.09$, $BF_{01} = 1.13$] after controlling for the baseline scores.

Table 9. Descriptive statistics of prenatal parenting and psychological distress, and the results from testing the between-groups differences in these outcomes.

	Control group (N = 44)			*Intervention group (N = 46)*			*Between-groups difference*				
	n	***Mean***	***SD***	***n***	***Mean***	***SD***	***df***	***t***	***p***	***Cohen's d*** [b]	***Bayes factor (B_{01})*** [a]
Baseline (<24 gwks)											
EPDS sum	35	8.0	4.1	45	8.9	5.6	78	-0.83	0.41		
		n/N	***%***		***n/N***	***%***	***df***	***X^2 p***			
EPDS (≥13)		4/35	11.4		12/45	26.7	1	2.86	0.09		
	n	***Mean***	***SD***	***n***	***Mean***	***SD***	***df***	***t***	***p***	***Cohen's d*** [b]	***Bayes factor (B_{01})*** [a]
MFAS index (7 items)	35	4.5	0.4	45	4.5	0.4	78	0.65	0.52		
P-PRFQ index (8 items)	35	5.4	0.9	44	5.3	0.8	77	0.28	0.78		
STAI sum	35	34.7	8.4	45	35.4	10.0	78	-0.36	0.72		

Table 9. continues.

	Control group (N= 44)			*Intervention group (N = 46)*			*Between-groups difference*				
Post-intervention (>34 gwks)	***n***	***Mean***	***SD***	***n***	***Mean***	***SD***	***df***	***t***	***p***	***Cohen's d*** [b]	***Bayes factor (B_{01})*** [a]
EPDS sum	28	7.1	4.5	41	6.2	5.0	67	0.82	0.42	0.19	3.11
		n/N	**%**		**n/N**	**%**			***p***		
EPDS (≥13)		4/28	14.3	41	2/41	4.9			0.21[c]		
	n	***Mean***	***SD***	***n***	***Mean***	***SD***	***df***	***t***	***p***	***Cohen's d*** [b]	***Bayes factor (B_{01})*** [a]
STAI sum	28	33.7	8.0	41	33.7	8.9	67	0.0	1.00	0	3.92
MFAS index	28	4.2	0.3	41	4.1	0.4	67	1.69	0.10	-0.28	0.87
Role taking [d]	28	4.6	0.4	41	4.5	0.5	67	0.78	0.44	-0.22	2.61
Differentiation [d]	28	4.3	0.6	41	4.2	0.5	67	0.56	0.58	-0.18	3.05
Interacting [d]	28	4.0	0.5	41	3.8	0.6	67	1.97	0.053	-0.36	0.48
Attributing [d]	28	4.0	0.4	41	3.8	0.5	67	2.03	0.046*	-0.44	0.67
Giving [d]	28	4.2	0.5	41	4.2	0.5	67	0.41	0.69	0	3.60
P-PRFQ index (14 items)	24	5.2	0.6	27	5.2	0.5	49	-0.35	0.73	0	3.46
F1 [e]	24	4.4	1.3	27	4.4	1.2	49	0.03	0.98	0	3.53
F2 [e]	24	5.9	0.6	27	5.9	0.6	49	0.20	0.84	0	3.00
F3 [e]	24	5.1	0.9	27	5.3	0.9	49	-0.83	0.41	0.22	3.27
Change from 1st to 2nd time point											
EPDS index	27	-0.07	0.44	41	-0.30	0.51	66	1.85	0.07	0.48	0.94
MFAS index (shared 7 items [f])	27	0.04	0.35	41	0.01	0.32	66	0.40	0.69	-0.09	3.68
P-PRFQ index (shared 8 items [g])	27	-0.03	0.63	40	0.13	0.68	65	-0.99	0.33	0.24	2.60
STAI index	27	-0.05	0.35	41	-0.05	0.46	66	-0.01	1.0	0	3.94

Note. [a] Bayes factor (B_{01}) values >1 are interpreted as evidence for the null hypothesis; Index = the total sum score of the measure divided by the number of items. [b] Effect size Cohen's *d*: 0.2 refers to small, 0.5 to medium and 0.8 to large effect (Cohen, 1988) ; [c] Fisher's exact test; EPDS = Edinburgh Pre/Postnatal Depression Scale; STAI = State-Trait Anxiety Inventory; MFAS = Maternal-Fetal Attachment Scale; MFAS factors: Role taking = *Role taking*, Differentiation = *Differentiation of self from fetus*, Interacting = *Interacting with the fetus*, Attributing = *Attributing characteristics to the fetus* and Giving = *Giving of self;* P-PRFQ = Prenatal Parental Reflective Functioning Questionnaire; [e] P-PRFQ factors: F1 = *Opacity of mental states,* F2 = *Reflecting on the fetus-baby and* F3 = *Dynamic nature of mental states*; [f] The change in the MFAS scores was calculated using the 7 items used in the pre-and post-intervention and [g] the change in P-PRFQ scores was calculated using 8 items included in the pre- and post-intervention. The table is modified from the tables presented in Jussila et al., (2020a) . * p-value < 0.05

5.1.2.5 Efficacy of the intervention on participation in obstetric care and perinatal outcomes (Study II)

Clinical sample characteristics revealed that nearly half (48%) of the pregnant women with recent or current harmful substance use suffered from complications during pregnancy, such as obesity, gestational diabetes, hypertension, pre-eclampsia or antenatal infections. Our findings did not establish evidence for between-groups differences in the number of prenatal obstetric consultations, emergency department visits, and hospital admissions (Table 10). However, 59% of the patients in the intervention group participated in all of the scheduled clinical visits in the context of treatment-as-usual in comparison with the participation rate of 83% in the control group ($X^2[1, N = 80] = 5.54, p = 0.02$).

Table 10. Descriptive statistics regarding participation in obstetric care and the results from testing the differences between the intervention group and control groups in these outcomes.

	Control group (N = 44)			***Intervention group (N = 46)***			***Between-group difference***	
	n	***Mean (SD)***	***Median (range)***	***n***	***Mean (SD)***	***Median (range)***	***p***	***r***
All consultations at the obstetric outpatient clinic	35	8.4 (4.0)	8.0 (3-23)	40	8.1 (3.5)	8.0 (3-22)	0.94 [a]	0.01
Emergency consultations at the obstetric outpatient clinic	35	1.3 (1.6)	1.0 (0-7)	40	1.0 (1.2)	1.0 (0-5)	0.39 [a]	0.10
Prenatal hospital admissions (obstetric care)	35	0.6 (1.2)	0 (0-7)	40	0.3 (0.8)	0 (0-4)	0.11 [a]	0.19
Prenatal hospital care (days) at the obstetric department	35	2.3 (6.3)	0 (0-31)	38	0.6 (1.5)	0 (0-8)	0.08 [a]	0.20
Emergency department visits	33	0.3 (0.6)	0 (0-2)	38	0.6 (1.1)	0 (0-4)	0.27 [a]	0.13
	N	***n***	***(n/N) %***	***N***	***n***	***(n/N) %***	***p***	***Cramer's ϕ***
Participants with withdrawn visits at the obstetric clinic	36	*6*	*17%*	44	*18*	*41%*	0.02[b] *	0.26

Note. The table is modified from the table presented in the original publication (Jussila et al., 2020b) .

N = data available, *n* = a number of relevant cases; The between-goups difference: [a] Mann Whitney U test, [b]Pearson Chi-Square test; [d] Effect size *r* = 0.1 is referring to small effect, *r* = 0.30 is referring to medium effect, and *r* = 0.5 is referring to large effect (Field, 2013) . **p* = < 0.05.

Seventy-one percent of the participants had an uncomplicated vaginal delivery, and a vacuum extraction was performed in 11% and a cesarean section in 18% of the participants. The median birth weight was 3310g ranging from 645g to 4870g. The

median pH of umbilical artery at birth was 7.25 (range 7.11–7.47). Thirty-five percent of the newborns needed treatment at the neonatal intensive care unit. One neonate born to the mother participating in the intervention group died from birth asphyxia. Our findings did not provide evidence of the between-groups differences in the perinatal child outcomes (Table 11).

Table 11. Descriptive statistics regarding the perinatal child outcomes and the results from testing the differences between the intervention group and control groups in these outcomes.

	Control group (N = 44)			***Intervention group (N = 46)***			***Between-group difference***	
	n	***Mean (SD)***	***Median (range)***	***n***	***Mean (SD)***	***Median (range)***	***p***	***r*** [d]
Gestational weeks at delivery	36	38.8 (2.5)	39.0 (28-42)	44	39.0 (2.8)	40.0 (25-41)	0.19 [a]	0.15
Birth weight standard deviation (*SD*)	35	-0.7 (1.2)	-1.0 (-2.5-2.2)	41	-0.7 (1.0)	-0.6 (-3.2-1.6)	0.72 [a]	0.04
Head circumference standard deviation (*SD*)	35	-0.4 (1.0)	-0.5 (-2.8-2.0)	38	-0.6 (0.8)	-0.8 (-2.6-1.6)	0.28 [a]	0.13
Apgar score at 5 minutes	34		9.0 (8-10)	41		9.0 (3-10)	0.66 [a]	0.05
Length of hospital stay, days (child)	35	6.1 (9.3)	4.0 (2-58)	43	9.3 (14.9)	5.0 (0-90)	0.21 [a]	0.14
	N	***n***	***(n/N) %***	***N***	***n***	***(n/N) %***	***p***	***Cramer's ϕ***
Small for gestational age (<2*SD*)	35	5	(5/35) 14%	41	4	(4/41) 10%	0.73 [c]	0.07
Low birth weight (<2500g)	36	4	(4/36) 11%	44	5	(5/44) 11%	1.00 [c]	0.004
Preterm (<37gwks)	36	4	(4/36) 11%	44	6	(6/44) 14%	1.00 [c]	0.04
Neonatal withdrawal symptoms	36	8	(8/36) 22%	40	4	(4/40) 10%	0.21 [c]	0.17

Note. The table is modified from the table presented in the original publication (Jussila et al., 2020b) .

N = data available, *n* = a number of relevant cases; Difference between the intervention and the control group: [a] Mann Whitney U test, [c] Fisher's exact test; [d] Effect size *r* = 0.1 is referring to small effect, *r* = 0.30 is referring to medium effect, and *r* = 0.5 is referring to large effect (Field, 2013) . * *p* = < 0.05

5.1.2.6 Efficacy of the intervention on fetal drug exposure (Study II)

We evaluated the efficacy of the intervention on fetal drug exposure by using the results from routinely assessed newborn meconium toxicology testing as an outcome. Meconium drug testing was available for 89% (71/80) of the neonates, 94% (34/36) in the control and 84% (37/44) in the intervention group. Based on the neonatal drug testing, 7% (5/71) of the newborns were exposed to illicit drugs or non-medical use of prescription drugs. Meconium was screened positive for illicit drugs in 3% (1/37) of the newborns in the intervention group and 12% (4/34) in the

control group. A difference between the intervention and control groups was not displayed in fetal drug exposure (Fisher's exact test, $p = 0.18$).

5.1.3 The role of maternal-fetal attachment and pregnancy-related anxiety in prenatal smoking behavior in the FinnBrain Birth Cohort study (Studies III and IV)

5.1.3.1 Sample characteristics and attrition

The prevalence of smoking in pregnancy was 16.5% (612 of 3698) in the FinnBrain Birth Cohort. Of the pregnant smokers, 58.1% (354 of 609) quit smoking and 41.9% (255 of 609) continued smoking during pregnancy. The data concerning smoking in pregnancy was missing in 1.8% (68 of 3766) of the participants, and regarding smoking cessation in 0.5% (3 of 612) of the pregnant smokers. By their delivery date, 7.6% (288 of 3766) of the pregnant women in the FinnBrain Birth Cohort discontinued their participation. The drop-out rate did not differ between the non-smokers and the smokers (6.9% vs. 5.4%, $F(1) = 1.8$, $p = 0.179$, respectively), or between those who had quit smoking and those who continued smoking during pregnancy (6.5% vs. 3.1%, $F(1) = 3.5$, $p = 0.063$, respectively).

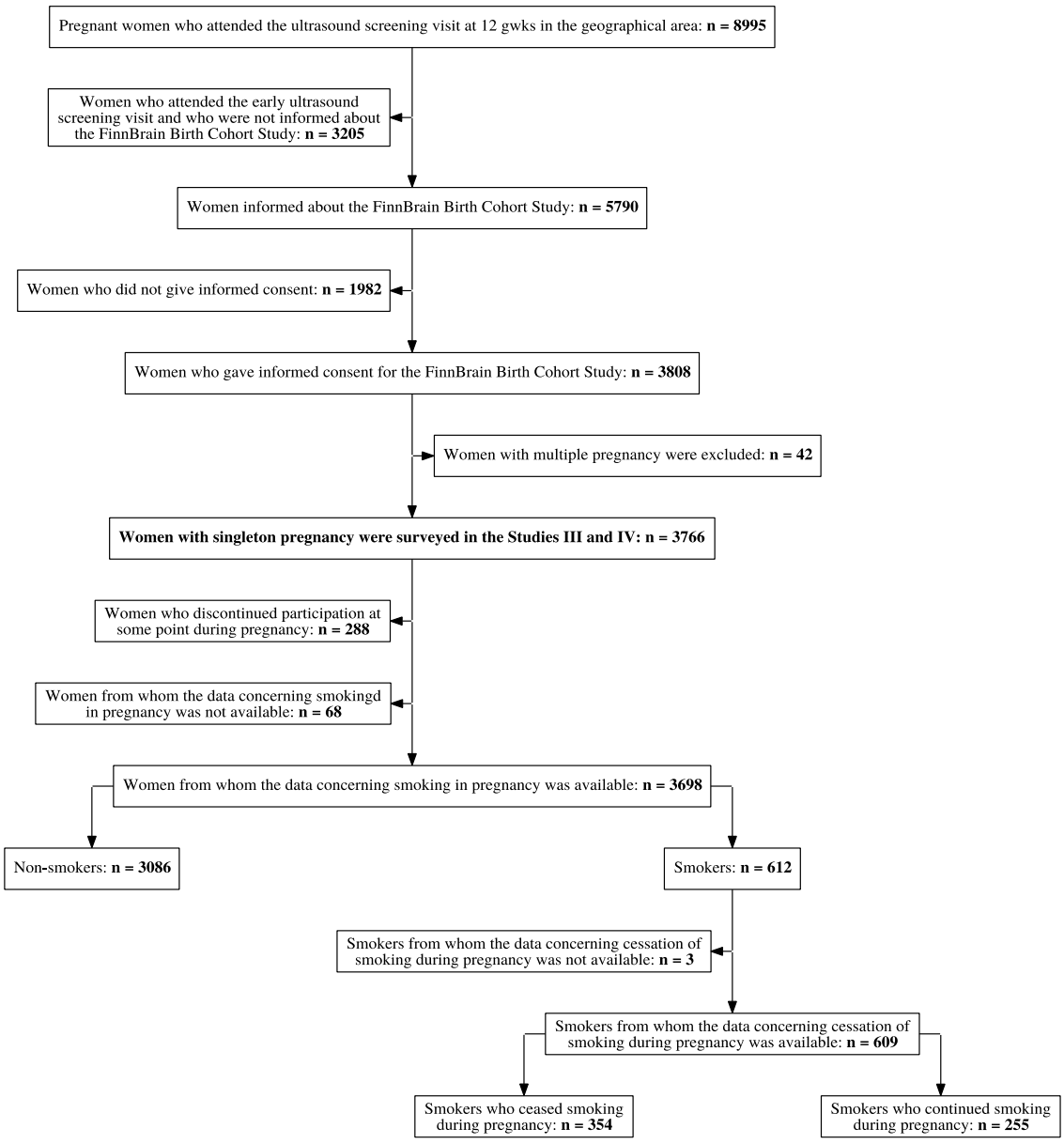

Figure 2. Flow chart of Studies III and IV conducted in the FinnBrain Birth Cohort Study sample. Ennrollment to the FinnBrain Birth Cohort Study took place between December 2011 and April 2015.

In the second and third trimester, attrition in the questionnaire responses was significantly higher among the women who smoked in comparison with the non-smoking women. In addition, higher attrition in the questionnaire responses was observed among the persistent smokers when compared with attrition among those women who quit smoking

during pregnancy. Attrition in the questionnaire responses by the participants' smoking status is presented in Table 12. The participants who had responded to the questionnaire measure of maternal-fetal attachment at least once during pregnancy were included in the statistical models of Study III (24 gwks n = 2858 [76%] and 34 gwks: n = 2836 [75%]). Those participants who had completed the questionnaire measure of pregnancy-related anxiety at least once during pregnancy were included in the statistical models of Study IV (24 gwks n = 2840 [75%]). In the subsample of women who smoked, those who had completed the questionnaire measure of maternal-fetal attachment at least once during pregnancy were included in the imputation and regression models regarding smoking cessation during pregnancy (24 gwks: n = 429 [70%]; 34 gwks: n = 426 [70%]). Similarly, the women who smoked and had completed the PRAQ-R2 at least once during pregnancy were included in the statistical models regarding smoking cessation (24 gwks n = 426 [70%]).

Table 12. Attrition in the questionnaire responses in The FinnBrain Birth Cohort Study by the participants' smoking status, and differences in attrition between the non-smoking and smoking women, and between those women who quit smoking and those women who continued smoking during pregnancy.

	Non-smoking *N* = 3086			**Smoking *N* = 612**			**Between-groups difference**
	n	***N***	***%***	***n***	***N***	***%***	***p***
24 gwks							
PRAQ-R2	770	3086	25.0%	206	612	33.7%	<0.001**
MFAS	755	3086	24.5%	203	612	33.2%	<0.001**
EPDS	769	3086	24.9%	204	612	33.3%	<0.001**
SCL-90 Anxiety	772	3086	25.0%	204	612	33.3%	<.001**
34 gwks							
MFAS	898	3086	29.1%	239	612	39.1%	<0.001**
EPDS	895	3086	29.0%	239	612	39.1%	<0.001**
SCL-90 Anxiety	900	3086	29.2%	238	612	38.9%	<0.001**
	Quit smoking *N* = 354			**Continued smoking *N* = 255**			**Between-groups difference**
	n	***N***	***%***	***n***	***N***	***%***	***p***
24 gwks							
PRAQ-R2	99	354	28.0%	104	255	40.8%	<0.001**
MFAS	97	354	27.4%	103	255	40.4%	<0.001**
EPDS	98	354	27.7%	103	255	40.4%	<0.001**
SCL-90 Anxiety	98	354	27.7%	103	255	40.4%	<0.001**
34 gwks							
MFAS	118	354	33.3%	118	255	46.3%	0.001**
EPDS	119	354	33.6%	117	255	45.9%	0.002**
SCL-90 Anxiety	119	354	33.6%	116	255	45.5%	0.003**

Note. The estimates are based on the original data, not the imputed dataset. *N* = the total number of participants, *n* = the number of participants with the missing questionnaire responses.
PRAQ-R2 = Pregnancy-Related Anxiety Questionnaire, revised version 2; MFAS = Maternal-Fetal Attachment Scale; EPDS = Edinburgh (Pre) Postnatal Depression Scale; SCL-90 Anxiety = Symptom Checklist -90, the Anxiety Subscale.
* p-value < 0.05, **p-value < 0.01

The demographic characteristics of the participants are presented in Table 13. The mean age of the participants was M_{years} = 30.2 years (SD 4.7, range 17–46). The women who smoked were younger than the non-smokers, M_{years} = 28.2(*SD* 5.2) vs. M_{years} = 30.7(*SD* 4.5) respectively, $t(799.1) = 11.1$, $p < 0.001$. Further, the women who smoked were statistically significantly more often primiparous and single parents-to-be, and they reported a lower level of educational attainment, income and had substantial mental health problems prior to pregnancy. Socio-economic situation and prior history of mental health problems also differentiated the persistent smokers from the pregnant women who were able to quit smoking during pregnancy. The pregnant women who continued smoking until late pregnancy reported lower educational achievements and income, and they were more often multiparous and single mothers. In addition, the persistent smokers reported more frequently a prior history of depression. The pregnant women who quit smoking in early pregnancy were approximately of the same age as the pregnant women who continued smoking in late pregnancy M_{years} = 28.4(*SD* 5.0) vs. M_{years} = 27.8(*SD* 5.5) respectively, $t(511.6) = 1.6$, $p = 0.12$.

Table 13. Sociodemographic and clinical characteristiscs of the pregnant women participating in the FinnBrain Birth Cohort Study, and the differences in the sample characteristics between the non-smoking and smoking pregnant women and, in the subsample of smoking women, the differences between the persistent smokers and those women who were able to quit smoking during pregnancy.

	Non-smokers	Smokers	Between-groups difference		Quit smoking	Continued smoking	Between-groups difference	
	N = 3086	*N* = 612			*N* = 354	*N* = 255		
	n/N (%)	***n/N (%)***	***df***	***X^2 p***	***n/N (%)***	***n/N (%)***	***df***	***X^2 p***
Primiparous	1432/3086 (46.4)	353/612 (57.7)	1	<0.001**	231/354 (65.3)	112/255 (47.1)	1	<0.001**
Single parent	80/3080 (2.6)	68/605 (11.2)	1	<0.001**	17/353 (4.8)	51/249 (20.5)	1	<0.001**
Education			2	<0.001**			2	<0.001**
low	828/2582 (32.1)	325/462 (70.3)			190/298 (63.8)	133/161 (82.6)		
middle	803/2582 (31.1)	81/462 (17.5)			62/298 (20.8)	19/161 (11.8)		
high	951/2582 (36.8)	56/462 (12.1)			46/298 (15.4)	9/161 (5.6)		
Income			3	<0.001**			3	0.015*
<1000€	544/2577 (21.1)	133/460 (28.9)			72/297 (24.2)	59/160 (36.9)		
1001-1500€	409/2577 (15.9)	112/460 (24.3)			71/297 (23.9)	41/160 (25.9)		
1501-2000€	870/2577 (33.8%)	140/460 (30.4)			101/297 (34.0)	39/160 (24.4)		
>2000€	754/2577 (29.3)	75/460 (16.3)			53/297 (17.8)	21/160 (13.1)		
Self-reported prior mental disorder (any)	419/2580 (16.2)	126/460 (27.4)	1	<0.001**	74/297 (24.9)	50/160 (31.3)	1	0.146
Self-reported prior depression	291/2580 (11.3)	93/460 (20.2)	1	<0.001**	51/297 (17.2)	40/160 (25.0)	1	0.046*
Self-reported prior anxiety disorder	137/2580 (5.3)	38/460 (8.3)	1	0.012*	23/297 (7.7)	14/160 (8.8)	1	0.707

Note. The table is modified from the table presented in the original publication (Jussila et al., 2020). The descriptive sample statistics are based on the original data, not the imputed dataset.

N = information available or relevant total *N*, *n* = a number of pregnant women with an affirmative response. * *p*-value < 0.05, ***p*-value < 0.01

Our results suggested that the group means of maternal-fetal attachment were significantly different depending on the expectant mothers' smoking behavior (non-smoking, smoking cessation in early pregnancy, continuation of smoking) (MFAS 24 gwks: $F(2, 2737) = 3.19$, $p = 0.041$; 34 gwks: $F(2, 2558) = 3.90$, $p = 0.020$). Post hoc comparison between the groups revealed that the non-smoking women self-reported a lower level of maternal-fetal attachment than the pregnant women who

quit smoking in early pregnancy (24 gwks: *M* = 86.78, SD = 10.48 vs. *M* = 87.50, *SD* = 10.00, *p* = 0.035, respectively; 34 gwks: *M* = 91.52, *SD* = 10.26 vs. *M* = 94.03, *SD* = 9.75, *p* = 0.018, respectively). Interestingly, the highest total scores of maternal-fetal attachment were observed among the pregnant women who smoked and who were able to quit smoking.

We investigated the group means of pregnancy-related anxiety by the expectant mother's smoking status (non-smoking, smoking cessation in early pregnancy, continuation of smoking). Our results demonstarted that the group means of pregnancy-related anxiety were significantly different depending on the expectant mothers' smoking behavior (PRAQ-R2 24 gwks: $F(2, 2719) = 10.58$, $p < .001$). Post hoc comparison between the groups revealed that the non-smoking women self-reported a lower level of pregnancy-related anxiety than the pregnant women who continued smoking throughout pregnancy (24 gwks: *M* = 22.70, *SD* = 6.54 vs. *M* = 24.79, *SD* = 7.82, *p* <.001, respectively). Further, the level of pregnancy-related anxiety was lower among the non-smoking women when compared with the level of pregnancy-related anxiety among pregnant women who quit smoking (24 gwks: *M* = 22.70, *SD* = 6.54 vs. *M* = 24.06, *SD* = 6.72, *p* = .007, respectively).

Further, we compared the smoking and non-smoking pregnant women in terms of prenatal parenting and prenatal psychological distress (Table 14). The level of maternal-fetal attachment (the total sum score of MFAS) was equivalent among the non-smokers and the smokers. However, the women who smoked scored higher in three factors of MFAS in the second trimester. In the third trimester, maternal-fetal attachment regarding two subscales of MFAS was higher among the women who smoked. The women who smoked suffered more from depressive and anxiety symptoms than the non-smoking women in the second and third trimester. The proportion of women exceeding the EPDS cut-off ≥10 was significantly higher among the women who smoked at both time points. In the second trimester, the level of pregnancy-related anxiety was significantly higher among the women who smoked. In addition, the women who smoked scored higher in all of the subscales of PRAQ-R2 in the second trimester.

In the sample of pregnant smokers, we investigated differences in prenatal parenting and psychological distress between the persistent smokers and those women who smoked and quit smoking in early pregnancy (Table 15). The pregnant women who ceased smoking scored higher in one subscale of MFAS, *Giving of self*, in the second and third trimester. The persistent smokers reported more depressive and anxiety symptoms than the women who were able to quit smoking at both time points. The between-groups difference in pregnancy-related anxiety was not substantiated in the second trimester. The prevalence of prenatal depression (EPDS ≥10) was higher among the persistent smokers.

Finally, we investigated the level of maternal-fetal attachment by maternal educational level (low, middle, high). The findings suggested that the group means of maternal-fetal attachment were significantly different at the different levels of maternal education (MFAS 24 gwks: $F(2, 2603) = 10.61$, $p < 0.001$; 34 gwks: $F(2, 2444) = 3.97$, $p = 0.019$). Interestingly, the women with the highest educational achievements displayed the lowest level of maternal-fetal attachment at both time points. Post hoc comparison between the groups suggested that the pregnant women with low education scored higher in the MFAS than the women with high education in the second trimester (24 gwks: $M = 87.7$, $SD = 10.19$ vs. $M = 85.61$, $SD = 10.30$, $p < 0.001$, respectively). Further, the pregnant women with a middle level of education self-reported stronger maternal-fetal attachment than the women with a high level of education (24 gwks: $M = 87.47$, $SD = 10.87$ vs. $M = 85.61$, $SD = 10.30$, $p < 0.001$, respectively). In the third trimester, the pregnant women with a low education reported stronger attachment than the women with a high level of education (34 gwks: $M = 92.54$, SD = 10.22 vs. $M = 91.36$, $SD = 10.32$, $p = 0.046$, respectively). Further, the women with a middle level of education displayed stronger attachment than the highly educated women (34 gwks: $M = 92.54$, $SD = 10.31$ vs. $M = 91.36$, $SD = 10.32$, $p = 0.047$).

Table 14. Descriptive data on prenatal parenting and psychological distress, and the comparisons between the smoking pregnant women and the non-smoking pregnant women.

	Non-smokers *N* = 3086			**Smokers** *N* = 612			**Between-groups difference**	
	n	***Mean (SD)***	***Median (range)***	***n***	***Mean (SD)***	***Median (range)***	***p*[a]**	***r***
24 gwks								
MFAS	2331	86.9 (10.6)	87 (51-116)	409	88.0 (10.0)	88 (44-113)	0.074	0.03
Role taking	2336	16.7 (2.8)	17 (6-20)	410	16.8 (2.7)	17 (7-20)	0.703	0.01
Differentiation	2340	15.4 (2.5)	15 (6-20)	410	15.7 (2.4)	16 (7-20)	0.032*	0.04
Interacting	2338	16.6 (3.1)	17 (5-25)	410	17.1 (3.0)	17 (8-24)	0.004**	0.05
Attributing	2335	18.5 (3.4)	19 (6-30)	409	19.0 (3.2)	19 (11-29)	0.006**	0.05
Giving	2338	19.7 (2.5)	20 (9-25)	410	19.5 (2.5)	20 (8-25)	0.091	0.03
PRAQ-R2	2316	22.7 (6.6)	22(10-48)	406	24.3(7.2)	24(10-46)	<0.001**	0.08
F1	2317	6.7(2.6)	6(3-15)	406	7.1(2.8)	7(3-15)	0.014*	0.04
F2	2317	8.5(3.4)	8(4-20)	406	9.2(3.5)	9(4-20)	<0.001**	0.07
F3	2316	7.5(2.9)	7(3-15)	406	8.1(3.1)	8(3-15)	<0.001**	0.07
SCL-90 Anxiety	2314	3.8 (4.2)	3 (0-30)	408	4.7 (4.6)	4 (0-24)	<0.001**	0.08
EPDS	2317	4.8 (4.1)	4 (0-25)	408	6.0 (4.3)	5 (0-23)	<0.001**	0.11
		n/N	**%**		**n/N**	**%**	***X*² *p***	**Cramer's ϕ**
EPDS≥10		299/2317	12.9%		73/408	17.9%	0.007**	0.05

Table 14. continues

	Non-smokers *N* = 3086			Smokers *N* = 612			Between-groups difference	
	n	***Mean (SD)***	***Median (range)***	***n***	***Mean (SD)***	***Median (range)***	***p*[a]**	***r***
34 gwks								
MFAS	2188	92.0 (10.2)	93 (52-116)	373	93.1 (10.2)	93 (55-117)	0.137	0.03
Role taking	2202	17.1 (2.6)	18 (7-20)	374	17.1 (2.5)	18 (8-20)	0.886	0.00
Differentiation	2204	15.9 (2.4)	16 (8-20)	374	16.2 (2.2)	16 (10-20)	0.111	0.03
Interacting	2202	18.1 (3.1)	18 (5-25)	374	18.5 (2.8)	19 (10-25)	0.037*	0.04
Attributing	2198	21.1 (3.4)	22 (9-30)	373	21.8 (3.4)	22 (12-30)	0.001**	0.07
Giving	2198	19.8 (2.4)	20 (10-25)	374	19.6 (2.5)	20 (10-25)	0.171	0.03
SCL-90 Anxiety	2186	3.1 (3.8)	2 (0-27)	374	3.8 (4.6)	3 (0-33)	0.012*	0.05
EPDS	2191	4.7 (4.0)	4 (0-26)	373	5.9 (4.5)	5 (0-23)	<0.001**	0.10
		n/N	**%**		**n/N**	**%**	**X^2 *p***	**Cramer's ϕ**
EPDS≥10		287/2191	13.1%		84/373	22.5%	<0.001**	0.09

Note. The table is modified from the table presented in the original publication (Jussila et al., 2020) . The estimates are based on the original data, not the imputed dataset. MFAS = Maternal-Fetal Attachment Scale, and the subscales of Maternal-Fetal Attachment Scale: *Role taking*, Differentiation = *Differentiation of self from fetus*, Interacting = *Interacting with the fetus*, Attributing = *Attributing characteristics to the fetus* and Giving = *Giving of self;* PRAQ-R2 = Pregnancy-Related Anxiety Questionnaire, revised version 2, and the factors of PRAQ-R2: F1 = *Fear of Giving Birth*, F2 = *Worries about Bearing a Physically or Mentally Handicapped Child*, and F3 = *Concerns about Own Appearance;* EPDS = Edinburgh (Pre) Postnatal Depression Scale; SCL-90 Anxiety = Symptom Checklist -90, the Anxiety Subscale.

[a] Mann-Whitney U test * *p*-value <0.05, ***p*-value <0.01

Table 15. Descriptive data on prenatal psychological distress and prenatal parenting, and the comparisons between the pregnant women who quit smoking and the pregnant women who continued smoking during pregnancy.

	Quit smoking *N* = 354			**Continued smoking** *N* = 255			**Between-groups difference**	
	n	***Mean (SD)***	***Median (range)***	***n***	***Mean (SD)***	***Median (range)***	***p*[a]**	***r***
24 gwks								
MFAS	257	88.6 (10.0)	88 (57-113)	152	87.0 (10.0)	87 (44-112)	0.102	0.08
Role taking	258	16.6 (2.7)	17 (8-20)	152	16.7 (2.6)	17 (7-20)	0.237	0.06
Differentiation	258	15.7 (2.4)	16 (9-20)	152	15.6 (2.3)	16 (7-20)	0.644	0.02
Interacting	258	17.1 (3.1)	17 (8-24)	152	17.0 (2.9)	17 (9-24)	0.574	0.03
Attributing	257	19.1 (3.2)	19 (11-29)	152	19.0 (3.2)	19.0 (11-29)	0.773	0.01
Giving	258	19.8 (2.4)	20 (13-25)	152	18.8 (2.6)	19 (8-25)	<0.001**	0.18
PRAQ-R2	255	24.1(6.7)	24(10-46)	151	24.8(7.9)	24(10-46)	0.564	0.02
F1	255	6.9(2.6)	6(3-15)	151	7.4(3.2)	7(3-15)	0.113	0.08
F2	255	9.0(3.5)	9(4-20)	151	9.5(3.7)	9(4-19)	0.254	0.06
F3	255	8.2(3.0)	8(3-15)	151	7.9(3.3)	8(3-15)	0.279	0.05
SCL-90 Anxiety	256	4.3 (4.5)	3 (0-24)	152	5.4 (4.7)	4 (0-20)	0.007**	0.13
EPDS	256	5.6 (4.1)	5 (0-20)	152	6.8 (4.5)	6 (0-23)	0.006**	0.14
		n/N	**%**		**n/N**	**%**	***X^2p***	**Cramer's ϕ**
EPDS≥10		36/256	14.1%		37/152	24.3%	0.009**	0.13

Table 15. continues

	Quit smoking *N* = 354			Continued smoking *N* = 255			Between-groups difference	
	n	***Mean (SD)***	***Median (range)***	***n***	***Mean (SD)***	***Median (range)***	***p*[a]**	***r***
34 gwks								
MFAS	236	93.9 (9.7)	93 (67-115)	137	91.8 (10.9)	91 (55-117)	0.093	0.09
Role taking	236	17.3 (2.5)	18 (8-20)	138	17.0 (2.5)	17 (8-20)	0.136	0.08
Differentiation	236	16.2 (2.3)	16 (10-20)	138	16.1 (2.2)	16 (10-20)	0.883	0.01
Interacting	236	18.5 (2.7)	19 (12-25)	138	18.4 (3.0)	18 (10-25)	0.555	0.03
Attributing	236	21.9 (3.3)	22 (12-28)	137	21.6 (3.7)	22 (12-30)	0.542	0.03
Giving	236	20.1 (2.5)	20 (12-25)	138	18.8 (2.5)	18 (10-25)	<0.001**	0.26
SCL-90 Anxiety	235	3.5 (4.5)	2 (0-33)	139	4.5 (4.7)	3 (0-26)	0.016*	0.12
EPDS	235	5.4 (4.2)	5 (0-20)	138	6.8 (4.9)	6 (0-23)	0.007**	0.14
		n/N	**%**		**n/N**	**%**	**X^2p**	**Cramer's ϕ**
EPDS≥10		42/235	17.9%		42/138	30.4%	0.005**	0.15

Note. The table is modified from the table presented in the original publication (Jussila et al., 2020) . The estimates are based on the original data, not the imputed dataset. MFAS = Maternal-Fetal Attachment Scale and the subscales of Maternal-Fetal Attachment Scale: *Role taking*, Differentiation = *Differentiation of self from fetus*, Interacting = *Interacting with the fetus*, Attributing = *Attributing characteristics to the fetus* and Giving = *Giving of self;*

PRAQ-R2 = Pregnancy-Related Anxiety Questionnaire, revised version 2, and the factors of PRAQ-R2: F1 = *Fear of Giving Birth*, F2 = *Worries about Bearing a Physically or Mentally Handicapped Child*, and F3 = *Concerns about Own Appearance;* EPDS = Edinburgh (Pre) Postnatal Depression Scale; SCL-90 Anxiety = Symptom Checklist -90, the Anxiety Subscale.

[a] Mann-Whitney U test

* p-value <0.05, **p-value <0.01

5.1.3.2 Association of maternal-fetal attachment with smoking in pregnancy (Study III)

Binary logistic regression analyses were conducted to estimate the relationship between maternal-fetal attachment and maternal prenatal tobacco smoking (Figure 3). We did not establish evidence of an association between the MFAS total scores in the second and third trimester and smoking in pregnancy (*MFAS* 24 gwks: $\beta = 0.00$, aOR = 1.00, 95% CI [0.99, 1.01], $p = 0.937$, multiplicity adjusted $p = 1.00$; *MFAS* 34 gwks: $\beta = 0.00$, aOR =1.00, 95% CI [0.99, 1.02], $p = 0.595$, multiplicity adjusted $p = 1.00$) or the associations between the MFAS subscales and smoking in pregnancy (aOR = 0.97–1.04, $p = 0.07$–0.90, multiplicity adjusted $p = 0.581$–1.00) while controlling for maternal age, education, single parenthood, parity, and concurrent symptoms of depression and anxiety.

5.1.3.3 Association of maternal-fetal attachment with smoking cessation during pregnancy (Study III)

In the sample of pregnant women who smoked, we performed binary logistic regression analyses to evaluate the association between maternal-fetal attachment and smoking cessation during pregnancy after controlling for maternal age, education, single parenthood, parity, and concurrent symptoms of anxiety and depression (Figure 3). We did not observe evidence of the association between maternal-fetal attachment (the total sum scores of MFAS at the 24th and 34th gwks) and smoking cessation during pregnancy (*MFAS* 24 gwks: $\beta = 0.02$, aOR = 1.02, 95% CI [1.00, 1.04], $p = 0.088$, multiplicity adjusted $p = 0.781$; *MFAS* 34 gwks: $\beta = 0.02$, aOR = 1.02, $p = 0.155$, multiplicity adjusted $p = 1.00$). After multiple testing correction, a marginally significant association was demonstrated between the *Giving of Self* subscale of the MFAS at 24 gwks and smoking cessation ($\beta = 0.13$, aOR =1.13, 95% CI [1.04, 1.24], $p = 0.007$, multiplicity adjusted $p = 0.062$). Further, a higher score in the MFAS subscale *Giving of self* at 34 gwks did associate significantly with an increased probability of smoking cessation ($\beta = 0.16$, aOR = 1.17, 95% CI [1.07, 1.29], $p = 0.0009$, multiplicity adjusted $p = 0.008$). Evidence of associations between the other subscales of the MFAS and smoking cessation during pregnancy was not demonstrated (aOR = 0.99–1.05, $p = 0.21$–0.88, multiplicity adjusted $p = 1.00$).

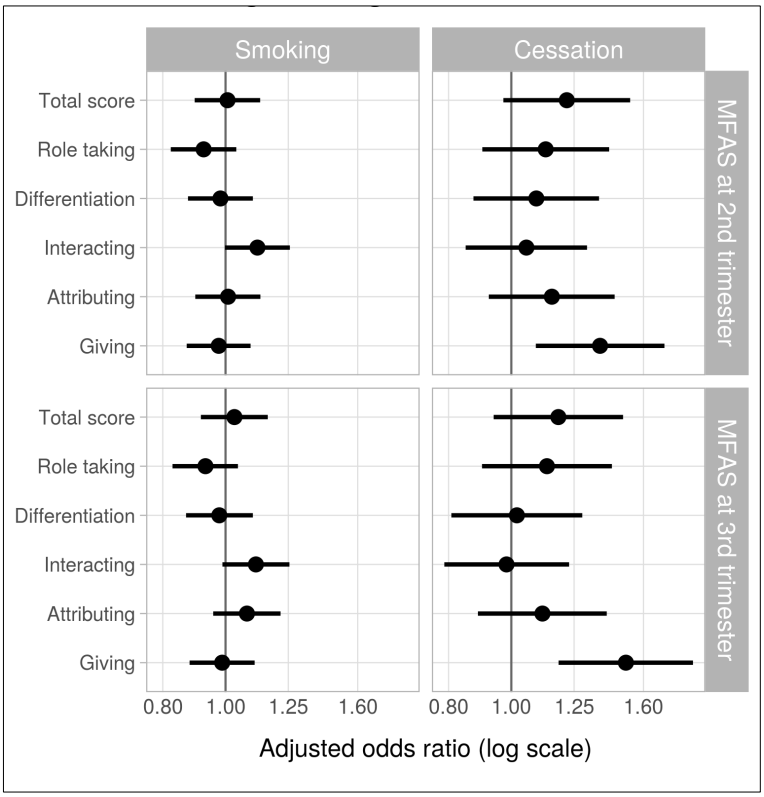

Figure 3. The associations between one standard deviation (SD) increase in the MFAS total score/subscale scores and smoking in pregnancy / smoking cessation during pregnancy. The standard deviations of the the MFAS total scores/subscale scores have been reported in Tables 14 and 15.

5.1.3.4 Maternal-fetal attachment modifying the effects of maternal education and prenatal psychological distress on smoking in pregnancy (Study III)

First, we estimated the main effects of education and prenatal psychological distress on smoking in pregnancy. These findings indicated that a lower level of maternal education and a higher level of depressive symptoms associated with an increased risk of smoking in pregnancy. The pregnant women with a middle level of education (aOR = 0.28–0.29, $p < 0.001$) or high level of education (aOR = 0.17, $p < 0.001$) were less likely to smoke during pregnancy than the pregnant women with the lowest level of education. The pregnant women who reported a higher level of depressive symptoms were more likely to smoke during pregnancy (*EPDS* 24 gwks: $\beta = 0.05$, aOR = 1.05, 95% CI [1.02, 1.09], $p = 0.004$; *EPDS* 34 gwks: $\beta = 0.05$, aOR = 1.06, 95% CI [1.02, 1.09], $p = 0.002$) while a relationship between prenatal anxiety symptoms and smoking in pregnancy was not substantiated (*the anxiety subscale of*

the SCL-90 at 24 gwks: $\beta = 0.00$, aOR = 1.00 , 95% CI [0.97, 1.03], $p = 0.854$; *the anxiety subscale of the SCL-90* at 34 gwks: $\beta = -0.02$, aOR = 0.98, 95% CI [0.94, 1.01], $p = 0.191$).

The findings indidated that maternal education and prenatal depressive symptoms associated statistically significantly with smoking in pregnancy. Therefore, the interaction effects *MFAS* × Education [low, middle, high] and *MFAS* × Prenatal Psychological Distress [*EPDS*] on smoking in pregnancy were investigated. Our findings did not substantiate the modifying effect of maternal-fetal attachment on the association between maternal education and smoking in pregnancy, or the association between prenatal depressive symptoms and smoking in pregnancy. Our preliminary finding suggested that a stronger maternal-fetal attachment at 24 gwks could associate with a decrease in the risk of prenatal smoking among the women with a middle level of education when compared to the risk of smoking among the women with low ($\beta = -0.03$, aOR = 0.97, 95% CI [0.95, 0.996], $p = 0.026$, multiplicity adjusted $p = 0.137$) or high education ($\beta = -0.04$, aOR = 0.96, 95% CI [0.93, 0.998], $p = 0.038$, multiplicity adjusted $p = 0.199$). Nevertheless, evidence for the modifying effect of maternal-fetal attachment on the association between maternal education and smoking in pregnancy was not considered sufficient because the statistical significance of the results did not remain after the correction for multiple comparisons (multiplicity adjusted $p = 0.137–1.00$). The effect of maternal education on smoking in pregnancy did not display any difference in the way it was dependent on the level maternal-fetal attachment at 24 gwks among the women with a high education compared to the women with a low education ($\beta = 0.006$, aOR = 1.006, 95% CI [0.98, 1.04], $p = 0.698$, multiplicity adjusted $p = 1.00$). Further, the modifying effect of maternal-fetal attachment (the total sum scores of MFAS at the 24th and 34th gwks) on the direction or strength of the association between prenatal depressive symptoms and smoking in pregnancy was not demonstrated ($p = 0.832–0.833$, multiplicity adjusted $p = 1.00$).

5.1.3.5 Maternal-fetal attachment modifying the effects of maternal education and prenatal psychological distress on smoking cessation during pregnancy (Study III)

In the population of pregnant women who smoked, we first estimated the main effects of maternal education and prenatal psychological distress on smoking cessation during pregnancy. The findings revealed that a higher level of maternal education predicted cessation of smoking during pregnancy whereas evidence of an association between prenatal psychological distress (neither depressive nor anxiety symptoms) and quitting smoking during pregnancy was not demonstrated. The women with a middle level of education (aOR = 2.20–2.45, p = 0.021–0.008) or high

level of education (aOR = 3.15–3.23, p = 0.007–0.008) were more likely to quit smoking during pregnancy than the women with the lowest level of education. A relationship between prenatal depressive / anxiety symptoms and smoking cessation during pregnancy was not substantiated (24 gwks *EPDS:* β = -0.03, aOR = 0.98, 95% CI [0.91, 1.04], p = 0.451and *the anxiety subscale of the SCL-90:* β = -0.02, aOR = 0.99, 95% CI [0.93, 1.04], p = 0.621; 34 gwks *EPDS:* β = -0.04, aOR = 0.96, 95% CI [0.90, 1.02], p = 0.179 and *the anxiety subscale of the SCL-90*: β = 0.00, aOR = 1.00, 95% CI [0.94, 1.06], p = 0.965).

The findings indidated that only maternal education associated statistically significantly with smoking cessation during pregnancy and therefore we estimated the interaction effect *MFAS* × Education [low, middle, high] on smoking cessation. We did not confirm that the association between maternal education and smoking cessation during pregnancy was modified depending on the level of maternal-fetal attachment. The effect of maternal education on smoking cessation during pregnancy did not display any difference in the way it was dependent on the level maternal-fetal attachment among the women with a high education or middle level of education compared to the women with a low education (aOR = 1.00–1.02, p = 0.545–0.943, multiplicity adjusted p = 1.00).

5.1.3.6 Association of pregnancy-related anxiety with smoking in pregnancy (Study IV)

Within the whole FinnBrain Birth Cohort sample, an association between second trimester pregnancy-related anxiety and smoking in pregnancy was investigated while controlling for maternal age, education, single parenthood, parity, and concurrent symptoms of depression and general anxiety. The results are presented in Figure 4. Our findings provided neither evidence for an association between the PRAQ-R2 total sum score in the second trimester and smoking in pregnancy (linear term: β = 0.01, *SE* = 0.04, aOR = 1.01, 95% CI = [0.92, 1.10], p = 0.866; quadratic term: β = 0, *SE* =0.001, aOR = 1.00, 95% CI [1.00, 1.00], p = 0.884) nor evidence supporting associations between the second trimester factor scores of the PRAQ-R2, i.e. *Fear of Giving Birth*, *Worries about Bearing a Physically or Mentally Handicapped Child*, and *Concerns about Own Appearance* and smoking in pregnancy (linear terms: aOR = 0.92–1.09, p = 0.232–0.950; quadratic terms: aOR = 1.00–1.01, p = 0.353–0.743).

5.1.3.7 Association of pregnancy-related anxiety at 24 gwks with smoking cessation during pregnancy (Study IV)

Within the subsample of participating pregnant women who smoked in the FinnBrain Birth Cohort Study, we investigated the association between second trimester pregnancy-related anxiety and cessation of smoking in early pregnancy (Figure 4). Adjusted for maternal age, education, single parenthood, parity, and concurrent symptoms of depression and general anxiety, our result did not establish evidence of an association between the PRAQ-R2 total sum score in the second trimester and cessation of smoking during pregnancy (linear term: β = 0.11, *SE* = 0.08, aOR = 1.11, 95% CI [0.94, 1.31], p = 0.204; quadratic term: β = -0.002, *SE* = 0.002, aOR = 1.00, 95% CI [1.00, 1.00], p = 0.145).

Next, we estimated the associations of the PRAQ-R2 factors with smoking cessation while pregnant. Our findings indicated that the PRAQ-R2 factor *Fear of Giving Birth* did associate with smoking cessation in early pregnancy (linear term: β = 0.39 , *SE* = 0.19, aOR = 1.47, 95% CI [1.02, 2.16], p = 0.038; quadratic term: β = -0.03, *SE* = 0.01, aOR = 0.97, 95% CI [0.95, 0.99] p = 0.012). The results are presented in Figure 4. The association between the dimesion of *Fear of Giving Birth* and cessation of smoking was found to be slightly curved and to indicate that the pregnant women who smoked and suffered from more severe fear of childbirth were less likely to quit smoking in early pregnancy than the pregnant women experincing little or some fear of childbirth (Figure 4, D). Our results did not provide evidence of associations between the other factors of the PRAQ-R2 at 24 gwks and cessation of smoking during pregnancy (linear terms: aOR = 0.97–1.24, p = 0.23–0.81; quadratic terms: aOR = 0.99–1.00, p = 0.28–0.93).

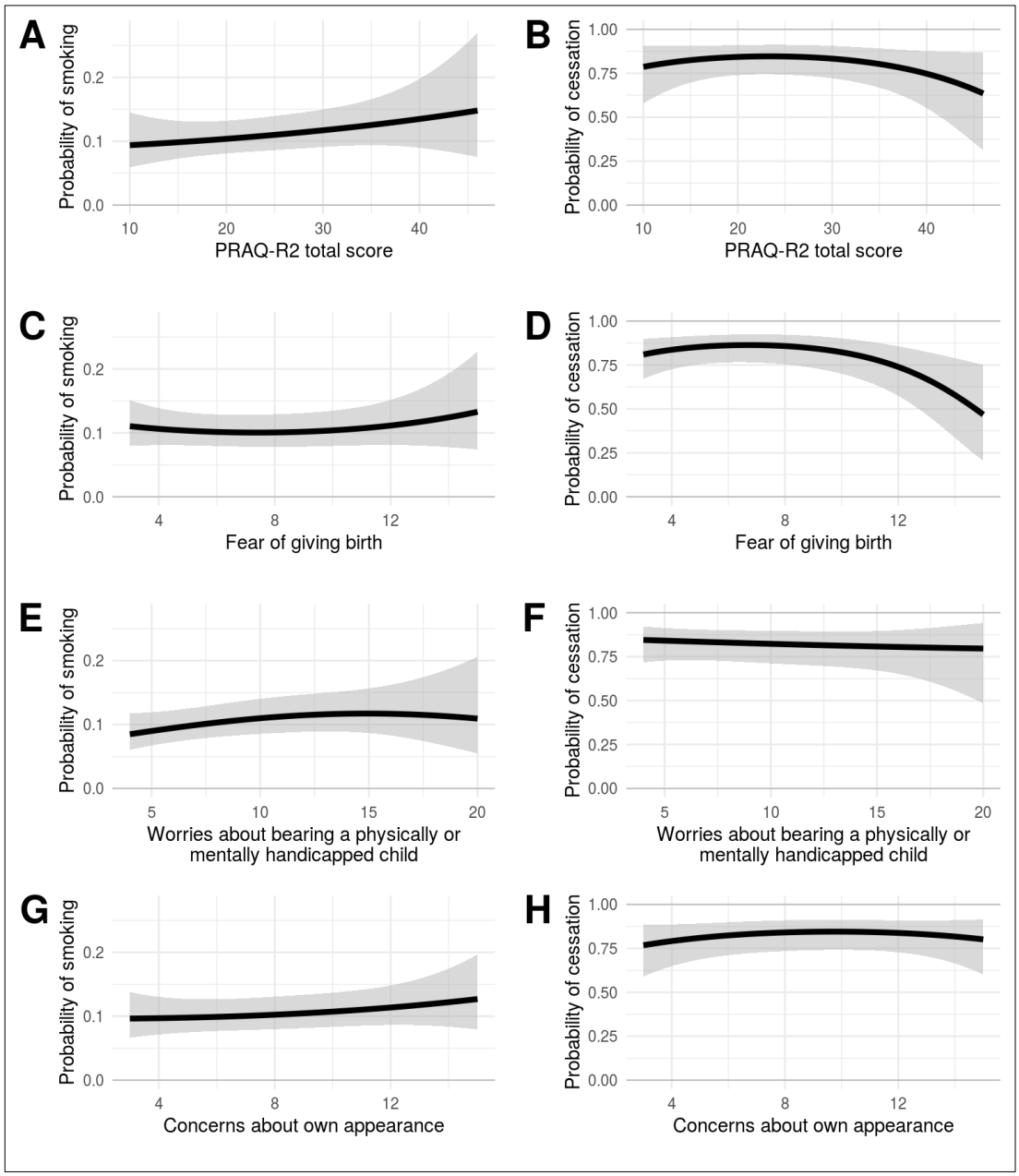

Figure 4. Probabilities for smoking/smoking cessation as a function of PRAQ-R2 total score / subscales scores, estimated by the analysis models. The covariates were set to their mean (continuos covariates) or most frequent values (categorical covariates) except education, which was set to "middle". The figure D presents the statistically significant association between the PRAQ-R2 factor *Fear of Giving Birth* and smoking cessation during pregnancy. The black line indicates the estimated probabilities of smoking / smoking cessation for different values of the PRAQ-R2 (total score or subscale scores) and the grey area consists of the 95% confidence intervals for these estimates.

6 Discussion

In the present dissertation research, we aimed at recognizing potential early focuses to intervene and break the intergenerational chain of adversity connected to prenatal tobacco and substance use disorders. We especially focused on exploring the potential protective momentum of prenatal parenting. Further, we examined the weight of burden due to prenatal psychological distress and its reflection on prenatal smoking behavior.

First, we tested with a randomized and controlled research design the efficacy of the novel parental mentalization focused 4D ultrasound intervention for treatment of pregnant women with recent or current harmful substance use. Contrary to the hypothesis, the efficacy of the intervention in terms of prenatal parental mentalization, maternal-fetal attachment, prenatal psychological distress, participation in obstetric care, perinatal child outcomes and fetal drug exposure was not substantiated with the methodology used. However, the study and intervention retention rates were found to be very good with this novel intervention approach. Particularly, the high attendance rate at the parenting focused interactive 4D ultrasound sessions was emphasized in the intervention group. Unexpectedly, our results indicated that the pregnant women in the intervention group displayed a weaker participation rate to standard obstetric care when compared with the compliance of the participants in the control group.

Second, we investigated the role of maternal-fetal attachment and pregnancy-related anxiety in determining maternal prenatal smoking behavior in the large population-based FinnBrain Birth Cohort Study sample. Our hypotheses were only partially supported. We did not establish a protective role for the total level of maternal-fetal attachment in the determination of prenatal smoking behavior. Nevertheless, the results addressed the fact that the pregnant women who smoked and who experienced stronger altruistic attachment towards the unborn child were more likely to quit smoking during pregnancy. In addition, the role of the total level of pregnancy-related anxiety in prenatal smoking behavior was not substantiated, but the pregnant women who smoked and experienced a more intense fear of childbirth in the second trimester were less likely to quit smoking during pregnancy than

pregnant women who smoked and experienced low or moderate level of fear of childbirth.

This dissertation research addressed the high-risk profile of pregnant women with substance use problems; it also pointed out the vulnerability of pregnant women who smoked, especially persistent smokers, in terms of the level of prenatal psychological distress, the proportion of women exceeding the EPDS cut-offs and socio-economic status. The newborns of pregnant women with substance use problems and of those women who continued smoking throughout pregnancy displayed the poorest neonatal outcomes among the newborns in both study samples. These observations call for early interventions of which efficacy, based on our experiences, is difficult to establish in the presence of several risks for maternal and fetal health. Breaking the intergenerational chain of adversity related to maternal tobacco and substance use disorders may require more intense and integrated care beyond single sector interventions (Brumana et al., 2017; Milligan et al., 2010; Niccols et al., 2012a; Niccols et al., 2012b; Shonkoff & Garner, 2012; Shonkoff, 2016; Smith et al., 2016).

However, integrated care is constituted of different elements. Despite our negative findings as regards the efficacy of the new parental mentalization focused 4D ultrasound intervention, efforts for the development and implementation of the prenatal parenting intervention for treatment of women with substance use problems and experiences gained from testing the intervention can be considered very valuable aspects in this research project and in achieving the aim to overcome prenatal and early life adversity (Shonkoff, 2016). To our knowledge, we conducted the first RCT evaluating the efficacy of parenting-focused intervention for pregnant women with substance use problems (Glover & Capron, 2017; Howard et al., 2014; Neger & Prinz, 2015; Terplan et al., 2015). Women with tobacco and substance use disorders can be considered to constitute a very challenging population from the perspective of scientific research as prenatal tobacco and substance use disorders, together with associative problems, often weaken expectant mothers' willingness and capacities to adhere to treatment and potentially to prenatal research (Barnett, Fealy, & Wilson, 2018; Dietz et al., 2010; Feijen-de Jong et al., 2012; Frazer et al., 2019; Kotelchuck et al., 2017; Roberts & Pies, 2011; Stone, 2015; Terplan et al., 2015). Thus, our findings suggesting very good study and intervention retention rates in the parental mentalization focused 4D intervention study are notable. Contrary to our expectations, the studies conducted in the large population-based pregnancy cohort did not substantiate the role of maternal-fetal attachment or pregnancy-related anxiety in determining of prenatal smoking behavior whereas the specific dimensions of these phenomena were found to be important. Our results replicated the previous finding suggesting the beneficial relationship between altruistic maternal-fetal attachment and smoking cessation in early pregnancy (Massey et al.,

2015) . Further, our results demonstrated, for the first time as we know, that fear of childbirth may constitute a specific barrier to smoking cessation. These findings have implications for further efforts to intervene in the intergenerational cycle of adversity by establishing new focuses for interventions to promote smoking cessation during pregnancy.

6.1 The efficacy of the novel mentalization focused 4D ultrasound intervention for pregnant women with recent or current harmful substance use

6.1.1 General findings from the testing of the intervention

The participants in the intervention study constituted a high-risk sample of pregnant women with severe substance use problems and cumulative burden of adversity related to socioeconomic and psychosocial situation and comorbid mental health problems. Over 80% of the pregnant women referred to specialized obstetric care due to harmful substance use reported recent or current use of illicit drugs, and nearly half of the participants had a history of intravenous drug use. The proportion of participants reporting primarily harmful alcohol use was unexpectedly low, around 20%. This percentage of substance use problems linked primarily to alcohol was lower than expected as the population-level prevalence rates of substance use disorders suggest that alcohol use disorders are considerably more common than drug use disorders in Finland. The prevalence of risky drinking has been reported to be relatively high, around 16%, in Finnish women of reproductive age (Koskinen, Lundqvist, & Ristiluoma, 2012). Further, the prevalence of alcohol use disorder has been demonstrated to be at least 2% among women in Finland (Koskinen et al., 2012; Raitasalo et al., 2014). The prevalence rates of illicit drug use have been found to be considerably lower, for problematic amphetamine use 0.7–1.1% and for opioid abuse 0.9–1.1%, in Finnish women between the ages of 25–34 years (Ollgren et al., 2014). In addition, one large population-based study has demonstrated that severe alcohol related problems leading to register records in health and social care registers are over twice as common as drug related problems among Finnish parenting women (Raitasalo et al., 2014). The TWEAK measure has been found appropriate in screening prenatal risky drinking (Burns et al., 2010). However, according to our findings, there is a concern that risky drinking and prenatal alcohol use disorders, even though relatively much more common than drug use disorders, may not be sufficiently identified in early pregnancy which constitutes the most critical time for fetal development and prenatal interventions.

The participants displayed several risk factors for perinatal mental disorders (Howard et al., 2014) and compromised pre- and postnatal parenting (Alhusen, 2008;

Earls et al., 2019; Suchman & DeCoste, 2018; Yarcheski et al., 2009). Almost 80% of the pregnant women had self-reported or clinically documented psychiatric comorbidity, and especially alarming was the high percentage (60%) of women reporting suicidal ideations or suicide attempts in the past. The socioeconomic status of the participants was low or even marginal, because more than half of them had completed only the compulsory basic education and belonged to the lowest income category. In addition, 41 % of the women had been involved in criminal activities. Living in a single parent household was common, as one third of the participants were living alone. Regarding two thirds of these pregnant women, the child´s father also suffered from substance use disorders, which may indicate a lack of social support for the expectant mother and, therefore, an increased risk of poor prenatal mental health, inadequate participation in prenatal care, compromised transition to the parenthood and difficulties in reducing substance use or maintaining abstinence (Alhusen, Gross, Hayat, Rose, & Sharps, 2012; Frazer et al., 2019; Howard et al., 2014; Roberts & Pies, 2011). Over 70% of the pregnancies were unintended, which has been demonstrated to increase the risk of prenatal depression (Fellenzer & Cibula, 2014), severe inter-parental conflicts including intimate partner violence (Yakubovich et al., 2018) and, most worryingly, child maltreatment (Guterman, 2015).

Considering the high-risk profile of the study population, the study retention of 89% within the whole sample and, especially the retention rate of 96% in the intervention group, can be considered very good, also in comparison with retention rates reported in previous studies conducted in samples of pregnant or parenting women with substance use disorders (Neger & Prinz, 2015; Terplan et al., 2015; Zedler et al., 2016). In studies investigating the efficacy of the psychosocial interventions, such as contingency management and a motivational interview based approach, for treatment of pregnant women with severe substance use disorders, intervention retention rates have varied between 28–100% (Terplan et al., 2015). Retention of participation in the parental mentalization focused 4D ultrasound intervention was found to be higher in comparison with treatment retention rates reported in the previous studies evaluating the efficacy of psychosocial interventions for treatment of pregnant or parenting women with drug use disorders, with the exception of one study with a sample size less than ten patients (Terplan et al., 2015). A recent systematic review has also reported a considerably high attrition rate of 22–33% in medication-assisted treatment programs for pregnant women with an opioid use disorder (Zedler et al., 2016) despite the fact that medication-assisted treatment is considered the most effective treatment modality for opioid addiction (Carroll & Weiss, 2017). In studies investigating the efficacy or effectiveness of parenting interventions for women with substance use disorders, treatment retention rates have been reported to vary from 16% to 100% and study retention rates from 33% to 93%

(Neger & Prinz, 2015). In the current study, one of the most important and clinically meaningful observation was that the study and treatment retention rates were found to be higher with this novel parenting focused ultrasound intervention than treatment retention rates reported in the most of the previous studies on interventions addressing parenting in the context of substance use disorders (Neger & Prinz, 2015).

Only 4% of the pregnant women in the intervention group dropped out during pregnancy. The drop-out rate was significantly higher in the control group in which 18% of the participants decided to discontinue their participation in the study. It is of note that the participants in the control group who withdrew their consent, did so immediately after randomization when they received the information on allocation to the control condition. It is of importance that, as the relatively high study and intervention retention rates suggest, the intervention was well-accepted by this high risk sample. The participants in the intervention group were offered the mentalization based parenting focused 4D interactive ultrasounds and psychosocial support for their prenatal parenting (Pajulo et al., 2016). The high study and intervention retention rates suggest that the intervention has potential to engage these high-risk mothers in treatment and possibly overcome barriers which these high-risk women often perceive in prenatal care (Roberts & Pies, 2011).

The high adherence to the study was especially observed in the intervention group and regarding the 4D ultrasound sessions. The interactive and concrete visualization of the fetus and paying special attention to the emerging parental-fetal relationship may have been particularly important, rewarding and supportive for these high-risk pregnant women, therefore possibly building an experience of meaningful encounters with health care professionals. Research to date suggest that ultrasound imaging strengthens the expectant mother's enthusiasm, positive emotions and attachment towards the unborn child (de Jong-Pleij et al., 2013) and constitutes the most promising intervention method to enhance parental-fetal relationship (Borg Cunen et al., 2017). Unfortunately, participants' attendance at the diary meetings was weaker. Verbal reflection on the experiences aroused by the parental mentalization focused pregnancy diary may have been difficult for these women who tend to have deficits in verbal learning and memory (Squeglia & Gray, 2016), insight (Goldstein et al., 2009) and reflective functioning related to parenthood and their own mental states (Camoirano, 2017; Pajulo et al., 2012; Suchman et al., 2010b). It is of note, however, that the participants were encouraged to implement the parental mentalization focused pregnancy diary in their daily life with the core idea that it would independently strengthen the expectant mothers' parental mentalization. Unfortunately, feedback on the individual usage of the diary was not collected. It is possible that the pregnancy diary has also contributed to the study retention by awakening the expectant mother's interest in the unborn child and her own well-being. We speculate that the attendance rate at the diary meetings could

perhaps be improved by scheduling the diary visits more closely with the ultrasound sessions. The participants' low attendance rate at the pregnancy diary meetings may, however, have negatively affected the potential efficacy of the intervention.

6.1.2 The efficacy of the intervention on prenatal psychological distress and parenting (Study I)

Contrary to our hypothesis, we did not establish evidence of the efficacy of the intervention on prenatal parenting and psychological distress with the current sample and research methods. This negative result may be attributed to the small sample size of our study, the assessment of outcomes only with the patient reported outcome measures, or a true lack of effect on prenatal parenting and/or psychological distress. Unfortunately, some of our results were inconclusive (the BF_{01} values within the range of 0.33–3) and, therefore further research should be undertaken to evaluate the efficacy of the intervention with a larger sample. This is of great importance as the intervention may have a true beneficial effect on prenatal parenting and psychological distress, but our sample size may have been too small to ensure sufficient statistical power to detect small or moderate effects.

As far as we know, the efficacy of psychosocial interventions focusing on prenatal parenting or psychological distress have not previously been investigated using a randomized and controlled research design in the context of maternal prenatal substance use disorders (Glover & Capron, 2017; Howard et al., 2014; Neger & Prinz, 2015; Terplan et al., 2015). Contrary to the hypothesis, our results did not provide evidence for the core hypothesized mechanism of action of the intervention, that is to say, the positive change in prenatal parenting in terms of parental mentalization and maternal-fetal attachment. This finding was unexpected. One possible explanation for the lack of effect is that we may not have been able to capture the essence of prenatal parenting with the patient-reported outcome measures. Even though prenatal parenting is considered protective especially in the presence of high risks (Glover & Capron, 2017), the conceptualization and assessment of maternal-fetal attachment is still being debated, despite decades of research (McNamara, Townsend, & Herbert, 2019). We assessed maternal-fetal attachment with a one single self-report measure which captures primarily behavioral aspects of prenatal maternal-fetal relationship (Brandon et al., 2009; Cranley, 1981). In addition, the patient-reported outcome measure for the evaluation of prenatal parental mentalization has recently been developed, and so far it has been construct-validated and tested only in a general population of pregnant women considered to be at low risk (Pajulo et al., 2015). During the data collection of the intervention study, the P-PRFQ questionnaire measure was in the process of development. In order to gain experiences from this new measure and evaluate

prenatal parental mentalization in a feasible way in this high-risk sample and clinical real-world setting, the P-PRFQ was implemented in the research protocol. Due to the development process on this new measure, only about half of the participants responded to the construct-validated 14-item version of P-PRFQ post-intervention. In addition, our reliability analyses referred to the fact that the P-PRFQ and the three subscales of the MFAS measure demonstrated a low degree of internal consistency in this sample of pregnant women with recent or current harmful substance use (Cronbach's $\alpha < 0.60$). However, previous literature suggests that when measuring psychological constructs also Cronbach's α values below 0.70 can realistically be expected due to the diversity of constructs measured (Field, 2013).

The assessment of outcomes with the patient-reported outcome measures may also be particularly challenging within this group of pregnant women for other reasons. In general, the parental mentalization capacity (Håkansson et al., 2018; Pajulo al., 2008; Pajulo et al., 2012; Suchman et al., 2017; Suchman et al., 2010b) as well as insight (Goldstein et al., 2009) have been shown to be weak among persons suffering from substance use disorders, which may be manifested in difficulties to recognize and self-report experiences related to prenatal parenting and mental health. In clinical practice as well as in previous research, the assessment of parental mentalization has previously been based predominantly on interview methods in which the quantity and quality of parents' verbal expressions and narration regarding her/his own experiences on mental states and the child's mental states are evaluated (Camoirano, 2017; Shai & Belsky, 2017; Slade, 2005; Zeegers et al., 2017). However, recent research suggests that, to some extent, parental mentalization may also take place beyond verbal narrative and language skills (Shai & Belsky, 2017; Zeegers et al., 2017). Parental embodied mentalization refers to the parental capacity to reflect the child's mental states from his or her nonverbal behavior, such as bodily based kinesthetic expressions (Shai & Belsky, 2017). The expectant mothers' emerging capacities for implicit and embodied parental reflective functioning may not be captured with self-report measures and in the prenatal period. Therefore, capturing the multidimensional and nuanced process implicated to awakening of reflective parenting and a maternal-fetal relationship during pregnancy, also at the level beyond words, can be considered challenging. We may not have been able to detect all possible beneficial effects of the intervention with the patient-reported outcome measures.

In diverse populations, maternal-fetal attachment has typically been found to strengthen over the course of pregnancy (Cannella, 2005; Tichelman et al., 2019; Yarcheski et al., 2009). This spontaneous deepening of the maternal-fetal relationship was not observed among the pregnant women participating in the intervention study. With respect to our findings on prenatal parenting, previous observations regarding the level of maternal-fetal attachment among disadvantaged

pregnant women have varied (Alhusen et al., 2012; Magee et al., 2014; Massey et al., 2015). The participants in the current study self-reported a higher level maternal-fetal attachment than the pregnant women in one previous study evaluating prenatal attachment with the MFAS measure in a sample of women with drug use disorders (Shieh & Kravitz, 2006). Unexpectedly, the high-risk pregnant women in the intervention study self-reported a higher level of prenatal parental mentalization than pregnant women participating in the population-based FinnBrain Birth Cohort Study conducted in the same geographical area (Pajulo et al., 2015). This observation is not in accordance with previous studies which have assessed parental mentalization with interview methods and suggested that women with substance use disorders are at an especially high risk for displaying weak parental mentalization (Håkansson et al., 2018a; Håkansson et al., 2018b; Pajulo et al., 2008; Pajulo et al., 2012; Suchman et al., 2017; Suchman et al., 2010b). The participants in the intervention study assessed their prenatal parenting rather positively considering the high-risk profile of the sample. Their way of responding may also indicate unbalanced and idealized prenatal representations, which have been observed in high-risk parents and among pregnant women with substance abuse in particular (Flykt et al., 2012; Isosävi et al., 2016). Previous studies have been inconclusive regarding the effect of these unbalanced representations on the early mother-infant interaction among women with substance use problems (Flykt et al., 2012; Isosävi et al., 2016). It is important to note, however, that one Finnish study has recognized this idealizing tendency in prenatal representations as a specific risk factor for the early mother-infant interaction (Flykt et al., 2012).

In addition, the participants also reported a relatively low level of prenatal psychological distress considering their cumulative burden of risks for prenatal mental disorders (Biaggi et al., 2015; Fellenzer & Cibula, 2014; Lancaster et al., 2010). The proportion of women reporting a high level of prenatal depressive symptoms (EPDS $\geq$ 13) was found to be lower at both time points than the prevalence rates of prenatal depression reported in previous studies with samples of women with substance use problems (Holbrook & Kaltenbach, 2012; Ordean et al., 2013). This may partially be related to a high access to prenatal care which has been demonstrated to improve maternal health in disadvantaged populations including pregnant women with substance use disorders (Aizer & Currie, 2014; Kotelchuck et al., 2017). Further, the participation in the randomized and controlled trial may have had a positive effect on the outcomes per se (Nijjar et al., 2017). The participants in the intervention study reported a higher level of prenatal psychological distress than the non-smoking women in the the FinnBrain Cohort Study sample. However, the high-risk women with substance use problems displayed only a moderately higher level of prenatal psychological distress than the pregnant women who smoked and participated in the FinnBrain Birth Cohort. The difference in the level of prenatal

psychological distress between the persistent smokers in the birth cohort and the high-risk pregnant women in the intervention study was found to be small (see Table 7).

The pregnant women in the intervention study displayed relatively positive representations regarding prenatal parenting and a surprisingly low level of prenatal psychological distress, which may partly be attributed to a social desirability bias. In the intervention study, the participants were requested to evaluate their prenatal mental health and parenting capacity in the public health care setting including the obligatory involvement of the Child Welfare Services. The hospital social worker collected the study questionnaires in the closed envelopes to maintain the confidentiality of the responses. However, according to the Child Welfare Act in Finland, professionals working in the health care system are obliged to submit an anticipatory child welfare notification and thus collaborate with the Child Welfare authorities before the birth of a child in the cases where there are reasons to assume that the child will need support from the Child Welfare services immediately after birth. These legal acts apply to identified prenatal substance abuse. The participants have been aware of the involvement of Child Welfare authorities which, combined with possible fears of losing the custody of child, may have influenced their way of responding and lead to a proneness to give an excessively positive picture of their prenatal mental health and parenting (Roberts & Pies, 2011; Terplan et al., 2015). However, the balance between costs and benefits of self-reporting is complex. In the intervention study, the patient-reported outcome measures were used for feasibility reasons. The study was carried out in the real-world clinical setting of prenatal obstetric care with limited resources to conduct extensive structural interviews for the evaluation of prenatal mentalizing and maternal mental health. Second, we did not want to constitute a barrier to prenatal care with an extensive and demanding research protocol. The pregnant women with substance use disorders often receive inadequate prenatal care (Kotelchuck et al., 2017) and perceive several barriers to seeking and maintaining treatment which may also be related to practices in health care system and encounters with health care professionals (Roberts & Pies, 2011).

This study was unable to demonstrate evidence of the efficacy of the parental mentalization focused 4D ultrasound intervention, which may also be attributed to an insufficient beneficial impact of the intervention on prenatal parenting and psychological distress within this very high-risk sample. Our results reflect those of Terplan et al. (2015) who conducted a systematic review and evaluated the efficacy of psychosocial interventions for treatment of pregnant women with drug use disorders. This systematic review did not establish evidence of the efficacy of studied specific psychosocial interventions, such as contingency management and motivational interviewing, on prenatal treatment retention, maternal substance use, fetal drug exposure and perinatal child outcomes over comprehensive treatment-as-

usual (Terplan et al., 2015). Further, another recent systematic review evaluated the efficacy of psychosocial interventions, such as cognitive behavioral therapy, mindfulness, psychoeducation, stress management, heart rate variability biofeedback combined with breathing exercises and peer-mentoring, in alleviating prenatal psychological distress in populations at risk of developing prenatal stress or already experiencing elevated levels of distress; however, the review concluded that the effects were largely inconsistent (Matvienko-Sikar et al., 2020). Therefore, research establishing optimal mechanisms and means to alleviate prenatal depressive and anxiety symptoms is scarce. Within this very high-risk group of pregnant women, the insufficient of efficacy of the intervention may be explained by the accumulation of adversity and multiple treatment needs of pregnant women with substance use disorders, and thus calls for more integrated care and intense support for prenatal parenting (Milligan et al., 2019; Niccols et al., 2012; Pajulo et al., 2016; Smith et al., 2016).

6.1.3 The efficacy of the intervention on the pregnant women's participation in obstetric care, perinatal outcomes and fetal drug exposure (Study II)

Contrary to the hypothesis, the intervention study did not provide evidence to substantiate the beneficial effects of the intervention on fetal drug exposure and perinatal outcomes or the pregnant women's participation in obstetric care as regards the number of obstetric care visits, emergency consultations at the obstetric outpatient clinic, emergency department visits, hospital admissions and days in prenatal obstetric hospital care.

An unexpected between-groups difference was observed in the number of participants withdrawing from visits at the obstetric clinic. Adherence to standard obstetric care was poorer among the participants in the intervention group, even though their study and intervention retention rates were found to be good. This finding should be considered carefully when implementing the intervention in clinical practice. On the one hand, this finding indicates that the pregnant women in the intervention group inadequately attended prenatal care, but on the other hand, had a good attendance rate especially at the intervention ultrasound sessions; this may have been due to the women preferring the intervention sessions to the standard obstetric care visits. The pregnant women seem to have perceived the new intervention method attractive and acceptable taking into account the very good study retention and the high rate of attendance at the parenting focused interactive 4D ultrasound sessions. It is of note that the attrition was higher in the control group. We speculate that even the most disadvantaged pregnant women may have been retained in the intervention group. Even though the baseline sample characteristics

did not reveal any between-groups differences, the accumulation of more severe cases in the intervention group could explain why greater difficulties to participate in standard obstetric care were observed among the intervention group. Moreover, despite of the successfully completed randomization procedure, we may not have been able to control all potential confounding factors related to the individually tailored content and intensity of treatment-us-usual (Kazdin, 2015) which may have influenced the expectant mothers' participation in routine care visits at the obstetric clinic. The finding may also be explained by the difference in how the pregnant women with substance use disorders were handled at the intervention sessions compared with standard obstetric care visits, which may have influenced the pregnant women's choices in favor of the intervention. The parental mentalization focused interactive 4D ultrasound intervention aimed at engaging these women to reflect their thoughts, beliefs and experiences regarding the awakening of prenatal parenting and the relationship with the unborn child, and the perspective of the unborn child in an interactive and dialogic manner in which the fetus was also concretely visualized. This novel approach when encountering these high-risk pregnant women may have differed from their encounters in the context of treatment-as-usual. Ultrasound imaging in general and parental mentalization focused interventions in treatment of women with addictions have been shown to induce mothers' positive representations of caregiving and positive emotions, such as joy, delight and an preoccupation with the unborn child/infant (de Jong-Pleij et al., 2013; Suchman & DeCoste, 2018). Existing research recognizes the importance of facing pregnant women with substance use disorders in a way which supports their self-efficacy and self-worth to promote their engagement with prenatal care (Davis & Yonkers, 2012; Patrick & Schiff, 2017; Terplan et al., 2015). However, the participants in the intervention group may have missed important prenatal visits during which the follow-up of maternal and fetal health, such as clinical examinations and laboratory tests, was conducted.

In the sample of pregnant women with substance use problems, the cumulative burden of psychosocial and health-related risks was reflected in the perinatal child outcomes that showed a high rate of prematurity (13%), a low birth weight (11%) and perinatal mortality due to one neonatal death caused by birth asphyxia. The neonatal outcomes were poorer than those observed the FinnBrain Birth Cohort sample (see Table 7). The national statistics derived from the Finnish Medical Birth Register show that, on average, around 5.9% of newborns are born preterm, 4.4% have a low birth weight and perinatal mortality is around four per thousand in Finland (Vuori & Gissler, 2016). Our findings accord with earlier observations which have established that birth outcomes of children born to women with substance use disorders are often severely impaired (Behnke et al., 2013; Forray & Foster, 2015; Kotelchuck et al., 2017; Ludlow et al., 2004). In the intervention study,

between-groups differences in the perinatal child outcomes were not substantiated. Previous studies evaluating the efficacy of prenatal psychosocial intervention for treatment of pregnant women with substance use have also failed to demonstrate the efficacy of psychosocial interventions, such as motivational interviewing and contingency management, on neonatal outcomes in comparison with comprehensive treatment-as-usual (Terplan et al., 2015). However, one very large population-based study has established that prenatal treatment for substance use disorders associates with improved neonatal outcomes (Kotelchuck et al., 2017). Overall, the previous literature indicates that probably very large samples are required to establish the effects of psychosocial treatment on perinatal child outcomes. In addition, the effectiveness of treatment-as-usual has often been found to be as good as specific interventions (Kazdin, 2015), and in this case treatment-as-usual consisted of a variety of public health services, such comprehensive maternity care and treatment for substance use disorders. However, our findings addressing poor pregnancy outcomes among women with substance use problems have significant implications for clinical practice and intervention research as disparities in health at the moment of birth constitute a significant source of health and wealth related inequality (Aizer & Currie, 2014; Bilgin et al., 2018).

Contrary to the hypothesis, we did not find evidence of the statistically significant difference between the groups in fetal drug exposure. Cochrane's systematic review (2015) has revealed that previous studies evaluating the efficacy of prenatal psychosocial interventions for treatment of women with illicit drug use have also failed to establish the efficacy of psychosocial interventions on maternal prenatal substance use outcomes over comprehensive control treatment (Terplan et al., 2015). Studies assessing the efficacy or effectiveness of brief interventions and integrated programs for treatment of pregnant women with substance use disorders have shown some promise in reducing fetal substance exposure (Farr, Hutchings, Ondersma, & Creanga, 2014; Haug et al., 2014; McLafferty et al., 2016). In the current study, the number of positive meconium screening results was found to be relatively small when considering the severity of substance use problems in the study population. Only 7% of the neonates were screened positive for drugs. In a similar sample of pregnant women with substance use disorders (n = 524) collected in the Helsinki metropolitan area between 1992–2001, 29% of the children were exposed to alcohol, 10% to illegal drugs, 10% to both alcohol and illegal drugs, and 51% had an unspecified fetal substance exposure, for example exposure to multiple substances (Koponen et al., 2019). However, in the study information regarding fetal substance exposure was based on clinical observations, the expectant mothers' self-reporting and urine toxicology (Koponen et al., 2019). Meconium drug screening is considered to be the gold standard for detecting fetal drug exposure (Wabuyele et al., 2018). However, meconium toxicology does not detect fetal drug exposure which has taken

place in early pregnancy (Wabuyele et al., 2018) or fetal alcohol exposure (McQuire et al., 2016). Further, it should be noted that it is impossible to differentiate fetal exposure to opioids due to prenatal medication assisted treatment for opioid use disorder (buprenorphine assisted withdrawal / opioid maintenance treatment with buprenorphine) from fetal opioid exposure due to prenatal abuse of buprenorphine products. In the current study, the former was not considered as fetal exposure to illicit drugs. The intervention may have favorably affected the risk of opioid abuse among the women attending opioid-assisted treatment program, but meconium drug screening is not able to capture this possible beneficial effect of the intervention.

Our negative findings may be related to the small sample size that was only able to detect medium to large treatment effects. In addition, the higher attrition in the control group and possible retention of more disadvantaged pregnant women in the intervention group (attrition bias) may have compromised the detection of the intervention efficacy. In addition, all the pregnant women participating in the intervention study were treated in a specialized obstetric outpatient unit, and most of them were also engaged in other treatment modalities. Presumably all the prenatal services have contributed to the outcomes and, thus the potential benefits of the intervention might have been difficult to differentiate in this diverse real-world setting (Kazdin, 2015). The negative findings may also simply result from the intervention not being effective enough within this very high-risk population. Our results suggest that one single intervention may not be sufficiently efficient to improve maternal and fetal outcomes in the context of severe prenatal substance use disorders, and more intense and integrated care for these high-risk pregnant women may be required to break the intergenerational chain of adversity (Britto et al., 2017; Brumana et al., 2017; Milligan et al., 2010; Niccols et al., 2012a; Niccols et al., 2012b; Shonkoff & Garner, 2012; Shonkoff, 2016). However, integrated care of pregnant women with substance use disorders involves several simultaneous focuses of treatment and parenting is considered an especially important modifiable factor to promote resilience of children facing prenatal/early life adversity (Bada et al., 2012; Glover & Capron, 2017; Shonkoff, 2016; Smith et al., 2016; Stein et al., 2014; Traub & Boynton Jarrett, 2017). The develoment and implementation of the essential elements of integrated care can be considered very important. At this stage, the parental mentalization focused 4D ultrasound intervention approach shows promise especially as a means to encounter high-risk pregnant women with substance use problems.

6.1.4 Strengths and limitations

Our study was a pioneer work in many respects and has several strengths. To our knowledge, we conducted the first clinical randomized and controlled parenting

focused intervention trial for treatment for pregnant women with substance use disorders. In the hierarchy of traditional evidence-based medicine (EBM), randomized and controlled trials represent the highest ranked evidence which is considered to be more trustworthy than evidence provided by uncontrolled observations, experiments, or clinical experience (Djulbegovic & Guyatt, 2017). The efficacy of the intervention was tested in a real-world clinical practice within a public health care setting, which gave a realistic perspective on development and implementation of the new intervention method for treatment of pregnant women with substance use disorders. In addition, intervening by focusing on prenatal parental mentalization and maternal-fetal attachment with ultrasound imaging and the reflective pregnancy diary presents a novel approach to breaking the intergenerational chain of adverse outcomes related to maternal prenatal substance use disorders. The new questionnaire measure was tested in the assessment of prenatal parental mentalization which can be considered important, as efforts to develop feasible measures for the parenting assessment process in large clinical populations are greatly needed. In addition, this clinical trial promoted a genuine collaboration especially as regards expertise from obstetrics and perinatal infant mental health work.

Several limitations should also be noted. In the context of the intervention study, clinical diagnostic interviews were not conducted. Therefore, we were not able to confirm that the participants met the diagnostic criteria for substance use disorders. However, all of the participants were screened as having recent or current substance use problems at a level that suggested risky drinking / alcohol abuse, abuse of illicit drugs, or substance addiction. In addition, the clinical characteristics of the sample refer to substance use problems meeting the diagnostic criteria of the DSM-5 / ICD-10 substance use disorders. The characteristics found were: a high percentage of women with a history of intravenous drug use (47%), current hepatitis C infection (27%), prenatal smoking (91%) and self-reported or documented substance use during the index pregnancy (56% before the positive pregnancy test and 33% after the positive pregnancy test). Further, 18% of the participants were in opioid maintenance treatment which, according to law in Finland, can be administered only for patients meeting the diagnostic criteria of opioid addiction.

The small sample size is the most severe limitation of the current study. The intervention may have had true beneficial effects on the outcomes, but the sample size is likely to have been too small to detect small or even moderate treatment effects. In addition, the drop-out rate was higher in the control group which may have had an influence on the balance of confounding factors among the study groups. It is likely that the participants in the control group may have withdrawn their consent because they were not allocated to receive the novel parental mentalization focused 4D ultrasound intervention. Nonetheless, the between-groups difference in

attrition constitutes a potential source of bias and therefore may diminish the experimental validity of the study. It is important to note that the present cornerstone of evidence-based medicine, the GRADE classification (The Grades of Recommendation, Assessment, Development and Evaluation), suggests that downgrading the quality and certainty of evidence from a randomized trial may be necessary when considering the risk of bias (Djulbegovic & Guyatt, 2017).

The use of only patient-reported outcome measures in the assessment of prenatal parenting and psychological distress within this high-risk sample and in the context of Child Welfare follow-up is a significant limitation in the intervention study. In addition, we may not have been able to capture the whole picture regarding the participants' utilization of prenatal care. Maternity clinics in primary health care are mainly responsible for prenatal care in Finland, and the participants in the intervention study have also been followed up in these maternity clinics. We were not able to obtain the data regarding the expectant mothers' participation in prenatal care at these local maternity clinics. In the current study, we only had access to medical records stored in the patient data repository in Turku University Hospital where the study was conducted.

This clinical intervention trial was implemented in routine care at the special obstetric outpatient clinic. The participants in both study groups received comprehensive treatment-as-usual which also constituted the control condition. In addition to specialized obstetric care, the treatment-as-usual aimed at offering psychosocial support for pregnant women with substance use problems with a multidisciplinary treatment approach. Further, the majority of the participants were also involved in other treatment modalities integrating addiction and mental health treatment and psychosocial support for the expectant mothers' transition to parenthood. In this real-world clinical practice, the content of the control condition has been individually tailored and diverse. Despite randomized and controlled research design, we may not have been able eliminate the influence of all possible confounding factors, for example those related to the content of standard care at the individual level (Kazdin, 2015). In addition, the intervention includes several components, i.e. the parental mentalization focused interactive 4D ultrasounds, the reflective pregnancy diary, and the session with an infant mental health specialist to work around the reflective pregnancy diary. The impact of these components was not investigated separately, which can be considered as a limitation.

6.1.5 Clinical implications and future directions

Previous research has established that prenatal parenting should be supported in populations at risk for adverse maternal and fetal/child outcomes (Glover & Capron, 2017; Stein et al., 2014). The support for prenatal parenting can be considered

especially important in the context of substance use disorders which robustly associate with an increased risk for prenatal/early life adversity, that is to say, detrimental prenatal environment, compromised postnatal nurturing care and adverse childhood experiences (Behnke et al., 2013; Neger & Prinz, 2015; Romanowicz et al., 2019; Suchman & DeCoste, 2018). The parental mentalization focused interactive 4D ultrasound intervention aims at enhancing parental mentalization and maternal-fetal attachment, which both have been found to constitute the precursors of positive parent-child interactions and secure child attachment (Dubber et al., 2015; Foley, 2018; Zeegers et al., 2017) – the most important protective environmental factors for child development in families affected by alcohol and drug disorders (Wlodarczyk et al., 2017). Strengthening positive emotions and reward that can be gained from the transition to parenthood and an awakening of a prenatal caregiving relationship with the fetus can be considered especially important among pregnant women with substance use disorders because their neural connections and networks, which are essential in reward related to caregiving and regulation of distress, have been found to be dysregulated in substance addictions (Rutherford & Mayes, 2017).

The most important clinical implications of this intervention study are related to the development and implementation of the novel way to encounter the high-risk pregnant women with substance use disorders. This novel intervention method which invites the pregnant woman with substance use disorders to the process of mentalizing the unborn child with the assistance of concrete and interactive 4D ultrasound visualization of the fetus, seemed to have engendered an experience of meaningful encounters for these high-risk pregnant women. We conclude, from all evidence provided by the very good study and intervention retention rates in the current study, that this novel way of encountering the pregnant women with substance use problems seems to be feasible in this high-risk group of pregnant women and might be beneficial if it could be integrated into routine obstetric care.

In the future, the very important next step would be to evaluate the efficacy of the intervention with a larger sample size and also with more objective methods, such as structured interviews for the assessment of maternal mental health and parental mentalization. Further, there is a special call for more intense mentalization-focused work and supervision with the assistance of videotaped 4D ultrasound sessions to achieve a strengthening of prenatal parenting (Pajulo et al., 2016). Qualitative research on the experiences of pregnant women with substance use disorders regarding this novel intervention approach would be valuable to understand the underlying reasons for the good study and intervention retention rates observed in the current study. In addition, during the last decade world has changed enormously as regards the development and culture around mobile phones, applications and digital media. The paper-and-pen version of the reflective

pregnancy diary has already been revised into the whole family version which is available through an electronic link for all maternity clinics and expectant parents nationwide. It could, however, be further developed in a digital interactive platform, such as a mobile phone application. In the future, it will also be extremely important to assess whether and how the parental mentalization focused 4D ultrasound intervention affects early mother-infant relationship and the quality of postnatal parenting (Pajulo et al., 2016). An extension of the indications for fetal ultrasound to support maternal-fetal attachment requires a constant scientific evaluation of the benefits, safety and costs as well as a process which involves scientific and ethical considerations and aims at a consensus on the use of fetal ultrasound in supporting maternal-fetal relationship (Abramowicz, 2013; Denbow, 2019; Van den Hof, 2018).

6.2 The role of maternal-fetal attachment and pregnancy-related anxiety in prenatal smoking behavior in The FinnBrain Birth Cohort Study

6.2.1 General findings from The FinnBrain Birth Cohort Study regarding prenatal smoking, parenting and psychological distress

Studies III and IV of this dissertation research project were designed to determine the role of maternal-fetal attachment and pregnancy-related anxiety in the expectant mothers' prenatal smoking behavior in order to recognize potential modifiable factors to promote abstinence from tobacco smoking and to increase a smoking cessation rate during pregnancy. The studies were conducted in the large FinnBrain Birth Cohort sample which has shown to represent well the general population in the geographical area (Karlsson et al., 2018). Nevertheless, the pregnant women's survey self-reports addressed a somewhat lower of prenatal smoking than observed in the general population of pregnant women living in the hospital district of Southwest Finland (12.7% vs. 16.6%, respectively) (Karlsson et al., 2018). Due to this observation, we combined the survey responses on maternal prenatal smoking behavior with the clinically derived register records regarding prenatal smoking behavior obtained from the Finnish Medical Birth Register. With this approach, the estimated of smoking in pregnancy was found to be approximately the same as the prevalence of prenatal smoking in the general population of pregnant women in the hospital district area (Karlsson et al., 2018) and the prevalence estimates of prenatal smoking presented in the official perinatal statistics in Finland (Vuori & Gissler, 2016). Our findings revealed that the prevalence of smoking in pregnancy was 16.5% and, therefore, still considerably higher than in the other Nordic countries (Ekblad et al., 2014) and in many regions of Europe where, on average, 6% of the pregnant

women smoke (Lange et al., 2018). Further, our findings demonstrated that 58% of the smokers quit smoking in early pregnancy and, therefore, the smoking cessation rate was somewhat higher than the smoking cessation rate of 39–49% reported in the national perinatal statistics in Finland during the data collection of the FinnBrain Birth Cohort Study (Vuori & Gissler, 2016). The smoking cessation rate was found to be a slightly higher than the smoking cessation rate of less than 50% reported in the previous population based studies among pregnant women who smoke (Lange et al., 2018). Nulliparous pregnant women, who are more likely to quit smoking in pregnancy than multiparous pregnant women (Riaz et al., 2018), have been found to be slightly overrepresented in the FinnBrain Birth Cohort sample (Karlsson et al., 2018). The slightly larger proportion of nulliparous women among the study sample, the participants' relatively high educational attainments and attendance in prenatal care may have contributed to the better smoking cessation rate than observed in previous studies (Riaz et al., 2018).

Our descriptive sample characteristics revealed that the expectant mothers' smoking behavior, that is to say the non-smoking status, smoking cessation in early pregnancy and persistent smoking during pregnancy, differentiated the level of maternal-fetal attachment. Interestingly, the highest total scores for maternal-fetal attachment were observed among the pregnant women who smoked but were able to quit smoking in early pregnancy. These results reflect those of Slade et al. (2006) who also found that pregnant women who smoke and consider smoking cessation experience stronger attachment towards the fetus than non-smoking pregnant women (Slade et al., 2006). Slade et al. (2006) explained this finding by cognitive dissonance due to an awareness of the harmful effects of smoking on the fetus and the simultaneous awakening of maternal-fetal attachment, and a tendency to solve this contradicting situation by contemplation of smoking cessation; the process which was presumed to affirm maternal-fetal attachment (Slade et al., 2006). Interestingly, one previous study has observed that women who smoke and quit smoking during pregnancy display better quality of mother–infant interaction in comparison with non-smoking pregnant women (Massey et al., 2018). Further, the outcomes of children whose mothers quit smoking during pregnancy are more favorable to the outcomes of children whose mothers have never smoked (Hutchinson, Pickett, Green, & Wakschlag, 2010; Pickett, Wood, Adamson, DeSouza, & Wakschlag, 2008).

Our findings did not establish evidence of a group difference in the total level of maternal-fetal attachment between the non-smokers and smokers, but the women who smoked scored higher in some of the subscales of the MFAS questionnaire. However, it is important to note that our descriptive sample characteristics demonstrated that of the women who smoked those who quit smoking in early pregnancy reported stronger altruistic maternal-fetal attachment, i.e. a higher score

in the *Giving of self* subscale of the MFAS. One prior study by Massey et al. (2015) has shown that the stronger level of this particular dimension of maternal-fetal attachment predicts smoking cessation during pregnancy (Massey et al., 2015).

Further, we investigated the level of maternal-fetal attachment by the level of maternal education (low, middle, high). It was somewhat surprising that the pregnant women with low education self-reported the highest level of maternal-fetal attachment. The reason for this finding is not clear but may be connnected with the way the women at different educational levels are preoccupied with and perceive their transition to the parenthood, or respond to the questionnaire measures regarding maternal-fetal attachment. It should be noted, however, that an overly positive tendency in prenatal representations regarding parenting can sometimes indicate a risk for early mother-infant interaction (Flykt et al., 2012). Prior research has reported conflicting findings regarding the relation of maternal-fetal attachment and the different levels of maternal education (Tichelman et al., 2019; Yarcheski et al., 2009).

The current study found that the pregnant women who smoked suffered more from prenatal psychological distress in all its dimensions in comparison with the non-smoking pregnant women in the second trimester. The pregnant women who smoked also self-reported a higher level of prenatal depressive and anxiety symptoms in the third trimester. Further, the sample descriptions revealed that the pregnant women who smoked and continued smoking suffered significantly more from anxiety and depressive symptoms in the second and third trimester in comparison with the pregnant women who smoked and quit smoking in early pregnancy whereas a difference between these groups was not observed in second trimester pregnancy-related anxiety. The proportion of women exceeding an EPDS cut-off of ≥ 10 was the highest among the persistent smokers: 24% in the second trimester and 30% in the third trimester. These findings support the work of other studies in this area addressing the adverse relationship between prenatal smoking and psychological distress, and the comorbidity of prenatal tobacco use and mental disorders in perinatal period (Alhusen et al., 2016; Riaz et al., 2018; Smedberg et al., 2015; Tong et al., 2016). As far as we know, the level of pregnancy-related anxiety has not previously been assesssed by the expectant mothers' prenatal smoking habits (Goedhart et al., 2009; Westerneng et al., 2017). One of the important implications that emerges from these findings is that the pregnant women who smoked, especially the persistent smokers, have a substantial risk of prenatal psychological distress and prenatal depression and they may need a referral to perinatal mental health services.

6.2.2 The role of maternal-fetal attachment in prenatal smoking behavior (Study III)

We hypothesized that stronger maternal-fetal attachment would contribute to positive maternal prenatal health practices in terms of maternal prenatal smoking behavior, in other words, a lower risk of smoking in pregnancy and a higher likelihood of smoking cessation in early pregnancy. In addition, we explored weather maternal-fetal attachment could contain a momentum to modify the effects of previously established risk factors, educational disadvantage and prenatal psychological distress, on maternal prenatal smoking habits. Contrary to expectations, our findings did not substantiate an association between the total level of self-reported maternal-fetal attachment and smoking in pregnancy or smoking cessation in early pregnancy. However, the pregnant women who smoked and experienced stronger altruistic maternal-fetal attachment, i.e. scoring higher in the "*Giving of self*" subscale in the MFAS questionnaire, were more likely to quit smoking during pregnancy. In addition, the preliminary finding from our data suggested that a stronger level of prenatal attachment towards the fetus associated with a decreased risk of smoking in pregnancy among the women with a middle level of education when compared with the risk of smoking among the pregnant women with a low or high education. However, the evidence of the modifying effect of maternal-fetal attachment on the association between maternal education and smoking at any time during pregnancy was not considered sufficient as the finding was no longer statistically significant after the correction for the multiple testing. Further, evidence supporting the modifying effect of maternal-fetal attachment on the strength or direction of the association between prenatal depressive symptoms and smoking at any time of pregnancy or the association between maternal education and smoking cessation in early pregnancy was not observed.

Contrary to expectations, our results did not substantiate a significant role of the total level of maternal-fetal attachment in maternal prenatal smoking behavior. This finding is contrary to previous studies which have suggested that stronger maternal-fetal attachment predicts positive prenatal health practices with a large effect (Cannella et al., 2018) and also associates with beneficial changes in prenatal smoking habits (Lindgren, 2001; Magee et al., 2014; Massey et al., 2015; Slade et al., 2006). Nevertheless, our most interesting finding was that a one unit higher score in the altruistic dimension of maternal-fetal attachment, the "*Giving of self*" subscale in the MFAS measure, associated with a 1.13–1.17 fold increase in the likelihood of smoking cessation in early pregnancy. Previous qualitative studies have addressed that expectant mothers' willingness to help and do the best for the unborn child strengthens their motivation for change and promotes smoking cessation in pregnancy (Barnett et al., 2018). In addition, becoming a caregiver for a significant other has been found to constitute the most significant life experience promoting

recovery from substance addictions (Jessup et al., 2014). It is of note that one recent large-scale meta-analysis did not yet recognize the role of maternal-fetal attachment as a predictor of smoking cessation during pregnancy (Riaz et al., 2018). However, it is encouraging to compare our finding with that found by Massey et al. (2015) who also demonstrated that a stronger level of altruistic maternal-fetal attachment associates with the higher likelihood of smoking cessation during pregnancy (Massey et al., 2015). Our finding replicates the previous finding by Massey et al. (2015) and thus confirms that especially the expectant mother's stronger altruistic attachment towards the unborn child is related to the motivational drive to quit smoking during pregnancy.

In the birth cohort study, the descriptive sample characteristics demonstrated that the pregnant women who smoked, and particularly those women who continued smoking throughout pregnancy, comprised high-risk populations among pregnant women due to a cumulative burden of excessive prenatal psychological distress and socioeconomic disadvantage. Our results substantiated the detrimental association of low maternal education as well as prenatal depressive symptoms with smoking in pregnancy, which is in accordance with previous research (Ekblad et al., 2014; Goodwin et al., 2017; Kandel et al., 2009; Smedberg et al., 2014). In contrast to earlier findings (Tong et al., 2016), however, evidence of an association between prenatal anxiety and smoking in pregnancy was not demonstrated. In addition, one unanticipated finding was that the findings from the birth cohort study did not provide evidence of an association between prenatal psychological distress (neither depressive nor anxiety symptoms) and smoking cessation during pregnancy. This finding is contrary to previous studies which have shown that prenatal psychological distress often compromises abstinence from tobacco among pregnant women who smoke (Riaz et al., 2018). Consistent with previous literature (Kandel et al., 2009), the birth cohort study established that the pregnant women with a lower level of education were less likely to quit smoking in early pregnancy. Our study aimed at exploring a potential momentum of maternal-fetal attachment to beneficially modify the associations between maternal education as well as prenatal psychological distress and the expectant mothers' prenatal smoking behavior, i.e smoking in pregnancy and smoking cessation during pregnancy among the pregnant smokers. The modifying effect of maternal-fetal attachment on the strength or direction of these associations was not confirmed. Our negative findings suggest that the awakening of maternal-fetal attachment may not be a sufficiently efficient force to moderate the effects of maternal educational disadvantage and prenatal psychological distress in prenatal smoking behavior. However, the results from these exploratory analyses should be interpreted with caution for several reasons. First, the variable describing maternal education was relatively basic and classified maternal education only in three levels. This relative simple classification of maternal

education may not capture detailed vertical and horizontal disparities in maternal educational attainment which have been found important in predicting prenatal smoking behavior (Härkönen et al., 2018). Further, a cross-sectional approach in which only the prenatal period constitutes the time frame of research may not be able to consider longitudinal interferences. Early socioeconomic disparities and preconception health practices have been found to strongly predict prenatal smoking behaviour (Bay et al., 2016; Brumana et al., 2017; Catalano et al., 2012; Kandel et al., 2009; Patton et al., 2018), which precede the awakening of maternal-fetal attachment. On the other hand, women's representations of the emerging caregiving relationship with the unborn child may already inspire a change in smoking behavior in the preconception period; many of the women who smoke, especially those with a higher education, quit smoking just before pregnancy (Curtin & Matthews, 2016; Schoenaker et al., 2017).

One possible explanation for our mainly negative results may be general limitations in the methodology to assess prenatal parenting. The phenomenon of maternal-fetal attachment has already been investigated for several decades, but there is still no consensus about the definition and assessment of the phenomenon (Brandon et al., 2009; McNamara et al., 2019). We assessed maternal-fetal attachment with Mecca Cranley's Maternal-Fetal Attachment Scale (MFAS) which captures mainly behavioral manifestations of prenatal caregiving relationship with the unborn child (Brandon et al., 2009; Cranley, 1981). The MFAS measure may not sufficiently represent all dimensions of maternal-fetal attachment, especially expectant mothers' fantasies, thoughts and feelings regarding the unborn child and her emotional bond with the fetus (Brandon et al., 2009; McNamara et al., 2019; Walsh, 2010). Further, the subscales of the MFAS have been criticized due to a lack of construct validity and poor psychometric properties (Brandon et al., 2009; Busonera, Cataudella, Lampis, Tommasi, & Zavattini, 2016; Doster et al., 2018). In the birth cohort study, the reliability of some subscales in the MFAS questionnaire was found to be relatively poor. Nevertheless, interpreting Cronbach's α values has been considered complex at times. When measuring psychological phenomena even the Cronbach's α values below < 0.7 can be realistically be expected due to the diversity of constructs which are measured (Field, 2013). In addition, the value of Cronbach's α is dependent on the number of items in the questionnaire measure; the larger number of items leads to a larger value for Cronbach's α (Field, 2013). The number of items in the MFAS subscales is relatively small, which could have lead to the low Cronbach's α values even if the correlation between the items had been acceptable (Field, 2013).

The relationship between maternal-fetal attachment and the expectant mother's smoking behavior may not yet be fully elucidated. The same risk factors, such as childhood adverse experiences and a lack of social and partner support, may have a

detrimental effect on both maternal-fetal attachment and smoking behavior during pregnancy (Doan & Zimerman, 2008; Pear, Petito, & Abrams, 2017; Sancho Rossignol et al., 2018). In addition, the neurobiology of substance use disorders has been found to overlap with the essential neurobiology of parenting (Rutherford & Mayes, 2017) which may also have implications for the awakening of maternal-fetal attachment in the context of a tobacco use disorder. The neuronal circuitries which are crucial in reward gained from caregiving experiences and the neuronal pathways responsible for controlling maternal distress have been demonstrated to be dysregulated in substance addictions (Rutherford & Mayes, 2017; Rutherford & Mayes, 2019; Strathearn et al., 2019). Nicotine is highly addictive and tobacco products have been considered to represent the strongest addictiveness among substances (Henningfield et al., 2011). Therefore, especially the very severe forms of nicotine dependence may override potential beneficial effects of maternal-fetal attachment on prenatal smoking behavior. Heavy smoking prior to pregnancy and more severe nicotine addiction has been found to predict a lower smoking cessation rate during pregnancy (Massey et al., 2015; Riaz et al., 2018). However, pregnancy has been shown be a protective time period during which the expectant mother's emerging caregiving relationship with the fetus and associative neurobiological changes may be able to interrupt the process of maternal addiction (Kendler et al., 2017; Massey & Wisner, 2018).

6.2.3 The role of pregnancy-related anxiety in prenatal smoking behavior (Study IV)

In Study IV, we aimed at investigating the role of pregnancy-related anxiety in prenatal smoking behavior in the large population-based pregnancy cohort. We were especially interested in identifying factors which could be modified during pregnancy to be able to intervene in negative health practices in terms of prenatal smoking behavior. Therefore, we focused on the role of second trimester pregnancy-related anxiety. Based on previous observations regarding the relationship between pregnancy-related anxiety and prenatal smoking behavior (Goedhart et al., 2009; Westerneng et al., 2017), we hypothesized that low and high levels of pregnancy-related anxiety would associate negatively with prenatal smoking habits. Contrary to expectations, our findings did not establish evidence of a linear or curved relationship between the total level of pregnancy-related anxiety and prenatal smoking behavior while controlling for maternal demographic characteristics and concurrent symptoms of depression and general anxiety. Nevertheless, the study revealed that one important dimension of pregnancy-related anxiety, "*Fear of Giving Birth*", did associate with smoking cessation in early pregnancy. The association between fear of childbirth and smoking cessation was found to be somewhat curved

indicating that the pregnant women who smoked and suffered from a more severe fear of childbirth were less likely to quit smoking in early pregnancy than the pregnant women who smoked and experienced low or moderate fear of childbirth (see Figure 4). Our finding suggests that severe fear of childbirth may constitute a specific barrier to smoking cessation during pregnancy.

Only a few studies have previously investigated the role of pregnancy-related anxiety in prenatal smoking behavior (Goedhart et al., 2009; Lobel et al., 2008; Westerneng et al., 2017). The study of Westerneng et al. (2017) have shown that pregnant women with low and high levels of pregnancy-related anxiety are more likely to smoke during pregnancy (Westerneng et al., 2017). Contrary to previous findings (Lobel et al., 2008; Westerneng et al., 2017), our results did not substantiate the relationship between the total level of pregnancy-related anxiety and smoking in pregnancy, also when the association was investigated by considering a possible non-linear pattern of relationship. Further, an association between the total level of pregnancy-related anxiety and prenatal smoking cessation was not demonstrated, which is contrary to the finding of Goedhart et al. (2009) who found that pregnant women who smoked and who experienced high and low levels of pregnancy-related anxiety were less likely to quit smoking during pregnancy (Goedhart et al., 2009). Nevertheless, our most important finding addressed the role of fear of childbirth, i.e. one of the key dimensions of pregnancy-related anxiety, in determining cessation of smoking in early pregnancy. The finding to emerge from our analysis suggests that the pregnant women who smoked and suffered from more intense fear of childbirth were less likely to quit smoking than the pregnant women who smoked but experienced a low or moderate fear of childbirth. A recent large-scale systematic review and meta-analysis did not identify fear of childbirth as a predictor of smoking cessation (Riaz et al., 2018). Previously, only a few studies have reported findings regarding the association between fear of childbirth and prenatal smoking behavior (Dencker et al., 2019; Laursen, Hedegaard, & Johansen, 2008; Ryding et al., 2015). One study by Ryding et al. (2015) found that daily smoking was more common among pregnant women suffering from more intense fear of childbirth (Ryding et al., 2015). In addition, Laursen et al. (2007) demonstrated that prenatal smoking associated with fear of childbirth with a small effect (Laursen et al., 2008).

The lower likelihood of smoking cessation among pregnant women with a high level of pregnancy-related anxiety could be explained by maternal smoking, especially nicotine administration, constituting a response to pregnancy-specific distress and a coping strategy for pregnant women who smoke to alleviate and modulate their negative affective states related to fear of childbirth (Benowitz, 2010; Flemming, Graham, Heirs, Fox, & Sowden, 2013; Goedhart et al., 2009; Westerneng et al., 2017). For this reason, pregnant women suffering from intense fear of childbirth may display greater difficulties in smoking cessation. Due to the cross-

sectional study design, the direction of association can not be established. However, underlying mechanisms through which smoking in pregnancy could induce anxiety about delivery, fear of painful contractions and loss of self-control during delivery, the key characteristics of fear of childbirth assessed in the PRAQ-R2 measure (Huizink et al., 2016), have not been presented in previous research (Dencker et al., 2019; Laursen et al., 2008; Ryding et al., 2015). In contrast, many mechanisms through which psychological distress can constitute a barrier to smoking cessation have been described in previous literature. Nicotine has been found to induce pleasure and alleviate stress, and smokers often modulate their emotional states with nicotine (Benowitz, 2010). Further, smokers with anxiety and distress experience more intense cravings and fear of withdrawal symptoms, and are deeply worried about how they will deal with negative affective states without smoking (Garey et al., 2020). The high co-occurrence of anxiety and smoking has been found to involve individual's vulnerability to negative affective states, a tendency to self-medicate anxiety with continued smoking, maladaptive cognitive beliefs and coping strategies regarding smoking cessation, and proneness to low self-efficacy (Garey et al., 2020). In addition, anxiety sensitivity and poor distress tolerance have been found to amplify those perceived effects of smoking which alleviate anxiety (Leventhal & Zvolensky, 2015). Three key mechanisms have been found to underlie smoking continuation in individuals who suffer from distress in terms of depression: low positive affect, high negative affect and cognitive deficits related to depression (Mathew et al., 2017). Even though fear of childbirth comprises a very unique type of phobic fear and anxiety (Nilsson et al., 2018), these underlying mechanisms could also explain why the pregnant women with intense fear of childbirth were less likely to quit smoking during pregnancy. Our finding from the birth cohort suggests that particularly the dimension fear of childbirth of pregnancy-related anxiety may constitute a specific barrier to smoking cessation during pregnancy, which has not been previously recognized (Dencker et al., 2019; Riaz et al., 2018).

The PRAQ-R2 questionnaire captures especially emotional and cognitive attributes of pregnancy-related anxiety and covers five important dimensions of the concept: anxiety and fears with respect to fetal health, loss of fetus, childbirth, body image and loss of control (Bayrampour et al., 2016). However, the PRAQ-R2 does not assess somatic symptoms of anxiety, such as sleeping difficulties, excessive autonomic arousal and pains (Bayrampour et al., 2016; Brunton et al., 2015). Further, the PRAQ-R2 does not capture pregnant women's worries related to subjective well-being, parenting capacity, encounters in health care, financial situation or the level of social support (Bayrampour et al., 2016) . The measures for the assessment of pregnancy-related anxiety have been criticized due a lack of clear definition of the concept and insufficient sensitivity and specificity for pregnancy-related anxiety (Brunton et al., 2015). However, prior studies with good or excellent methodological

quality have suggested that the factors in the PRAQ-R2 measure are accurate indicators of pregnancy-related anxiety (Sinesi, Maxwell, O'Carroll, & Cheyne, 2019).

6.2.4 Strengths and limitations

An important strength of Studies III and IV is the well-designed large population-based pregnancy cohort in which the sample has been demonstrated to represent well the general population of pregnant women living in the geographical area (Karlsson et al., 2018). In addition, we obtained the data on prenatal smoking behavior from two different sources by combining the survey self-reports and the clinically derived register records from The Finnish Medical Birth Register. This approach has probably strengthened our methodology, and the estimates on smoking in pregnancy and smoking cessation in early pregnancy are likely to be less prone to bias.

Limitations should also be noted. Attrition in the questionnaire responses concerning maternal-fetal attachment and prenatal psychological distress including pregnancy-related anxiety was higher among the women who smoked and the highest among those pregnant women who continued smoking throughout pregnancy. Reducing the effect of this possible source of bias was attempted through multiple imputations which has found to be a valid and even more accurate method than a complete case analysis to handle the problem of missing data in surveys studies, also in the context of prenatal epidemiological research (Allotey & Harel, 2019). Further, the studies conducted in the FinnBrain Birth Cohort sample focused on the prenatal period and thus utilized a cross-sectional research design. For this reason, causality or directions of associations can not be established. Further, we may not have been able to control for all the possible confounding factors. Prenatal smoking behavior and changes in smoking habits during pregnancy were not biochemically verified, and the severity of nicotine use disorder and possible interventions to promote smoking cessation during pregnancy were not controlled for. In addition, the expectant mothers' altruistic personality traits have been shown to promote smoking cessation during pregnancy (Massey & Compton, 2013), but maternal personality characteristics were not adjusted for in the current study.

6.2.5 Clinical implications

Smoking in pregnancy has remained a significant public health concern as only 13% of pregnant women who smoke reach permanent abstinence after receiving smoking cessation interventions (Jones et al., 2016). In the FinnBrain Birth Cohort Study, the prevalence of smoking in pregnancy was still considerably high, 16.5%, and 42% of the pregnant women who smoked continued smoking throughout pregnancy.

According to previous research, pregnant women who smoke often experience that smoking cessation interventions do not enhance their attempts to change towards smoking cessation (Barnett et al., 2018). However, many pregnant women who smoke quit smoking for the child's sake, and willingness to be a good mother and to protect the fetus often facilitate smoking cessation (Barnett et al., 2018). Our results suggest that the pregnant women who smoke and experience stronger altruistic maternal-fetal attachment are more likely to quit smoking during pregnancy. Ultrasound imaging represents the most promising approach to enhance the maternal-fetal relationship during pregnancy (Borg Cunen et al., 2017). In addition, psychosocial treatment during which expectant mothers' curiosity and interest in the unborn child's perspective, development and individuality is strengthened may offer new routes to support altruistic attachment towards the fetus (Pajulo et al., 2016). Our findings also address the fact that severe fear of childbirth seems to represent a specific barrier to smoking cessation during pregnancy. According to a recent systematic review and meta-analysis, antenatal education and self-hypnosis training can alleviate fear of childbirth, and educational interventions seem to be more effective (Moghaddam Hosseini, Nazarzadeh, & Jahanfar, 2018). In addition, a mindfulness based approach has shown some promise in treating fear of childbirth (Moghaddam Hosseini et al., 2018). Strengthening altruistic maternal-fetal attachment and alleviating fear of childbirth may help to increase the smoking cessation rate among pregnant women who smoke and therefore constitute interesting novel focuses for interventions promoting prenatal smoking cessation.

7 Conclusions

The primary interest of this dissertation was to investigate the aspects of prenatal parenting and psychological distress during the prenatal transition to motherhood in the context of maternal tobacco and substance use disorders. The aim was to find and establish potential new routes for prenatal intervention, i.e. momentums that can break the intergenerational chain of adverse outcomes related to prenatal tobacco and substance use disorders. Two different samples and research designs were used to gain a wider perspective on interactions between prenatal health behavior, parenting and psychological distress.

First, the efficacy of a new prenatal parenting intervention was evaluated using a randomized and controlled research design in the high-risk clinical sample of women with substance use problems. To our knowledge, this was the first randomized and controlled clinical trial investigating the efficacy of prenatal parenting focused psychosocial intervention for women with substance use disorders. Contrary to expectations, the results did not provide evidence of the beneficial effects of the intervention on the following assessed outcomes: maternal prenatal parenting, psychological distress, participation in obstetric care, fetal drug exposure and perinatal child outcomes. However, the intervention was well-accepted by these high-risk pregnant women who often experience several barriers to attending prenatal care. An especially high attendance rate at the interactive parenting focused 4D ultrasound sessions was found. We conclude, from evidence provided by the very good study and intervention retention rates observed, that the novel intervention approach, especially the method of encountering these high-risk pregnant women, is feasible, and could be integrated into standard obstetric care. The reflective and interactive manner in carrying out the intervention may have constituted meaningful encounters for these high-risk women. However, further research should be undertaken to evaluate the efficacy of the intervention with a larger sample size and more objective methods instead of only patient-reported outcome measures.

Second, the role of maternal-fetal attachment and pregnancy-related anxiety in prenatal smoking behavior was investigated in the large population-based FinnBrain Birth Cohort Study. Contrary to expectations, our results did not substantiate the

association between the total level of maternal-fetal attachment / pregnancy-related anxiety and prenatal smoking behavior, i.e. smoking in pregnancy and smoking cessation during pregnancy. Nevertheless, the results demonstrated that pregnant women who smoked and experienced stronger altruistic maternal-fetal attachment were more likely to quit smoking during pregnancy. In addition, the findings suggested that the pregnant women who smoked and suffered from severe fear of childbirth were less likely to quit smoking in early pregnancy than the pregnant women who smoked but had a lower or more moderate level of fear of childbirth.

Prenatal tobacco and substance use disorders constitute a significant source of health related inequality and frequently expose the child to adverse environmental conditions, both pre- and postnatally (Aizer & Currie, 2014; Behnke et al., 2013; Smith et al., 2016; Tandon et al., 2013). Efforts to protect unborn children from fetal exposure to tobacco and substances are essential to ensure that all children can achieve their full developmental potential (Behnke et al., 2013; Ekblad et al., 2015; O'Leary et al., 2013; Roozen et al., 2016). Focusing on supporting both, parenting and maternal mental health, have been recognized to be effective in building the resilience of children who have faced adversity (Traub & Boynton Jarrett, 2017). To overcome very early life adversity, there is an especial need for prenatal and early interventions (Glover & Capron, 2017; Shonkoff, 2016; Stein et al., 2014). The underlying idea of this dissertation was to establish momentums which could help to intervene in the intergenerational adversity connected to prenatal tobacco and substance use disorders. In the main, our results did not support our hypothesis, which addressed the complexity and weight of burden related to prenatal tobacco and substance use disorders. Further, these mainly negative results may reflect challenges in establishing practically and scientifically feasible research metholodology to capture the essence and effects of relatively complex psychological phenomena of prenatal parenting and psychological distress within women with tobacco and substance use disorders. However, this dissertation recognized a few potentially modifiable factors through which it could be possible to intervene in the intergenerational chain of adverse outcomes in the context of prenatal tobacco and substance use disorders. In conclusion, strengthening altruistic maternal-fetal attachment to promote prenatal smoking cessation and alleviating fear of childbirth to overcome this specific barrier to smoking cessation during pregnancy may offer novel routes for early interventions. Further, the new parental mentalization focused 4D ultrasound intervention shows promise in encountering high-risk pregnant women with substance use disorders in a reflective, interactive and patient-centered way which succeeds in gaining their acceptance and commitment.

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