HEALTH OF PRENATALLY BUPRENORPHINE-EXPOSED CHILDREN TO THREE YEARS OF AGE

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ACADEMIC DISSERTATION

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ABBREVIATIONS

ACh  acetylcholine
ADHD attention deficit hyperactivity disorder
AEF auditory evoked magnetic field
ANOVA analysis of variance
AS active sleep
BNS Bayley Infant Neurodevelopmental Screener
Brief-P Behavior Rating Inventory of Executive Function Preschool Version
cAMP cyclic adenosine monophosphate
CNS central nervous system
CYP2C8 cytochrome P450 2C8
DAMGO [D-Ala², N-MePhe⁴, Gly-ol] -enkephalin
dmfs decayed/missing/filled tooth surfaces index
dmft decayed/missing/filled teeth index
dNA d-ribose nucleic acid
DQ developmental quotient
dt decayed teeth index
EEG electroencephalography
EMCDDA European Monitoring Centre for Drugs and Drug Addiction
EOG electo-oculography
EUROCAT European Concerted Action on Congenital Anomalies and Twins
FAS fetal alcohol syndrome
FASD fetal alcohol spectrum disorder
GTP-y guanosine 5’-O-(gamma-thio)triphosphate
HBV hepatitis B virus
HCV hepatitis C virus
HIV human immunodeficiency virus
HUCH Helsinki University Central Hospital
KOP kappa opioid receptor
LAAM levobuprenoacetamid
MCAS McCarthy Scales of Children’s Abilities
MDI Mental Developmental Index
MEG magnetoencephalography
MOP mu opioid receptor
MRI magnetic resonance imaging
NAS neonatal abstinence syndrome
NEPSY developmental NEuroPSYchological Assessment
NF nerve growth factor
NICHD National Institute of Child Health and Human Development network
NOP nociceptin/orphanin FQ receptor
PCR polymerase chain reaction
PDA patent ductus arteriosus
PKC protein kinase C
QS quiet sleep
RNA ribonucleic acid
SDQ Strengths and Difficulties Questionnaire
SFF somato-sensory evoked magnetic field
SGA small for gestational age
SIDDS sudden infant death syndrome
SSRI selective serotonin reuptake inhibitor
ToM Theory of Mind
TfSFI Test of Sensory Functions in Infants
tSSS Spatiotemporal Signal Space Separation method
UNODC United Nations Office of Drug and Crime
VEP visual evoked potential
WHO World Health Organization
WPPSI-R Wechsler Preschool and Primary Scale of Intelligence-Revis

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following publications, referred to in the text by their Roman numerals:


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1 ABSTRACT

**Background:** Illicit use of prescription opioids has increased markedly in recent years, especially in Europe and North America. In Finland, the number of opioid problem users constantly increased through the 2000s, levelling off in 2012. Buprenorphine is a semisynthetic opioid that was originally administered as an analgesic, but later also used in opioid detoxification and maintenance treatment. However, buprenorphine abuse has been reported in many countries. In Finland, buprenorphine is the most common injection drug. Buprenorphine use in late pregnancy leads to neonatal abstinence syndrome (NAS) in roughly 60% of newborns. Data on buprenorphine-exposed children’s health after the neonatal period is scarce. Our aim was to identify the health problems of these children from infancy to three years of age.

**Patients and methods:** The study population comprised altogether 108 children with a positive drug screen for buprenorphine as a newborn. Children were born between August 2000 and November 2008 in Helsinki University Central Hospital (HUCH). All mothers had smoked in pregnancy and some mothers had also used other substances. Children had regular pediatrician’s appointments after neonatal age based on the HUCH Children Hospital’s established practice for substance-exposed children. Our study included four substudies. In Study I, the data of 102 prenatally buprenorphine-exposed children’s physical health outcomes and child welfare reports made in HUCH to three years of age were analyzed. In Study II, we investigated 51 buprenorphine-exposed children’s oral health and potential dental neglect at 3-4 years of age when children were invited for the dental appointment. In Study III, we enrolled 21 three-year-old buprenorphine-exposed children with their biological or foster mothers in a psychological evaluation. The Bayley-III Cognitive, Language, and Social-Emotional Scales, the Emotional Availability Scale, and the Self-Efficacy for Parenting Tasks Index -Toddler Scale were performed. In Study IV, we measured with magnetoencephalography (MEG) 11 buprenorphine-exposed newborns with neonatal abstinence syndrome (NAS) to determine somatosensory and auditory evoked potentials. For each of the studies (II-IV), we recruited a control group of children who had not been prenatally exposed to opioids.

**Results:** One main finding was that pediatricians observed multiple types of child abuse and neglect in the study population. They made altogether 70 child welfare reports. Repeated...
failure to come to an appointment, which was considered medical neglect, constituted 64% of the child welfare reports. In four children, physical abuse was suspected. Another main finding was that buprenorphine-exposed children had significantly more early childhood caries than control children. The study raised concern for dental neglect in buprenorphine-exposed children. We also discovered that 10% of buprenorphine-exposed children had been diagnosed with strabismus and 5% had a major congenital anomaly. Of 102 children, four had an umbilical or inguinal hernia and three had infantile pyloric stenosis. Two children died by the age of three years. The psychological study revealed poorer cognitive abilities in buprenorphine-exposed children than in controls as well as diminished performance in mother-child dyads in terms of emotional availability and perceived maternal self-efficacy. In the MEG study, somatosensory and auditory evoked potentials did not show significant differences between the buprenorphine-exposed group and the control group.

**Conclusions:** Prenatally buprenorphine-exposed children exhibit more early childhood caries and dental neglect than control children. In addition to dental neglect, the children are exposed to multiple types of child maltreatment as well as to unfavorable emotional features in the caregiver-child relationship. Based on health and maltreatment issues revealed here, a pediatric follow-up with a multi-professional team, including a dentist, is essential.
2 INTRODUCTION

Opiate abuse is a global health problem. The number of patients receiving opioid maintenance treatment was estimated to be 700,000 in Europe in 2013 (European Monitoring Centre for Drugs and Drug Addiction, 2015). Methadone and buprenorphine are the main options for opioid maintenance treatment. Buprenorphine is a semisynthetic opioid derived from thebaine. It has mixed agonist-antagonist effects on opioid receptors (Martin et al., 1976; Huang et al., 2001; Walsh and Eissenberg, 2003). Illicit use has been reported in several countries (Harper, 1983; Strang, 1985; Lavelle et al., 1991; Robinson et al., 1993; Obadia et al., 2001; Jenkinson et al., 2005; Aalto et al., 2007; Hakansson et al., 2007; Hughes et al., 2007; Spiller et al., 2009; Dasgupta et al., 2010; Moratti et al., 2010; Vicknasingam et al., 2010; Larance et al., 2011; Wish et al., 2012). In Finland, the number of opioid problem users in treatment has constantly increased in the 2000s up to the year 2012. Buprenorphine is the most common injected street drug in Finland (Varjonen, 2015).

Data on prenatally buprenorphine-exposed children’s health, especially beyond the neonatal period, are limited. To date, studies have mainly concentrated on NAS, which occurs in roughly 60% of buprenorphine-exposed newborns (Fischer et al., 2000; Johnson et al., 2003; Kayemba-Kay and Laclede, 2003; Lacroix et al., 2004; Kahila et al., 2007b; Kakko et al., 2008; Jones et al., 2014). Children exposed to other types of opioids are described as having mild neurocognitive deficits (Wilson et al., 1979; Ornry et al., 1996; Bunikowski et al., 1998; Messinger et al., 2004). In addition, congenital disorders have been suggested to occur after gestational opioid exposure (Broussard et al., 2011).

The children of substance-abusing parents are at risk for child abuse and neglect. Substance-abusing parents may have weaknesses in parenting skills and difficulties in taking care of a child’s basic needs (Rizzo et al., 2014). Substance abuse-related problems, such as financial problems, criminality, parental mental health problems, and repeated out-of-home placements, may exacerbate the suboptimal home circumstances for a child. Child maltreatment has long-term effects on an individual’s mental and physical health (Gilbert et al., 2009a), and thus, it is essential to know more about child abuse and neglect also in buprenorphine-exposed children.

This study is among the first attempts to elucidate the health problems of buprenorphine-exposed children after gestational age. The number of study patients at three years of age (n=102) clearly exceeds the number of subjects in previous reports exploring the health of

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This study is among the first attempts to elucidate the health problems of buprenorphine-exposed children after gestational age. The number of study patients at three years of age (n=102) clearly exceeds the number of subjects in previous reports exploring the health of
buprenorphine-exposed children beyond neonatal age. We aimed to investigate buprenorphine-exposed children's physical health and possible maltreatment from infancy to three years of age and to compare their oral health, child development, and caregiver-child relationships with control children. In addition, the physiological basis of NAS and brain electrical activity in response to somatosensory and auditory impulses was explored with MEG.
3 REVIEW OF THE LITERATURE

3.1 Opioids

German pharmacist Friedrich Sertürner (1783-1841) applied chemical analysis to plant drugs by purifying the main active ingredient of opium poppy at the beginning of the 1800s. Sertürner gave this drug the name “morphi um” recalling Morpheus, a god of dreams in Greek mythology. The name morphium later became morphine (Hamilton and Baskett, 2000). In 1874, the English chemist C.R. Alder Wright discovered heroin (diacetylmorphine) by adding two acetyl groups to the morphine molecule (Sneader, 1998). The term opiates refers to over 20 alkaloids derived naturally from the opium poppy plant (Papaver somniferum), including morphine, codeine, and thebaine (McMurry, 2003; Vallejo et al., 2011). Opioids are a generic term applied to alkaloids from opium poppy and their synthetic analogs that binds to opioid receptors (Vallejo et al., 2011). Since the discovery of morphine and heroin, numerous opioids have been synthesized for medical use. Their analgesic effects have made them valuable in treatment of severe pain, e.g. in cancer and after surgery.

3.2 Opioid receptors

Opioid receptors are categorized into the three classical types of opioid receptors, mu opioid receptor (MOP), delta opioid receptor (DOP), and kappa opioid receptor (KOP) (McDonald and Lambert, 2005). In addition, the non-classical receptor nociceptin/orphanin FQ peptide (NOP) exists (McDonald and Lambert, 2005). Opioid receptors appear in the central nervous system (CNS) and are especially abundant in the nuclei of the tractus solitarius, periaqueductal gray area, cerebral cortex, thalamus, and substantia gelatinosa of the spinal cord, but also exist in the heart, lungs, liver, kidneys, spleen, adrenal glands, and gastrointestinal and reproductive tracts (Wittert et al., 1996; McDonald and Lambert, 2005; Le Merrer et al., 2009). These receptors are stimulated by opioids or endogenous peptides produced in response to nociceptive stimuli (Froehlich, 1997; Zadina et al., 1997). Heroin metabolizes to 6-monoacetylmorphine and morphine, which act as opioid agonists (Inturrisi et al., 1983; Rossi et al., 1996).
Binding of agonist to MOP receptors will result in supraspinal analgesia, euphoria, serenity, respiratory depression, reduced gastrointestinal motility, urinary retention, pruritus, prolactin release, physical dependence, anorexia, sedation, and miosis (Trescot et al., 2008; Fields, 2011). Agonist attachment to KOP receptors may induce spinal analgesia, pupil constriction, sedation, dyspnea, dysphoria, diuresis, and respiratory depression (Trescot et al., 2008; Crowley and Kash, 2015). Agonist binding to DOP receptors has been suggested to result in respiratory depression, reduced gastrointestinal motility, antinociception, euphoria, reduced anxiety, and tissue protection in hypoxia (McDonald and Lambert, 2005; Gendron, 2015). They have also been suggested to be involved in the biochemical mechanisms of learning and memory (Gendron, 2015). The function of NOP receptors involves spinal antinociception, anxiolysis, antidepressive effects, antitussive effects, vascular vasodilation, inhibition of gastrointestinal motility, and inhibition of immunoocyte activity (Lambert, 2008).

At the cellular level, MOP, DOP, KOP, and NOP share similar coupling mechanisms with inhibitory G-proteins. This classic pathway of opioid receptor signal transduction is related to modulation of calcium and potassium channels. When an opioid or endogenous peptide binds to opioid receptor on the presynaptic terminals of the nociceptive C-fibers and A delta fibers, a number of actions occur: closing of voltage-sensitive calcium channels, stimulation of potassium efflux leading to hyperpolarization, reduced cyclic adenosine monophosphate (cAMP) production, and inhibited release of pain neurotransmitters such as glutamate, substance P, and calcitonin gene-related peptide (McDonald and Lambert, 2005; Trescot et al., 2008; Al-Hasani and Bruchas, 2011). The overall effect is a reduction in neuronal cell excitability, which in turn results in diminished transmission of nociceptive impulses (McDonald and Lambert, 2005; Trescot et al., 2008; Al-Hasani and Bruchas, 2011).

### 3.3 Opioid abuse and opioid dependence

Substance abuse comprises all hazardous use of psychoactive substances in conflict with medical guidelines or legislation. Drug abuse may have an impact on an individual’s mental and physical health, and it is related to increased mortality, criminality, social problems, and economic costs (International Drug Control Programme Austria, 1998; European Monitoring Centre for Drugs and Drug Addiction, 2015). Addiction, physical dependence, and tolerance are different kinds of phenomena connected to opioid abuse.
Addiction is established to be a chronic relapsing brain disorder (Leshner, 1997; American Academy of Pain Medicine et al., 2001; Koob, 2009). It is characterized by one or more of the following behaviors: impaired control over substance use, compulsive use, craving, and continued use in spite of harm (American Academy of Pain Medicine et al., 2001). Heroin use creates in its acute phase euphoria and detachment from emotions, and this state may become an object of intense desire that governs the individual’s everyday life. It is nevertheless not clear-cut how addiction progresses and why some persons become addicted. The neurobiological process in addiction is described as a dysfunction in the brain reward process based on an imbalance of the circuitry of positive-reinforcing properties in ventral striatal-pallidal-thalamic loops and negative-reinforcing properties in the extended amygdala (Koob, 2009). Physiological vulnerabilities of the individual may make the person more prone to addiction and/or background factors in the environment may favor an individual succumbing to drug addiction (Dube et al., 2003; Uhart and Wand, 2009). Genetic surveys have appraised heritability to account for 43-60% of opioid abuse (Tsang et al., 1996; Goldman et al., 2005; Li and Burmeister, 2009). To date, OPRD1, GAL, ABCB1, and OPRM1 have been presented as potential candidate genes for opioid misuse (Beer et al., 2013).

Physical dependence has been classified as “a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist” (American Academy of Pain Medicine et al., 2001). Sudden discontinuation or decrease in opioid supply after repeated and usually prolonged use may result in such withdrawal symptoms as agitation, anxiety, muscle ache, lacrimation, insomnia, rhinorrhea, sweating, yawning, abdominal cramping, diarrhea, weight loss, mydriasis, piloerection, nausea, and vomiting (Wesson and Ling, 2003).

Tolerance is defined as “a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time” (American Academy of Pain Medicine et al., 2001). Opioids can induce tolerance, and doses may escalate both in pain treatment and in illicit opioid use. Downregulation of opioid receptors following prolonged opioid agonist exposure, G protein uncoupling, opioid receptor desensitization, and opioid receptor internalization has been suggested to be involved in tolerance, but an integrative theory of the mechanisms is lacking (Gomes 2002; Al-Hasani and Bruchas, 2011; Allouche, 2014).
Opioid dependence is a medical diagnosis for uncontrollable, compulsive use of opioids despite obvious harm. Dependence has been designated by the International Statistical Classification of Diseases and Related Health Problems as “a cluster of physiological, behavioral, and cognitive phenomena in which the use of a substance or a class of substances takes on a much higher priority for a given individual than other behaviors that once had greater value. A central descriptive characteristic of the dependence syndrome is the desire (often strong, sometimes overpowering) to take psychoactive drugs (which may or may not have been medically prescribed), alcohol, or tobacco. There may be evidence that return to substance use after a period of abstinence leads to a more rapid reappearance of other features of the syndrome than occurs with nondependent individuals” (World Health Organization, 1992).

A diagnosis of dependence can usually be made only if the patient has had three or more of the following symptoms present simultaneously during the previous year:

(a) a strong desire or sense of compulsion to take the substance;
(b) difficulties in controlling substance-taking behavior in terms of its onset, termination, or levels of use;
(c) a physiological withdrawal state when substance use has ceased or been reduced, as evidenced by: the characteristic withdrawal syndrome for the substance; or use of the same (or a closely related) substance with the intention of relieving or avoiding withdrawal symptoms;
(d) evidence of tolerance, such that increased doses of the psychoactive substances are required in order to achieve effects originally produced by lower doses (clear examples of this are found in alcohol- and opiate-dependent individuals who may take daily doses sufficient to incapacitate or kill nontolerant users);
(e) progressive neglect of alternative pleasures or interests because of psychoactive substance use, increased amount of time necessary to obtain or take the substance or to recover from its effects;
(f) persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts to recover from its effects;
(g) persisting with substance use despite clear evidence of overtly harmful consequences, such as harm to the liver through excessive drinking, depressive mood states consequent to periods of heavy substance use, or drug-related impairment of cognitive functioning; efforts
should be made to determine that the user was actually, or could be expected to be, aware of the nature and extent of the harm” (World Health Organization, 1992).

3.3.1 Epidemiology of opioid abuse

Opiate abuse is a worldwide health problem. The United Nations Office on Drugs and Crime (UNODC) estimated that 13-21 million opiate users and 28-38 million opioid users existed in the world in 2012 (United Nations Office on Drugs and Crime, 2014). Asia and Eastern Europe have been the main regions of opiate consumption (United Nations Office on Drugs and Crime, 2014). The report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimated the presence of 1.3 million problem opioid users in Europe in 2013 (European Monitoring Centre for Drugs and Drug Addiction, 2015). About 700 000 patients received opioid maintenance treatment in Europe in 2013 (European Monitoring Centre for Drugs and Drug Addiction, 2015).

In recent years, the nonmedical use of prescription opioids has been a topical concern. Increased use of prescription drugs has been reported in Europe, North America, and Australia (United Nations Office on Drugs and Crime, 2011, 2013; Manchikanti et al., 2012; European Monitoring Centre for Drugs and Drug Addiction, 2015). Regarding buprenorphine, the first reports of its injection misuse emerged in the 1980s (Harper, 1983; Strang, 1985). Since then, buprenorphine abuse has been reported in many countries, including Australia (Jenkinson et al., 2005), Finland (Aalto et al., 2007), France (Obadia et al., 2001), UK (Lavelle et al., 1991), Italy (Moratti et al., 2010), New Zealand (Robinson et al., 1993), Sweden (Hakansson et al., 2007), US (Hughes et al., 2007; Spiller et al., 2009; Dasgupta et al., 2010; Wish et al., 2012), Malaysia (Vicknasingam et al., 2010), and several other South Asian countries (Larance et al., 2011).

A review of nationwide hospitalizations for deliveries found that the prevalence of opioid abuse or dependence during pregnancy increased from 0.17% to 0.39% in the US between 1998 and 2011 (Maeda et al., 2014). In the UK, 2% of young women are estimated to use opiates in early pregnancy (Crome and Kumar, 2007). In Denmark, 608 pregnant women took part anonymously in a urine drug screening. Of the drug screens, 3.6% were positive, and 86.4% of confirmed positive samples contained opiates (Rausgaard et al., 2015).

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3.3.1 Epidemiology of opioid abuse

Opiate abuse is a worldwide health problem. The United Nations Office on Drugs and Crime (UNODC) estimated that 13-21 million opiate users and 28-38 million opioid users existed in the world in 2012 (United Nations Office on Drugs and Crime, 2014). Asia and Eastern Europe have been the main regions of opiate consumption (United Nations Office on Drugs and Crime, 2014). The report of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) estimated the presence of 1.3 million problem opioid users in Europe in 2013 (European Monitoring Centre for Drugs and Drug Addiction, 2015). About 700 000 patients received opioid maintenance treatment in Europe in 2013 (European Monitoring Centre for Drugs and Drug Addiction, 2015).

In recent years, the nonmedical use of prescription opioids has been a topical concern. Increased use of prescription drugs has been reported in Europe, North America, and Australia (United Nations Office on Drugs and Crime, 2011, 2013; Manchikanti et al., 2012; European Monitoring Centre for Drugs and Drug Addiction, 2015). Regarding buprenorphine, the first reports of its injection misuse emerged in the 1980s (Harper, 1983; Strang, 1985). Since then, buprenorphine abuse has been reported in many countries, including Australia (Jenkinson et al., 2005), Finland (Aalto et al., 2007), France (Obadia et al., 2001), UK (Lavelle et al., 1991), Italy (Moratti et al., 2010), New Zealand (Robinson et al., 1993), Sweden (Hakansson et al., 2007), US (Hughes et al., 2007; Spiller et al., 2009; Dasgupta et al., 2010; Wish et al., 2012), Malaysia (Vicknasingam et al., 2010), and several other South Asian countries (Larance et al., 2011).

A review of nationwide hospitalizations for deliveries found that the prevalence of opioid abuse or dependence during pregnancy increased from 0.17% to 0.39% in the US between 1998 and 2011 (Maeda et al., 2014). In the UK, 2% of young women are estimated to use opiates in early pregnancy (Crome and Kumar, 2007). In Denmark, 608 pregnant women took part anonymously in a urine drug screening. Of the drug screens, 3.6% were positive, and 86.4% of confirmed positive samples contained opiates (Rausgaard et al., 2015).
In Finland, it is estimated that 0.38-0.45% of the total population are opioid users (Varjonen, 2015). Buprenorphine is the most common illicitly used opioid. It accounted for at least 74% of all opioid misuse in 2011 and was mainly used by injection (Varjonen, 2012). At the same time, regular heroin use was rare. Buprenorphine abuse increased when the availability of heroin crashed in the Finnish drug markets after 2001 (Varjonen et al., 2012). An estimated 4400-5200 opioid-using women exist in Finland and they are mostly of a child-bearing age (Varjonen, 2015). In the Helsinki area, the first child who had a positive urine screen for buprenorphine was born in 2000 (unpublished statistics of Social Pediatrics Outpatient Clinic, HUCH). Between 2001 and 2008, some 12-18 such newborns were born yearly in HUCH; the number of these newborns after the year 2008 is not available (unpublished statistics of Social Pediatrics Outpatient Clinic, HUCH).

### 3.4 Opioid maintenance therapy

Maintenance therapy was first presented in 1965, when Dole and Nyswander (1965) discovered that a daily dose of oral methadone relieved morphine addiction. Since then, methadone has been the golden standard for opioid maintenance. Maintenance therapy is often combined with psychosocial counselling in treatment of opioid dependence (Kakko et al., 2003).

In Finland, opioid substitution treatment was accepted as part of the official therapy for opioid dependence in accordance with the regulation of the Ministry of Social Affairs and Health in 1997 (Sosiaali- ja terveysministeriön määräyskokoelma 1997:28). The preconditions for opioid maintenance treatment comprise diagnosed opioid dependence, lack of contraindications, and failed opioid withdrawal. Patients are presumed to be motivated for treatment. Provision of maintenance drugs is supervised in Finland, and patients get their medicines mainly from healthcare centers and addiction treatment units. The objectives of the treatment are to decrease or end opioid abuse, decrease injection of drugs, reduce overdose risk and crimes linked to drug abuse, and enhance the physical and mental health of the patient (World Health Organization, 2009). Maintenance therapy is not a curative treatment for all patients, but it has proven to have clear benefits: decreased heroin use, increased treatment retention, improved psychosocial functioning, reduced crimes, and decreased morbidity and mortality (Mello and Mendelson, 1980; Marsch, 1998; Mattick et al., 2009, 2014; Evans et al., 2015). Substitution therapy in pregnancy is suggested to lead
to earlier enrollment in prenatal care, improved maternal nutrition, better compliance with psychosocial rehabilitation, less risk for premature birth, and less admissions to special care nursery (Finnegan, 1991; Burns et al., 2007).

Maintenance therapy of opioid dependence is mainly accomplished with methadone, buprenorphine, or buprenorphine/naloxone. Levo-alpha-acetylmethadol (LAAM), naloxone, codeine, heroin, and morphine have also been used in maintenance treatment (Hall and Mattick, 2007; Tetraithil and Fiellin, 2012). Methadone and buprenorphine-containing products have also been applied for treating opioid dependence in pregnancy (Fischer et al., 2000; Kayemba-Kay and Laclede, 2003; Lacroix et al., 2004; Lejeune et al., 2006; Kahila et al., 2007b; Minozzi et al., 2013). In Finland, there were a total of 2439 patients in opioid maintenance treatment at the end of 2011 (Partanen et al., 2014). Of these patients, 58% used buprenorphine-naloxone, 38% methadone, and 4% buprenorphine.

3.4.1 Buprenorphine

Buprenorphine is a semisynthetic opioid derived from the morphine alkaloid thebaine. It was first discovered in the late 1960s in the laboratory of Reckitt & Colman company in England (Lewis, 1973). Buprenorphine is a potent analgesic administered either parenterally, sublingually, or transdermally. Illicit use also includes snorting. Buprenorphine is between 25 and 40 times more potent than morphine after parenteral injection in rodents (Cowman et al., 1977). It has a partial agonist activity at the MOP receptors (Martin et al., 1976; Huang et al., 2001) and an antagonist activity at the KOP receptors (Walsh and Eisenberg, 2003). Buprenorphine additionally binds to the DOP and NOP receptors, but effects of these actions are unclear (Wnendt et al., 1999; Hawkins et al., 2000; Huang et al., 2001; Cami-Kobeci et al., 2011). About 75% of buprenorphine is N-dealkylated to norbuprenorphine in the liver mainly by microsomal enzyme cytochrome P450 3A4 (CYP3A4), accounting for 65% of this metabolism, and by cytochrome P450 2C8 (CYP2C8), accounting for 30% (Irribane et al., 1997; Picard et al., 2005). Most buprenorphine is excreted in feces and only about 10–30% via the kidneys in urine (Cone et al., 1984; Elkader and Sproule, 2005). Bioavailability of 51.4% has been measured in the sublingual route in humans (Kuhlman et al., 1996).

The advantages of buprenorphine are suggested to be decreased overdose risk, potential for dosing once every two days, low abuse potential (Walsh and Eisenberg, 2003) and, after 18 to earlier enrollment in prenatal care, improved maternal nutrition, better compliance with psychosocial rehabilitation, less risk for premature birth, and less admissions to special care nursery (Finnegan, 1991; Burns et al., 2007).

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prenatal exposure, shorter NAS (Jones et al. 2010). Buprenorphine exhibits a ceiling effect at a moderate dose, after which increasing the dose will not increase intoxication risk or respiratory depression (Walsh and Eissenberg, 2003; Center for Substance Abuse Treatment, 2004). In sublingual tablets, buprenorphine is available either alone or combined with naloxone. Naloxone is an opioid antagonist and in combination with buprenorphine it may prevent abuse by precipitating withdrawal symptoms in intravenous use (Mendelson et al., 1996; Orman and Keating, 2009). Side-effects of buprenorphine are those common to other opioids (Walsh and Eissenberg, 2003). Buprenorphine alone is seldom the reason for intoxication deaths, but deaths in conjunction with polydrug use do occur (Walsh and Eissenberg, 2003; Simonsen et al., 2015).

3.5 Animal studies of prenatal opioid exposure

Heroin has a high degree of lipid solubility and it diffuses across the placenta as well as the blood–brain barrier (Gareri et al., 2006). Morphine, buprenorphine, and methadone also enter the fetal circulation via the placenta (Nanovskaya et al., 2002; Gareri et al., 2006). Animal studies have conclusively shown that gestational opioid exposure can lead to neonatal abstinence syndrome (Pinto et al., 1986; Barr et al., 1998, 2011; Richardson et al., 2006).

In rats, prenatal heroin exposure results in lower birth weight than in controls (Zhu and Stadlin, 2000). The weight gain after birth was reduced particularly in female pups, which also displayed elevated ambulation, increased rearing, and diminished habituation rate. Another study revealed that prenatal heroin exposure in mice results in deficits in behavioral performance tested in the eight-arm radial maze, increased hippocampal M(1)-muscarinic receptor expression, and increased muscarinic receptor-mediated IP formation (Steingart et al., 2000). When adult mice received fetal neural grafting, this reversed both the behavioral deficits and the muscarinic hyperactivity. Prenatally heroin-exposed mice have also been found to have reduced dendrite length and diminished number of branches in pyramidal neurons in the somatosensory cortex as well as a tendency to explore less objects in novel locations (Lu et al., 2012). One study determined the function of protein kinase C γ (PKCγ), an enzyme related to behavioral effects, in prenatally heroin-exposed mice (Shahak et al., 2003). Nonexposed control mice had increased level of hippocampal cell membrane PKCγ in young adulthood after incubation with carbachol, the muscarinic cholinergic receptor.

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agonist, which is indicative of translocation from the cytosol. Antenatally heroin-exposed mice did not show this response, which suggests a role of PKCy in heroin’s neurobehavioral effects (Shahak et al., 2003).

In rats, perinatal methadone exposure has proved to decrease brain wet weights (Zagon and McLaughlin, 1977a; Zagon and McLaughlin, 1977b; Ford and Rhines, 1979; Zagon and McLaughlin, 1982a; Zagon and McLaughlin, 1983), decrease brain dry weight (McLaughlin et al., 1978), decrease cerebellar wet weight (Zagon and McLaughlin, 1977a; Zagon ad McLaughlin, 1978), decrease cerebellar width (Zagon and McLaughlin, 1977), reduce thickness of the cortex and number of cells of the neocortex (Ford and Rhines, 1979), and decrease deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or protein concentration in the brain and cerebellum (Zagon and McLaughlin, 1977b; Zagon and McLaughlin, 1978; Zagon and McLaughlin, 1982a). Prenatal methadone exposure also results in smaller head circumference in rat pups (McLaughlin et al., 1978). Other findings that have been reported after methadone exposure in rat pups are a diminished amount of nerve growth factor (NGF) in the striatum (Robinson, 2000; Wu et al., 2001), reduced enkephalin levels in the striatum (Tiong and Olley, 1988), reduced level of acetylcholine (ACh) in striatal neurons, which tend to be smaller than normal (Robinson, 2000), and reduced number and density of internal granule neurons in the brain (Zagon and McLaughlin, 1982b).

In utero exposure to buprenorphine has been reported in transient downregulation of MOP receptors (Belcheva et al., 1994; Belcheva et al., 1998) as well as upregulation of KOP1 receptors in the brains of rat pups (Belcheva et al., 1998). One study showed that buprenorphine gestational treatment attenuates [D-Ala², N-MePhe⁴, Gly-ol]-enkephalin (DAMGO) –induced guanosine 5'-O-[gamma-thio]triphosphate (GTPγS) binding in some male P2 mesolimbic regions, but stimulates NOP-induced GTPγS binding in male P2 nucleus accumbens and lateral septum (Hou et al., 2004). The effect of prenatal exposure was gender-dependent, with male rats being more sensitive to gestational buprenorphine exposure than females. Perinatal exposure to buprenorphine has been shown to change striatal ACh content (Robinson, 2002) and diminish the expression of NGF content in the striatum of rats (Wu et al., 2001). However, buprenorphine seems not to change met- or leu-enkephalin levels in the brain, contrary to methadone (Tiong and Olley, 1988).
Perinatally buprenorphine-, methadone-, or morphine-exposed rat pups have been observed to quickly develop tolerance to morphine injected after birth (Robinson and Wallace, 2001; Chiang et al., 2010). Buprenorphine has also been suggested to decrease birth weight in rat pups (Evans et al., 1989), but this has not been noted in all studies (Hutchings et al., 1995; Chiang et al., 2010). Some researchers have suggested that buprenorphine increases prenatal mortality in animals (Hutchings et al., 1996; Robinson and Wallace, 2001).

In visceral and skeletal examination of rats after morphine exposure, no anomalies were found (Fujinaga and Mazze, 1988). However, gestational opioid exposure has in some studies shown potential effects on the nervous system. One study reported that in utero morphine exposure in rats delayed the formation of the neural tube and diminished its thickness (Nasiraei-Moghadam et al., 2005). CNS anomalies have occurred after opioid exposure in hamsters (Geber and Schramm, 1975). Mouse embryos have been reported with exencephaly, rachischisis, and spinal cord kinking after prenatal opioid exposure (Jurand, 1973). Taken together, previous studies have indicated that gestational opioid exposure modulates cellular level mechanisms and neurobehavior and may have effects on morphology and structures of the neural system in animals.

### 3.6 Human studies of prenatally opioid-exposed children’s health

#### 3.6.1 Pregnancy and the fetus

Opioid-dependent pregnant women encounter similar symptoms of opioid dependence and withdrawal as opioid-dependent patients in general. Complications related to substance abuse are skin abscesses, cellulitis, septic thrombophlebitis, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, endocarditis, and malnutrition (Kuczkowski, 2007).

The mother’s opioid use has depressive effects on the fetus, reflected in less motor activity, decreased breathing movements and heart rate, and decreased heart rate variability (Woudes et al., 2004; Jansson et al., 2005, Schmid et al., 2010). One study reported, however, no significant differences in asphyxia markers erythropoietin, cardiac troponin T, and S100 (Kahila et al., 2008).

Opioid use in pregnancy has been suggested to increase risk for antepartum hemorrhage and prematurity (Hulse et al., 1998b; Minozzi et al., 2013; Patrick et al., 2015). Low birth weight and prematurity (Hulse et al., 1998b; Minozzi et al., 2013; Patrick et al., 2015). Low birth weight

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weight, low birth length, and small circumference have been reported in opioid-exposed newborns (Lifschitz et al. 1983; Lifschitz et al. 1985; Chasnoff, 1986; Kaltenbach et al., 1987; Minozzi et al., 2013; Bell et al., 2008; Patrick et al., 2015). Kahila et al. (2007b) have presented the outcome of 67 Finnish buprenorphine-using women’s pregnancies. Of newborns, 4.5% were premature (delivery <37 weeks), which was less than the corresponding figure of 5.2% in the total population in Finland in 2004. Birth weight was below 2500 g in 7.5% of buprenorphine-exposed newborns, exceeding the figure of 4.4% in the total Finnish population.

3.6.2 Neonatal abstinence syndrome

NAS is a withdrawal syndrome of newborns after prenatal exposure to substances, most commonly opioids. In the US, the incidence of NAS nearly tripled between 2000 and 2009, being 3.39 per 1000 hospital births in 2009 (approximately 13 000 affected newborns) (Patrick et al., 2012). The reported frequency of NAS varies greatly, from 5% up to 94% (Kocherlakota, 2014). Maternal use of buprenorphine in late pregnancy leads to NAS in 40-85% of newborns (Fischer et al., 2000; Johnson et al., 2003; Kayemba-Kay's and Laclyde, 2003; Lacroix et al., 2004; Kahila et al., 2007b; Kakko et al., 2008; Jones et al., 2010).

NAS is a clinical diagnosis with characteristic signs of hyperirritability, respiratory distress, and gastrointestinal dysfunction as well as symptoms of the autonomic nervous system (Velez and Jansson, 2008; Hudak et al., 2012). Newborns prenatally exposed to buprenorphine show withdrawal symptoms normally within 1-2 days after birth and symptoms may last for up to several weeks, resulting in prolonged hospitalization (Kahila et al., 2007b).

The mother’s methadone or buprenorphine use has not been shown to have a dose-response effect on neonatal outcome (Seligman et al., 2008; Jones et al., 2013; Jones et al., 2014). Compared with methadone-exposed newborns, buprenorphine-exposed newborns with NAS require smaller doses and shorter duration of morphine treatment, and their hospital stay is shorter (Jones et al., 2010). Later gestational age (Seligman et al., 2008; Liu et al., 2010; Kaltenbach et al., 2012), a newborn at a good birth weight (Kaltenbach et al., 2012), male gender (Unger et al., 2011; O’Connor et al., 2013), mother’s benzodiazepine use (Seligman et al., 2008), mother’s cigarette smoking (Choo et al., 2004; Winklbaur et al., 2009; Kaltenbach et al., 2012), and mother’s use of selective serotonin reuptake inhibitors (SSRIs)
in pregnancy (Seligman et al., 2008, Wachman et al. 2011; Kaltenbach et al., 2012) may add risk for more severe NAS. Newborns exposed to both cocaine and opioids in utero exhibit more central and autonomous nervous system signs than newborns exposed to opioids alone (Bada et al., 2002). One study suggested that prenatal alcohol does not, however, increase the severity of NAS (Kreitinger et al., 2015). Increased methylation within the OPRM1 gene promoter is associated with worse NAS outcomes (Wachman et al., 2014). Genotypes OPRM1 118A>G AG/GG and COMT 158A>G AG/GG have been associated with shortened length of hospital stay and less need for treatment than the OPRM1 AA genotype (Wachman et al., 2013; Kocherlakota, 2014).

The exact pathophysiology of NAS remains obscure. Kocherlakota (2014) summarized in his review article that the sudden cessation of opioid supply to opioid receptors after birth leads to increased cyclic adenosine monophosphate (cAMP) production in cells, which in turn leads to increased amounts of protein kinase and transcription factors. Next, the release of neurotransmitters noradrenaline, corticotrophin, and acetylcholine increases, and serotonin and dopamine production diminishes.

Attempts have been made to determine the quantity of gestational drug exposure. Mothers can be interviewed about substance abuse during pregnancy, and maternal urine samples can be collected for toxicology screening. Drug exposure in late pregnancy can potentially be measured from a newborn’s urine sample (Kocherlakota, 2014). In our hospital district, the urine sample for a newborn’s drug screen detects exposure to amphetamine, cocaine, cannabinoids, benzodiazepines, buprenorphine, methadone, and other opiates. Mecumion analysis is another frequently used method (Launiainen et al., 2013). Hair and umbilical cord samples have been submitted to drug screening as well (Kocherlakota, 2014). Urine screening can also be used for detecting norbuprenorphine, a metabolite of buprenorphine, since the highest urine concentration of norbuprenorphine in the first three days of life predicts the length of morphine treatment and hospital stay after buprenorphine exposure (Hytinantti et al., 2008).

Only a few studies have attempted to measure the effects of prenatal opioid exposure on CNS function in humans. One study reported that compared with nonexposed newborns, opioid-exposed newborns had less electroencephalography (EEG) measurements that could be classified as normal (van Baar et al., 1989). Opioid-exposed newborns have also been assessed for alterations in the sleep-wake cycle, revealing an increase of active sleep (AS) and a concomitant reduction of quiet sleep (QS) (Dinges et al., 1980; Pinto et al., 1988).
Their sleep disturbances, namely sleep deprivation, disorganization, and fragmentation, are related to the severity of NAS (O’Brien and Jeffery, 2002). Morphine used in NAS treatment can also cause EEG changes (Young and da Silva, 2000). In addition to EEG studies, the cry of methadone-exposed infants is characterized by higher levels of vocal fold vibratory perturbation than the cry of nonexposed infants (Quick et al., 2009).

The need for initiating pharmacological NAS treatment and determination of the dosing and length of pharmacological treatment are evaluated with abstinence scoring systems such as Finnegan, Lipsitz, or Ostree Tools (Finnegan et al., 1975; American Academy of Pediatrics, 1998). Finnegan scoring is used at HUCH, and newborns with scores >8 three times successively or >12 two times successively receive oral morphine hydrochloride treatment (Finnegan et al., 1975). Overall, morphine hydrochloride is the preferred drug for treatment of opioid-induced NAS. Other drugs used include buprenorphine, chlorpromazine, clonidine, methadone, phenobarbital, and paregoric (American Academy of Pediatrics, 1998; Kocherlakota, 2014). Compared with supportive care only, opioids may reduce the time to regain birth weight and the duration of supportive care, but increase the duration of hospital stay (Osborn et al., 2010b). Opioids have also been reported to reduce the incidence of seizures relative to phenobarbital (Osborn et al., 2010b). One study, however, indicated that the length of opioid treatment may be shorter in methadone-treated than morphine-treated newborns (Brown et al., 2015). Supplementing phenobarbital with opioid therapy may diminish withdrawal severity (Osborn et al., 2010a). However, the Cochrane review states that sufficient evidence of the safety of opioids in NAS treatment is lacking (Osborn et al., 2010b). Treatment of NAS has been frequently accomplished in neonatal intensive care units. Weaning at postnatal wards, in the outpatient setting, or at home has also been performed (Saiki et al., 2010; Backes et al., 2012; Kelly et al., 2015).

Nonpharmacological care is generally recommended for treatment of NAS. It can be used either as the first-phase treatment in mild NAS symptoms or in addition to pharmacological treatment. Swaddling, holding, kangaroo treatment, pacifiers, frequent feeding, and water beds have been used in supportive care. Gentle handling, avoiding noise, and dimming room lights create a calmative environment (Committee on Drugs, 1998; Velez and Jansson, 2008; Kocherlakota, 2014). Breastfeeding may decrease NAS symptoms (Pritham, 2013). Supportive measures are inexpensive and are generally viewed as unharful for newborns, although scientific evidence for their effectiveness is lacking.

Withdrawal symptoms are associated with the risk for early mother-infant attachment, which is
known to be important for later emotional development – other long-term health effects of NAS remain unclear (Velez and Jansson, 2008). For society, treatment of NAS is expensive. In the US, there were 9674 unweighted discharges for NAS, with a mean hospital charge of 53 400 USD in 2009 (Patrick et al., 2012).

3.6.3 Visual evoked potential responses and ophthalmic disorders

Visual evoked potential (VEP) responses have been used to measure visual maturation of opioid-exposed newborns. The VEPs from methadone-exposed newborns have been reported less likely to be of typical waveform and more likely to be immature, nondetectable, and smaller in amplitude than those of control newborns (McGlone et al., 2008; McGlone et al., 2013). After one week, the VEPs of methadone-exposed newborns matured, but they remained of lower amplitude than VEPs of control newborns and were nondetectable in 15% (McGlone et al., 2008). The Australian study of Whitham and colleagues (2010) found that 4-month-old methadone-exposed children had prolonged VEP latencies compared with buprenorphine-exposed and control children. After adjustment of covariates, methadone-exposure remained a significant predictor of VEP response to a checkerboard pattern of 48° of retinal arc, but not to pattern of 69° of retinal arc. The authors concluded that buprenorphine could possess an advantage over methadone in terms of visual maturation at 4 months of age, and responses to smaller stimuli, which require greater maturation of visual pathways, may be affected easier than responses to larger stimuli in methadone-exposed children. The prognostic value of VEPs for long-term neurological development of opioid-exposed children is not known. However, the abnormal features of the VEPs predict adverse outcomes in term newborns with birth asphyxia (Kato and Watanabe, 2006) and in children with visual attentiveness (Inuma et al., 1997).

A variety of ophthalmic problems have been suggested in opioid-exposed children. Nelson et al. (1987) examined 40 substance-exposed children as newborns. Of this group, 29 children were examined at regular intervals up to 5 years of age; 17 children were exposed to heroin or some other opioid. Strabismus was found in 24% of children. Gill et al. (2003) assessed the ophthalmological examination for 29 children aged 6-39 months exposed to heroin, methadone, or other opioids. Several types of eye problems were noted: exotropia, exotropia, strabismus after treating persistent hyperplastic primary vitreous, and hypermetropia. Strabismus was found in 7 patients (24%), and one patient had a previous
history of squint. Mulvihill et al. (2007) included in their study 12 children aged 6-118 months who had been exposed to heroin or methadone. Ophthalmic disorders such as nystagmus, esotropia, exotropia, optic nerve hypoplasia, and delayed visual maturation were found. Hamilton et al. (2010) examined 20 heroin- and methadone-exposed children (aged from 3 months to 7 years) and found that 30% of patients had strabismus, 70% had nystagmus, 95% had reduced acuity, 30% had refractive errors, 50% had delayed visual maturation, and 25% had cerebral visual impairment. In the study of Gupta et al. (2012), 24 opioid-exposed children (aged 4-65 months) were diagnosed with a variety of ophthalmic disorders such as nystagmus, esotropia, exotropia, bilateral optic nerve hypoplasia, bilateral hyperopia of +2.5 diopters or greater, mild myopia, and delayed visual maturation. Strabismus was found in 64% of patients, and bilateral hyperopia was diagnosed in 56% of patients.

Study populations in former research are relatively small (<30 patients), and often no control group is provided. Confounding factors, such as polydrug exposure, exist in several studies so the link between the eye disorders and opioid exposure cannot be ensured. However, maternal substance abuse overall has been associated with a higher prevalence of strabismus and nystagmus in siblings (Spiteri Cornish et al., 2013). In some children, these findings persist and may result in a lack of binocularity and poor visual acuity (Spiteri Cornish et al., 2013).

3.6.4 Congenital disorders

Congenital disorders are pathological conditions that exist already during pregnancy and may be discovered in pregnancy, at birth, or later. During the past decades efforts have been made to determine whether prenatal opioid exposure causes any specific congenital disorders in humans.

Saxen (1975) studied 599 children with cleft palate or cleft lip (with or without cleft palate) and found that their mothers had used opioid analgesics (mainly codeine) more frequently than the control group in pregnancy. The greatest difference between groups for codeine use was in the drug consumption in the first trimester of pregnancy. Yet, a case-control study in Connecticut revealed that exposure to narcotic analgesics in the first trimester was more frequent in mothers of children who had inguinal hernias, ventricular and atrial septal defect, other heart and circulatory system defects, cleft lip and palate, dislocated hip, and other

history of squint. Mulvihill et al. (2007) included in their study 12 children aged 6-118 months who had been exposed to heroin or methadone. Ophthalmic disorders such as nystagmus, esotropia, exotropia, optic nerve hypoplasia, and delayed visual maturation were found. Hamilton et al. (2010) examined 20 heroin- and methadone-exposed children (aged from 3 months to 7 years) and found that 30% of patients had strabismus, 70% had nystagmus, 95% had reduced acuity, 30% had refractive errors, 50% had delayed visual maturation, and 25% had cerebral visual impairment. In the study of Gupta et al. (2012), 24 opioid-exposed children (aged 4-65 months) were diagnosed with a variety of ophthalmic disorders such as nystagmus, esotropia, exotropia, bilateral optic nerve hypoplasia, bilateral hyperopia of +2.5 diopters or greater, mild myopia, and delayed visual maturation. Strabismus was found in 64% of patients, and bilateral hyperopia was diagnosed in 56% of patients.

Study populations in former research are relatively small (<30 patients), and often no control group is provided. Confounding factors, such as polydrug exposure, exist in several studies so the link between the eye disorders and opioid exposure cannot be ensured. However, maternal substance abuse overall has been associated with a higher prevalence of strabismus and nystagmus in siblings (Spiteri Cornish et al., 2013). In some children, these findings persist and may result in a lack of binocularity and poor visual acuity (Spiteri Cornish et al., 2013).

3.6.4 Congenital disorders

Congenital disorders are pathological conditions that exist already during pregnancy and may be discovered in pregnancy, at birth, or later. During the past decades efforts have been made to determine whether prenatal opioid exposure causes any specific congenital disorders in humans.

Saxen (1975) studied 599 children with cleft palate or cleft lip (with or without cleft palate) and found that their mothers had used opioid analgesics (mainly codeine) more frequently than the control group in pregnancy. The greatest difference between groups for codeine use was in the drug consumption in the first trimester of pregnancy. Yet, a case-control study in Connecticut revealed that exposure to narcotic analgesics in the first trimester was more frequent in mothers of children who had inguinal hernias, ventricular and atrial septal defect, other heart and circulatory system defects, cleft lip and palate, dislocated hip, and other
musculoskeletal defects (Bracken and Holford, 1981). Narcotic analgesics exposure in the second trimester was more common in mothers of children with alimentary tract defects (Bracken and Holford, 1981). Another case-control study described a potential association between neuroblastoma and in utero exposure to codeine (Cook et al., 2004). Furthermore, Brousard et al. (2011) presented a population-based case-control study including data of 17,449 children with congenital disorders and 6701 controls. Their analysis suggested associations between mothers’ opioid treatment and spina bifida, gastrochisis, conoventricular septal defects, atrioventricular septal defects, and hypoplastic left heart syndrome. In addition, a Croatian study of 86 newborns exposed to heroin and/or methadone found that 8% had an anomaly (Vucinovic et al., 2008). Congenital heart defects were the most common anomalies (Vucinovic et al., 2008). A Swiss study of 78 newborns of methadone-using mothers reported 15% to have some type of congenital malformation (Arlettaz et al., 2005).

Few brain magnetic resonance imaging (MRI) studies have been performed for opioid-exposed children. One MRI study showed no major structural anomalies in brains of opioid-exposed newborns (Kahila et al., 2007a), but another study detected morphometric changes, with opioid-exposed children’s basal ganglia being significantly smaller and lateral ventricular volumes being larger than the population’s mean values (Yuan et al., 2014).

Not all studies have found the number of congenital disorders to be increased following prenatal opioid exposure. A Norwegian study did not find a significant difference in the number of malformations in offspring of 2666 women who used codeine during pregnancy compared with 65,316 women who did not use opioids during pregnancy (Nezvalova-Henriksen et al., 2011). In an Australian study of 879 substance-exposed children, only about 2% had a congenital disorder (congenital heart defects, gastrochisis, or Down’s syndrome) (Abdel-Latif et al., 2013). Methadone- and buprenorphine-exposed newborns had no overt anomalies in the study of Kakko et al. (2008). In summary, previous research has not shown any clear connection between gestational opioid exposure and congenital disorders (Behnke et al., 2013).

3.6.5 Mother-infant relationship
Attachment theory originates from the pioneering work of psychiatrist John Bowlby. Attachment behavior is “seeking and maintaining proximity to another individual”
Attachment can be seen as lasting psychological connectedness between humans, and it is thought to develop in phases, with the process continuing beyond infancy. A significant amount of interaction with a caregiver is needed to achieve optimal attachment. Four attachment patterns have been categorized: secure, avoidant, resistant, and disorganized (Benoit, 2004).

Secure attachment supports favorable development, mental health, and success in future relationships (Benoit, 2004). Attachment security could thus serve as an important protective factor also for opioid-exposed children. However, opioid-using women appear less positive with their newborns and less responsive to their children than control mothers (Bernstein et al., 1986; Bernstein and Hans, 1994). One study observed that methadone-using mothers display disorganized and avoidant behavior and less contact-maintaining behavior than mothers of control children (Goodman et al., 1999).

Emotional availability is a relationship construct reflecting the adaptive exchanges that affect emotional communications between children and parents (Emde, 1980). Secure attachment in infancy has been associated with emotional availability. Emotionally available mothers are likely to have children who have secure attachment (Ziv et al., 2000). Salo et al. (2010) assessed mother-infant relationships with Emotional Availability Scales for three groups: buprenorphine-using mothers and their infants, mothers with depression and their infants, and healthy control mothers and their infants. Infants were 7-9 months of age. Buprenorphine-exposed infants showed lower scores in infant involvement than the two other groups. Furthermore, buprenorphine-using mothers had lower scores in maternal sensitivity, structuring, and nonintrusiveness than mothers in the other groups. Criminal record and mother’s foster care in childhood were significantly related to lower sensitivity and higher intrusiveness.

One study examined parenting skills of 32 pregnant women receiving buprenorphine maintenance treatment. Adult-Adolescent Parenting Inventory version 2 and Childhood Experience of Care and Abuse Questionnaire were used in an interview (Rizzo et al., 2014). The study found that the mothers had low empathy, unrealistic expectations of the child, belief in corporal punishment, reversal perception of parent-child roles, and oppressive features in behavior related to their children. Mothers were concerned about their child’s health and NAS, but did not express concern about their own parental skills (Rizzo et al., 2014). Socioemotional interactions between children and their opioid-using mothers pose a concern and require treatment and prevention. Parenting interventions for high-risk families

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have concentrated mainly on improving maternal sensitivity, and they have been shown to be clinically effective (Wright et al., 2015).

### 3.6.6 Behavioral and developmental problems in early childhood

Methadone-exposed children have been presented as having mental and motor developmental delays at 1-2 years of age (Strauss et al., 1979; Rosen and Johnson, 1982; Johnson et al., 1984). In recent years, studies have elucidated also the neurocognitive outcome of prenatally buprenorphine-exposed children (Safari et al., 2009; Whitham et al., 2010; Salo et al., 2010; Konijnenberg and Melinder, 2013; Melinder et al., 2013; Sundelin Wahlsten and Sarman, 2013; Konijnenberg and Melinder, 2013a; Konijnenberg and Melinder, 2015b). The main results of studies of buprenorphine-exposed children’s health are presented in Table 1.

Some researchers have tried to distinguish the effects of prenatal opioid exposure and later environment on cognitive development. Wilson et al. (1979) enrolled in their study four groups of 3- to 6-year-old children: heroin-exposed children, nonexposed children living in a “drug environment”, control children with other types of medical risks, and children with a socioeconomic background similar to that of heroin-exposed children. Results did not significantly differ between groups in the Columbia Mental Maturity Scale, but heroin-exposed children had the lowest scores in the General Cognitive Index of McCarthy Scales of Children’s Abilities and in the Illinois Test of Psycholinguistic Abilities subtests measuring organizational processes. Heroin-exposed children also showed impulsiveness, aggressiveness, and problems in peer relations. The authors concluded that the noticed problems in heroin-group may derive from prenatal substance exposure rather than being consequences of environmental factors after birth.

An Israeli study conducted by Ornoy and colleagues (1996) comprised 83 heroin-exposed children between 0.5 and 6 years of age, 44 of whom were adopted soon after birth. Control groups were 76 children born to heroin-dependent fathers, 50 children living in a deprived environment, 50 children living in families of moderate or high socioeconomic status, and 80 normal control children recruited from kindergartens. For measuring developmental quotient (DQ) and motor ability, Bayley Developmental Scales were used for children up to two years of age. For measuring intelligence quotient and motor ability, McCarthy Scales were used for children over three years of age. The children of heroin-dependent mothers have concentrated mainly on improving maternal sensitivity, and they have been shown to be clinically effective (Wright et al., 2015).
scored significantly lower on the Bayley or McCarthy Cognitive Developmental Scale than normal controls. The children who lived in a severely deprived environment had the lowest results, even when compared with heroin-exposed children living at home. Children born to heroin-dependent mothers and raised at home obtained significantly lower mental scores on the Bayley test and poorer mental and motor scores on the McCarthy test than adopted children of heroin-dependent mothers. The adopted heroin-exposed children had a lower incidence of behavioral disorders than heroin-exposed children raised at home. Behavioral disorders (hyperactivity, inattention, impulsivity, and aggression) were found in 74% of children of heroin-dependent mothers living at home, 20% of adopted children of heroin-dependent mothers, 42% of children of heroin-dependent fathers, 37% of children who lived in environmental deprivation, and 5% of normal controls.

Ornoy et al. (2001) studied children aged between 5 and 12 years and compared heroin-exposed children living at home, heroin-exposed children adopted at a young age, control children living with a drug-dependent father, control children in families with a low socioeconomic status, and control children living in families with an average socioeconomic status. Children born to parents with heroin dependency and raised at home and children of low socioeconomic status exhibited impairments in verbal, performance, reading, and arithmetic skills. Adopted children born to mothers with heroin dependency had otherwise normal intellectual and learning abilities, except for reduced results on performance. The study found a high rate of ADHD among all children with a heroin-using parent as well as among children with a low parental socioeconomic status; mothers of these children also had high rate of ADHD. Of children, the highest ADHD rate (54%) was in heroin-exposed children raised at home, being twice that noted in the other groups.

Environmental factors in development have also been emphasized in the American study of Hans and Jeremy (2001). In the first two years of life, opioid-exposed children exhibited poorer results than the demographically comparable control group on Bayley Scales Mental and Psychomotor Development indices and on Infant Behavior Record ratings of mental and motor functioning. Still, in both groups performance fell within the normal range during infancy, and scores in both groups dropped during the second year of life relative to norms. The authors found that poorer performance of opioid-exposed children in mental development was related to social-environmental risk factors, and results in psychomotor development were associated with reduced birth weight. Furthermore, Messinger et al. (2004) assessed in a longitudinal study the scores on Bayley Scales of Infant Development II scored significantly lower on the Bayley or McCarthy Cognitive Developmental Scale than normal controls. The children who lived in a severely deprived environment had the lowest results, even when compared with heroin-exposed children living at home. Children born to heroin-dependent mothers and raised at home obtained significantly lower mental scores on the Bayley test and poorer mental and motor scores on the McCarthy test than adopted children of heroin-dependent mothers. The adopted heroin-exposed children had a lower incidence of behavioral disorders than heroin-exposed children raised at home. Behavioral disorders (hyperactivity, inattention, impulsivity, and aggression) were found in 74% of children of heroin-dependent mothers living at home, 20% of adopted children of heroin-dependent mothers, 42% of children of heroin-dependent fathers, 37% of children who lived in environmental deprivation, and 5% of normal controls.

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at 1, 2, and 3 years of corrected age for infants exposed to cocaine (n = 474), opiates (n = 50) and cocaine and opiates (n = 48). The control group comprised 655 nonexposed children. Opiate-exposed infants scored 3.8 Psychomotor Development Index points below nonexposed infants, but the effect of opiate exposure was not significant after controlling for covariates. In all groups, low birth weight and nonoptimal caregiving were associated with poorer results on the Mental Development Index, Psychomotor Development Index, and Behavioral Record Score.

The German study of Bunikowski et al. (1998) reported that 27 one-year-old opioid-exposed children’s average Griffiths Developmental Quotient, and the “locomotor” and “intellectual performance” subscales were significantly poorer than in control children. Of opioid-exposed children, 67% were living in foster families at one year of age. This study did not find a significant difference in outcome between children living in foster families and those living at home. Twelve mothers had drug relapse during their child’s first year of life, and children were by that time living in the care of other relatives. This may have moderated the results to reduce the difference nonsignificant between children living at home and those in foster care.

A substantial number of factors may vary between studies of opioid-exposed children and be explanatory in outcome, e.g. polydrug exposure in pregnancy, quality of prenatal and neonatal care, emotional relationship between child and caregiver, and support from child welfare services. The discrepancies in results of neurocognitive outcome of opioid-exposed children living at home versus in foster care/adoption family can be explained by multifaceted environmental circumstances that may either protect or harm normal development.
Table 1. Studies on health and development of buprenorphine-exposed children after neonatal age.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Prenatal exposure and size of study/control population</th>
<th>Outcome measures</th>
<th>Main Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sarfi et al. 2009</td>
<td>35 opioid-exposed (24 methadone-exposed and 11 buprenorphine-exposed) children were considered as a single group. 36 control children.</td>
<td>Distributions and frequencies of sleep, wakefulness and distress measured in hours and episodes on sleep charts recorded by the mothers at 3 months age.</td>
<td>No significant difference to controls.</td>
</tr>
<tr>
<td>Whitham et al. 2013</td>
<td>30 buprenorphine-exposed children, 22 methadone-exposed children, 33 control children not exposed to opioids.</td>
<td>Emotionality of patterns of visual VEP at 4 months age.</td>
<td>Methadone-exposed children had prolonged latencies compared to buprenorphine-exposed and control children. After covariables’ adjustment methadone-exposure remained a significant predictor of VEP response to checks of 48”, but not 60”.</td>
</tr>
<tr>
<td>Salo et al. 2010</td>
<td>15 buprenorphine-exposed children and their mothers, 15 control children and mothers who had depression 57 control children and their mothers</td>
<td>Cognitive development measured with Bayley-II MDI and mother-child interaction with Emotional Availability Scale at 7-9 months of age.</td>
<td>Cognitive development measured with Bayley-II MDI and mother-child interaction with Emotional Availability Scale at 7-9 months of age. Buprenorphine-exposed children performed lower scores at Bayley-II MDI test and in infant involvement than children in two other groups. Buprenorphine-exposure: mothers had lower scores in maternal sensitivity, structuring and nonintrusiveness than mothers in two other groups. Mothers’ criminal record and foster care in childhood were significantly related to lower sensitivity and higher intrusiveness.</td>
</tr>
<tr>
<td>Sarfi et al. 2011</td>
<td>16 opioid-exposed, 15 methadone-exposed and 11 buprenorphine-exposed children of smoking mothers were considered as a single group. 35 control children.</td>
<td>Quality of mother–infant relationship when the infants were 6 months old. Vidopedal mother–infant interactions rated on a global scale (NICHD) and child development evaluated with BINS and TSFI tests.</td>
<td>Quality of mother–infant relationship when the infants were 6 months old. Video’doped mother–infant interactions rated on the NICHD rating scale (based on the free-play situation) contributed significantly with dyad adherence. The importance of group status (exposed vs. non-exposed) diminished after controlling variables such as maternal depression and prenatal stress.</td>
</tr>
<tr>
<td>Konjajzberg et al. 2013</td>
<td>15 methadone- or buprenorphine-exposed children were considered as a single group. 35 control children.</td>
<td>Oculomotor directed eye movements, visual attention from NEPSY and subtest Perception from the Bender Gestalt II, fine motor function (subtest Fine motor from Bender Gestalt II and subtest Hand positions from NEPY), goal belief understanding (ToBI) measured at 4 years age.</td>
<td>Oculomotor directed eye movements, visual attention from NEPSY and subtest Perception from the Bender Gestalt II, fine motor function (subtest Fine motor from Bender Gestalt II and subtest Hand positions from NEPSY), goal belief understanding (ToBI) measured at 4 years age. Buprenorphine-exposed children had less proactive goal-directed eye movements than control children. No differences were found in visual perception or goal understanding.</td>
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<td>Sundén Wahlén and Sarman, 2013 (Sweden)</td>
<td>25 buprenorphine-exposed children. No comparison group.</td>
<td>Neurobehavioral development at 5-6 years of age (WPPSI-R, MCSA, BROWN and SDQ). Growth.</td>
<td>Results in WPPSI-R Performance Scales were below normal. In the MCSA evaluation, the children had lower scores, compared with normal population, on the Motor, the Memory, the Verbal and General Cognitive scales. Teachers' estimations showed significantly elevated levels of hyperactivity, impulsivity on the ADHD scale in BROWN and in SDQ tests. The somatic growth was normal.</td>
</tr>
<tr>
<td>Melinder et al. 2013 (Norway)</td>
<td>26 opioid-exposed (18 methadone-exposed and 8 buprenorphine-exposed) children were mainly considered as a single group (some separate analyses for methadone and buprenorphine were made). 23 control children.</td>
<td>Eye movements and smooth pursuit were recorded at 4 years age with Tobii 1750 Eyetracker. Vestibular functions were examined by Bender test.</td>
<td>Excerice function was measured with neuropsychological tests: Statue subtest from NEPSY and subtests Animal Pegs, Sensomotor, Day-night, Comprehension and Block Design from WPPSI-R. BRIEF-P was also performed. Children were aged between 48 and 57 months.</td>
</tr>
<tr>
<td>Konjezuberg et al. 2013a (Norway)</td>
<td>36 opioid-exposed (24 methadone-exposed and 11 buprenorphine-exposed) children, additionally mentioned that seven children were exposed to some other opioid as well). 31 control children.</td>
<td>Eye movements and smooth pursuit were recorded at 4 years age with Tobii 1750 Eyetracker. Vestibular functions were examined by Bender test.</td>
<td>Executive function was measured with neuropsychological tests: Statue subtest from NEPSY and subtests Animal Pegs, Sensomotor, Day-night, Comprehension and Block Design from WPPSI-R. BRIEF-P was also performed. Children were aged between 48 and 57 months.</td>
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<td>Konjezuberg et al. 2013b (Norway)</td>
<td>22 methadone-exposed children and 9 buprenorphine-exposed children. 25 control children.</td>
<td>Visual selective attention measured with a Tobii 1750 Eye Tracker using a spatial negative priming paradigm, and attention problems - measured using the Child Behavior Checklist at 4 years age.</td>
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3.6.7 Hepatitis B, hepatitis C, and human immunodeficiency virus infections

Intravenous opioid use of the mother increases her risk for HBV, HCV and HIV infection and predisposes also the newborn and child for contagion. In Finland, 71-80% intravenous drug users are positive for HCV and around 3% for HBV, and about 1-2 % of intravenous drug users have HIV infection (Varjonen, 2015).

If mother is positive for hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg), 40%-90% of infants will acquire HBV infection (Margolis et al., 1995; Centers for Disease Control and Prevention, 2012). Approximately 90% of infected infants develop chronic HBV infection (Centers for Disease Control and Prevention, 2012). For infants born to HBsAg-positive women, immunoprophylaxis is reported to be 85% to 95% effective in preventing perinatally acquired chronic HBV infection. For HCV, vertical transmission is about 3-6% (Arshad, 2001; Benova et al., 2014). Transmission of HIV has been avoided in all HIV positive pregnancies in Finland. In 2009, there were two cases of mother to child transmission of HIV, but transmission had occurred before arrival in Finland (European Centre for Disease Prevention and Control, 2013).

3.6.8 Growth

Growth of opioid-exposed children has been evaluated in several studies. Chasnoff et al. (1986) reported that prenatally opiate exposed newborns were smaller than control newborns at birth. They caught up with control children by nine months of age in weight and length, but their head circumference remained significantly smaller to two years of age (Chasnoff et al., 1986). Another study reported that the mean birth lengths of opioid-exposed children were under the length of control children, but the mean height was comparable between groups at 3 years of age (Lifschitz et al., 1983). In a study of 1094 children, of which 137 were HIV-positive and 383 were exposed in utero to opioids or cocaine, both HIV-1 infection and drug exposure were associated with a smaller head circumference at 4 months of age, but at 24 months of age only HIV-1 infection remained associated with head circumference (Macmillan et al., 2001). Furthermore, in the thesis of Whitham (2012), she reported that growth of prenatally buprenorphine-exposed children was normal over the first two years of life, but methadone-exposed children had significantly lower weight, compared to non-exposed control children, until two years of age.
3.6.9 Mortality
A meta-analysis of studies published between 1966 and 1996 suggested an increased risk for neonatal mortality in opioid-exposed children (Hulse et al., 1998a). Kahlert et al. (2007) reported an elevated risk for sudden infant death syndrome (SIDS) in opioid-using HIV-infected mothers' children relative to control children. Ostrea et al. (1997) reported 6.7 SIDS deaths per 1000 live births and a mortality rate of 18.4 per 1000 live births in opioid-exposed children to two years of age. Kelly et al. (2012) did not observe an increased risk for mortality in methadone-exposed children to one year of age.

3.7 Prenatal exposure to other substances: overview of effects

3.7.1 Alcohol
Poor habituation and low levels of arousal along with motor abnormalities have been identified in newborns whose mothers have consumed significant amounts of alcohol during their pregnancy (Pierog et al., 1977; Streissguth et al., 1983). Alcohol use of the mother during pregnancy can cause fetal alcohol spectrum disorder (FASD). FASD is an umbrella term describing a range of several types of effects that alcohol has on children. Fetal alcohol syndrome (FAS) is the most serious type of FASD. The criteria for FAS diagnosis are growth deficits, CNS abnormality, and three facial abnormalities: smooth philtrum, thin vermilion, and small palpebral fissures (Astley, 2004). In addition to CNS abnormalities, several other anomalies may occur in children with FAS, although their existence is not needed for FAS diagnosis (Astley, 2004). Vision impairment and ophthalmological problems appear in children with FAS (Strömland, 2004).

3.7.2 Tobacco
Maternal smoking during pregnancy increases the risk for prematurity (U.S. Department of Health and Human Services, 2014). Prenatally tobacco-exposed newborns have presented with impaired orientation and autonomic regulation, hypertonicity, excitability, stress/abstinence signs, tremors, and diminished auditory habituation (Fried and Makin, 1987; Dempsey et al., 2000; Law et al., 2003). Prenatal tobacco exposure reduces birth weight, birth length, and head size of the newborn (Hardy and Mellits, 1972; Rantakallio, 1987; Dempsey et al., 2000; Law et al., 2003). Prenatal tobacco exposure reduces birth weight, birth length, and head size of the newborn (Hardy and Mellits, 1972; Rantakallio, 1987; Dempsey et al., 2000; Law et al., 2003).
1983; Vik et al., 1996; Roza et al., 2007; U.S. Department of Health and Human Services, 2014; Eckblad et al. 2015). Growth delay at birth may resolve in the first year of life (Hardy and Mellits, 1972; Day et al., 1992; Conter et al., 1995). The long-term effect on growth is attributable to a disproportionate weight for height, with prenatally tobacco-exposed children more likely being obese (DiFranza et al., 2004).

Maternal smoking has been associated with an elevated risk of strabismus in the child, increasing with number of cigarettes smoked per day (Torp-Pedersen et al., 2010). Tobacco exposure has also been related to orofacial clefts (Little et al., 2004; Hackshaw et al., 2011; U.S. Department of Health and Human Services, 2014), musculoskeletal anomalies (Hackshaw et al., 2011) and congenital heart defects (Hackshaw et al., 2011). Prenatal tobacco exposure may be related to behavioral disorders, especially to attention deficit hyperactivity disorder. In addition, maternal smoking may cause reduced lung function in childhood and increased risk for SIDS (U.S. Department of Health and Human Services, 2014).

### 3.7.3 Benzodiazepines

Symptoms and signs of hypertonicity, hypoventilation, hyperirritability or “floppy infant syndrome” with hypotonia, feeding problems, and lethargy have been suggested after gestational benzodiazepine exposure (Gilberg, 1977; Rementeria and Bhatt, 1977). A birth register study in Sweden detected an increased risk for preterm birth and low birth weight in children exposed to benzodiazepines and/or benzodiazepine receptor agonists (Wikner et al., 2007). No clear connection has been found between congenital disorders and maternal benzodiazepine use (Dolovich et al., 1998; Wikner et al., 2007; Ban et al., 2014).

### 3.7.4 Cannabis

Cannabis may be associated with fetal growth restriction in pregnancy (El Marroun et al., 2009). However, there is insufficient evidence that cannabis causes a specific type of anomaly. Prenatal cannabis exposure does not lead to a neonatal withdrawal syndrome as obvious as that caused by opioids, but slight neurobehavioral symptoms may occur. Exaggerated and prolonged startle reflexes (Fried, 1995), changes in crying characteristics (Lester and Dreher, 1989), and sleep cycle disturbances (Scher et al., 1988) have been
reported after gestational exposure. One study associated prenatal exposure to cannabis with aggressive behavior in 18-month-old girls (El Marroun et al., 2011). Increased externalizing behavior (Fried et al., 1998; Goldschmidt et al., 2000) and deficits in visuoperceptual functioning (Fried et al., 1998; Fried, 2002) have been suggested to exist in school-aged children.

3.7.5 Amphetamine

Congenital disorders have not been associated with gestational amphetamine (alpha-methylphenethylamine) exposure. Effects on newborn neurobehavior are presumably subtle and do not generally require pharmacological treatment. Research data of possible long-term consequences of prenatal amphetamine exposure are scarce (Oei et al., 2012).

3.8 Magnetoencephalography

MEG is a noninvasive imaging technique that can measure brain electrical activity. Neuronal activity creates weak extracranial magnetic fields and superficial sources, e.g. in cerebral sulci, can be measured with MEG. These magnetic fields are hard to reach with EEG, but they can be detected with MEG with a temporal resolution of a millisecond (Hari et al., 2010). MEG is insensitive to strictly radial currents relative to EEG, which measures currents of all orientations. MEG is also practically transparent to tissue defects in brain and skull between the active brain source and the measuring device (Hämäläinen et al., 1993). MEG has been used in detecting epileptic seizures and localizing sensory, motor, and auditory areas prior to operations (Paetau and Mohamed, 2013). However, it has also been shown to be a useful tool in predicting outcome of high-risk newborns (Majnemer et al., 1990; Pike and Marlow, 2000; Rahkonen et al., 2013).

3.9 Child maltreatment

Pediatrician Henry Kempe and his colleagues published the landmark paper “The Battered Child Syndrome” in 1962 (Kempe et al., 1962). He was the first ones to identify child abuse and brought it to the attention of physicians. Concepts of child maltreatment may vary depending on whether they are used in the field of medicine, law, or child welfare. Cultural


discrepancies exist about what is understood to be child maltreatment. Medical literature typically distinguishes four main types of child maltreatment: child neglect, physical abuse, sexual abuse, and emotional abuse, which are also the categories outlined in the WHO (Butchart, 2002). The terms “child maltreatment” and “child abuse and neglect” are often used interchangeably. Some definitions of child maltreatment are presented in Table 2.

**Table 2. Definitions of child maltreatment.**

<table>
<thead>
<tr>
<th>Type of Abuse</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child maltreatment</td>
<td>is defined as “all forms of physical and/or emotional ill-treatment, sexual abuse, neglect or negligent treatment, or commercial or other exploitation, resulting in actual or potential harm to the child’s health, survival, development, or dignity in the context of a relationship of responsibility, trust, or power” (Butchart, 2002).</td>
</tr>
<tr>
<td>Child neglect</td>
<td>comprises “both isolated incidents, as well as a pattern of failure over time on the part of a parent or other family member to provide for the development and well-being of the child – where the parent is in a position to do so – in one or more of the following areas: health, education, emotional development, nutrition, shelter, and safe living conditions” (Butchart, 2002).</td>
</tr>
<tr>
<td>Dental neglect</td>
<td>is classified as “the persistent failure to meet a child’s basic oral health needs, likely to result in the serious impairment of a child’s oral or general health or impairment” (Harris et al., 2009).</td>
</tr>
<tr>
<td>Medical neglect</td>
<td>arises from “a failure to provide prescribed care or treatment or failure to seek appropriate medical care in a timely manner” (Jenny et al., 2007).</td>
</tr>
<tr>
<td>Physical abuse</td>
<td>is defined as “the intentional use of physical force against a child that results in – or has a high likelihood of resulting in – harm for the child’s health, survival, development, or dignity” (Butchart, 2002).</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>is defined as “the involvement of a child in sexual activity that he or she does not fully comprehend, is unable to give informed consent to, or for which the child is not developmentally prepared, or else that violates the laws or social taboos of society. Children can be sexually abused by both adults and other children who are – by virtue of their age or stage of development – in a position of responsibility, trust, or power over the victim” (Burchart, 2002).</td>
</tr>
<tr>
<td>Emotional abuse</td>
<td>is “the failure of a caregiver to provide an appropriate and supportive environment, and includes acts that have an adverse effect on the emotional health and development of a child. Such acts include restricting a child’s movements, denigration, ridicule, threats and intimidation, discrimination, rejection, and other non-physical forms of hostile treatment” (Butchart, 2002).</td>
</tr>
<tr>
<td>Medical child abuse</td>
<td>(alternative names Munchausen syndrome by proxy, pediatric condition falsification, factitious disorder by proxy, child abuse in the medical setting) is defined as “a child receiving unnecessary and harmful or potentially harmful medical care at the instigation of a caretaker” (Roesler and Jenny, 2009).</td>
</tr>
</tbody>
</table>
### 3.9.1 Epidemiology of child maltreatment

It has been estimated that in US 9.1 per 1000 children in a population and a total number of 679,000 children encountered child abuse and neglect in 2013 (U.S. Department of Health and Human Services, 2015). Information of reports to child protective services showed prevalence’s of 79.5% for neglect, 18.0% for physical abuse, 9.0% for sexual abuse, and 8.7% for psychological abuse. In UK, approximately 1 of 5 children have experienced severe maltreatment (Radford et al., 2011). The Canadian Incidence Study of Reported Child Abuse and Neglect reported primary categories of substantiated child maltreatment in Canada in 2008 (Public Health Agency of Canada, 2010). Child neglect was the primary category in 34%, exposure to intimate partner violence in 34%, physical abuse in 20%, emotional maltreatment in 9%, and sexual abuse in 3% of case. In general, child neglect is acknowledged to be the most common form of child maltreatment (Hussey et al., 2006).

There is considerable overlap between different maltreatment types, and the same child may encounter multiple types of maltreatment. Estimates of child maltreatment prevalence are often based on cases reported to officials, most typically to child welfare statistics. The prevalence of child maltreatment has also been evaluated with interviews or questionnaires inquiring whether subjects have been victims of child maltreatment. Alternatively, the study population has been asked whether they themselves have been perpetrators. It is commonly acknowledged that child abuse and neglect are likely underrecognized and underreported and that statistics thus reflect only a fraction of all maltreatment.

Research in child abuse and neglect has leaned on Urie Bronfenbrenner’s ecological model to describe the way in which factors related to child, family, community, and society affect a child’s risk for maltreatment (Bronfenbrenner, 1977). The ecological model originally described a theory for child development as a process in which children and environment interact mutually. Children affect their environment and the environment shapes their development. The model is often sketched as an onion-like structure where the individual is at the core and the outer layers are in successive order of family, community and neighborhood, and society and cultural values. The structure of the ecological model has been later adapted to explain background factors in child maltreatment (Figure 1).

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Proposed indicators for maltreatment risk are listed in Table 3. This list does not take into account, however, the impact of specific factors on different child maltreatment groups, but instead is a generalization of suspected risk factors. For instance, a large meta-analysis evaluated that the strongest risk factors for neglect were parent-child relationships and a parent’s perception of a child as a problem, while child physical abuse was most clearly associated with a parent’s anger/hyper-reactivity, high family conflict, and low family cohesion (Stith et al., 2009). Another example is the child’s gender; girls are thought to be more prone to sexual victimization and boys to physical abuse (Gilbert et al., 2009b).

Moreover, child maltreatment often emerges after cumulation of several risk factors (Brown et al., 1998; Nair et al., 2003). It is noteworthy that protective factors in the environment may shelter the child from being maltreated, even in the presence of risk factors. The protective factors can be seen much as opposites to risk factors (Australian Institute of Family Studies, 2013; Christian et al., 2015).

<table>
<thead>
<tr>
<th>Ecological level</th>
<th>Factors associated to child maltreatment</th>
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<tbody>
<tr>
<td><strong>Individual child factors</strong></td>
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<td></td>
<td>• Child gender</td>
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<td></td>
<td>• Persistent crying</td>
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<td></td>
<td>• Child’s social competence</td>
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<td>• Externalizing behaviors</td>
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<tr>
<td><strong>Family/parental factors</strong></td>
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<td></td>
<td>• Parent gender</td>
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<td>• Young parent</td>
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<td>• Single parent</td>
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<td>• Low level of parental education</td>
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<td>• Parental substance abuse</td>
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<td>• Mental health problems</td>
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<td>• Parent’s low self-esteem</td>
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<td>• Parent’s poor relationship with own parents</td>
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<td></td>
<td>• Parental history of child abuse and neglect</td>
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<td></td>
<td>• Criminal behaviors</td>
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<td>• Large family size</td>
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<td>• Stress over parenting or other personal stress</td>
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<td>• Lack of access to social support and child welfare services</td>
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<td>• The nature and extent of health care of children including preventive health care</td>
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<td>• The nature and responsiveness of criminal justice system in issues considering children</td>
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3.9.2 Consequences of child maltreatment

Child abuse and neglect is linked to a wide range of consequences. Manifestations of child maltreatment in childhood include physical symptoms, disability, sleep problems, attachment disorders, emotional problems, reduced self-esteem, problems in socialization, language delay, cognitive skills delay, behavioral psychopathology such as aggression, conduct disorder and ADHD (Kellogg, 2005; Jones DPH, 2008; Naughton et al., 2013; Christian et al., 2015). At worst, child maltreatment may be fatal (Sidebotham et al., 2011; Damashek et al., 2013; Palusci and Covington, 2014; Christian et al., 2015). An estimated 1520 children died of child maltreatment at a fatality rate of 2.04 children per 100,000 children in 2013 in the U.S. (U.S. Department of Health and Human Services, 2015).

Past research has shown that the consequences of child maltreatment extend to adulthood. Norman et al. (2012) conducted an extensive meta-analysis of how non-sexual maltreatment affects health in adulthood, including 124 studies in the final analysis. They found significant associations between non-sexual maltreatment and depressive disorders, drug use, suicide attempts, sexually transmitted infections, and risky sexual behavior. Moreover, a 30-year longitudinal study of 987 participants (509 females) in New Zealand examined the relationship of sexual abuse that occurred under the age of 16 years with health in later life (Fergusson et al., 2013). Research subjects participated in structured interviews at the ages of 21, 25, and 30 years. After adjusting for confounding covariates (sociodemographic, family-related, and child factors), the extent of sexual abuse exposure was associated with increased rates of major depression, anxiety disorder, suicidal thoughts, suicide attempt, alcohol dependence, and illicit drug dependence. Moreover, sexual abuse was associated with a high rate of post-traumatic stress disorder symptoms, diminished self-esteem, diminished life satisfaction, younger age at onset of sexual activity, elevated number of sexual partners, more medical contacts for physical health issues, and dependence on social welfare.

The review of Gilbert et al. (2009a) summarized the long-term outcome of child maltreatment and evaluated the strength of evidence between maltreatment and later health. They evaluated that studies have proved strong evidence of the link between child maltreatment and behavioral problems in childhood and in adolescence, criminal behavior and post-traumatic stress disorder. They also postulated that there is evidence that child maltreatment is associated to a low educational achievement, employment, depression, alcohol dependence, and illicit drug dependence. Moreover, sexual abuse was associated with a high rate of post-traumatic stress disorder symptoms, diminished self-esteem, diminished life satisfaction, younger age at onset of sexual activity, elevated number of sexual partners, more medical contacts for physical health issues, and dependence on social welfare.

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attempted suicides, alcohol problems, drug misuse or dependence, prostitution or sex trading, teenage pregnancies and obesity.

In addition to the wide range of effects that child maltreatment has on an individual, it also results in marked economic costs for society. It has been estimated that the average lifetime cost per victim of non-fatal child maltreatment was 210,012 USD in 2010 in US (Fang et al., 2012). The total lifetime economic costs resulting from new cases of fatal and non-fatal cases of child maltreatment in US in 2008 was approximately 124 billion USD (Fang et al., 2012). Child welfare costs comprise part of the expenses of child maltreatment. The costs of out-of-home care were 620 million euros in Finland in 2010 (Heinonen, 2012). When the costs of prevention and support measures in open care were added, the child welfare expenses were nearly one billion euros. Child maltreatment has substantial long-term effects on child as well as society and this advocates active improving of prevention strategies.
Our general aim was to uncover novel information on prenatally buprenorphine-exposed children’s health to three years of age. We additionally determined the types of child maltreatment in our study population. Specific aims of Studies I-IV were as follows:

I To elucidate the health problems of prenatally buprenorphine-exposed children up to three years of age. We also identified major issues underlying child welfare reports by pediatricians regarding suspected maltreatment.

II To assess oral health and dental neglect of buprenorphine-exposed children.

III To examine child development of buprenorphine-exposed children at three years of age. Furthermore, we evaluated parental self-efficacy and emotional availability in child-mother relationships.

IV To measure brain electrical activity in response to somatosensory and auditory stimuli in newborns with NAS by magnetoencephalography.
5 STUDY DESIGN

This population-based study comprised altogether 108 children born at HUCH between August 2000 and November 2008 with a positive urine screen for buprenorphine as a newborn. Of these children, 102 were included in the study of children’s general health (I), 51 in the dental study (II), 21 in the psychological study (III), and 11 in the MEG study (IV).

From 2000 to 2008, about 14 000 children were born annually in HUCH, which has a total population coverage of one million in the Helsinki metropolitan area. Substance-abusing women were referred to the tertiary maternity clinics of the Department of Obstetrics and Gynecology at HUCH’s Women’s Hospital for prenatal care and delivery. Newborns of substance-abusing mothers underwent similar neonatal screenings as other newborns, and, furthermore, urine samples for drug screening were collected. Buprenorphine-exposed newborns were supervised at a neonatal ward in case of NAS and evaluated with the Finnegan scale (Finnegan et al., 1975). If Finnegan scores were 8 or more three times successively, medication with oral morphine mixture (and/or phenobarbital) was initiated. All newborns were administered hepatitis B immunoglobulin and the first dose of HBV vaccination before discharge from hospital. Some of the buprenorphine-exposed children with their mothers had also participated in two former studies (Kahila et al., 2007b; Hytinantti et al., 2008).

It has been a well-established practice since 2001 that all substance-exposed children in the Helsinki area have regular visits with a pediatrician at the Social Pediatrics Outpatient Clinic in Children’s Hospital after neonatal age until the age of seven years. This procedure was applied to our study population, including the first patient who was born in 2000. In the first year of life, there are four appointments, and thereafter two appointments per year. The pediatricians who met the children were two of the researchers (S.K.-K. and S.T.). The visits focused on child health and development and possible signs of child maltreatment. Pediatricians cooperated closely with social workers of child welfare. The Child Welfare Act in Finland obligates healthcare professionals "to notify the municipal body responsible for social services without delay and notwithstanding confidentiality provisions if, in the course of their work, they discover that there is a child for whom it is necessary to investigate the need for child welfare on account of the child’s need for care, circumstances endangering the child’s development, or the child’s behavior” (Finlex, 2013). A first report of a child was made to child welfare services about substance abuse of the mother in...
A total of 102 children (61 males and 41 females) born between August 2000 and December 2007 were included in the study. Their mothers’ mean age was 25 (range 18-40) years. The child was born as the first child for 63 mothers, the second child for 23 mothers, the third child for 9 mothers, the fourth child for 5 mothers, and the fifth child for 2 mothers. Of mothers, 51 received buprenorphine in pregnancy as a medical treatment for opioid dependence and 51 had illicit use of buprenorphine. Some of the mothers on opioid maintenance therapy may have also had additional illicit use of buprenorphine. All mothers smoked during pregnancy. Some of them also used benzodiazepines (n=64), cannabis (n=23), amphetamine (n=21), alcohol (n=13), heroin (n=5), methadone (n=1), paracetamol + codeine (n=1), tramadol (n=1), and ecstasy (n=1) during pregnancy. Four mothers had consumed selective serotonin reuptake inhibitors (SSRIs) and ten had used some psychoactive drug other than those mentioned above.

HCV infection presented in 73 mothers and 1 mother had HIV infection. Seven mothers had been infected with HBV, although none had chronic hepatitis B infection. Other underlying diseases and pregnancy complications comprised pre-eclampsia (n=3), hepatogestosis (n=2), gestational diabetes (n=2), type 1 diabetes (n=1), cholestasis of pregnancy (n=1), Rh disease (n=1), polyhydramnion (n=1), and oligohydramnion (n=1). Delivery was performed by elective or emergency Cesarean section on 21 mothers. Ten newborns were born prematurely (<37 weeks of gestational age) and one was born at less than 32 weeks of pregnancy. Of the study population, 58 newborns received medication for NAS treatment, majority of them morphine and 6 newborns born before the year 2007 received phenobarbital with or without morphine. More characteristics of newborns are presented in Table 4.
Table 4. Characteristics of buprenorphine-exposed children (n=102) in Study I.
*mean (range)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Gestational age at delivery (weeks)</td>
<td>39.3 (28.6-42.3)*</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3172 (840-4610)*</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>48 (23.8-54.4)*</td>
</tr>
<tr>
<td>Head circumference at birth</td>
<td>34 (24.9-37)*</td>
</tr>
<tr>
<td>Prematurity 32 to &lt;37 weeks, n (%)</td>
<td>9 (9%)*</td>
</tr>
<tr>
<td>Prematurity 28 to &lt;32 weeks, n (%)</td>
<td>1 (1%)*</td>
</tr>
</tbody>
</table>

5.1.2 Study II

The dental trial comprised a population of 65 prenatally buprenorphine-exposed 3- to 4-year-old children born to tobacco-smoking mothers between February 2002 and February 2006. Of 65 children, 10 (15.4%) had dropped out of the pediatrician’s follow-up after 3.0 years of age, 1 child (1.5%) had been kidnapped and could not be reached by authorities, 2 children (3.1%) had died, and 1 child’s caregiver (1.5%) declined to participate in the study. A total of 51 (29 males and 22 females) children’s guardians (78.5% of 65) signed the informed consent to take part in the trial. In addition to buprenorphine, 16 children were prenatally exposed to benzodiazepines, 2 to amphetamine, 1 to tramadol, and 1 to codeine.

When the dental examination took place, 21 children (41%) were living with a biological parent, 25 children (49%) were in foster care, 4 children (8%) were in emergency placement in residential care, and 1 child was adopted (2%). The total duration of out-of-home care by the time of the examination had varied from 1 month to 52 months. The adopted child was included in the foster care group in the data analysis.

The control group was compiled by nurses from five child health clinics of five Helsinki districts: Haaga, Kallio, Tuomarinkylä, Vallila, and Vartiokylä. The nurses were asked to offer the possibility to participate in the study successively to each Finnish-speaking three-year-old’s parent when the family visited the child health clinic. If the caregiver was willing to attend the study with the child, a research nurse telephoned the family and set an appointment with a dentist and a pediatrician. The control group contained 68 children (39 males and 29 females) born between October 2003 and May 2006. The control children had been living with a biological parent since birth, and they had not been exposed to opioids.
during pregnancy. The mother’s substance use was inquired about at the study appointment. Both buprenorphine-exposed and control children were entitled to public dental care services.

5.1.3 Study III

The caregivers of 28 buprenorphine-exposed children born between December 2002 and January 2005 were informed about the study. Information was given to three-year-old children’s caregivers during their visit to the pediatrician at the Social Pediatrics Outpatient Clinic, and all agreed to participate. The main reason for drop-outs (n=7) was that the participant did not come to a scheduled appointment. Mothers had smoked during pregnancy. Furthermore, 9 children were exposed to benzodiazepines, 9 children to amphetamine, 4 children to alcohol, and 2 children to cannabis. Of the study population, 7 children were living with their biological mother and 14 children with their foster mother (2 children were in kinship care) at the age of three years. Seventeen children had been in out-of-home care for more than a few weeks.

The control group included 13 children and their biological mothers. These children had not been exposed to substances during pregnancy and had lived with their biological mother since birth. They were recruited from six randomly selected well-baby clinics in Turku and Helsinki, Finland. The nurses at the clinics invited every third family to participate in the study, and approximately 90% agreed to participate. Characteristics of buprenorphine-exposed children and control children are shown in Table 5.
Table 5. Characteristics of buprenorphine-exposed children and control children in Study III. Each value is reported as mean (SD). *Education level: 1=compulsory school education, 2=additional occupational education, 3=high school education, 4=academic or higher professional training. ** p<0.01, one-way ANOVA, ***p<0.001, one-way ANOVA

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine-exposed children in parental care n=7</th>
<th>Buprenorphine-exposed children in foster care n=14</th>
<th>Control children n=13</th>
<th>F value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>40.29 (1.38)</td>
<td>39.85 (1.65)</td>
<td>40.92 (1.81)</td>
<td>0.70</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>2990 (422)</td>
<td>3264 (493)</td>
<td>3486 (373)</td>
<td>2.98</td>
</tr>
<tr>
<td>Birth length (cm)</td>
<td>48.4 (1.3)</td>
<td>48.9 (2.7)</td>
<td>50.1 (2.0)</td>
<td>1.60</td>
</tr>
<tr>
<td>Total number of foster placements</td>
<td>2.11 (1.34)</td>
<td>2.70 (1.65)</td>
<td>-</td>
<td>33.82***</td>
</tr>
<tr>
<td>Length of living in current residence (months)</td>
<td>13.70 (10.11)</td>
<td>9.07 (2.84)</td>
<td>-</td>
<td>20.00***</td>
</tr>
<tr>
<td>Mother’s age (years)</td>
<td>28.29 (2.84)</td>
<td>33.93 (4.77)</td>
<td>29.08 (3.20)</td>
<td>7.27**</td>
</tr>
<tr>
<td>Mother’s education level*</td>
<td>2.70 (0.48)</td>
<td>2.42 (0.64)</td>
<td>3.00 (0.71)</td>
<td>2.65</td>
</tr>
</tbody>
</table>

5.1.4 Study IV

Buprenorphine-exposed newborns were enrolled in the MEG study between March 2007 and November 2008. During this period 37 newborns were born with a positive urine screen for buprenorphine. After birth, we managed to reach 19 mothers who were informed about the study and 15 agreed to participate. However, 3 newborns did not fall asleep before MEG and could not get measured, and 1 newborn’s measurement was excluded from the analysis because the stimulus had not worked sufficiently. Thus, we succeeded in measuring 11 buprenorphine-exposed children well. During pregnancy all mothers had smoked, 3 mothers had used alcohol, 2 had used benzodiazepines, and 1 had used amphetamine. Five newborns...
had started morphine treatment for NAS, and four were still on this medication when the MEG was performed. The control group comprised 12 healthy full-term newborns whose mothers did not report any substance abuse (tobacco, alcohol, or drugs). Table 6 shows the characteristics of buprenorphine-exposed newborns and control newborns.

### Table 6. Characteristics of buprenorphine-exposed newborns and control newborns in Study IV. *p=0.001, **p=0.005, independent samples Student’s test.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Buprenorphine-exposed newborns (n=11)</th>
<th>Control newborns (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (days)*</td>
<td>12.3 (3-30)</td>
<td>1.6 (1-3)</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>40.5 (38.1-42.3)</td>
<td>40.4 (39.0-41.7)</td>
</tr>
<tr>
<td>Postmenstrual age (weeks)**</td>
<td>42.2 (39.7-44.7)</td>
<td>40.7 (39.3-42.0)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>3324 (2500-3920)</td>
<td>3635 (3110-4318)</td>
</tr>
<tr>
<td>Umbilical artery pH</td>
<td>7.24 (7.14-7.30)</td>
<td>7.24 (7.12-7.42)</td>
</tr>
<tr>
<td>Apgar scores</td>
<td>8.2 (1-9)</td>
<td>9.2 (9-10)</td>
</tr>
</tbody>
</table>

### 5.2 METHODS

#### 5.2.1 Study 1

The buprenorphine-exposed children were invited to a pediatrician’s appointment four times until one year of age and thereafter two times annually. Data were collected by pediatricians’ medical interviews of caregivers and by examination of the child at follow-up visits. Furthermore, all children’s medical records from HUCH were thoroughly explored retrospectively. We also analyzed the child welfare reports submitted by pediatricians after the child had left the maternity hospital. The endpoint of data collection was 3.0 years of age. One child’s data were missing after six months of age because the child was kidnapped abroad and could not be located.

Children with developmental problems or medical conditions that needed more specific evaluation or treatment were referred to an appropriate medical specialist. If the child did not have single words by two years of age or if there were no 2- to 3-word sentences by three years of age, the child was sent to the evaluation of speech therapist. An ophthalmologist further examined children with eye problems. At 4 months of age, HCV...
was tested with the polymerase chain reaction (PCR) method and at 1.5 years by measuring HCV antibodies. Information about maternal substance abuse (tobacco, alcohol, and other drugs) was gathered from three sources: (1) neonatal medical records (including data of substance use based on what mothers revealed at tertiary maternity clinic appointments and urine drug screens in pregnancy), (2) neonatal drug urine screens, and (3) medical interview of the mother at the first visit to the pediatrician at the Department of Social Pediatrics.

5.2.2 Study II

Study subjects and children in the control group underwent a dental examination at 3-4 years of age. It was carried out in a dental unit with a dental mirror, a dental probe, fiber-optic illumination, and appropriate dental lighting. Radiographs were not taken. The intra-examiner reliability for caries showed a kappa value of 0.99. The oral hygiene level was recorded based on existence of visible plaque on the buccal surfaces of the upper incisors (present/absent). We defined caries by using decayed, missing, and filled teeth and tooth surfaces indices. Caries lesions involving dentine were included (World Health Organization, 1997). The dentist also recorded any developmental enamel defects (hypomineralized and hypoplastic defects). Oral soft tissues were evaluated by visual examination for pathological signs.

A semistructured interview was conducted with each child’s guardian regarding the child’s health, medication, history of dental trauma, tooth brushing, fluoride use, use of pacifier, dietary habits (breast-feeding, bottle-feeding, and candy eating), previous dental care appointments, and family’s socioeconomic situation. We used in the interview a modified questionnaire that has been used in the Finnish Family Competence Study (Mattila, 2001). Dental neglect was observed with the questions “How regularly does your child brush his or her teeth?”, “Who usually brushes his or her teeth?”, and “Does your child have regular appointments with a dentist or dental hygienist?” We interviewed 17 biological mothers, 3 biological fathers, 18 foster mothers, and 3 grandmothers of the buprenorphine-exposed children. Ten patients came to the study appointment with someone who was not capable of answering the questions because she/he had known the child for only a short period of time. Of control children’s parents, 62 biological mothers and 6 biological fathers were interviewed.
5.2.3 Study III

Psychological testing and observation of mother-child interaction were performed on buprenorphine-exposed children and control children at three years of age. Children were evaluated by a licensed clinical psychologist blinded to the study aims and group status. Examinations of mother-child pairs were videotaped. Coders blind to the study hypotheses and group membership made the score rating.

Information on maternal background factors and education level were obtained through questionnaires developed for this study. Maternal education level was assessed using a 4-point scale: rating 1 for compulsory school education, 2 for additional occupational education, 3 for high school education, and 4 for academic or higher professional training.

Data of neonatal characteristics and primary residence (with biological mother or in foster care) were obtained from medical records and the study questionnaire.

Emotional availability of the mother-child pairs was rated from videotaped observations of 5 min of mother-infant free play with a ball, a doll, blocks, a mirror, and a teddy bear by using the Emotional Availability Scales (Emotional Availability Scales, 3rd edition; Biringen et al., 1998) and prior to the Bayley-III testing. Emotional Availability Scales have four maternal scales (Sensitivity, Structuring, Non-intrusiveness, and Non-hostility) and two child scales (Responsiveness to Mother and Involvement of Mother). Sensitivity (9-point scale) refers to a mother’s positive affect, responsiveness, acceptance, and awareness of the child’s cues and appropriate response to them. Structuring (5-point scale) involves the mother’s ability to structure or scaffold the child’s environment and play. Nonintrusiveness (5-point scale) involves the degree to which the mother can be available without interfering with the child’s autonomy and space. Nonhostility (5-point scale) refers to maternal behavior that is free of impatience, harshness, or malice. Child Responsiveness (7-point scale) refers to the degree to which the infant invites the mother to interact with him/herself. Two trained raters coded videotapes, with 10% of the tapes (randomly selected) coded with the method trainer (Z.B.). Interrater reliabilities (r) were from 0.70 to 0.90 between the raters and from 0.85 to 0.92 with the method trainer.

We observed maternal self-efficacy with the Self-Efficacy for Parenting Tasks Index – Toddler Scale (SEPTI T5; Coleman and Karraker, 2003). The seven subdomains are (1) emotional availability: “When my child needs me, I am able to easily put aside whatever
else I may be doing.”; (2) nurturance, valuing the child, and empathetic responsiveness: “My toddler knows that I understand when his/her feelings are hurt.”; (3) protection from harm or injury: “I am very good about never leaving my child unattended.”; (4) discipline and limit setting: “Setting limits for my toddler is relatively easy for me.”; (5) play: “I can always think of something to play with my child.”; (6) teaching: “I believe my toddler learns a great deal from my efforts to show him/her things.”; and (7) instrumental care and establishment of structure and routines: “I have been able to establish a daily routine with my toddler that feels comfortable for both of us.”. Each item is rated on a 6-point Likert scale, with answers ranging from Strongly Agree to Strongly Disagree. Total scores are from 53 to 318, with higher scores indicating stronger self-efficacy. The Cronbach’s alpha coefficient for the full scale was 0.76.

Child development was evaluated with Bayley Scales of Infant and Toddler Development, 3rd edition (Bayley-III; Bayley, 2006), which contains a Cognitive Development Index, Language Development Index (sum of Receptive and Expressive Communication), and Social-Emotional Development Index. The raw scores of the Cognitive and Receptive and Expressive Communication Scales are changed to standard scores (M = 10, SD = 3) according to the US norms. A composite score for the Language Scale was created by adding the scaled scores of Receptive and Expressive Communication (M = 20, SD = 6). The Bayley-III Social-Emotional Scale is an adaptation of the Greenspan Social-Emotional Growth Chart: A Screening Questionnaire for Infants and Young Children (Greenspan, 2004). The Social-Emotional Scale is a parent-completed questionnaire with a 5-point Likert scale for evaluating social and emotional milestones in young children, including mastery of functional emotional skills, such as self-regulation and interest in the world; communicating needs; engaging with others and establishing relationships; using emotions in an interactive, meaningful manner; and using emotional gestures or signals to solve problems. Total scores for three-year-olds have a potential range of 35-175. Cronbach’s alpha coefficient was 0.85.

5.2.4 Study IV

MEG was measured in a magnetically protected room (Euroshield Ltd., Eura, Finland) with a whole-head helmet-formed MEG sensor array containing 306 sensors, including 204 planar gradiometers and 102 magnetometers (Elekta Neuromag, Helsinki, Finland). MEG was recorded together with EEG electro-oculography (EOG). For EEG, one to three silver-
silver chloride disposable electrodes were positioned at F4, P4, Cz, or P3, and for EOG one electrode was attached above the left eye canthi and another below the right eye canthi. The reference electrode was situated on the left mastoid and the ground electrode on the forehead. MEG and EEG signals were bandpass-filtered at 0.03-257 Hz. The sampling rate was 1002 Hz. We defined an individual Cartesian coordinate system with a 3-dimensional digitizer (Polhemus) before the recording. The r-axis connected to preauricular points (positive values towards the right ear), the y-axis connected the x-axis and nasion (positive values towards the nose), and the z-axis was perpendicular to the xy-plane (positive values upwards). The positions of four indicator coils placed on the newborn’s head were determined with the digitizer relative to anatomic landmarks. The newborn was fed before the measurement if necessary and then placed on the bed next to the MEG device in a supine position, with the left hemisphere of the head downwards over the occipital part of the adult-sized helmet. One or two researchers stayed beside the newborn. The researcher held the tactile stimulus on the newborn’s index finger, watched the newborn’s behavior, and coded when the newborn was awake and his/her assumed sleep stage onto trigger channels linked to the raw data file. The stimulation and recording started when the newborn was asleep and stopped when she/he woke up. No sedation was used. Each MEG measurement took from two to three hours.

The tactile and auditory stimuli alternated during the measurement. The interstimulus interval between modalities was 1 s and between the same modality 2 s. The stimulation arrangement is described in detail by Pihko et al. (2011). The tactile stimulus was a gentle tap on the tip of the right index finger from a thin elastic membrane expanded by pressurized air (Somatosensory Stimulus Generator, 4-D Neuroimaging Inc.* San Diego, CA, US). The auditory stimuli were conducted to the right ear via a plastic tube and an earpiece at 75 dB sound pressure level. The auditory stimuli consisted of utterances of separated vowels a: and i: read by a Finnish adult female. Both vowel sounds lasted 300 ms and they were delivered in a semi-random sequence so that 85% of the auditory stimuli (standards) were the vowel (a:) and 15% were deviants (i:). After a deviant, there were always at least two standards before the next deviant. Our study presents only the responses to the standards. The number of deviants was not enough for analysis, and for practical reasons it was not possible to lengthen the MEG recording to obtain a sufficient number of deviants.

To remove possible magnetic artifacts, we processed the MEG data with a Spatiotemporal Signal Space Separation method (tSSS) (II) of MaxFilter software (Elekta Neuromag, ...
Helsinki, Finland) using a correlation limit of 0.98 and a 4-s time window, thus suppressing frequencies below 0.25 Hz. After tSSS, data were thoroughly inspected before offline averaging according to sleep stages, disregarding time periods with movement artifacts. The sleep stage was evaluated based on MEG, EEG, EOG, and coded behavioral observations. Only periods of QS without movement artifacts were included in the analysis. The sleep stage was defined as QS when the closed-eye newborn had a rhythmic breathing cycle and his/her eyes were closed, MEG and EEG showed high-voltage low-frequency activity or trace alternant, and no rapid eye movements existed in the EOG. We averaged approximately 300 tactile responses for each newborn. The location, strength, and orientation of the active neural sources were evaluated by the equivalent current dipole model. Equivalent current dipoles were computed using data from an individually chosen subset of MEG sensors close to the measured hemisphere displaying clear responses. The baseline was a 100-ms period before the stimulus. Single dipoles with 1-ms intervals were modeled around the visually determined peaks, and the equivalent current dipole with the greatest dipole moment was chosen for further analysis. The selected dipoles had a dipolar field pattern and goodness-of-fit values over 70%.

5.3 Ethics
The study was approved by the Ethics Committee for Gynecology and Obstetrics, Pediatrics, and Psychiatry of the Hospital District of Helsinki and Uusimaa.

5.4 Statistics
In Study II, nonparametric numerical data were analyzed using the Mann-Whitney U-test, and categorical data with a two-sided Fisher’s exact test (2 x 2 tables or contingency tables) or Pearson’s Chi-square test. Statistical significance level was predetermined at p<0.05. Analyses were conducted with PASW Statistics 18.0 (IBM Corporation, Armonk, NY, USA).

In Study III, demographic and perinatal data were compared with one-way Analysis of variance (ANOVA). Analysis of covariance (ANCOVA) was performed to investigate the associations between groups, dimensions of Emotional Availability Scales, Maternal Self-Efficacy Scale, and the Bayley-III Cognitive, Language, and Social-Emotional Scales. A set
of covariates was used to control for their effects in each of the analyses. Covariates included infant birth weight and height, gestational age, maternal age, maternal socioeconomic status, and number of placements. Multiple regression statistics for all Bayley-III scales and for Emotional Availability infant scales of involvement and responsiveness were also performed.

In Study IV, postmenstrual age was significantly lower with buprenorphine-exposed newborns (Student’s t-test, p=0.005). As it is known that postmenstrual age correlates with AEFs of newborns, the AEF parameters (peak latency, location of source, and strength of source) were correlated against postmenstrual age with simple regression or Spearman’s rho if the data were not normally distributed. If there was a value that was not dependent on postmenstrual age, the results of buprenorphine-exposed newborns were compared with control newborns with mixed 2 x 2 ANOVA, with group (patients/controls) as a between-subjects factor and response (auditory M250/M550) as a within-subjects factor. When a significant correlation with postmenstrual age was noted, ANCOVA was applied with postmenstrual age as a covariate to the ANOVA design mentioned above. SEFs are not known to depend on postmenstrual age and SEF characteristics were analyzed with ANOVA. Mann-Whitney U-test was used if the data did not follow the normal distribution. Retrospective power calculations were conducted to determine the mean difference in AEF and SEF parameters between control and patient groups, which can be detected with 80% power and a significance level of 0.05 (two-sided test). Pooled standard deviations were used in power calculations.
6 RESULTS

6.1 Study I

6.1.1 Congenital disorders

Major structural anomalies were found in 5 (5%) of 102 children. One male had duplex thumb and left-sided duplex urinary collecting system, one female palatal cleft and ankyloglossia, one male Pierre Robin syndrome, one male microtia and stenotic external ear canal in the right ear, and one male tetralogy of Fallot, high forehead, hypoplastic midhead, unusually short proximal parts of the hands and legs, two thoracic hemivertebrae and one lumbar hemivertebra, and further, one extra vertebra and thymic aplasia. In addition, three children (3%) had minor structural anomalies. One male had pulmonary artery stenosis, one female ventricular septal defect, and one female multiple ventricular septal defects.

To be mentioned, one male was diagnosed with primary vesicoureteral reflux grade III and another male with primary vesicoureteral reflux grade III-IV accompanied by hydronephrosis. For 51 newborns, neonatal brain ultrasound was performed during treatment in the neonatal ward: 47 newborns had a normal brain ultrasound, 3 newborns had one choroid plexus cyst without clinical consequences and not classified as a congenital disorder, and one premature newborn with multiple anomalies, including tetralogy of Fallot, had slightly dilated lateral ventricles. Fetal alcohol spectrum disorder (FASD) had not been diagnosed in any child.

6.1.2 Ophthalmological findings

An ophthalmologist had diagnosed ocular findings in 11 (11%) of the 102 children. Strabismus appeared in 10 children (10%). One child had esotropia since birth and this persisted to three years of age. Another 9 children with strabismus were over seven months of age at the time of diagnosis. Ophthalmological diagnosis was unilateral intermittent exotropia in two males, unilateral esotropia in one male and one female, intermittent esotropia in one female and one male, unilateral exotropia in one female, bilateral intermittent exotropia in one female, concomitant convergent strabismus in one male, bilateral strabismus in one female, and opticus atrophy and nystagmus in one female.

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6.1.3 Other morbidities

One full-term male had bilateral sensorineural hearing loss. One full-term female needed surgical repair of the patent ductus arteriosus (PDA) at one year of age. One full-term male with spontaneously closed PDA was diagnosed with acute lymphoblastic leukemia at 1 year and 5 months of age. Three males were operated on for pyloric stenosis. Mild hypospadias occurred in one male. One male who also had Pierre Robin syndrome was diagnosed with an undescended testicle. One prematurely born male had an umbilical hernia. Another prematurely born male had both an umbilical and an inguinal hernia. One male born full-term with an ear anomaly had a right-side inguinal hernia in infancy and a left-side inguinal hernia at 2 years of age. One prematurely born male was diagnosed with bilateral inguinal hernias (he also had tetralogy of Fallot, multiple skeletal anomalies, and thymic aplasia). One child was diagnosed with HCV transmitted by the mother. No child had HBV or HIV infection. Ten children (10%) were diagnosed with asthma and eight children (8%) with atopic eczema. Tympanostomy was performed on 11 children (11%), adenotomy and tonsillectomy on 10 children (10%), and adenotomy and tonsillectomy on one child (1%).

Speech delay was noted in 16 children (16%, 12 males and 4 females) at 3 years of age (speech was unclear speech, vocabulary was limited, or the child did not use simple sentences). One male with speech delay was born prematurely. One male with speech problems also had bilateral sensorineural hearing loss. Four children were referred to a psychologist or child psychiatrist for behavior problems. One child had melatonin medication because of sleeping problems at the age of 2 years. One prematurely born female was diagnosed with motor delay in infancy. She also had multiple ventricular septal defects, nystagmus, and optic atrophy. At 3 years of age, two males were sent for further investigations to the child neurology unit: one for ataxy and the other for developmental delay of language and motor skills. Major medical outcomes of the study patients are presented in Table 7.

Fourteen children (14%) were small for gestational age (SGA) (unpublished results) based on Finnish growth references (Sankilampi et al., 2013). Their medical outcomes are presented in Table 8.

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Table 7. Major medical outcomes and mortality of buprenorphine-exposed children (total n=102) to three years of age in Study I.

<table>
<thead>
<tr>
<th>Medical outcome</th>
<th>Number of buprenorphine-exposed children with this medical outcome (%)</th>
<th>Occurrence in general population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Speech delay</td>
<td>16 (16%)</td>
<td>Prevalence of speech problems 2.0-17.5% in 3-year-olds (Silva et al., 1983, Tomblin et al., 1997; Horwitz et al., 2003; de Koning et al., 2004); mean prevalence of speech delay and specific language impairment 2.5% in a Finnish study of children up to 6 years of age (Hannus, 2009)</td>
</tr>
<tr>
<td>SGA</td>
<td>14 (14%)</td>
<td>Prevalence 3.1% in singleton births in Finland (Räisänen et al., 2013)</td>
</tr>
<tr>
<td>Strabismus</td>
<td>10 (10%)</td>
<td>Prevalence 2-6% in Western countries (Graham, 1974; Chew et al., 1994; Williams et al., 2008; Cotter et al. 2011)</td>
</tr>
<tr>
<td>Asthma</td>
<td>10 (10%)</td>
<td>Lifetime prevalence 5.9% for children under 5 years of age in US. (National Health Interview Survey, 2013); 7.9% of children have diagnosed asthma and about the same number of children have asthma-like symptoms (Suomalaisen Lääkärisäätiö, Suomen Lääkäriyritys ry:n, Suomen Lääkäritutkimusyhdistys ry:n, Suomen Lastenlääkäritutkimusry:n, Suomen Lääkäritutkimusyhdistys ry:n, Suomen Lääkäritutkimusry:n, Suomen Lääkäritutkimusry:n)</td>
</tr>
<tr>
<td>Heart defect</td>
<td>4 (4%)</td>
<td>Prevalence 8/1000 live births in Europe (van der Linde, 2011)</td>
</tr>
<tr>
<td>Behavior problems</td>
<td>4 (4%)</td>
<td>Prevalence for ADHD about 3% and for any behavioral disorder about 9-15% at preschool age (Egger and Angold, 2006)</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>3 (3%)</td>
<td>Incidence 1.1–3.5/1000 live births (de Laffolie et al., 2012)</td>
</tr>
<tr>
<td>Inguinal hernias</td>
<td>3 (3%)</td>
<td>Incidence 1.5-5.5% in term infants and 13% in infants born at &lt;33 weeks of gestational age (Wang, 2012)</td>
</tr>
<tr>
<td>HCV</td>
<td>1 (1%)</td>
<td>Prevalence 0.05-0.36% in Europe and USA (Baker, 2015)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (2%)</td>
<td>0.1% of children aged under 3 years died in Finland in 2005 (Statistics Finland, Ps-Web-Database)</td>
</tr>
</tbody>
</table>

Table 8. Major medical outcomes and mortality of buprenorphine-exposed children (total n=102) to three years of age in Study I.

<table>
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<tr>
<th>Medical outcome</th>
<th>Number of buprenorphine-exposed children with this medical outcome (%)</th>
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<td>Speech delay</td>
<td>16 (16%)</td>
<td>Prevalence of speech problems 2.0-17.5% in 3-year-olds (Silva et al., 1983, Tomblin et al., 1997; Horwitz et al., 2003; de Koning et al., 2004); mean prevalence of speech delay and specific language impairment 2.5% in a Finnish study of children up to 6 years of age (Hannus, 2009)</td>
</tr>
<tr>
<td>SGA</td>
<td>14 (14%)</td>
<td>Prevalence 3.1% in singleton births in Finland (Räisänen et al., 2013)</td>
</tr>
<tr>
<td>Strabismus</td>
<td>10 (10%)</td>
<td>Prevalence 2-6% in Western countries (Graham, 1974; Chew et al., 1994; Williams et al., 2008; Cotter et al. 2011)</td>
</tr>
<tr>
<td>Asthma</td>
<td>10 (10%)</td>
<td>Lifetime prevalence 5.9% for children under 5 years of age in US. (National Health Interview Survey, 2013); 7.9% of children have diagnosed asthma and about the same number of children have asthma-like symptoms (Suomalaisen Lääkärisäätiö, Suomen Lääkäriyritys ry:n, Suomen Lääkäritutkimusyhdistys ry:n, Suomen Lääkäritutkimusry:n, Suomen Lääkäritutkimusry:n, Suomen Lääkäritutkimusry:n)</td>
</tr>
<tr>
<td>Heart defect</td>
<td>4 (4%)</td>
<td>Prevalence 8/1000 live births in Europe (van der Linde, 2011)</td>
</tr>
<tr>
<td>Behavior problems</td>
<td>4 (4%)</td>
<td>Prevalence for ADHD about 3% and for any behavioral disorder about 9-15% at preschool age (Egger and Angold, 2006)</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>3 (3%)</td>
<td>Incidence 1.1–3.5/1000 live births (de Laffolie et al., 2012)</td>
</tr>
<tr>
<td>Inguinal hernias</td>
<td>3 (3%)</td>
<td>Incidence 1.5-5.5% in term infants and 13% in infants born at &lt;33 weeks of gestational age (Wang, 2012)</td>
</tr>
<tr>
<td>HCV</td>
<td>1 (1%)</td>
<td>Prevalence 0.05-0.36% in Europe and USA (Baker, 2015)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (2%)</td>
<td>0.1% of children aged under 3 years died in Finland in 2005 (Statistics Finland, Ps-Web-Database)</td>
</tr>
</tbody>
</table>
Table 8. Medical outcome of 14 children small for gestational age (SGA) in Study 1.

<table>
<thead>
<tr>
<th>Gender</th>
<th>Medical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>Pulmonary artery stenosis</td>
</tr>
<tr>
<td>Male</td>
<td>Tetralogy of Fallot, multiple skeletal anomalies, thymic aplasia, bilateral inguinal hernias</td>
</tr>
<tr>
<td>Male</td>
<td>Bilateral sensorineural hearing loss, speech delay</td>
</tr>
<tr>
<td>Male</td>
<td>Speech delay, atopic eczema</td>
</tr>
<tr>
<td>Female</td>
<td>Hepatitis C</td>
</tr>
<tr>
<td>Male</td>
<td>Asthma</td>
</tr>
<tr>
<td>Female</td>
<td>Atopic eczema</td>
</tr>
<tr>
<td>Female</td>
<td>Esotropia</td>
</tr>
<tr>
<td>Female</td>
<td>Recurrent otitis media, tympanostomias performed</td>
</tr>
<tr>
<td>Male</td>
<td>Inguinal hernia, herniotomy performed; adenotomy performed</td>
</tr>
<tr>
<td>Male</td>
<td>No findings</td>
</tr>
<tr>
<td>Female</td>
<td>No findings</td>
</tr>
<tr>
<td>Female</td>
<td>No findings</td>
</tr>
<tr>
<td>Female</td>
<td>No findings</td>
</tr>
</tbody>
</table>

6.1.4 Mortality

Two children died by the age of 3 years. One female died of SIDS at one month of age, and one male died of congenital heart disease at 22 months of age.

6.1.5 Child welfare reports

Pediatricians reported 70 cases of suspected maltreatment to child welfare. These reports encompassed 37 children (36% of the total population, 16 females and 21 males). Reports were made of 18 children once, 11 children twice, 6 children three times, 1 child five times, and 1 child seven times.

Of the 70 reports, 45 (64%) concerned the family’s repeated failure to come to the pediatrician’s appointment. These reports were categorized as medical neglect. Physical abuse was suspected in four cases: one female at 4 months of age had temazepam poisoning,
one female at 4 months of age appeared with a skull fracture of unknown origin, one male at 11 months of age had a radius fracture of unknown origin, and one male at 3 years of age had bruises on the head of unknown origin. Medical child abuse consisted of one case in which the caregiver gave the child melatonin at much higher doses than advised. Other issues for reports were parental substance abuse (n=11), emotional maltreatment (n=5), neglect of child’s basic needs (n=3), and chaotic home environment (n=1). See also Figure 2 for results.

6.1.6 Primary residence after birth

After discharge from maternity hospital, 31 children settled home with at least one biological parent and 30 children went with a biological parent to an institution: either a mother-and-child home, an assisted living facility, a family rehabilitation center for substance-abusing parents and their children, or a prison ward for mothers and their children. Moreover, 9 children moved to foster care and 32 children to residential care. At one year of age, 54 children lived at home with a parent or parents, 8 lived with a parent or

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Figure 2. Reasons for child welfare reports of buprenorphine-exposed children (Study I).
parents in an institution, 23 were in foster care, and 15 were in residential care. At two years of age, 56 children lived at home with a parent or parents, 3 lived with a parent or parents in an institution, 34 were in foster care, 5 were in residential care, and 1 was adopted. At three years of age, 48 children lived at home with a parent or parents, 44 were in foster care, 6 were in residential care, and 1 was adopted. One child died at one year of age and two children had died to two years of age. One child’s data were missing from the age of one year onwards. See also Figure 3 for results.

Figure 3. Buprenorphine-exposed children’s primary residence (Study I).

parents in an institution, 23 were in foster care, and 15 were in residential care. At two years of age, 56 children lived at home with a parent or parents, 3 lived with a parent or parents in an institution, 34 were in foster care, 5 were in residential care, and 1 was adopted. At three years of age, 48 children lived at home with a parent or parents, 44 were in foster care, 6 were in residential care, and 1 was adopted. One child died at one year of age and two children had died to two years of age. One child’s data were missing from the age of one year onwards. See also Figure 3 for results.
6.2 Study II

6.2.1 Dental health

Buprenorphine-exposed children had greater mean decayed/missed/filled teeth index, greater mean decayed teeth index, greater mean decayed/missed/filled teeth per tooth surfaces index, and more visible plaque than control children. There were more caries-free children in the control group than in the buprenorphine-exposed group. No significant differences emerged in signs of dental trauma between groups. Moreover, no significant difference was found in occurrence of developmental enamel defects, but buprenorphine-exposed children had more affected primary incisors than control children. No significant differences in caries indices, dental trauma or enamel defects existed between buprenorphine-exposed children living with a biological mother and buprenorphine-exposed children living in foster care. A separate analysis of the buprenorphine-exposed children showed that mean gestational age was smaller (38.8 months vs. 39.9 months, p<0.01) in children with developmental enamel defects. There was no such significant difference in mean birth weights (3072 g vs. 3338 g, p=0.129) between those with and without enamel defects. Main findings of dental health are presented in Table 9.

After the study appointment, the children in need of dental treatment were referred to a dentist in public dental services. Four buprenorphine-exposed children and one child in the control group needed dental treatment under local analgesia, and four buprenorphine-exposed children under general anesthesia.

6.2.2 Dental neglect

As compared with buprenorphine-exposed children, the teeth of children in the control group were brushed more often, their parents were more involved in children’s tooth brushing, and they had experienced more dental check-ups. All children in both groups used toothpaste. Results are shown in Table 9.
<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine-exposed children (n=51)</th>
<th>Control children (n=68)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>3.3 (0.5)</td>
<td>3.5 (0.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Dmft index*, mean (range)</td>
<td>0.82 (0-9)</td>
<td>0.09 (0-5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Dr index**, mean (range)</td>
<td>0.62 (0-9)</td>
<td>0.01 (0-1)</td>
<td>0.001</td>
</tr>
<tr>
<td>Dmfs index***, mean (range)</td>
<td>1.51 (0-34)</td>
<td>0.10 (0-6)</td>
<td>0.004</td>
</tr>
<tr>
<td>No caries, n (%)</td>
<td>42 (82.3)</td>
<td>66 (97.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Enamel defect, n (%)</td>
<td>26 (50.9)</td>
<td>39 (57.4)</td>
<td>0.46</td>
</tr>
<tr>
<td>Dental trauma in primary teeth, n (%)</td>
<td>12 (23.5)</td>
<td>18 (26.5)</td>
<td>0.83</td>
</tr>
<tr>
<td>Visible plaque, n (%)</td>
<td>17 (33.3)</td>
<td>7 (10.3)</td>
<td>0.003</td>
</tr>
<tr>
<td>Tooth brushing, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weekly</td>
<td>1</td>
<td>1</td>
<td>0.001</td>
</tr>
<tr>
<td>Daily</td>
<td>27</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Twice a day</td>
<td>13</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>Who brushes child’s teeth, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Child</td>
<td>0</td>
<td>1</td>
<td>0.042</td>
</tr>
<tr>
<td>Child and parent</td>
<td>33</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>7</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Dental examinations before the study, n</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>24</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Dmft=decayed, missing, filled teeth index, ** Dr=decayed teeth index, *** Dmfs=decayed, missing, filled teeth per tooth surfaces. Statistics: Mann-Whitney U-test (numerical data), two-sided Fisher’s exact test or Pearson Chi square test.
Table 10. Personal and sociodemographic factors in buprenorphine-exposed children and control children are presented in Study II. Statistics performed with two-sided Fisher’s exact test or Pearson Chi square test.

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine-exposed children (total n=51)</th>
<th>Control children (total n=68)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Used pacifier when under 2 years old</td>
<td>39/39 (100%)</td>
<td>46/68 (68%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Used pacifier at 3 years of age</td>
<td>6/41 (15%)</td>
<td>0/68 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>No candy eating</td>
<td>2/41 (5%)</td>
<td>17/68 (25%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Mother had no cavities at last check-up</td>
<td>12/46 (33%)</td>
<td>48/68 (71%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother &lt;25 years old</td>
<td>24/51 (47%)</td>
<td>1/68 (1%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother’s education over 11 years</td>
<td>18/38 (47%)</td>
<td>63/68 (93%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother is blue-collar worker</td>
<td>30/40 (75%)</td>
<td>14/67 (21%)</td>
<td></td>
</tr>
<tr>
<td>Mother is white-collar worker</td>
<td>10/40 (25%)</td>
<td>53/67 (79%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Father &lt;25 years old</td>
<td>6/38 (16%)</td>
<td>1/68 (1%)</td>
<td>0.008</td>
</tr>
<tr>
<td>Father’s education over 11 years</td>
<td>12/36 (33%)</td>
<td>61/68 (90%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Father is blue-collar worker</td>
<td>31/38 (82%)</td>
<td>7/68 (10%)</td>
<td></td>
</tr>
<tr>
<td>Father is white-collar worker</td>
<td>7/38 (18%)</td>
<td>61/68 (90%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother smoked during pregnancy</td>
<td>51/51 (100%)</td>
<td>1/68 (1%)</td>
<td>~0.001</td>
</tr>
</tbody>
</table>

Table 10. Personal and sociodemographic factors in buprenorphine-exposed children and control children are presented in Study II. Statistics performed with two-sided Fisher’s exact test or Pearson Chi square test.

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<td>~0.001</td>
</tr>
<tr>
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<td>0/68 (0%)</td>
<td>0.002</td>
</tr>
<tr>
<td>No candy eating</td>
<td>2/41 (5%)</td>
<td>17/68 (25%)</td>
<td>0.044</td>
</tr>
<tr>
<td>Mother had no cavities at last check-up</td>
<td>12/46 (33%)</td>
<td>48/68 (71%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother &lt;25 years old</td>
<td>24/51 (47%)</td>
<td>1/68 (1%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother’s education over 11 years</td>
<td>18/38 (47%)</td>
<td>63/68 (93%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother is blue-collar worker</td>
<td>30/40 (75%)</td>
<td>14/67 (21%)</td>
<td></td>
</tr>
<tr>
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<td>10/40 (25%)</td>
<td>53/67 (79%)</td>
<td>~0.001</td>
</tr>
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</tr>
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<td>~0.001</td>
</tr>
<tr>
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<td>31/38 (82%)</td>
<td>7/68 (10%)</td>
<td></td>
</tr>
<tr>
<td>Father is white-collar worker</td>
<td>7/38 (18%)</td>
<td>61/68 (90%)</td>
<td>~0.001</td>
</tr>
<tr>
<td>Mother smoked during pregnancy</td>
<td>51/51 (100%)</td>
<td>1/68 (1%)</td>
<td>~0.001</td>
</tr>
</tbody>
</table>
6.2.3 Personal and sociodemographic factors

The duration of breastfeeding differed between buprenorphine-exposed children and children in the control group, as no one in the former group was breastfed (0 vs. 11 months, p<0.01). The number of bottle-feeding months was 21 months in buprenorphine-exposed children and 6 months in control children (p<0.01). Other personal and sociodemographic factors are presented in Table 10.

6.3 Study III

6.3.1 Emotional availability

Emotional availability scales of mothers contained four aspects: sensitivity, structuring, nonintrusiveness, and nonhostility. Buprenorphine-exposed mothers and foster mothers scored lower than mothers of nonexposed children in sensitivity (F-value 5.89, p<0.01) and in nonhostility (F-value 6.61, p<0.05). Buprenorphine-exposed children living with biological mothers and foster mothers had lower scores than children in the nonexposed group in responsiveness (F-value 4.59, p<0.05) and involvement (F-value 4.68, p<0.05). No significant differences were measured in mothers’ scales of structuring or nonintrusiveness. Results are also shown in Table 11.

6.3.2 Maternal self-efficacy

Scores of the buprenorphine-exposed group living with a biological mother and the buprenorphine-exposed group living with a foster mother were lower in maternal self-efficacy than the nonexposed group (F-value 6.55, p<0.01). Detailed results are provided in Table 11.

6.3.3 Bayley-III Scales

Buprenorphine-exposed children living with a biological mother and buprenorphine-exposed children living with a foster mother performed worse in Bayley Cognitive and Language Scales than control children. In addition, we found some covariate effects, with older maternal age related to higher language scores F-value (2,33) = 8.31, p<0.01 and fewer
gestational weeks related to lower cognitive scores F-value (2,33) = 17.02, p<0.001. Results of Bayley-III Scales are shown in Table 11.

Table 11. Results of Emotional Availability Scales, Maternal Self-Efficacy Scale and Bayley-III test presented as mean (SD). Statistics performed with ANCOVA (table modified from the original publication of Study III, Salo et al., 2009).

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine-exposed children with biological mother</th>
<th>Buprenorphine-exposed children with foster mother</th>
<th>Control children</th>
<th>F-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EA Scales - Mother’s sensitivity</td>
<td>4.57 (1.17)</td>
<td>5.68 (0.93)</td>
<td>7.03 (0.69)</td>
<td>5.89**</td>
</tr>
<tr>
<td>EA Scales - Mother’s structuring</td>
<td>3.42 (0.53)</td>
<td>3.71 (0.61)</td>
<td>4.23 (0.48)</td>
<td>1.27</td>
</tr>
<tr>
<td>EA Scales - Mother’s intrusiveness</td>
<td>4.43 (0.78)</td>
<td>4.36 (0.63)</td>
<td>4.77 (0.43)</td>
<td>0.86</td>
</tr>
<tr>
<td>EA Scales - Mother’s nonhostility</td>
<td>3.64 (0.85)</td>
<td>4.16 (0.72)</td>
<td>4.96 (0.13)</td>
<td>6.61*</td>
</tr>
<tr>
<td>EA Scales - Infant responsiveness</td>
<td>4 (0.91)</td>
<td>4.82 (0.82)</td>
<td>6.04 (0.54)</td>
<td>4.59*</td>
</tr>
<tr>
<td>EA Scales - Infant involvement</td>
<td>4.29 (1.07)</td>
<td>4.61 (0.81)</td>
<td>5.96 (0.51)</td>
<td>4.68*</td>
</tr>
<tr>
<td>Maternal self-efficacy</td>
<td>200.08 (7.02)</td>
<td>209.34 (7.26)</td>
<td>215.77 (11.86)</td>
<td>6.55**</td>
</tr>
<tr>
<td>Bayley-III Cognitive Scale</td>
<td>8.14 (0.38)</td>
<td>9.29 (0.91)</td>
<td>10.54 (1.26)</td>
<td>8.33**</td>
</tr>
<tr>
<td>Bayley-III Language Scale</td>
<td>18.00 (2.00)</td>
<td>19.21 (2.80)</td>
<td>23.69 (2.13)</td>
<td>9.91***</td>
</tr>
<tr>
<td>Bayley-III Social-emotional Scale</td>
<td>9.14 (1.77)</td>
<td>8.29 (1.38)</td>
<td>11.08 (2.59)</td>
<td>4.57*</td>
</tr>
</tbody>
</table>

6.3.4 Predictors for cognitive and socioemotional outcome

The covariates of gestational age, birth weight, birth height, number of placements, caregiver age, caregiver education, sensitivity, structuring, nonhostility, nonintrusiveness, self-efficacy, group status buprenorphine-exposed vs. nonexposed, and also group status parental care vs. foster care were regressed on the Bayley-III Scales as well on the child variables of Emotional availability.

For the Bayley Cognitive Scale, gestational age was a significant predictor variable (β 0.65, p<0.001).

For the Bayley Language Scale, gestational age (β 0.40, p<0.01), caregiver age (β -0.06, p<0.05), maternal self-efficacy (β 0.35, p<0.05), and group status of buprenorphine-exposed children in parental care vs. foster care (β 0.62, p<0.05) were significant predictor variables.

6.3.4 Predictors for cognitive and socioemotional outcome

The covariates of gestational age, birth weight, birth height, number of placements, caregiver age, caregiver education, sensitivity, structuring, nonhostility, nonintrusiveness, self-efficacy, group status buprenorphine-exposed vs. nonexposed, and also group status parental care vs. foster care were regressed on the Bayley-III Scales as well on the child variables of Emotional availability.

For the Bayley Cognitive Scale, gestational age was a significant predictor variable (β 0.65, p<0.001).

For the Bayley Language Scale, gestational age (β 0.40, p<0.01), caregiver age (β -0.06, p<0.05), maternal self-efficacy (β 0.35, p<0.05), and group status of buprenorphine-exposed children in parental care vs. foster care (β 0.62, p<0.05) were significant predictor variables.
For the Bayley Social-Emotional Scale, the only significant predictor was maternal self-efficacy ($\beta = 0.50, p<0.001$).

For child involvement, caregiver age ($\beta = 0.28, p<0.05$) and mother’s sensitivity emerged as significant predictor variables ($\beta = 0.71, p<0.001$).

For child responsiveness, mother’s sensitivity ($\beta = 0.50, p<0.05$) and mother’s structuring ($\beta = 0.27, p<0.01$) were significant predictors. Results are more specifically shown in Table 12.

Table 12. Predictors for cognitive and socioemotional outcome for buprenorphine-exposed children in Study III. Multiple regression analysis was used for statistics (table modified from the original publication of Study III, Salo et al., 2009). $R^2$ is an additional variance accounted for each step. $\beta$ is a regression coefficient. * $p<0.05$, # $p<0.01$, • $p<0.001$

<table>
<thead>
<tr>
<th>Step</th>
<th>Predictor variable</th>
<th>Bayley-III Cognition Scale</th>
<th>Bayley-III Language Scale</th>
<th>Bayley-III Social-emotional Scale</th>
<th>Involvement</th>
<th>Responsiveness</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gestational age</td>
<td>0.65•</td>
<td>0.40•</td>
<td>0.04•</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>Birth weight</td>
<td>0.33</td>
<td>0.09</td>
<td>0.03</td>
<td>0.19</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Birth length</td>
<td>0.49</td>
<td>-0.17</td>
<td>-0.13</td>
<td>0.08</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td>Number of placements</td>
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<td>-0.10</td>
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<td></td>
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<tr>
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<td>Sensitivity</td>
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<td>Mother’s sensitivity</td>
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<td></td>
<td>Parental care</td>
<td>-0.12</td>
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<td>0.27</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Self-efficacy</td>
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<td>0.15•</td>
<td>0.16</td>
<td>0.50•</td>
<td>0.03</td>
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<tr>
<td></td>
<td>Exposed vs. control</td>
<td>0.03</td>
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<td>0.04</td>
<td>0.32•</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Parental care vs. foster care</td>
<td>0.03</td>
<td>0.01</td>
<td>0.62•</td>
<td>0.08•</td>
<td>0.32</td>
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</table>

For the Bayley Social-Emotional Scale, the only significant predictor was maternal self-efficacy ($\beta = 0.50, p<0.001$).

For child involvement, caregiver age ($\beta = 0.28, p<0.05$) and mother’s sensitivity emerged as significant predictor variables ($\beta = 0.71, p<0.001$).

For child responsiveness, mother’s sensitivity ($\beta = 0.50, p<0.05$) and mother’s structuring ($\beta = 0.27, p<0.01$) were significant predictors. Results are more specifically shown in Table 12.

Table 12. Predictors for cognitive and socioemotional outcome for buprenorphine-exposed children in Study III. Multiple regression analysis was used for statistics (table modified from the original publication of Study III, Salo et al., 2009). $R^2$ is an additional variance accounted for each step. $\beta$ is a regression coefficient. * $p<0.05$, # $p<0.01$, • $p<0.001$
6.4 Study IV

6.4.1 Auditory evoked magnetic fields

The first main auditory response M250 was measured in all 11 buprenorphine-exposed children and in 8 of 12 control children and the later response M550 in all 11 buprenorphine-exposed children and in 7 of 12 control children. The results of M250 and M550 responses, including peak latencies, source strengths, and source locations (coordinates in x, y, and z axes) are presented in Table 13.

M250 response was further generated by a dipolar source modeled with an equivalent current dipole (ECD). ECD pointed upwards in 10 patients and 7 controls and downwards in 1 patient and 1 control. Location of ECD correlated approximately with the location of the primary auditory cortex on the superior temporal gyrus (when taking into account the anatomical landmarks defining the coordinate frame).

M550 response was generated so that dipolar source pointed upwards – in two newborns in whom the M250 pointed downwards also the M550 pointed downwards. The M550 source location was 3.4±7.3 mm more posterior to the M250: ANOVA, main effect for response F(1,16)=5.5, p=0.03. The M550 source location was also 2.7±5.6 mm more inferior to the M250: ANOVA, main effect for response: F(1,16)=4.6, p=0.046. No auditory responses were detected in 4 control newborns.

After plotting AEF sources against postmenstrual age, a significant correlation with postmenstrual age was detected for source strengths of M250 (Pearson’s R=0.64, p=0.001) and M550 (Pearson’s R=0.78, p=0.001). In ANCOVA analysis, where the effect of postmenstrual age was taken into account, no significant difference existed between exposed and nonexposed newborns in source strength. No correlation was detected with postmenstrual age for AEF peak latencies and locations. In addition, no latency differences were present between exposed and nonexposed newborns with ANOVA test.

Pooled standard deviations were used in power calculations. Post-hoc power calculations indicated that we had 80% power to detect a 14.5 (AEF M250) and 17.9 (AEF M550) mean difference in source strength (unpublished results).
6.4.2 Somatosensory evoked magnetic fields

The first SEF response M60 was measured in 10 of 11 buprenorphine-exposed children and in all 12 control children and the later response M200 in 7 of 11 buprenorphine-exposed children and in 11 of 12 control children.

M60 and M200 responses did not differ significantly between exposed and nonexposed newborns in source strength, peak latency, or ECD location (ANOVA/Mann-Whitney U-test). The results of M60 and M200 responses regarding peak latencies, source strengths, and source locations (coordinates in x, y, and z axes) are presented in Table 13.

The underlying ECD of M60 (located on the primary somatosensory cortex SI) pointed anteriorly and ECD of M200 (located on the secondary somatosensory cortex) pointed upwards.

Pooled standard deviations were used in power calculations. Post-hoc power calculations indicated that we had 80% power to detect a 5.8 (SEF M60) and 14.3 (SEF M200) mean difference in source strength (unpublished results).

### Table 13. Auditory evoked magnetic field (AEF) responses (M250 and M550) and somatosensory evoked magnetic field (SEF) responses (M60 and M200).

<table>
<thead>
<tr>
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<th>Controls Patients</th>
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<tbody>
<tr>
<td><strong>M250</strong></td>
<td>272±36 289±36</td>
<td>9.0±9.0 16.1±11.9</td>
<td>-24±8</td>
<td>-33±7</td>
<td>7.7±7</td>
<td>-21±10</td>
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<tr>
<td><strong>M550</strong></td>
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<td>9.8±12.5 24.4±12.3</td>
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<td>-28±5</td>
<td>1.1±16</td>
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<tr>
<td><strong>M60</strong></td>
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<td>249±109 242±40</td>
<td>15.2±10.9 9.2±8.9</td>
<td>-23±9</td>
<td>-25±8</td>
<td>4±9</td>
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</table>
7 DISCUSSION

In this study, we had a unique opportunity to observe prenatally buprenorphine-exposed children’s health from infancy to three years of age. Our study included a total of 108 children. To our knowledge, the study population included the largest number of buprenorphine-exposed children in studies of health beyond the neonatal age in this patient group. One of the major findings here was that prenatally buprenorphine-exposed children had significantly more early childhood caries than control children. Dental neglect, which has been very limitedly investigated in young children, posed a concern. In addition, pediatricians recognized several types of child maltreatment in these patients. We found that buprenorphine-exposed children achieved lower scores than control children in Bayley-III Cognition, Language, and Social-Emotional scales and in Emotional Availability Scales at three years of age. Their mothers scored lower than the mothers of control children in Self-Efficacy (Parenting Tasks Index – Toddler Scale) and in sensitivity and nonhostility in Emotional Availability Scales. Furthermore, we showed that despite NAS, brain electrical activity measured with MEG is not affected in response to somatosensory and auditory stimulation in buprenorphine-exposed newborns.

7.1 Congenital disorders

A major congenital anomaly with functional or cosmetic significance was present in five children (5%) and a minor structural anomaly in three children (3%) in Study 1. Compared with national statistics, the number of congenital anomalies in buprenorphine-exposed children was slightly more than average; the National Register of Congenital Malformations reports 3.6% of Finnish newborns to have major congenital anomalies (major congenital structural anomaly, chromosomal defect, or congenital hypothyroidism) (National Institute for Health and Welfare, 2014). Statistics in the US also reveal a major structural or genetic birth defect in approximately 3% of newborns (Centers for Disease Control and Prevention, 2008). The European Concerted Action on Congenital Anomalies and Twins (EUROCAT) presented a prevalence of 2.6% for birth deficits from 2008 to 2012 (data included live births, still births from 20 weeks’ gestation, and termination of pregnancy for fetal anomaly following prenatal diagnosis) (EUROCAT, 2015).

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The intense observation of buprenorphine-exposed children at a neonatal unit after birth for NAS may benefit the precise identification of birth deficits in this group compared with the general population. On the other hand, the accuracy of birth deficit registers depends on the extent of inclusion of data. Underrecognition and underreporting of birth defects may occur, resulting in lower prevalence rates in registers than in actually the case. It is to be noted, that the Finnish National Register of Congenital Malformations collects data on anomalies continuously, with no upper age or time limit for notification of an anomaly.

In our study population, the most common congenital disorders involved the heart – congenital cardiac deficits also globally are among the most common congenital disorders, along with chromosomal deficits. Other deficits in our study population involved the urinary tract and skeletal system, the latter including malformations of the palate and oral cavity. Previous research has revealed heterogeneous findings when trying to link gestational opioid exposure and birth defects. However, heart defects, cleft palates, and skeletal system malformations have been presented after opioid exposure (Saxen, 1975; Bracken and Holford, 1981; Vacinovic et al., 2008; Broussard et al., 2011; Abdel-Latif, 2013). It is noteworthy that all children in our study were exposed to tobacco, which has also been suggested to be associated with anomalies, e.g. with orofacial clefts (Little et al., 2004; Hackshaw et al., 2011; U.S. Department of Health and Human Services, 2014). Our study sample is too small to draw any conclusions about the effect of buprenorphine on formation of congenital disorders; to this end, larger patient samples are needed.

7.2 Ophthalmological disorders

One of the main findings in our study was the presence of ophthalmological disorders in buprenorphine-exposed children. Strabismus was found in 10% of children, which is more than the 2-6% reported in children in Western countries (Graham, 1974; Chew et al., 1994; Williams et al., 2008). One child in our study had nystagmus and opticus atrophy. The eye findings in our study population mirror earlier reports that opioid-exposed children exhibit ophthalmological problems. Strabismus, nystagmus, refractive errors, reduced acuity, optic nerve hypoplasia, and cerebral visual impairment have been described in heroin- or methadone-exposed children (Rosen and Johnson, 1982; Nelson et al., 1987; Gill et al., 2003; Mulvhill et al., 2007; Hamilton et al., 2010). Strabismus occurred in previous studies in 24-64% of heroin- and methadone-exposed patients, which is a larger proportion than the 2-6% reported in children in Western countries (Graham, 1974; Chew et al., 1994; Williams et al., 2008). One child in our study had nystagmus and opticus atrophy. The eye findings in our study population mirror earlier reports that opioid-exposed children exhibit ophthalmological problems. Strabismus, nystagmus, refractive errors, reduced acuity, optic nerve hypoplasia, and cerebral visual impairment have been described in heroin- or methadone-exposed children (Rosen and Johnson, 1982; Nelson et al., 1987; Gill et al., 2003; Mulvhill et al., 2007; Hamilton et al., 2010). Strabismus occurred in previous studies in 24-64% of heroin- and methadone-exposed patients, which is a larger proportion.
than in our study. Whether buprenorphine causes less ophthalmological problems than heroin and methadone remains to be clarified in future studies.

In addition to prenatal buprenorphine exposure, other drugs that mothers had used could explain the strabismus findings. All study subjects with ophthalmological problems were exposed to tobacco and some also to other substances such as alcohol and benzodiazepines. Both tobacco and alcohol exposure has been linked to eye problems (Chew et al., 1994; Stromland, 2004; Torp-Pedersen et al., 2010; Hackshaw et al., 2011). Some researchers have described eye disorders in benzodiazepine-exposed children, but data is very limited (Mulvihill et al., 2007; Hamilton et al., 2010). We cannot conclude whether the reason for strabismus is prenatal exposure to buprenorphine and/or other substances or some unknown factor underlies these findings. Regardless of the reason for strabismus, eye disorders should be carefully recorded in buprenorphine-exposed children at pediatrician follow-up. In some cases, strabismus can lead to vision impairment (Spiteri Cornish et al., 2013).

7.3 Other physical morbidities and mortality

Three males of the 102 children were diagnosed with infantile pyloric stenosis in Study I. This incidence is higher than the report of 1.1–3.5 per 1000 births in Western countries in the 2000s (de Laffolie et al., 2012). The male predominance in infantile pyloric stenosis has been recognized earlier (Krogh et al., 2012). All three children were also exposed to tobacco, and maternal smoking has been presented as a risk factor for pyloric stenosis (Sørensen et al., 2002). Familial clustering of infantile pyloric stenosis indicates heritability as a risk factor (Krogh et al., 2010). We do not know whether children in our study had a family history of pyloric stenosis.

Four children in the study population had either umbilical or inguinal hernia. Inguinal hernias have been suggested to relate to prenatal opioid exposure (Bracken and Holford, 1981). Prematurity is a risk factor for inguinal hernias (Peery et al., 1986) and may also be an explanatory factor, as three of the buprenorphine-exposed children with inguinal hernia were premature.

We found that 14% of the study population was SGA as newborns, which is more than the SGA rate of 3.1% in singleton pregnancies in the Finnish general population (Räisänen et al., 2013). Similarly, several studies have reported low birth weight and/or low birth length than in our study. Whether buprenorphine causes less ophthalmological problems than heroin and methadone remains to be clarified in future studies.

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in opioid-exposed newborns (Lifschitz et al. 1983; Lifschitz et al. 1985; Chasnoff, 1986; Kaltenbach et al., 1987; Minozzi et al., 2013; Patrick et al., 2015).

Two children died, one child of SIDS and another of congenital heart defect. Our study population is too small for a specific evaluation of mortality in this patient group.

7.4 Child maltreatment recognized by pediatricians

A total of 70 child welfare reports were made concerning 37 (36%) of the 102 children. Most of the child welfare reports (64%) comprised repeated failure to attend the pediatrician’s appointment, which was classified as medical neglect. This figure is strikingly more than that uncovered in child protective services’ investigations, in which medical neglect accounted for about 2.4% of child welfare reports in the US in 2013 (U.S. Department of Health and Human Services, 2015). The prominence of medical neglect noted in pediatrician’s follow-up mirrors the finding of less dental check-ups for buprenorphine-exposed children compared with control children in Study II. In Study I, the children’s regular appointments with a pediatrician were based on the general treatment practice for substance-exposed children in the hospital area. Families were actively contacted if they did not come to the appointment. Repeated failure to attend an appointment was classified as medical neglect.

The second leading cause for child welfare reports was parental substance abuse (16%), which is not surprising as the study patients were already prenatally exposed to drugs. Dubowitz et al. (2011) showed that parental substance abuse increases the risk for child welfare report in children with no prior child welfare reports. Children of substance-abusing parents are also at risk for recurrent reports to child welfare (Wolock and Magura, 1996).

Four reports to child welfare (6% of all reports) were considered suspected physical abuse. All of these cases were further processed in child welfare services as well as with other authorities. Young age of the child is a known risk factor for physical abuse, and infants and toddlers are at the highest risk for severe and fatal maltreatment (Christian and Committee on Child Abuse and Neglect, 2014). The identification of physical abuse can be difficult, especially in infants, for whom verbal evidence from the child cannot be obtained. The National Child Abuse and Neglect Data System (NCANDS) in the US showed that between 2009 and 2013 about 18% of child maltreatment cases dealt with physical abuse (U.S. Department of Health and Human Services, 2015). The prominence of medical neglect noted in pediatrician’s follow-up mirrors the finding of less dental check-ups for buprenorphine-exposed children compared with control children in Study II. In Study I, the children’s regular appointments with a pediatrician were based on the general treatment practice for substance-exposed children in the hospital area. Families were actively contacted if they did not come to the appointment. Repeated failure to attend an appointment was classified as medical neglect.

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Department of Health and Human Services, 2015). The true prevalence of all child maltreatment in our study population cannot be concluded based on this study, as this child maltreatment was only that noted by pediatricians in the hospital.

It has been established that physicians tend to more easily make a child welfare report if a child is young, if a discrepancy exists between the physical injury and history of the injury, if a child ends up in the hospital with injuries, if a child has already been reported to child welfare, if a family is poor, if a physician has received formal or recent education in child maltreatment, if a physician is confident in his/her ability to manage child maltreatment, and if a physician has a positive attitude towards domestic violence screening (Zellman, 1992; Flaherty et al., 2000; Oral et al., 2003; Flaherty et al., 2004; Flaherty et al., 2006; Flaherty et al., 2008; Jones R et al., 2008; Gilbert et al., 2009b). Factors impacting the physician’s decision not to make a child welfare report include fear of interfering with the patient-doctor relationship or other negative consequences, past negative experiences in working with child welfare, not knowing how to make a child welfare report, suspicion that the report would not improve the patient’s situation, and belief that child maltreatment will not be repeated (Flaherty et al., 2000; Flaherty et al., 2004; Gunn et al., 2005; Flaherty et al., 2006; Schweitzer et al., 2006; Jones R et al., 2008).

In our study, the same two pediatricians had treated the buprenorphine-exposed children from infancy to toddler age. Both pediatricians who worked with our study patients had a subspecialty in social pediatrics (child maltreatment), and they were accustomed to collaborative work with child welfare. This background probably facilitated the active making of child welfare reports, minimizing the insecurities that have been reported to make physicians reluctant to contact child welfare (Flaherty et al., 2000; Flaherty et al., 2004; Gunn et al., 2005; Flaherty et al., 2006; Schweitzer et al., 2006; Jones R et al., 2008). Our study clearly shows that it is possible in the prospective pediatrician’s follow-up visits in a tertiary hospital to detect several types of maltreatment in buprenorphine-exposed children. Previous data have also demonstrated that children who have a substance-abusing parent are at risk for child abuse and neglect (Kelleher et al., 1994, Jaudes et al., 1995, Chaffin et al., 1996, De Bellis et al., 2001). Moreover, the children at maltreatment risk have been suggested to be regularly seen by a pediatrician to enhance child health, to provide guidance for parents, and to recognize risk factors and possible signs of child maltreatment (Flaherty et al., 2010; Marchand et al., 2012). Based on maltreatment findings in this study, we can...
also recommend a schedule of routine visits to a pediatrician for buprenorphine-exposed children.

### 7.5 Primary residence to three years of age

Study I revealed that a large number of buprenorphine-exposed children in the HUCH area are in out-of-home care. The number of children in foster care increased from birth, reaching 43% by three years of age. There are two main groups entering public care in Finland: young children and teenagers (Hiilamo, 2008). In the first group, the reasons for out-of-home care are mainly parent-based (Hiilamo, 2008).

Studies have presented parental substance abuse as a risk factor for out-of-home care or have at least recognized that a large number of children in out-of-home care have a parent with a substance abuse problem (Besinger et al., 1999; Marcenko et al., 2000; Myllärniemi 2006; Young et al., 2007; Hiilamo, 2008; Sarkola et al., 2012; Simkiss et al., 2013). Parental substance abuse is also suggested to predict a risk for repeated entries to foster families (Brook and McDonald, 2009). A population-based analysis of 749 children in San Francisco revealed that parents’ substance abuse was a reason for placement in 30% of cases (Takayama et al., 1998). The data of the National Survey of Child and Adolescent Well-Being in the US revealed that 61% of infants and 41% of older children in out-of-home care are from families with active alcohol or drug abuse (Wulczyn et al., 2011). Of 134 children who were placed out-of-home in the Helsinki area in 2004, parental substance was documented in 43% of cases (Mylärniemi, 2006). The number was higher in younger children; in children aged under 3 years, substance abuse was one of the reasons behind the placement in 72% and in children aged 3-6 years in 64% of incidents. The study of Leventhal et al. (1997) reported that prenatally cocaine-exposed children possessed an increased risk for out-home care to two years of age compared with a control group with a similar socioeconomic background. After controlling confounding factors, however, the substance abuse alone was not a strong predictor for out-home care (Leventhal et al., 1997). Accumulation of adverse life circumstances increases the risk for maltreatment (Sidebotham and Heron, 2006), and parental substance abuse may not be the only risk factor for child maltreatment and out-of-home care in our study population either.
7.6 Dental health and dental neglect

In Study II, we found poorer oral health in buprenorphine-exposed children than in control children. Buprenorphine-exposed children had higher caries-related indices and worse oral hygiene than the controls. This is a novel finding, as data on dental problems in substance-exposed children are scarce. Two trials have described oorental problems or insufficient dental care in over 10-year-old offspring of fathers with substance abuse (Cornelius et al., 2004; Mezzich et al., 2007).

We found seven buprenorphine-exposed children and one child in the control group whose decayed/missed/filled teeth index was over 2.0. The majority of children had no caries. This finding reflects caries polarization, with a small percentage of the population having most of the caries and most of the population having no caries (Vehkalahti et al., 1997). The prevalence of early childhood caries varies greatly in developed countries from 24% to 42% (Tomar and Reeves, 2009; Davies et al., 2011), but no nationwide Finnish statistics exists regarding early childhood caries or caries tooth indices. However, in the Helsinki public dental services, the mean decayed/missed/filled teeth index was 0.16 at three years of age and 0.51 at five years of age in 2008. A mean decayed/missed/filled teeth index of 0.85 has been suggested for 5-year-olds in Finnish public dental services in 2003 (Suominen-Taipale et al., 2009). Thus, the mean decayed/missed/filled teeth index of 0.82 in 3- to 4-year-old buprenorphine-exposed children was almost the same as in Finnish children at 5 years of age. The corresponding mean decayed/missed/filled teeth index of 0.09 in control children in our survey was lower than that in Finnish children at 5 years of age.

We found that buprenorphine-exposed children possessed several well-known risk factors of early childhood caries relative to the control group; in buprenorphine-group, children had used a pacifier longer, had more mothers who had smoked in pregnancy, had more mothers who had caries, had younger mothers, had caregivers with a lower education, had caregivers with a lower income, and a lower proportion of children ate no candies (Mattila et al., 2000; Tsi et al., 2001; Poort et al., 2006; Ollila and Larmas, 2007; Yonezu and Yakushi, 2008; Majorana et al., 2014). In addition, buprenorphine-exposed children were bottle-fed, not breastfed. A long bottle-feeding has also been associated with early childhood caries (Schroth et al., 2013). The reports of whether prolonged breastfeeding increases risk for early childhood caries are contradictory (Tanaka and Miyake, 2012; Schroth et al., 2013).
Our study indicated dental neglect of buprenorphine-exposed children: their teeth were washed less frequently, parents were less involved in the tooth brushing, and these children had less dental check-ups than control children. The research on dental neglect is very limited although dental neglect is undoubtedly a risk factor for early childhood caries. Bhatia et al. (2014) conducted a systematic review of research from 1947 to 2012 on dental neglect of subjects aged under 18 years; they included 9 studies (2 case-control studies) in their final analysis. The studies mainly considered children over 3 years of age, and the concept of dental neglect mostly entailed failure to seek dental treatment or a delay in seeking adequate treatment (Bhatia et al., 2014).

Some of the identified risk factors of early childhood caries in our study – young parental age, low education, and low social position – have been previously associated also with a risk for child maltreatment (Post et al., 2006; Finlayson et al., 2007; Gilbert et al., 2009a). There is, however, very limited data on how often dental neglect accompanies other forms of child maltreatment. One study discovered high levels of tooth decay in 66 maltreated children aged from 2 to 6 years (Valencia-Rojas et al., 2008).

### 7.7 Parenting and behavioral findings

Study I found that 4% of buprenorphine-exposed children had been referred for consultation with a psychologist or child psychiatrist for behavioral problems. Approximately 7% of 3- to 5-year-olds have emotional or behavioral problems according to Norwegian and German studies (Wichstrom et al., 2012; Klein et al., 2015). One Finnish study included 1287 children, 7.2% of whom had received professional services because of behavioral problems between 3 to 12 years of age, and a further 3.3% of children were deemed to need professional services, but had not received them (Pihlakoski et al., 2004). Some studies have suggested that prenatally opioid-exposed children have a risk for ADHD or behavioral problems (Wilson et al., 1979; Ornoy et al., 2001; Sundelin Wahlsten and Sarman, 2013; Yolton et al., 2014). In our study, 43% of children were in foster care at three years of age. Children in foster care have been shown to have emotional difficulties (Lawrence et al., 2006), and behavioral problems are one of the most common reasons for disrupted out-of-home placement (Oosterman et al., 2007).
Study I evaluated behavioral problems based on only how many children had been referred for consultation with a psychologist or a child psychiatrist. The number of children (n=4, 4%) noted with behavioral difficulties in our study is lower than the number in previous studies. It is possible that behavioral problems are underrecognized. The children who were referred to the child psychiatric unit are supposed to be those whose symptoms were the most obvious or most severe. In minor symptoms, support of the parents and regular evaluation of the child's symptoms at a pediatric outpatient clinic may be sufficient measures.

In Study I, speech delay was observed in 16% of buprenorphine-exposed children. Prevalence of speech problems ranges from 2.0% to 17.5% in 3-year-olds (Silva et al., 1983; Tomblin et al., 1997; Horwitz et al., 2003; de Koning et al., 2004). The mean prevalence of delayed language development and specific language impairment (SLI) combined has been reported to be 2.5% in a Finnish study of children up to 6 years of age (Hannus et al., 2009). Relative to this Finnish study, the percentage of children with speech delay in our study seems high. Weak language skills at the age of two years predict specific language problems at five years in very low birth weight infants (Stolt et al., 2014). The study of Rice et al. (2007) also showed that a greater proportion of 7-year-old children who had been late talkers performed below normative expectations in language skills compared with control children. Of the children who had been late talkers, 20% performed below normative expectations in general language ability, 7% in speech, 18% in syntax, and 9-23% in morphosyntax.

However, the children in Study I had just turned 3 years, and after this age more specific diagnosis of language and behavioral disorders can often be done and it remains to be studied what is the true number of these problems later in childhood.

We further clarified buprenorphine-exposed children's cognitive and language development in Study III. Buprenorphine-exposed children living at home or in foster care scored lower on the Bayley-III Cognitive Scales, Language Scales, and Social-Emotional Scales than control children. Standardized scores were though mainly within normal limits. Evidence of cognitive and language outcome in our study population is consistent with previous research that children exposed to opioids may have some neurocognitive impairments (Strauss et al., 1979; Wilson et al., 1979; Johnson et al., 1984; Ornoy et al., 1996; Bunikowski et al., 1998; Ornoy et al., 2001; Messinger et al., 2004; Sundelin Wahlsten and Sarman, 2013) or,
their mental and motor skills are within the normal limits (Chasnoff et al., 1986; Kaltenbach and Finnegan, 1987; Hans and Jeremy, 2001; Konijnberg and Melinder, 2013).

In Study III, we evaluated the child-caregiver relationships. Buprenorphine-exposed children and their mothers scored lower than control children in perceived maternal self-efficacy, and among the Emotional Availability subscales, in mother’s sensitivity, mother’s non-hostility, child’s responsiveness, and child’s involvement. Mothers’ self-efficacy predicted children’s results in Bayley-III Language Scale and Social-Emotional Scale. For child involvement, mother’s sensitivity appeared to be a significant predictor variable, and for child responsiveness, mother’s sensitivity and mother’s structuring were significant predictors. In the light of our results, the caregiver environment is of importance for buprenorphine-exposed children’s cognitive and emotional performance. The problems in mother-child interactions of substance-exposed children have also been suggested in previous studies. Hostility and intrusiveness (Johnson et al. 2002), low levels of positive parenting behaviors (Johnson et al. 2002), and diminished emotional responsivity (Fitzgerald et al., 1990) have been reported.

The results in study III were fairly similar between buprenorphine-exposed children living at home and buprenorphine-exposed children living in foster care. There is not clear explanation for this, but one reason could be the timing of out-of-home care. Some of the buprenorphine-exposed children who were living with a biological parent had been earlier in out-of-home care and, majority of children in foster families had been living previously with a biological mother. Some children had experienced numerous out-of-home placements and, thus, many disruptions in their caregiver environment. Prior research suggested that opioid-exposed children living at home have reduced performance in mental skills compared to opioid-exposed children who were adopted (Ornoy et al., 1996). The impact of environment, in the perspective of foster care, has been demonstrated in children living in very deprived conditions. Nelson et al. (2007) compared young severely neglected Romanian children who had a poor early experience in an orphanage with children who had not been in an orphanage, and also with children who were moved from an orphanage to foster care at early age. The results showed marked improvements in cognitive outcomes at 42 and 54 months of age in the children placed in foster care, especially in the children who were youngest when entering the foster family. Another study showed that children who were placed in foster care from an institutional care quite early before 24 months of age, were more likely to have secure attachments (Smyke et al. 2010). Earlier placement was associated with less
likely disorganized or insecure-other attachments. In similar setting comparing severely neglected children in residential care with children who were placed early in foster care it was noted that, in extreme cases, severe neglect may affect brain white matter development (Bick et al., 2015).

In the light of results of study I and III, some buprenorphine-exposed children exhibit behavioral and developmental problems that need further treatment. Special emphasis is to be given for supporting mother-child –relationship as the maternal dimensions of emotional availability and mother’s self-efficacy suggested to have impact on child performance in cognitive tests as well as on child’s emotional interactions with a mother. Interventions are needed to determine what are the strengths in buprenorphine-exposed children’s families and the optimal ways to support the families. More research is needed to evaluate later outcome of these children in biological families and foster families and the effects of timing of foster care, when it is to be considered.

### 7.8 Somatosensory and auditory evoked magnetic fields

Newborns with NAS are generally described to be sensitive to stimulus, and avoidance of excessive stimulation is often the first step in NAS treatment. We measured MEG of buprenorphine-exposed newborns with NAS and control newborns who were not exposed to substances. No significant differences were detected between buprenorphine-exposed and nonexposed newborns in the measured AEFs and SEFs.

Atypical somatosensory-evoked responses SI and SII in newborns are suggested to be markers for later neurodevelopmental problems (Majnemer et al., 1990; Pike and Marlow, 2000; Rahkonen et al., 2013). Auditory event-related potentials in newborns predict later language development and reading skills (Guttorp et al., 2005). Our finding of no significant differences in measured SEFs and AEFs between groups indicates normal conditions for later development in buprenorphine-exposed newborns. However, in four buprenorphine-exposed newborns and one control newborn, no SII response was seen. In premature newborns, missing M200 response has been related to adverse neuromotor outcome at two years of age (Rahkonen et al., 2013).

Mother’s buprenorphine exposure treatment during pregnancy has some advantages over methadone exposure; NAS of buprenorphine-exposed newborns requires morphine
treatment at smaller doses and over a shorter time, and their hospital stay is shorter than in methadone-exposed newborns (Jones et al., 2010). In prenatally methadone-exposed infants, the VEPs showed more pathological features than in buprenorphine-exposed infants who had normal VEPs (Whitham, et al. 2010). Whether prenatal buprenorphine exposure shows an advantage over methadone also regarding auditory and sensory processing remains to be elucidated.

7.9 Limitations of the study

We cannot draw conclusions about the specific effect of prenatal buprenorphine exposure based on the findings of this thesis. Buprenorphine-exposed children had been exposed to other substances as well, and separating the effects of gestational exposure to different chemicals was not possible here.

Study I examined the health of buprenorphine-exposed children to three years of age. The birth deficits and other findings in Study I should be evaluated more precisely in a larger patient sample. A control group and more specific data on socioeconomic factors, polydrug exposure, and family history of mental and physical diseases are necessary before conclusions can be drawn about risk factors for medical outcomes of buprenorphine-exposed children.

We had data regarding the drugs that opioid-using mothers consumed in pregnancy, but we do not know the exact doses or timing of the substance use in pregnancy. A newborn’s urine drug screen reflects the mother’s substance use in late pregnancy. Regarding birth defects, it would be important to know the timing of drug exposure because the embryonic period is an especially sensitive time for some birth defects. However, determination of the detailed drug consumption of heavy opioid users throughout pregnancy is nearly impossible. Child maltreatment data would be useful in combination with health data for analysis of potential interactions. In study I, child welfare reports were coded for only the primary underlying reason. However, an isolated type of maltreatment rarely exists, and in some reports there were several subtypes of maltreatment that co-existed.

In Study II, the control group comprised parents from a higher socioeconomic class than parents of the buprenorphine group. This happened by chance as nurses in the well-baby clinics were asked to inform every 3-year-old’s parent about the study, but we do not have treatment at smaller doses and over a shorter time, and their hospital stay is shorter than in methadone-exposed newborns (Jones et al., 2010). In prenatally methadone-exposed infants, the VEPs showed more pathological features than in buprenorphine-exposed infants who had normal VEPs (Whitham, et al. 2010). Whether prenatal buprenorphine exposure shows an advantage over methadone also regarding auditory and sensory processing remains to be elucidated.

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data on how many declined to participate. The finding that control children had a higher socioeconomic position could partly explain the finding of more early childhood caries in the buprenorphine group, as low socioeconomic status is a risk factor for child maltreatment. It would be of interest to examine whether a link exists between other types of child maltreatment and dental neglect.

In Study III, a larger group of patients and controls would have yielded a more profound view of the development of buprenorphine-exposed children and the child-mother interactions. More precise data on child maltreatment, socioeconomic factors, mother’s substance use after pregnancy, mother’s mental health morbidities, and background factors gathered also from fathers would be useful in interpreting the causal links to results. In the control groups in Studies II and III, the information regarding mothers’ substance abuse was based solely on what was reported to the researcher in the interview, and thus, underreporting is possible.

One limitation of Study IV is the small patient sample. NAS of buprenorphine-exposed newborns was assessed with the Finnegan scale in the neonatal unit. Some children with mild symptoms had already been discharged from the neonatal ward and had come back to the hospital for the MEG. Precise knowledge of the severity of NAS symptoms at the time of MEG measurement would have facilitated the interpretation of results.
8 CONCLUSIONS

Our study revealed the novel information that buprenorphine-exposed children had more early childhood caries and higher caries indices than control children. The early childhood caries was detected in 17.6% of buprenorphine-exposed children and in 2.9% of control children. Dental neglect is a concern in buprenorphine-exposed children. The teeth of buprenorphine-exposed children were washed less often, the children had experienced less dental check-ups, and their parents were less involved in their child’s tooth brushing than in the control group.

Another main finding of the thesis is that buprenorphine-exposed children under three years of age are exposed to a wide range of child maltreatment. The maltreatment in the child welfare reports made in HUCH comprised medical neglect (64% of reports), parental substance abuse (16%), emotional maltreatment (7%), physical abuse (6%), neglect of child’s basic needs (4%), medical child abuse (1%), and chaotic home environment (1%).

Our study uncovered that 10% of prenatally buprenorphine-exposed children to three years of age were diagnosed with strabismus.

We discovered that prenatally buprenorphine-exposed children has reduced scores in Bayley-III Cognitive, Language, and Social-Emotional Scales as well as in Emotional Availability Scales in child responsiveness and child involvement compared with control children. Their mothers also score lower than mothers of control children in Maternal Self-Efficacy Scale and in Emotional Availability subscales mother’s sensitivity and nonhostility. We found that mother’s self-efficacy and maternal sensitivity and structuring predict children’s performance in Bayley-III Scales and Emotional Availability Scales suggesting the influence of child-caregiver environment in the cognitive and emotional outcome of children.

In MEG study, we showed that somatosensory and auditory evoked fields of buprenorphine-exposed newborns with NAS did not significantly differ from those of healthy newborns. This finding suggests that buprenorphine-exposed newborns exhibit by this time-point a normal baseline for later neuromotor development and auditory learning.

In summary, prenatally buprenorphine-exposed children encounter child maltreatment and unfavorable elements in caregiver environment that require attention. Child neglect is often difficult to notice, but “a look into the mouth” may be one of the most concrete methods to
identify neglect in the form of early childhood caries and dental neglect. A pediatrician’s follow-up with a multiprofessional team including a dentist is recommended for buprenorphine-exposed children due to multifaceted health and child maltreatment issues. Because of the magnitude of medical neglect, healthcare personnel must actively contact these patients’ parents to ensure that appointments are made and kept. The aim must be to discover what are the best strategies in health care to reduce child abuse and neglect in substance-exposed children - child maltreatment with its consequences should be considered preventable.
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