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Prenatal, Perinatal and Postnatal Adverse Conditions and their Impact on Psychosomatic Health in Children

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Adverse Conditions and their Impact on Psychosomatic Health in Children

Prenatal, perinatal and postnatal adverse conditions and their impact on psychosomatic health in children

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“When Dreams became Reality – Miracles of Life”

TO MY HUSBAND AND OUR STILL UNBORN BABY

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Abbreviations

11-β-HSD2	11-Beta-Hydroxysteroid Dehydrogenase enzyme Type 2
ACTH	Adrenocorticotropic Hormone
APGAR	1', 3' and 5' after birth evaluation of the newborn: 1. Heart Rate, 2. Respiratory Effort, 3. Muscle Tone, 4. Response to Stimulation and 5. Skin Color. A score of 8 to 10 indicates the best possible conditions. An APGAR score of 6 is defined as low (Apgar, 1953; WHO, 2001)
BP	Blood Pressure
CRH	Corticotropin-Releasing Hormone
GC	Glucocorticoids
GCsynth	Synthetic Glucocorticoids
GW	Gestational Week
HPA	Hypothalamus-Pituitary-Adrenal axis
MPF	Maternal-Placental-Fetal system
H-PNS-Gr	High Prenatal Stress Group
L-PNS-Gr	Low Prenatal Stress Group
M-PNS-Gr	Medium-high Prenatal Stress Group
OR	Odds Ratio
RDS	Respiratory Distress Syndrome
RR	Relative Risk
SAM	Sympathetic-Adrenal-Medullary axis
SES	Socio-Economic Status
WHO	World Health Organization

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Abstract

Various lines of research evidence have demonstrated that adverse pre-, peri- and postnatal life conditions might have negative influences on life stage neurodevelopment as well as on psychological and somatic health in children, adolescence and adult life. In particular, findings in children are still scarce and the etiological and maintaining underlying mechanisms are not fully understood. For this reason, we aimed to examine the influence of pre-, peri- and postnatal adverse conditions, such as prenatal stress, week of gestation, low birth weight and birth size on psychosomatic health as well as on psychosocial functioning in ten-year-old children. The main focus was on prenatal stress and its influence on birth outcomes and psychosomatic health between birth and the age of ten years.

Data I: Therefore, 96 ten-year-old children were investigated after being categorized into the groups of high, medium or low prenatal stress children. The categorization was based on the operational process considering two main prenatal factors: a complication-free pregnancy or the occurrence of preterm contractions and accordingly a risk of preterm birth and thus the administration of synthetic glucocorticoids. Glucocorticoid application serves to accelerate fetal lung maturation and consequently to prevent the newborn morbidity and mortality in cases of a childbirth before the 34th gestational week. Data analyses show significant group differences in the psycho-social level of functioning and psychological abnormalities. Perinatal outcomes seem to have no significant influence on children's psychosocial status at age ten years. A total variance of 8.6% to 13.10% of the independent psychological variables is explained through pre- and postnatal adverse conditions. Furthermore, children with high prenatal stress have a near 8-fold higher risk of psychological abnormalities. Children with medium prenatal stress have an almost five times higher risk compared to children of the low

prenatal stress group. Postnatal adverse conditions also lead to an up to 11-fold heightened risk of psychological abnormalities.

Data II: Further data analyses show that children with high and medium prenatal stress levels had lower gestational week, lower birth weight and birth size compared to children with low prenatal stress. No significant differences were found for somatic health indicators between birth and the age of ten years. Children with high prenatal stress experiences show lower diastolic blood pressure compared to children with low prenatal stress. No significant differences were found in systolic blood pressure and pulse pressure. Prenatal stress and lower birth weight seem to have a significant predictive value for blood pressure. Moreover, children with high prenatal stress reported experiencing significantly more headaches and abdominal pain, followed by children with medium prenatal stress, and finally children with low prenatal stress.

To conclude, prenatal stress might be an important but not sufficient factor in explaining etiology and maintenance of psychosomatic disorders. It seems more likely that the co-occurrence of adverse pre- peri- and postnatal life conditions, causing neurodevelopmental disturbances and programming maladaptive physiological patterns, might be responsible for health disparities in children, adolescents and in adult life.

1. Introduction

Different lines of research provide empirical evidence that pre-, peri- and postnatal development phases are crucial in association with the development of mental and somatic health in children and adolescents (Lupien et al., Seckl & Holmes, 2009; Cottrell and Seckl, 2009; O'Regan et al., 2008; Van den Berg et al., 2007; Ward et al., 2010). Periods of important development steps such as high cell mitosis activity and brain development during the prenatal phase are sensitive to endogenous and exogenous influences of adverse life conditions (Barker, 2002; Lupien et al., 2009; Newman & Newman, 2009; O'Regan et al., 2008). Adverse life conditions such as prenatal stress are considered to be a predictor of lower gestational week, lower birth weight and size as well as hypertension, cardiovascular morbidity and mortality in adulthood (Barker, 2002; Braveman & Barclay, 2009; Cottrell & Seckl, 2009; Seckl & Homes, 2007; Ward et al., 2010). Moreover, prenatal stress seems to be also associated with long-term cognitive, psychological, social and behavioral diseases in children and adolescents (Andersen & Teicher, 2008; Lupien et al., 2009; Seckl and Holmes, 2007; Van den Berg et al., 2005; Ward et al., 2004). Lower gestational week, lower birth weight and size are correlated with heightened risk of neonatal and infant morbidity and mortality (Braveman & Barclay, 2009; Forssas et al., 1999; Pedersen et al., 2007; Seckl & Holmes, 2007) as well as with long-term influences on adult blood pressure and the incidence of cardiovascular morbidity and mortality (Barker et al., 2006; Ericsson et al., 2002; Kajantie et al., 2005; Nuyt et al., 2009; O'Regan et al., 2008; Woods & Weeks, 2006). There is also clinical evidence of associations between perinatal adverse birth outcomes and psychological diseases such as depression (Abe et al., 2007; Nomura et al., 2007). Furthermore, animal and human research showed that the postnatal period is also very important for development, and there are also sensitive phases for the influence of negative environmental effects due to the

further maturation process of different brain structures such as the prefrontal cortex or amygdale (McEwen, 2008; Newman & Newman, 2009; Petermann et al., 2004; Vasconcelos et al., 2007). There is empirical evidence that early life events are strongly associated with numerous psychological and physiological disorders (Heim et al, 1998; Heim et al., 2000; Heim et al., 2001; Maniglio, 2009; Zielinski, 2010). Furthermore, empirical research also gives rise to the hypothesis that beyond pre- and perinatal as well as adverse early life conditions, there might be further life events correlated with negative health outcomes in children and adolescents. These are low socioeconomic status (Braveman, 2009; Gilman et al., 2003; Latinen et al., 2001; Lawlor et al., 2002; Lidtfeldt et al., 2007; Waylen & Stuart-Brown, 2009; Zielinski, 2009), parental divorce (Cartwright, 2006; Herland et al., 2002; O'Conner et al., 1999), psychiatric disorder of the mother and/or of the father (Waylen&Stuart-Brown, 2009), as well as birth of sibling, child psychiatric and/or somatic disorder, environmental disasters and transitional events. Life events seem to have an influence on the onset of depressive disorder as well as an impact on higher rates of depression in older age (Comjis et al., 2007; Horsch et al., 2008), somatic symptoms (Furniss et al. 2009; Liakopoulou-Kairis, 2002; Robinson et al, 1989) such as higher rates of abdominal pain in children (Hodges et al., 1984; Liakopoulou-Kairis, 2002; Robinson et al., 1990) and headache (Rhee, 2001) as well as generally on mental well-being (Bouma et al., 2008; Fruniss et al., 2009).

Quite often, numerous life events have a positive and a negative side. Challenging life conditions are required for a regular development. Stress, for example, is also considered to have positive effects. Dalziel et al. (2005), for instance, found no negative effect of prenatal stress in 31-year-old subjects. In school-aged children treated prenatally with glucocorticoids, Hirvikoski et al. (2008) showed no negative effects compared to the control group. The

different findings might reflect the various effects of pre-, peri, and postnatal adverse conditions depending on multiple bio-psycho-social factors.

We planned to explore the impact of adverse life conditions during pre-, peri-, and postnatal periods on psychological and somatic health. We aimed to investigate the single impact of prenatal stress. Furthermore, we wished to examine the combined effect of interactions between pre-, peri- and postnatal adverse life conditions on psychosomatic health in children.

This thesis is subdivided into three main parts: the theoretical background, including the methodological procedures, the empirical investigation and the general discussion. The first part introduces developmental and sensitive phases, as well as health as a basis for the development of mental and somatic health. Both serve as basis for the chapter on adverse life conditions, with the essential developments of the stress concept, prenatal stress, perinatal adverse conditions and postnatal critical life events. These constructs are summarized under the macro-category of life adversities and depict the basic principles of general influences of adverse pre-, peri- and postnatal conditions. The theoretical background is followed by the presentation of the study idea, the hypothesis and general methodological procedures. Part II presents the findings of the empirical research, followed by a general discussion in part III.

Part I – Theoretical Background

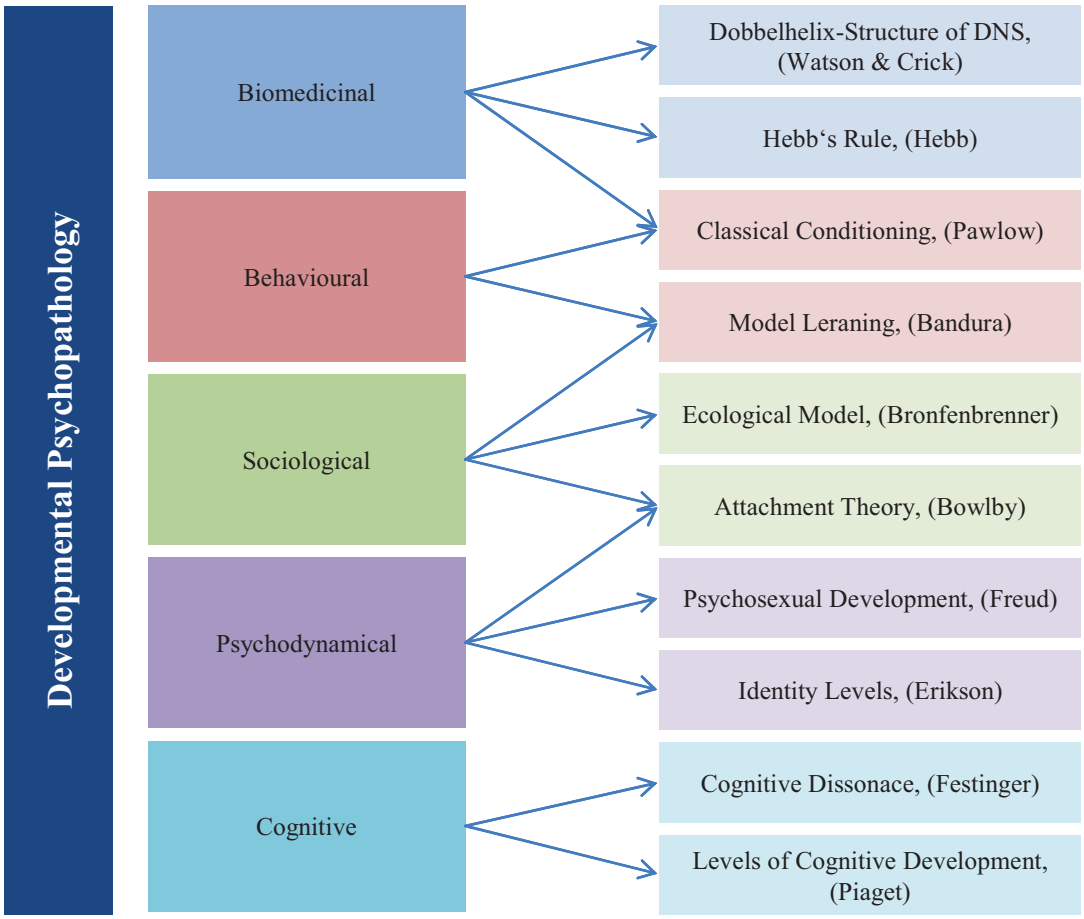
2. Pre-, Peri- and Postnatal Developmental and Sensitivity Phases for Adverse Life Conditions

Pre-, peri- and postnatal developmental phases are defined through natural developmentally given factors such as pregnancy, birth or puberty period as well as through social norms, e.g. school age or maturity (Keverne, 2004; Newman & Newman 2009; Petermann et al., 2004). Human development for its part is influenced through genetic, physical and social environmental factors as well as structural and personal factors. Hence, depending on timing, intensity and frequency, there are sensitive periods that might interact with possible influences through numerous adverse life conditions (Newman & Newman 2009; Petermann et al., 2004). Adverse life conditions can be generally classified into exposure to damaging substances (e.g. toxins, drugs, nicotine), natural or man-made disasters or exposure to violence, maltreatment or psychological stress. Empirical animal and human studies show negative health consequences based on complex multifactorial interactions, which can lead to health-threatening long-term mental and physical influences (Cottrell & Seckl, 2009; Newman & Newman 2009; Petermann et al., 2004). These complex interactions are investigated and integrated in the so-called developmental sciences, which are briefly described in the following.

Development science has only existed as an autonomous, interdisciplinary scientific method for three decades (Bronstein & Lamb; 2005; Petermann et al., 2004). The roots of developmental science can be found in “Developmental Psychobiology”, which dates back to 1888 from the term Psychobiology coined by Clarence Luther Herrick (1858-1904).

Development science is a specific approach that includes multiple levels of developmental analyses such as Psychology, Endocrinology, Neurophysiology, Embryology, Zoology, …..Cultural Anthropology and Psychiatry, for investigating, understanding and explaining human behavior (Gilbert, 2002; in Petermann et al., 2004). Therefore, a definition of the term development is not easily accessible, because there are several theories among numerous research disciplines (Lerner et al.; in Bornstein & Lamb, 2005). In 1990, Achenbach presented his broad interdisciplinary approach of Developmental Psychopathology (Figure 1).

Figure 1. Developmental Psychopathology – an interdisciplinary approach (adapted from Achenbach, 1990; in Petermann et al., 2004)

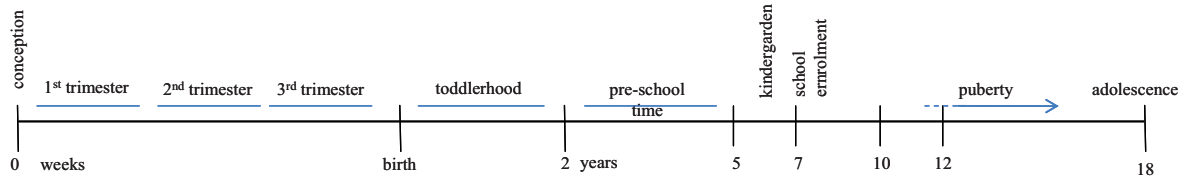


Each of the presented theories has its own theory-specific definition of Development as well as theory-specific research methods. The high variability of developmental theories and the disciplines on which they rely, are a good indicator of the broad field of Development (Cicchetti & Cohen, 1995; Petermann et al., 2004). In contemporary developmental science, the basic process of development shows multifactoral relations between different levels of organization, ranging from biology through individual and social functioning to physiological, cultural, ecological and historical contexts of development of a human being. The developmental hypothesis includes direct effects of unique exogenous or endogenous adaptive or maladaptive circumstances as well as interactional effects, including genetic, environmental and individual characteristics (Lerner et al.; Bornstein & Lamb, 2005). It is a convergence of all three development models: dispositional, environmental and interactional (Petermann et al., 2004).

Based on considerations of different research lines, the term development can be defined as a multidisciplinary, multifactoral as well as life-stage and life-long research discipline. First, the approaches stem from different research areas such as Genetics, Microbiology, Obstetrics, Medicine, Endocrinology, Pediatrics, Psychiatry and Developmental Psychology. Second, it includes numerous factors of relevance for development, such as biological, emotional, behavioral, social and microbiological factors. Finally, it contains the time factor from the beginning of a life – conception – until the end of a human life – death (Bernstein & Lamb, 2005; Newman & Newman, 2009; Petermann et al., 2004). In the following, we will focus especially on the prenatal period, the pregnancy and the perinatal period, and also on childhood until puberty because of their importance for this thesis. The considerations will be two-poled, taking a developmental and sensitivity perspective for negative health effects. Figure 2 provides an overview of important developmental phases of these periods. Each of

them might have also sensitive windows for negative influences of adverse pre-, peri- and postnatal conditions.

Figure 2. Developmental stages and potential sensitive phases for adverse pre-, peri- and postnatal conditions



2.1 Pregnancy – Prenatal Development

For most women, pregnancy and birth are an extraordinary experience. In addition to distinctive physiological modifications, such as hormonal and anatomic changes, there are psychological adjustment processes required, such as coping with the challenges of the physical changes and the role and responsibility as mother (Bühling & Friedmann, 2004; Ehlert et al., 2003; Petersen et al., 2009). During a pregnancy, there are bidirectional influences of the fetus and the pregnant woman within her social and cultural environments (Bühling & Friedmann, 2004; Newman & Newman, 2009; Stauber & Weyerstahl, 2005). Such interactions are also important in terms of the mother's experiences of stressful situations and can consequently have influences on the fetal development (Davis et al., 2007; Schneider, 2000; Wadhwa et al., 1997; Wadhwa et al., 2004). Important stress-reactive systems such as the hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic and parasympathetic nervous system are explained in section 4.1.2.

2.1.1 Developmental and Sensitive Phases of Pregnancy

A pregnancy is defined as the time after conception and before the childbirth. The pregnancy can be divided into three equivalent time periods.

First trimester – Gestational Weeks (GW) 1 to 13

Second trimester – GW 14 to 26

Third trimester – up to the 27th gestational week until birth (40th GW)

In humans, birth commonly occurs at a gestational age of about 40 weeks. A normal birth range is from 37 to 42 GW. Childbirth before fulfilling the 37th week of gestation is described as preterm (premature), whereas birth after 42 GW is considered postterm (too late) (The American Congress of Obstetricians and Gynecologists, ACOG, 2002; Petermann et al., 2004). Premature birth and its consequences will be described in the pregnancy complications in section 2.1.3.1.

In the following, the most important fetal developmental steps and fetal sensitive phases for endogenous and exogenous adverse conditions are described (Figure 4).

Fetal development during the first trimester – GW 1 to 13

In the first 10-13 days after the conception, rapid cell mitosis leads to the initiation of the embryogenesis, including basic neurodevelopmental building of the ecto-, endo- and mesodermal-layer and the first part of the central nervous system, the neural plate. From the neural plate, the neural groove is generated, and in the next step the neural tube. On the 24th day after conception, through high mitotic cell activity, three vesicles are built from the neural tube: the basal forebrain (prosencephalon), the midbrain (mesencephalon) and the hindbrain (rhombencephalon). From the prosencephalon, the hypothalamus is developed, an important organ of the hypothalamus-pituitary-adrenal (HPA) axis. The HPA is crucial in all human reactions associated with adverse life conditions (e.g. physical or psychological stress) and for maintaining homeostasis in the organism (Cannon, 1929a, b; Cannon, 1939; Goldstein & Kopin, 2007; McEwen & Wingfield, 2009; Petermann et al., 2004). Based on these three

anatomic structures, there is a further growth and cell differentiation for all parts of the central as well as the vegetative nervous system – which is ongoing until adolescence, e.g. frontal cortex and amygdale (Lupien et al., 2009; Newman & Newman, 2009; Petermann et al., 2004). At the end of the first trimester, all organs are established, the blood building cells in the bone marrow begin to build blood, and in the brain stem, the first electrical signals can be detected (Newman & Newman, 2009; Petermann et al., 2004).

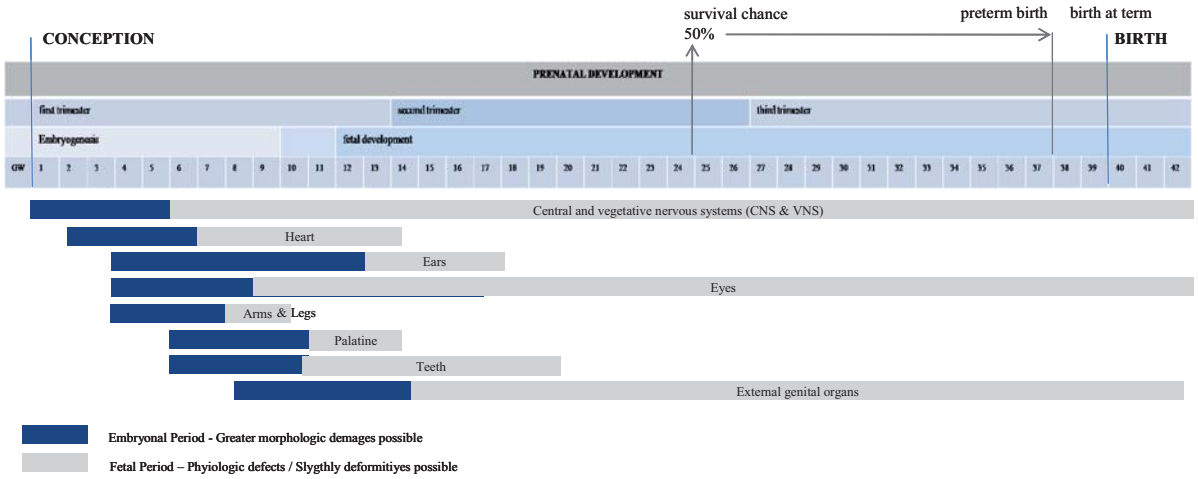
Fetal development during the second trimester – GW 14 to 26

During this time, genitals, bones and joints are formed and the disjunction of the two halves of the brain is visible. Numerous reflexes are present, including sucking and swallowing reflex. Up to the 24th GW, the fetus is in the fore and has a survival chance of 50% (Newman & Newman, 2009; Petermann et al., 2004).

Fetal development during the third trimester – up to the 27th GW until birth (40th GW)

In this pregnancy period, the fetus lung begins to build surfactant, which is an important substance (surface active agent) to protect the lungs from a collapse, and by the end of the 7th month of gestation, breathing is possible. The development of the central nervous system (CNS) is advanced and the fetus gains weight and is ready for the birth process and the beginning of a life in the environment. In the course of all of these periods of a pregnancy, adverse intrauterine and environmental conditions can lead to damages of different levels depending on timing, frequency and duration of these negative conditions (Lupien et al., 2009; Newman & Newman, 2009; Petermann et al., 2004).

Figure 3. Prenatal development and sensitive stages for environmental influences (adapted from Bühling & Friedmann, 2004; Petermann et al., 2004; Newman & Newman, 2009)



Sensitive phases for possible negative influences during pregnancy

Sensitive phases can be defined as time periods in which a human being is more sensitive to certain impulses and through the human being's own behavioral reactivity, there can be an increased vulnerability to exogenous stimuli (de Kloet et al., 2005; Petermann et al., 2004). The embryo / fetus is especially sensitive during pregnancy, with the highest vulnerability in the embryonic period (Figure 3). Depending on the time of pregnancy, the nature of the influencing substance, and finally the duration and intensity of the harmful exposure, greater fetal damages can result (Bühling & Freidmann, 2004; Schwab, 2007; Welberg & Seckl, 2001). Prenatal damages are generally possible by application of medical substances, drugs, toxins, radiation, infections, hormones, metabolic illness and hypoxia of the pregnant woman (Newman & Newman, 2009; Petermann et al., 2004; Stauber & Weyerstahl, 2005). Commonly, the highest sensitivity exists during phases of rapid cell division in the developing organs or nervous system (Cameron & Demerath, 2002; Kajantie & Phillips, 2006). The most highly sensitive time for exogenous teratogenic noxis is the time between the conception and

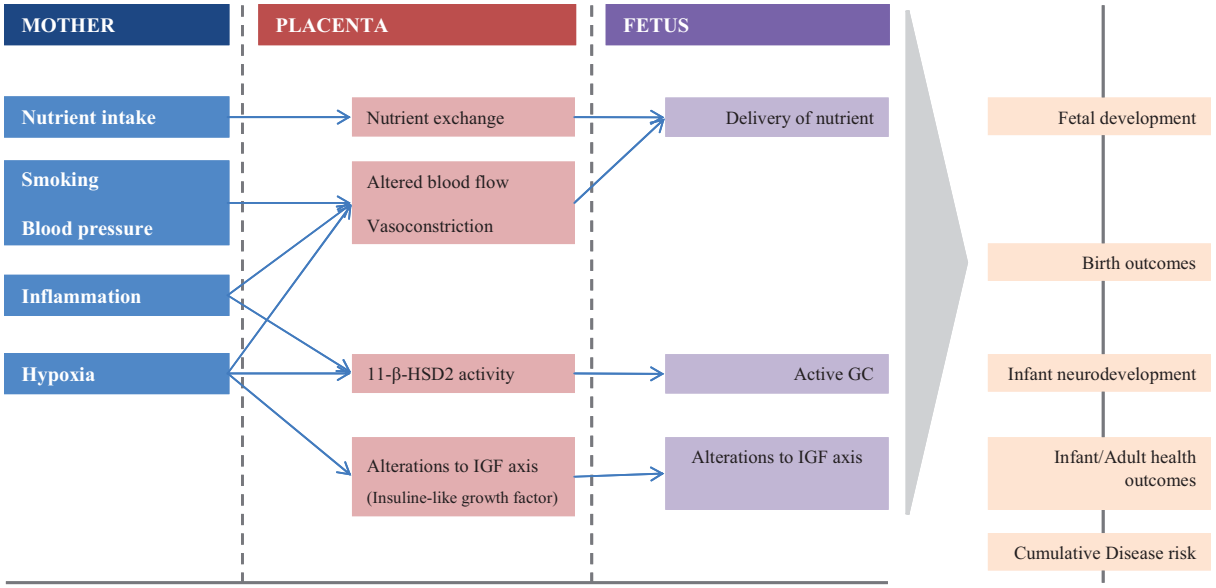
the 10th GW, which is why miscarriages might often occur during the first trimester. The central nervous system is especially vulnerable to morphological damages in the 3rd to 6th GW. Up to the 6th GW, physiological defects are possible (Bühling & Friedmann, 2004; Stauber & Weyerstahl, 2005). In addition to these severe damages in the fetal pregnancy period (up to the 8th GW), discreet physiological changes might occur, which can be persistent for a long time and have a long-term impact on the childhood and adolescence (Bühling & Friedmann, 2004; Seckl, 2001). Such alterations are based on the fetal programming hypothesis, which will be explained in section 4.2.1 and presents the background for the long-term impact of prenatal stress. Before proceeding with further risk factors and complications during a pregnancy, the conceptual framework of the entity mother, placenta and the fetus will be described, since the developing organism and the host environment are in interaction at every stage. They influence each other in a process of simultaneous reciprocal determinism and accordingly can have benign or malicious effects on the newborn (Bühling & Friedmann, 2004; Fowden et al., 2009; Lupien et al., 2009; Petermann et al., 2004; Van den Berg et al., 2009).

2.1.2 Maternal-Placental-Fetal Entity

Generally, through the entire fetal time, the fetus is nourished, provided with oxygen and protected through the mother's body and blood supply. Therefore, the body of the mother is connected with the developing fetus environment. The connection organ is the placenta, which begins to develop upon implantation of the fertilized cell in the endometrium (inner membrane of the mammalian uterus). Functions of the placenta are: nutrition, metabolic, immune and endocrine function (Carsten & Lu, 2004; Devereux et al., 2001; 2002; Emmert & Gerstorter, 2005; Hofmann &Geist, 1999). Figure 4 illustrates some interactions between the

mother and placenta and fetus, which are crucial for the control of fetal growth and health disturbances.

Figure 4. Maternal-Placental-Fetal interactions and potential consequences for psychosomatic health in children and adolescents (adapted from Murphy et al.; Wadhwa & Frederenko; in Hodgsen & Coe, 2005)



In the following, the neuroendocrine function and the mother's HPA-Placenta- and fetal HPA system will be described due to their importance for this work.

Parallel to the proceeding of the gestational week, there is an increase in corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH) and cortisol due to the secretion of CRH through to the placenta in addition to the mother's and fetus CRH production. Placental CRH has a stimulating effect on both the mother's and fetus secretion of ACTH through the pituitary (Egarter & Husslein, 1998; Wadhwa et al., 1997) and this consequently leads to increased cortisol levels in the mother and fetus. In contrast to the negative feedback loop to the hypothalamus and pituitaries, heightened cortisol levels have a

stimulating effect in the CRH-expression of the placenta (Egarter & Husslein, 1998; Wadhwa & Federenko; in Hodgson & Coe, 2005). The crucial protective factor, which protects the fetus from overexposure to GC, is the placental 11-β-hydroxisteroid dehydrogenase type 2 (11-β-HSD2). By 11-β-HSD2, glucocorticoids are oxidated into inactive derivates (Kerzner et al., 2002; Stewart et al., 1995; Vackova et al., 2009; Wadhwa & Federenko; in Hodgson & Coe, 2005; Welberg et al., 2000). Although the underlying mechanisms are still not fully understood, various lines of research provide sufficient evidence that the maternal, placental and fetal neuro-endocrine systems play a critical role in fetal maturation, physical processes and parturition (Ehlert et al., 2003; Wadhwa et al., 1997; Wadhwa & Federenco; in Hodgson & Coe, 2005). The maternal-placental-fetal (MPF) neuroendocrine axis promote in early gestation uterine quiescence and in late gestation uterine contractility. There seems to be a shift from a progesterone-dominant to an estrogen-dominant uterine environment over the course of the gestation. This process results in promoting labor, expression of oxytocin receptors and synthesis of prostaglandins (Challis et al., 2000; Ehlert et al., 2003; Grammatopoulus et al., 1999; Smith, 2001; Wadhwa et al., 1997; Wadhwa & Federenko; in Hodgson & Coe, 2005). Women in preterm birth have significantly elevated CRH-levels, in some studies already in the 15th GW, preceding the onset of spontaneous preterm birth, (Holzman et al., 2001; Wadhwa, 1998; Warren et al., 1992) as compared to controls. In contrast, women delivering postterm (> 41 GW) have lower levels of CRH (McLean et al, 1995; Wadhwa, 2004). The MPF neuroendocrine axis seems to be stress-sensitive (Wadhwa & Federenko; in Hodgson & Coe, 2005; Wadhwa, 2004). Clinical evidence suggests that the mechanism of placental CRH production over the course of gestation might be elevated by an adverse intrauterine environment characterized by physiological stress (Hobel et al., 1999; Wadhwa & Federenko; in Hodgson & Coe, 2005). Elevated CHR in the mother or fetus has been observed in women with occurrence of pregnancy complications such as pre-eclampsia,

reduced uteroplacental perfusion, intrauterine infection, and in cases where fetal distress has led to elective preterm childbirth (Wadhwa & Federenko; in Hodgson & Coe, 2005). Numerous in vitro studies have shown that CRH is released from cultured placental cells in a dose-response manner as a reaction to all of the major biological effectors of stress, including cortisol, epinephrine and norepinephrine as well as proinflammatory cytokines (Petraglia et al., 1987; 1989; 1990). Significant correlations among maternal HPA axis stress hormones ACTH and cortisol and placental CRH were found in vivo studies (Erickson et al., 2001; Petraglia et al., 1990). Furthermore, maternal psychological stress is significantly correlated with maternal HPA axis hormones ACTH and cortisol. Accordingly, in some studies, direct associations were found between maternal psychosocial stress and placental CRH function (Erickson et al., 2001; Hobel et al., 1999). Adverse prenatal stress effects on the fetus and child development as well as consequences for psychosomatic health are described in section 4.2.

In the next section, other risk factors such as numerous complications are briefly presented, which can appear during the pregnancy and might be very stressful and painful for the mother and fetus. Such adverse prenatal conditions might even have life-threatening effects on the fetus/newborn.

2.1.3 Complications of Pregnancy and their Treatment

In course of a pregnancy, different complications with negative influences on the fetus can emerge, including (Wen et al., 2004; Lopez Bernal, 2007):

- Pregnancy hypertension, which has a prevalence of 1.47% in Switzerland (StatSanté, 2007a)
- Preeclampsia, with a prevalence of 2.78% in Switzerland (StatSanté, 2007); 3-5% of all pregnancies (Kajantie & Phillips, 2006)

- Gestational diabetes, with a prevalence of 1.54% in Switzerland (StatSanté, 2007a)
- Premature rupture of membrane – no data available
- Hyperemesis gravidarum, with a incidence of 0.03-2% (Goodwin, 1998; in Ehlert, 2003; Schmidt-Matthisen & Schnauf, 2005c)
- Preterm Contractions ,with a prevalence of 5-9%; causal for preterm birth in 1/3 of all cases (Breckwoldt & Pfleiderer, 2008; StatSanté, 2007)

The complication with the highest incidence is the occurrence of preterm contractions (Iannucci et al., 1996; Krähenmann et al., 2005), which can result in a reduced gestational duration and subsequently to preterm birth with lower birth weight and size in newborn. The etiology and maintaining factors are multifactorial. One of these factors seems to be prenatal stress (Brett et al., 1997; Ehlert et al., 2003; Eskenazi et al, 2007; Kajantie & Phillips, 2006; Rieger et al., 2004; Rizzardo et al., 1988). This framework will be described in the following.

2.1.3.1 Preterm Contractions and the Risk of Preterm Birth

Preterm Contractions can be defined following the medical criteria which are listed in the following (Beinder & Vetter, 2007; Challis et al., 2001; Sidor & Bühling, 2004). Preterm contractions seems causal for 1/3 of preterm birth cases.

- Uterine contractions (painful, palpable, contractions have a duration of more than 30 seconds and a frequency higher than 3 times / 30 minutes) and
- Functional cervix reduction in the length and/or
- Opened mouth of uterus and/or
- A positive test of fibronectin (extracellular matrix glycoprotein) in vaginal secretion

Preterm contractions seems causal for a high portion of preterm birth cases (Breckwoldt & Pfleiderer, 2008; Lopez Bernal, 2007; Wenab et al., 2004). Preterm birth is a major challenge in perinatal health care (Tucker & McGuire, 2006; Lopez Bernal, 2007). It is a crucial factor of perinatal death and a major predictor of neonatal and infant morbidity and mortality. Premature birth might have an emotional and social impact on infants and their families (Adams, 1995; Berkowitz, 1993; Porter et al). In 75-95% of cases, neonatal mortality is due to premature birth (Hobel et al., 2003; Schneider, 2000; Rath, 2006; Wenab et al., 2004). Most developed countries have a 6-10% preterm labor rate. 1-2% of the newborns are born before 32+0 GW (Beinder & Vetter, 2007; Lumley, 2003; Tucker & McGuire, 2006). In this case, the morbidity and mortality of the babies is particularly high (Beinder & Vetter, 2007). Highest rates are found in the USA, with about 12% (Blumenfeld & Lyell, 2009; Tucker & McGuire, 2006). Worldwide, an increase in the rate of premature labor can be observed, in contrast to the decrease in the newborns' morbidity and mortality due to new developments in medicine and neonatal efficacy (Beinder & Vetter, 2007; Lumley, 2003). Interactions of many medicinal and non-medicinal factors can contribute to premature delivery (Friese et al., 2003; Lopez Bernal, 2007). There is evidence that myometrial contractility during human pregnancy is modulated by CRH (Tyson et al., 2009), reflecting the importance of the endocrinological role of the matermal-placental-fetal entity. The highest odds ratio (OR) for preterm birth is found in multiple pregnancies (OR=8.8), diabetes (OR=6.4), miscarriages in the past (OR=4.4) or bleeding before 24th GW (OR=2.5). Non-medical risk factors are gestational age of the pregnant woman, socio-economic status, consumption of caffeine, alcohol, nicotine or drugs, periodontitis, BMI, sport, sexual behavior, low social support and stress (Friese et al., 2003; Lobel et al., 1992; Petermann et al., 2004; Newman & Newman, 2009). Empirical indications based on psychobiological research show that stress is an etiological risk as well as maintaining factor for preterm delivery (Dunkel-Schetter, 1998; Dole et al., 2003; Ehlert,

2004). Maternal stress has remained a significant predictor of spontaneous premature birth, even after data were adjusted for adverse behavior and other complications during the pregnancy (Bandelow et al., 2002; Stein et al., 1987; Facchinetti et al., 2007). Research on stress and birth outcomes originated approximately 30 years ago, with the earliest published empirical studies on the role of stress in preterm contractions and accordingly delivery appearing in the 1970s (Dunkel-Schetter, 1998; Newton et al., 1979; Schwartz, 1977; Speilberger & Jacobs, 1979). Dole et al. (2003) found an increased risk of preterm delivery among women with high counts of pregnancy-related anxiety (risk ratio RR=2.1, 95% confidence interval (CI): 1.5-3.0), in terms of life events to which the mothers assigned a negative impact (RR=1.8; CI: 1.2-2.7), and in mothers with a perception of racial discrimination (RR=1.4; CI: 1.0-2.0).

In contrast to a number of studies indicating a strong association of mothers' stress with the incidence of pregnancy complications and in particular the occurrence of preterm contractions and thus the risk of preterm delivery, empirical studies investigating the effect of the appearance of symptoms of preterm contractions and mothers' psychological and physical well-being are lacking. Naturally, it can be strongly suggested that there is a negative influence on mothers' psycho-physiological well-being and increased pregnancy-related anxiety, also in mothers who experience a time period with a risk of preterm contractions. King et al. (2010) found that pregnant women with a diagnosis of a medical disorder are significantly more anxious and depressed than pregnant women with a complication-free course of pregnancy. Generally, many women report increased worries and anxiety during the pregnancy period, as well as depression-like symptoms (Alder et al, 2007). Enhanced levels of anxiety during pregnancy may affect maternal blood flow, blood pressure (Teixeira et al., 1999) and accordingly contribute to adverse obstetric, fetal and neonatal outcomes (Alder et

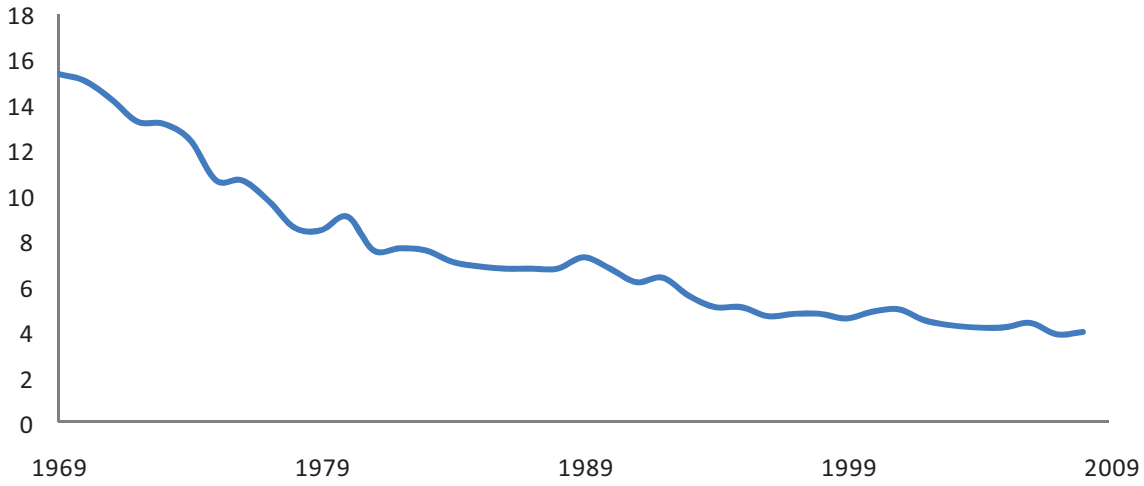
al., 2007; van den Berg et al., 2005). Hence, medical treatment of the symptoms of preterm contractions and conseqeuntly the risk of premature birth as well as maternal psycho-social care are very important. The following section illustrates the common medical treatment with tocolytica and/or glucocorticoids for preventing premature birth.

2.1.3.2 Treatment with Tocolytics and/or Glucocorticoids

Preterm contractions symptoms are generally treated through bed rest, avoidance of stress and physical effort (Anotayanonth et al., 2004; Goerke & Valet, 2006, WHO, 2007). The next treatment step is the application of tocolytics and in the case of a risk of preterm delivery before 34th GW, additionally the administration of synthetic glucocorticoids (GCsynth). Tocolytics (from the Greek tokos=childbirth and lytic=capable of dissolving) are substances which have an anti-contraction or labor-suppressing influence. Application of tocolytics is not indicated before 24th GW and after 34th GW. The main effect of a tocolytic treatment is an extension of the gestational duration of 2-7 days and a subsequent improvement of neonatal outcome (Blumenfeld & Lyell, 2009; Beinder & Vetter, 2007). All tocolytic medications have side effects, some of them potentially life-threatening. Medical decisions whether to use a tocolytic, if so which, require the clear diagnosis of preterm birth, knowledge of the mother's gestational age, medical anamnesis and cost. Once tocolysis is initiated, attention must be paid to the patient's reactivity, side effects and adverse effects (Blumenfeld & Lyell, 2009; Beinder & Vetter, 2007). In the time gained due to a tocolytic, a GC administration (Dexamethasone or Betamethasone) is possible. This treatment needs 1-2 days and accelerates greatly fetal lung maturation (Blumenfeld & Lyell, 2009; Krähenmann et al., 2005). Due to this accelerating maturation effect on the lung administration of synthetic GC, there seems to be a successful reduction of morbidity and mortality in preterm infants (Crowther et al., 2006; 2007; Lee et al., 2006; Roberts & Dalziel, 2006; Tegethoff et al., 2009). The pioneering work

of Liggins & Howie in the early 1970s has led to a widespread use of synthetic GC to treat mothers with a risk of premature delivery (Liggins & Howie, 1972). Figure 5 shows a decrease in mortality of newborns in Switzerland for the time since GC treatment in hospitals was induced.

Figure 5. Mortality rate of babies in the population of Switzerland. Values given in rate pro 1000 live births (adapted from StatSanté, 2009)



GR application can lead to structural functional changes in brain and other organs such as the kidneys after intrauterine exposure (Bolt et al., 2001; Grier et al., 2004), including HPA axis (Matthews, 1999; Tegethoff et al., 2009) cognitive, psychological or behavioral development (Owen et al., 2005; Seckl, 2004; Sloboda, 2005). A detailed description of the effects of endogenous or exogenous GR exposure on the fetus will be provided in chapter 4.

After describing the prenatal development and vulnerable phases for antenatal endogenous and exogenous factors in the next sections, the focus will be on the perinatal and postnatal developmental period.

The perinatal and postnatal phases are important for the further neuro-biological as well as socio-psychological development. In each individual period of development, there are appropriate stimuli needed for a healthy development, such as visual, auditory, and tactile stimuli as well as socio-emotional impulses such as feeding and attachment behavior. The following citation demonstrates the long-term importance of these developmental periods. "All aspects of adult human capital, from work force skills to cooperative and lawful behavior, build on capacities that are developed during childhood, beginning at birth" (The Science of Early Childhood).

2.2 Perinatal Development and Sensitivity Phases

The perinatal period begins with the birth. The WHO defines a neonate as a living child with vitality signs such as breathing and pulse pressure (Emmert & Gersthofer, 2005). The neonatal time can be defined as the early neonatal period, 1-7 days of life, and as the late neonatal period, 8-28 days of life (Emmert & Gersthofer, 2005; Khaf, in Hofmann & Geist, 1999). This period is primarily identified through the following birth outcomes: Week of gestation at birth, APGAR score; birth weight and size as well as first adaptation to the environment including swallowing reflex, gastro-intestinal function and first motor and sensory reflexes. With the APGAR score, the newborn physical status is evaluated by assigning numerical values (0 to 2) to each of the 5 criteria: 1. Heart Rate, 2. Respiratory Effort, 3. Muscle Tone, 4. Response to Stimulation and 5. Skin Color. A score of 8 to 10 indicates the best possible conditions. An APGAR score of 6 is defined as low (WHO, 2001). The newborn's body has to adapt to the environment. Autonomous breathing, ingestion and digestion, temperature regulation etc. are required. Animal studies in rats show an interaction of prenatally occurring complications or drug administration and perinatal developmental processes. There may be an interfering effect of gene expression during the determined program of perinatal developmental processes and thus

disorganized perinatal ontogenesis. The perinatal ontogenesis is characterized by intensive cell differentiation and receptor formation in already (prenatal) shaped organs such as endocrine and immune organs or brain. It seems that neonatal stress in rats can disturb the nociceptive system and cause long-term behavioral changes persisting until adulthood (Rokyota et al., 2008). Generally, early life adversity such as emotional or physical deprivation, abuse or violence has widespread effects on both the brain and the rest of the body (Felitti et al., 1998; Heim & Nemeroff, 2001;McEwen, 2008) and can lead to long-lasting emotional problems in children and adolescents (Kaufmann & Charney, 1999; Kaufmann et al., 2000; Rapetti et al., 2002, McEwen, 2008). The perinatal time is crucial for the development of the newborn, because of the immense cell differentiation and adaption to the environmental processes. The brain is constructed to be shaped by the environment. Either the absence of or overexposure to environmental stimuli can lead to light to severe neurodevelopmental damages (Lupien et al., 2009; The Science of Early Child Development, Shonkoff, 2010; van den Berg et al., 2005) (Figure 2 p.6).

2.3 Postnatal Development and Sensitivity Phases

The postnatal developmental period can be defined as in the following timetable (Table 1). Defining criteria are based on bio-psycho-social developmental processes as well as cultural norms. In all life phases, there are characteristic developments on brain functions, neuron neurogenesis and building of new synaptic connections, cognitive, verbal, emotional and social behavior as well as social competences (Paetsch, 2006; Petermann et al., 2004; Newman & Newman, 2009). In each age- and field-specific development step, there is a continuity from simple to complex processes in neurobiological functions and cognitions, emotions as well as social skills (Gardiner, 2007; Gluckmann & Hanson 2004; Paetsch, 2006; Petermann et al., 2004; Newman & Newman, 2009).

Table 1. Postnatal age periods from birth to adulthood (on the basis of: Petermann, et al., 2004; Newman & Newman, 2009)

Age	Developmental Period
1 – 4 weeks postnatal	Newborn / Neonate (described in the section above)
1 - 24 months	Infancy
2 - 5 years	Toddlerhood
5 – 7	Play Age / Preschooler
7 – 10	Primary School Age
10 -1 2	Preteen
12 – 16	Puberty
> 18	Adulthood

In the following, the single age periods are briefly described. Infancy can be defined as the time window between the perinatal phase and the age of two years. It is a crucial phase of sensory and motor development. The visual system and language, sitting, standing, walking as well as the development of the autonomy motivation are important challenges of this phase. Infancy is, moreover, an important period of bonding. First experiences of bonding are gathered by the newborn/infant and contact behavior skills to the social environment grow. This is possibly due to the development of infants' perception skills such as seeing and hearing, his "verbal" behavior (chattering, first words, two-words language, asking) as well as through his smile, shyness with strangers and seeking closeness to attachment figures (Newman & Newman, 2009; Petermann et al., 2004; Steinhausen, 2005). At this time, emotional deprivation, development disturbances and physical handicaps might have harmful effects for the further development (Newman & Newman, 2009; Petermann et al., 2004; Steinhausen, 2005). During toddlerhood, there is ongoing development in all of the fields described above. The child is able to manage his physical behavior at a higher level, is curious and engaged in fantasy and role-specific games. The child begins to develop his own personal

and gender identity, pro-social and group-related behavior. In the case of greater developmental disturbances, internalizing and externalizing disorders as well as eating and sleep disorders can be observed (Newman & Newman, 2009; Petermann et al., 2004; Steinhausen, 2005). With ongoing age, multiple factors influence the development of children, including the family, kindergarten and school, peers, the media and other factors of the social environment of the child (Bronfenbrenner, 1977; 1986; in Petermann et al., 2004; Newman & Newman, 2009). The onset of the school time constitutes a special challenge because of its multiple demands on children such as coping with separation from their parents, and dealing with the teacher, peers and group dynamics. The middle childhood is also characterized by the development of the internal behavior steering (conscience), and skills of concept and rule building (period of concrete operation). Psychopathological diseases might be observed in social and emotional behavior, psychosomatic, compulsive, tics and learning and impairment-related diseases (Newman & Newman, 2009; Petermann et al., 2004; Steinhausen, 2005). The next life challenge is the time of puberty, with crucial psychological, hormonal as well as physical challenges such as one's own identity, sexuality and authority. It is a critical time for developing delinquency, drug abuse behavior, affective disorder, suicidal behavior, compulsive disorder, schizophrenia and psychological diseases with somatic symptoms (Newman & Newman, 2009; Petermann et al., 2004; Steinhausen, 2005). After puberty comes the adolescent and early adulthood period, which are characterized by the end of the obligatory school period, the professional orientation and the beginning of working life (Newman & Newman, 2009; Petermann et al., 2004; Steinhausen, 2005).

In summary, from the time of birth, one life challenge follows the next. Each of them fits into specific development windows and accordingly, developmental steps are needed in order to deal with them. Disturbances through adversities such as low socio-economic status, racial

discrimination, parents' illness as well as emotional deprivation and sexual or physical abuse, are possible in each developmental period and might influence the children's coping with life challenges. A crucial and basic factor for successfully coping with all of these life challenges is good physical and psychological health of the children. Health will be described in the next section.

3. Health – Definition and Theories of Health

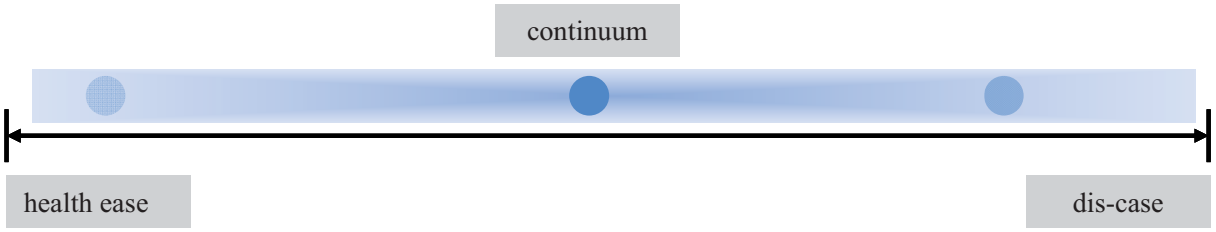
On April 7th 1948, the United Nations ratified the formation of the World Health Organization (WHO). Their fundamental objective was "the attainment by all peoples of the highest possible level of health". The WHO defined health in 1948 as being "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity". Studies that used the health concept for their investigations highlight its lack of operational value and the problem created by the use of the word "complete" (Jadad & O'Grady, 2008). Consequently, in 1986, the WHO redefined health in the Ottawa Charter for Health Promotion as follows: "a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities." Health is also defined in classification systems such as the WHO Family of International Classifications (WHO-FIC), which is composed of the International Classification of Functioning, Disability, and Health (ICF) and the International Classification of Diseases (ICD) (Eriksson & Lindström, 2008). Overall health is composed and achieved through a combination of physical, mental, emotional and social well-being. In the following, health theories used in scientific research are briefly described: the bio-medical model, the bio-social model and especially the salutogenic model.

The bio-medical model has existed since the middle of the 19th century and remains widely used to this day. In this model, health is defined as the absence of illness (Faltermaier, 2005; Reimann & Hammelstein, 2006; Wampold et al., 1997) and can be classified as pathogenetic model. Every illness has a specific cause. Therefore, medical examination is restricted to the body and its functions. The patient is classified as a passive carrier of the illness without an active role in the illness or healthy occurrence. Personal characteristics such as lifestyle, risk behavior or environmental influences are neglected (Faltermaier, 2005; Reimann & Hammelstein, 2006; Shah & Mountain, 2007; Wampold et al., 1997).

The bio-social model contains biological factors as well as psychological and social characteristics including resources and protective variables. There is the hypothesis of an existing continuum between illness and health, and professional evaluation is important in the process of etiology, maintenance, diagnosis and therapy (Faltermaier, 2005; Reimann & Hammelstein, 2006). This model characterizes health as being more than the absence of illness. The possibility exists that a person is not healthy despite a lack of physical illness symptoms (Brannon & Feist, 2007).

The health model of salutogenesis (Antonovsky, 1979; 1987), in contrast to the two models of health described above, contains a new perspective. Antonovsky asked “why some people stay healthy, despite, in some cases extreme life adversities?” His focus is directed towards personal characteristics and health protective factors (e.g. coping strategies) that lead to stable health in individuals. Antonovsky proposes an association between health (“health ease” and disease (“dis-case”) as a two-poled continuum called the health-ease-dis-case-continuum (HEDE-continuum, Figure 6).

Figure 6. Health-ease-dis-case-continuum – Fluent transition between health and disease (adapted from Antonovsky, 1979; 1987)



Exceptional benefits of the salutogenesis model are the fluid transition that indicates both the possibility to move in the direction of health or disease as well as the flexibility to change the situation – also in the case of an illness. Central points in the health model are also the general resistance through personal resources and the sense of coherence (SOC). Resistance is defined as a repertoire of coping strategies in order to deal with adverse life-threatening situations without becoming ill, and is developed up to the age of childhood and adolescence. SOC is characterized as a global individual orientation, which describes the intensity of the personal stable sense of confidence that life occurrences are understandable, have a sense of meaning, and one can cope with them. Interestingly – in contrast to the illness-focused models – in the salutogenesis model, stressors can have pathological or salutogenic (beneficial for health) consequences and the focus is directed towards the resources that intensify adaptive coping with adverse life situations.

3.1 Health in children and adolescents - Epidemiology

Each year, nearly 10 million children under the age of five die – more than 1000 every hour. However, most of these children could survive threats and thrive through access to simple, affordable interventions (WHO, 2008). The highest risk of death is in the perinatal phase during the first month of life. The high newborn mortality is explained through preterm birth,

birth asphyxia (e.g. respiratory distress syndrome) and infections. In the toddlerhood and childhood period until five years, the main causes of death are pneumonia, diarrhea, malaria, measles and human immunodeficiency virus (HIV). Malnutrition is estimated to contribute to more than one third of the mortality rate (WHO 2008). Survival rate increases with the advancing age of the child (WHO 2008). Generally, a change in the causes of child mortality can be discerned. At the turn of the 20th century, 90% of deaths were due to infections. In industrial states, mortality is nowadays explained by infections in only 1% of cases. Currently, the main causes of death in children aged between 1 and 15 are exposure to violence, injuries, intoxications or accidents (Schubert, 2004; Swiss Health Observatory, 2008; WHO, 2008). Generally, psychosomatic complaints are a challenge in pediatric institutions (Schulte et al., 2010; Walker et al. 1994).

The health quality from the prenatal period to childhood and adolescence has a significant importance for the further health, cognitive and intellectual development (Lampert & Richter, 2006). During childhood, the development of an imagination about diseases and health is initiated comparable to that of adulthood (Petermann et al., 2004; Seiffge-Krenke, 1997). In the following, epidemiological data will be described for children's and adolescents' psychopathology and physical health.

3.1.1 Epidemiology of Mental Health

Psychological diseases in children and adolescents can be defined as the existence of abnormal behavior and/or experiences in children and adolescents under consideration of their developmental age. Additionally, there is a concomitance of a handicap through this disturbance (e.g. incidence of separation anxiety at the age of 12) (Petermann et al., 2004; Petersen et al., 2006; Steinhausen, 2006). In the developmental period of childhood and

adolescence, several psychological diseases can occur, with differing prevalences. Table 2 provides an overview of epidemiological data for children aged 5 to 15 years.

Table 2. Epidemiological data on prevalence of psychological disorders in children and adolescents aged 5-15 years, diagnosed under consideration of DSM-IV. British sample (N=10428) (adapted from Petermann et al., 2005; Eschmann et al., 2007)

DIAGNOSIS	Frequencies in %
Any Diagnosis	**9.47**
Anxiety Disorders	3.77
Separation Anxiety	1.17
Specific Phobia	1.00
Social Phobia	0.32
Generalized Anxiety	0.65
Compulsive Disorder	0.25
Panic Disease	0.14
Posttraumatic Disorder	0.14
Agoraphobia	0.07
Unspecified Anxiety Disorders	0.93
Depressive Disorders	0.92
Major Depression	0.68
Unspecified Depressive Disorders	0.24
Externalizing Disorders	**5.90**
Attention-deficit/hyperactivity disorder (ADHD)	2.23
Oppositional Defiant Disorder	2.31
Social Behavioral Disorder	1.47
Unspecified Externalizing Disorders	1.05
Profound Developmental Disorders	**0.29**
Eating Disorders	**0.21**
Tic Disorder	**0.07**

Empirical studies show a strong association between psychological diseases during childhood and adolescence as well as adulthood. Having a psychological disease in the personal health anamnesis is considered as a risk factor in the etiology and maintenance of psychological disorders (Newman & Newman, 2009; Petermann et al., 2004).

3.1.2 Epidemiology of Somatic Health

Somatic health in children is important for an undisturbed developmental course during childhood and adolescence. In the following, different diagnoses of children's somatic diagnoses for the year 2008 in Swiss hospitals are presented (Table 3).

Table 3. Confirmed diagnosis in hospitals (Main diagnoses, ICD-10), 0-14 years, (adapted from Swiss Federal Statistics Office, 2008)

	Cases per 1000 residents
Endocrine, nutritional and metabolic diseases	4.1
Mental and behavioral disorders	1.2
Diseases of the Nervous System	0.6
Diseases of the eye and **ocular** adnexa	0.9
Diseases of the ear and mastoid process	7.4
Diseases of the circulatory system	1.4
Diseases of the respiratory system	0.9
Diseases of the digestive system	1.4
Diseases of the skin and subcutaneous tissue	0.7
Diseases of the musculoskeletal system and connective tissue	14.3
Diseases of the genitourinary system	5.6
Pregnancy, childbirth and puerperium	1.3
Certain conditions originating in the perinatal period	1.9
Diseases of the digestive system	3.8
Congenital malformations, deformations and chromosomal abnormalities	0.0
Symptoms and abnormal clinical and laboratory findings, not elsewhere classified	21.1
Injuries, poisoning and certain other consequences of external cause	6.1

External causes of morbidity and mortality	3.9
Factors influencing health status and use of primary healthcare	14.0

Figures 7 and 8 provide an overview of the distribution of different somatic health in Swiss children from the time of birth to 15 years old. A recent health problem in Swiss children is overweight and accordingly the heightened risk of diabetes mellitus type 2, and cardiovascular and arteriosclerotic diseases (Swiss Federal Statistics Office, 2007).

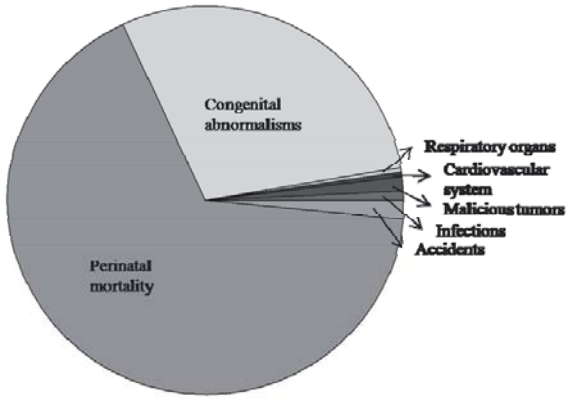


Figure 7. Mortality causes for children aged 0 months to 1 year (Swiss Federal Statistics Office, 2007)

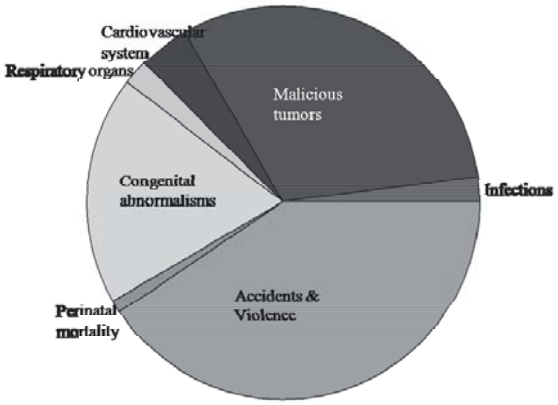


Figure 8. Mortality causes for children aged 15 years (Swiss Federal Statistics Office, 2007)

The American Academy of Pediatrics presented in 2008 a report entitled "A new urgency given the current epidemic of childhood obesity with the subsequent increasing risk of type2 diabetes mellitus, hypertension, and cardiovascular disease in older children and adults" (Shonkoff, 2010). Obesity, Diabetes mellitus type 2, hypertension, cardiovascular and idiopathic chronic pain diseases are also increased in children with antenatal stress exposure (Anda et al., 2006; Cottrell and Seckl,

2007; Felitti et al, 1998; Heim et al., 2001; James, 1996). Smolders-de Haas and colleagues (1990) found in 10-12 years children who were exposed prenatally to glucocorticoids, more hospital admissions because of infectious diseases during the first years of their life compared to a placebo group.

Generally, there are health protective and risk factors. These can be common, such as environmental or violent life threatening factors, or they can be specific for mental or somatic diseases. In the following, adverse pre-, peri- and postnatal life conditions are presented, beginning with the concept of stress. Stress can be adaptive or maladaptive. In this work, the focus is on the adverse effects of stress due to its relevance as an etiological and maintaining risk factor for numerous mental and somatic diseases.

4. Pre-, Peri- and Postnatal Adverse Life Conditions

Adverse life conditions can be defined as life conditions that threaten the psychological, somatic and social well-being of a subject (Antonovsky, 1979; 1987; Gardner et al., 2009; Matz et al., 2010). They can be of differing nature, such as exposure to natural disasters, to toxic substances or other health-threatening factors. Based on animal and human research, the following areas can also be defined as characterized by health- as well as life-threatening conditions: Stress, Prenatal Stress, Early Life Stress and Critical Life Events (Antonovsky, 1979; 1987; Gardner et al., 2009; Matz et al., 2010; Sanchez et al., 2001; Schilling et al., 2007). In the following, these concepts will be presented.

4.1 Stress

4.1.1 Definition and Theories of Stress

Stress research of the last decades shows that stress can lead to mental and somatic diseases (Chrousos, 2000; Ehlert, 2003; Kirschbaum & Hellhammer, 2007; Kudielka et al., 2004). The term stress was first used in the 18th century (Oxford English Dictionary, 2005) and originated in the English language to mean pressure, constraint or generally a burden. The roots of the stress concept as currently used can be found in the masterpiece "Introduction à la medicine expérimentale" of Claude Bernard (1813 – 1878) with the term of "milieu intérieur" (Bernard, 1965), which is still the underlying principle of homeostasis today (Cannon, 1929a, b; Cannon, 1939; Goldstein & Kopin, 2007). Claude Bernard used the term of "milieu intérieur" in several works between 1854 until his death and described with this term the ability of an organism to maintain a constant fluid environment in body cells as essential for life, independent of the external environment. Walter Bradford Cannon (1871 – 1945) subsequently coined the term "homeostasis" to describe the maintenance of several physiological variables, such as oxygen level, blood glucose or interior temperature within acceptable ranges (Cannon, 1929a, b; Cannon, 1939). Maintaining this stability requires the regulation of mechanisms as sensors to recognize discrepancies between the sensed and the physical norm values and needs effectors to reduce these discrepancies, i.e. negative feedback systems. In the early 1900s, in the course of observations during the First World War, Cannon described for the first time the acute changes in adrenal gland secretion associated with so-called "fight or flight" responses (Cannon, 1915). According to Cannon, a wide range of threats of homeostasis, such as traumatic pain, emotional distress, insulin-induced hypoglycemia, and hypotensive hemorrhage, provoke activation of the adrenal medullary and sympathetic nervous system. The function of the "sympathico-adrenal" system is to restore homeostasis. Whenever an organism perceives a threatening situation, the preparation of the

organism for a fight-or-flight reaction is activated and leads, among other things, to a rise of catecholamines, an increase of heart rate (HR), blood pressure (BP) and breathing frequency as well as the dilatation of the pupils, reduced secretion of saliva and vasoconstriction. This concept of an emergency reaction was expanded by the findings of Selye. Hans Selye (1907 – 1982) established and popularized the concept of stress. Endocrinological experiments with mice formed the background of his concept of a "general adaptation syndrome", which defines stress as a uniform response pattern to "acute nonspecific nocuous agents". In his stress theory, Selye characterized an "alarm", a "resistance" and an "exhaustion" phase of a stress reaction (Selye, 1936). First, in the alarm phase, the body is prepared to deal with threatening situations. Threatening situations lead to a disturbance of homeostatis; therefore, the sympatho-adrenal axis is alarmed and the emergency activation is induced, and further, the HPA is activated and leads to an increase of glucocorticoid (GC) secretion. Furthermore, immunosuppressive effects can be observed (Selye, 1950). Next in the resistance phase, adaptive reactions are intensified. If the stress exposure endures, the parasympathicus is activated as counter-steering process, diminishing the influence of the sympathicus. Nevertheless, catecholamines and GC levels remain high. Finally, in the exhaustion phase, the adaptive capacity is exhausted and the organism has difficulties to allocate energy (glucose as well as muscle energy), resulting in long-lasting adaptation problems. In the case of an empty storage of the adrenal cortex and a chronic stress situation, the organism can no longer cope with stress. This implicates physiological disturbances and diseases. Possible long-term consequences are disturbance of reproduction and growth processes, immune defense, enlargement of the adrenal cortex, shrinkage of the thymus, weight loss and gastrointestinal disturbances. For a long time period, stress research was based on animal research and it was consequently thirty years later before psychological factors were also included and stress was considered as psycho-biological phenomenon and psychological variables accounted for the

meaning of the stimulus to a stressed human being (Antonovsky, 1979; Lazarus, 1966; Lazarus & Cohen, 1977; Lazarus & Folkman, 1984; Mason, 1971).

Influenced by the existing stress theories, Aaron Antonovsky (1923 – 1994) presented his innovative idea of investigating the individual's concept in coping with stress or other critical life events by asking why stay people healthy (Antonovsky, 1972). Antonovsky's concept was presented in detail in the previous section due to its relevance as salutogenic health model.

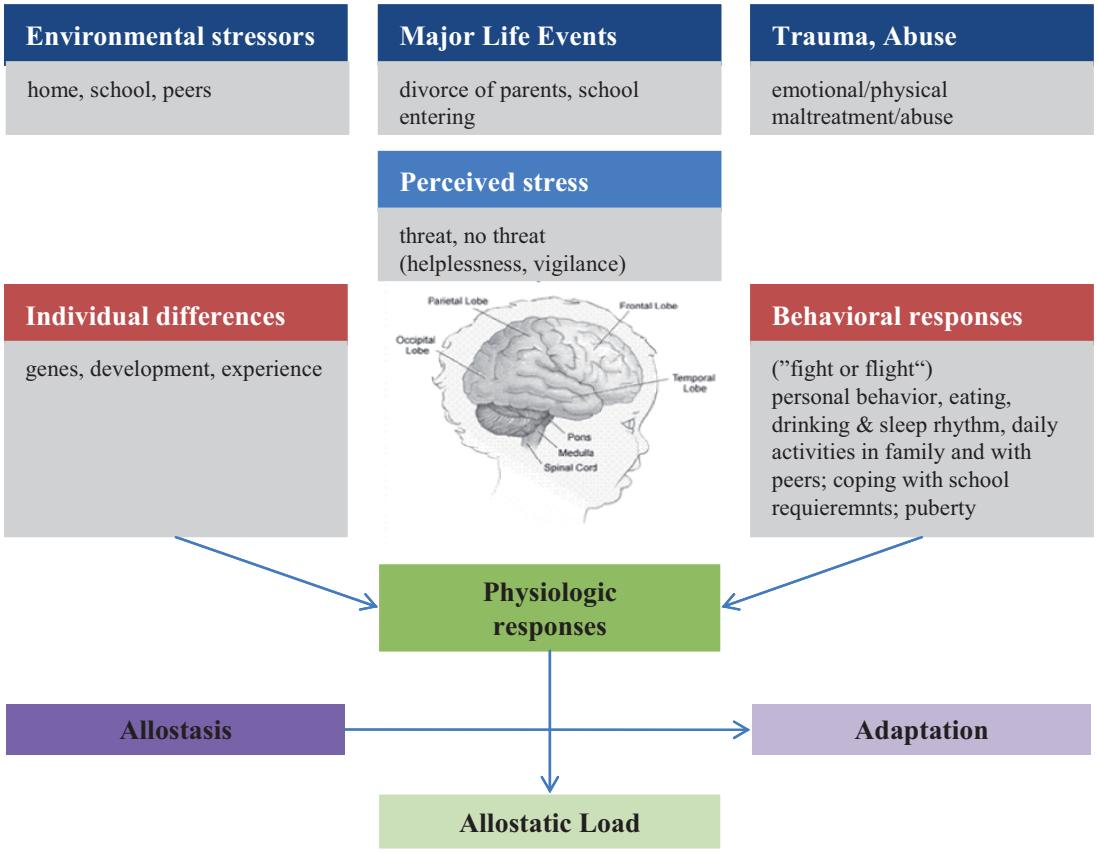
At about the same time period, Richard S. Lazarus (1922 – 2002) and colleagues developed and published their "transactional model of stress and coping", accentuating the importance of appraisal processes and coping mechanisms in the stress situation as well as the perception of one's own resources to cope with them (Lazarus, 1966; Lazarus & Cohen, 1977; Lazarus & Launier, 1978; Lazarus & Folkman, 1984). Lazarus and Antonovsky were convinced that individual perception of stress plays a key role and to a great extent develops the individual's evaluation of a situation (Lazarus, 1966). The transactional stress model has been modified and extended over the last decades and is based on two successive processes: primary appraisal and secondary appraisal. The primary appraisal depends on the attribution of the relevance of the situation. Therefore, a situation can be either irrelevant or relevant for the person. If considered as relevant, it can be perceived as harmless, challenge or threat. The second appraisal focuses on which competencies to cope with them are available and have to be used. The term "coping" is defined as a "constantly changing cognitive and behavioral efforts to manage specific internal and/or external demands that are appraised as taxing or exceeding the resources of the person" (Lazarus & Folkman, 1984, p. 141). Subsequent versions of the transactional model distinguish between problem-focused and emotion-focused coping mechanisms, and extend the model with a third process: the reappraisal

(Folkman, 1997). After coping with a situation, the outcome is evaluated and compared to the initial situation and if necessary, cognitions and emotions are altered – a reappraisal process occurs. In summary, the contemporary transactional theory of stress is based on two main concepts, appraisal and coping. It considers that individual beliefs and goals interact with environmental demands, constraints, personal resources and opportunities to shape the appraisal of what is happening, the stress reaction and how the subject copes with the situation (Lazarus, 1998).

Homeostatic activities as described by Cannon, as well as contemporary neurobiological research, allow the hypothesis of a main direction by the brain and of being determined by highly coordinated actions of a variety of effector systems, i.e. the HPA (Goldstein & Kopin, 2007). This provides the basis for the development of the concept of "allostasis" and "allostatic load". Allostasis is a term used by Sterling and Eyer in 1988 (McEwen, 1998) and refers to levels of activity required for the individual to "maintain stability through change" (McEwen, 1998; Schulkin et al., 1998; McEwen, 2000). Contemporary "allostasis" refers to a set of apparent steady-states maintained by numerous central and peripheral effectors. Among individuals, blood pressure, metabolism, glucose levels, body temperature, and so forth are normally held stable at different levels – between biological norm values – with different patterns of effector activation (Goldstein & Kopin, 2007). Highly frequent stress experiences or chronic stress can lead to prolonged continuous or intermittent activation involved in allostasis and refers to the term "allostatic load" (Juster, 2009; McEwen & Stellar, 1993). The "allostatic load" stress model represents the "wear or tear" of the body experiences when repeated allostatic responses are activated during stressful situations (McEwen & Stellar, 1993). Real or interpreted threats to homeostasis of an organism activate the sympathetic-adrenal-medullary (SAM) axis, which releases catecholamines (epinephrine and

norepinephrine) and the hypothalamic-pituitary-adrenal (HPA) axis, which leads to secretion of glucocorticoids that mobilize energy needed for fight-or-flight responses (Goldstein & McEwen, 2002; Sapolsky et al., 2000). Therefore, coordination of allostasis depends on the brain's perception and evaluating processes of the threat in adverse life conditions. In this process, involved brain areas are: hippocampus, amygdale, prefrontal cortex and prefrontal cortical regulation (Herman et al., 2005; McEwen, 2007). Figure 9 presents a graphical description of the interactions between biological characteristics, individual characteristics and environmental factors, adapted for children.

Figure 9. The allostatic load model for children and adolescents (adapted from McEwen, 1998a)



In the following the SAM and the HPA are described, as both are crucial in every reaction due to adverse life conditions in fetus, newborns, toddlers, children, adolescents and adults.

4.1.2 Biological Components of Stress

In a stress reaction, different biological systems are involved, such as the brain and especially the sympathetic-adrenal-medullary (SAM) axis as well as the hypothalamus-pituitary-adrenal (HPA) axis. Brain structures involved in stress reactions are: the limbic system with amygdale as a crucial structure related to emotional processes, prefrontal cortex, gyrus cingulum, hypothalamus, pituitary and other structures such as memory areas and executive functions. Each experience – stress – or not stressful – is based on brain-directed perceiving, controlling and executive functions. Further on, there are basic electrical signals between neurons and peripheral cells including important neurotransmitter systems (Adam et al.; in Coch et al., 2007; Cacioppo et al., 2007; Charmandari et al., 2003; 2005).

SAM – The sympathetic-adrenal-medullary axis is a part of the vegetative nervous system, which controls and regulates the function of the inner organs and helps to maintain the internal milieu (homeostasis). It is also responsible for acute adaptation to endogenous and environmental demands (i.e. increasing blood pressure, heart rate, glucose availability, breathing and decreasing reproductive functions in stress situations) (Birnbaumer & Schmidt, 2003; Cacioppo et al., 2007; Charmandari et al., 2005; Coch et al., 2007; Ehlert, 2003; Pinel, 2007) (Table 4).

Table 4. Human central and vegetative nervous system and their connections with different organs of the human organism as well as functions (adapted from Birnbaumer & Schmidt, 2003; Cacioppo et al., 2007; Pinel, 2007)

Sympathetic Nervous System (arousing)		**Central N. System (CNS)**		**Parasympathetic Nervous System (calming)**
Organ	**Function**	**Brain**	**Function**	**Organ**
Eye	Dilates pupil	**Spinal Cord**	Contracts pupil	Eye
Heart	Accelerates Heart Beat		Slows Heart Beat	Heart
Stomach	Inhibits digestion		Stimulates digestion	Stomach
Pancreas	Insulin secretion – reduces blood sugar		Decrease pancreas secretion Glucogen secretion – increases blood sugar	Pancreas
Liver	Stimulates glucose release by liver		Stimulates gallbladder	Liver
Adrenal Gland	Stimulates secretion of epinephrine/norepinephrine		Epinephrine secretion	Adrenal Gland
Kidney			Increased rennin secretion and sodium respiration	Kidney
Bladder	Relaxation		Contraction	Bladder
Sex organs	Vascular dilation in sex organs; ejaculation		Vascular constriction; Uterine muscle: Relaxation/contraction from gestation	Sex organs

As a consequence of an activation of the SAM, there is an increased secretion of both catecholamines, epinephrine and norepinephrine. Epinephrine is responsible among other things for increased heart rate and blood pressure as well as heightened levels of glucose in blood circulation. Norepinephrine has a vasoconstrictive effect on the human heart and also influences the blood pressure. Both have numerous nervous connections to other interior

organs and their interactions are often antagonistic (Table 3) (Birnbaumer & Schmidt, 2003; Cacioppo et al., 2000; Cacioppo et al., 2007; Charmandari et al., 2003; 2005; Coch et al., 2007; Ehlert, 2003).

HPA – The hypothalamus-pituitary-adrenal axis is, beyond the SAM, the essential stress system in the human body and is also called the "stress axis". The HPA is responsible for homeostasis processes in the human body and is composed of the hypothalamus, the pituitary and the adrenal cortex. There is a functional cascade from top to bottom and additionally feedback loops in the contrary direction to the pituitary and the hypothalamus (Birnbaumer & Schmidt, 2003; Cacioppo et al., 2007; Charmandari et al., 2003; 2005; Coch et al., 2007; Ehlert, 2003; Pinel, 2007). In common conditions, the following process can be described: through the sensory system, the environmental stimuli are perceived. This information is evaluated in specific brain structures, compared with past experiences and appraised for their emotional value. Subsequently, as a summary of this process, the decision is made of whether or not there is a threat for the organism. If the occurrence is attributed as a threat, the activation of the SAM and HPA is initiated and there is a secretion of corticotrophin-releasing hormone (CRH) in the hypothalamus, followed by the secretion of adrenocorticotropin hormone (ACTH) in the pituitary and finally cortisol in the adrenal cortex. In this way, an optimal reaction is possible. Energy resources are provided for the "fight or flight" reaction, and non-essential functions such as gastrointestinal or reproductive symptoms are suppressed (Birnbaumer & Schmidt, 2003; Cacioppo et al., 2007; Coch et al., 2007; Ehlert, 2003; Gazzaniga et al., 2002; Pinel, 2007). Negative feedback loops provide the information for the pituitary and the hypothalamus for suppressing their secretions of ACTH and CRH, respectively. In prolonged or chronic stress situations, long-term hypo- or hyper-reactivity of the HPA axis might arise, and might lead to mental and/or somatic diseases (Cacioppo et al.,

2007; Charmandari et al., 2003; 2005; Ehlert et al., 2003; Lupien et al., 2009; Cottrell and Seckl, 2009) .

In summary, the SAM and HPA axis are two crucial effector systems in the maintenance of homeostasis and prevention of allostatic load in adverse life conditions throughout the whole life. Additionally, as presented in section 2.1.2, the maternal-placental-fetal entity is stress-sensitive. Hence, in the following, pre-, peri- and postnatal adverse conditions and their impact on psychosomatic health in children and adolescents are presented, and selected animal and human findings are described.

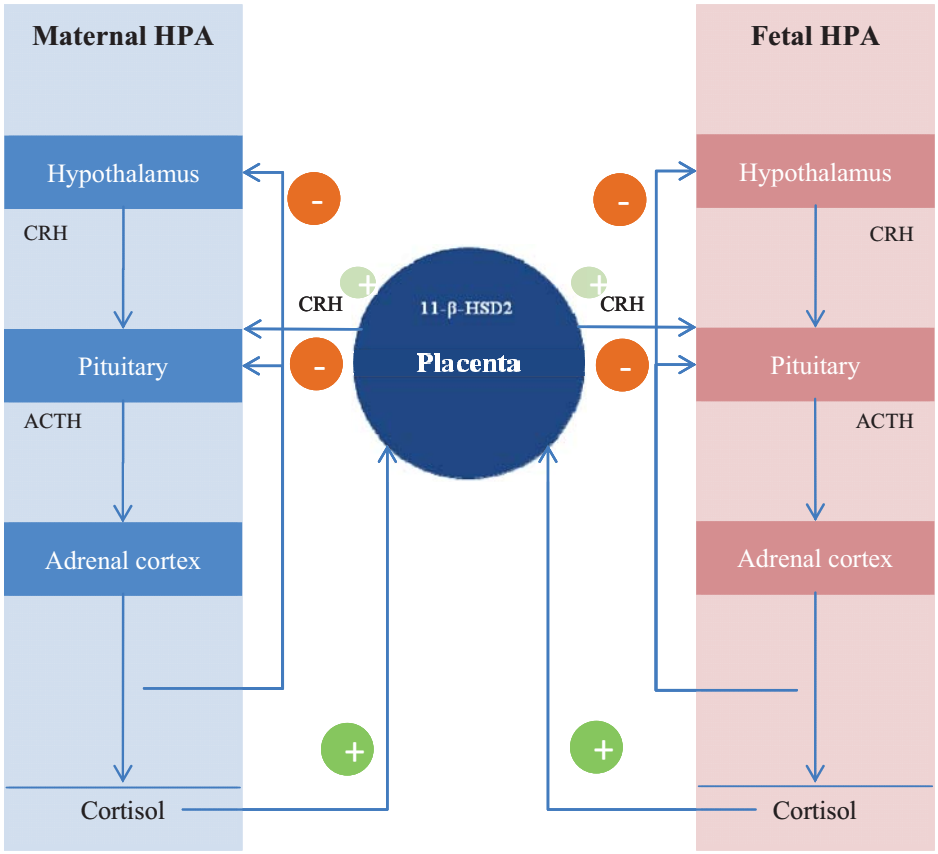
4.2 Prenatal Stress and its Influence on Psychosomatic Health

Prenatal stress can be defined as exposure of the embryo or fetus to a stressful environment between conception and time of birth (Cottrell & Seckl, 2009; Glover & O'Conner, in Hodgson & Coe, 2006; Schwab et al., 2007). Maternal malnutrition, psychological stress, exposure to toxic substances, drugs, alcohol or nicotine, or disturbed hormonal status – e.g. hyperinsulinemia associated with gestational diabetes or GC overexposure – transmit signals to the developing fetus. Depending, on timing, frequency and duration of these exposure, permanent effects on the tissue structure and function might be possible (Cottrell & Seckl, 2009; Hodgson & Coe, 2006; Lupien et al., 2009; Newnham et al., 2002; Schwab et al., 2007; Talge et al., 2007; Van den Berg et al., 2005; Wadhwa et al., 1996; 1997).

Moreover, the underlying and affected system involved in the case of adverse life conditions seems to be the maternal-placental-fetal HPA axis (Austin, 2002; de Weerth & Buitelaar, 2005; Ward, 2004; Watterberg, 2006), the vegetative (de Weerth & Buitelaar, 2005; Mulder et al., 2004) as well as the central nervous system with brain structures such as the prefrontal cortex, hippocampus and amygdale (Cottrell & Seckl, 2009; Heim & Nemeroff, 1999; Lupien

et al., 2009; Fowden, 2008; Matthwes, 1999; Van den Berg et al., 2005). In the following, the maternal-placental-fetal endocrine axis (maternal HPA, placenta and fetal HPA, Figure 10) is described in relation to prenatal stress.

Figure 10. Interactions between maternal HPA, placenta and fetal HPA (adapted from Drake et al., 2007; Ehlert et al., 2003)



Exposure to prenatal stress seems to lead to higher secretion of maternal stress hormones such as corticotrophin-releasing hormones (CRH), adrenocorticotropin hormones (ACTH) and cortisol, which are suggested to lead to increased fetal CRH, ACTH and cortisol levels (Cottrell & Seckl, 2009; diPietro et al., 2003; Ehlert et al., 2003; Ward, 2004; Watterberg, 2006). Glucocorticoids (GC) are highly lipophilic and can rapidly cross biological barriers such as the placenta. Generally, fetal GC levels are considerably lower than maternal GC

levels (Campbell & Murphy, 1997; Ehlert et al., 2003; Ehlert et al., 2004; Tegethoff et al., 2009; Watterberg, 2006). This gradient is due to the feto-placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). 11β-HSD2 is responsible for a rapid metabolism of cortisol and corticosterone to the physiologically inert 11-keto inactive forms cortisone and 11-dehydrocorticosterone (Seckl, 1997; Seckl, 2004; Tegethoff, 2009; Vackova et al., 2009). In the context of pregnant women with premature delivery risk before completion of the 34th week of gestational age (Kay et al., 2000; Matthews, 2000), there is a clinical indication of synthetic glucocorticoid (GCsynth) administration in order to accelerate lung maturation. This medical intervention leads to prevention of respiratory distress syndrome and accordingly newborn morbidity and mortality (Beinder & Vetter, 2007; Crowly, 2000; Lee et al., 2006; Roberts & Dalziel, 2006). Empirical findings demonstrate that intrauterine exposure to GCsynth can have clinically relevant influences on organs other than the lung, including structural and functional alterations in kidney and brain, HPA axis function as well as long-term effects on cognitive, psychological or behavioral development (Austin, 2000; 2005; Cattarelli et al., 2002; Owen et al., 2005; O'Shea & Doyle, 2001, Seckl, 2004, Sloboda et al., 2005; Tegethoff et al., 2009).

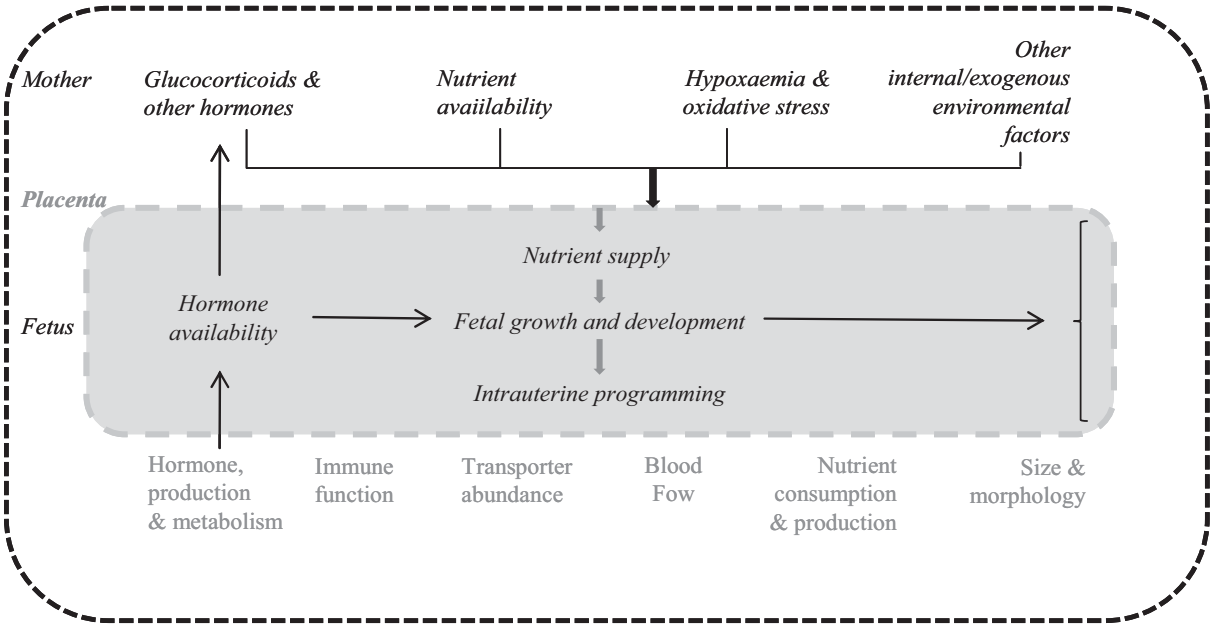
Furthermore, prenatal stress was for many years assumed to be associated with long-term effects during childhood and adolescence, but research was not conducted until the last 20 years (O'Conner et al., 2002; 2003; Schwab et al., 2007). Currently, it is widely recognized that exposure to an adverse environment during the prenatal development can have long-lasting effects on an individual's risk of psychological and somatic diseases (Cottrell & Seckl, 2009; Glover & O'Conner, in Hodgson & Coe, 2006; Newnham, 2001; Niederhofert & Reiter, 2004). The underlying mechanisms are still not fully understood. The "programming

hypothesis" provides an explanatory basis, which is often used in empirical research. The programming hypothesis is presented in the following.

4.2.1 Programming Hypothesis

In 1998, Barker postulated the fetal programming hypothesis. Fetal programming can be defined as alterations in brain steering processes through environmental changes. These alterations might be persistent for a long time period of the life (Barker, 1995; 1997; 1998; Barker et al., 2002; Cottrell & Seckl, 2009; Dötsch & Schild, 2004; Eriksson et al., 2000; Van den Berg, 2009). The fetal programming hypothesis has often been used since the time of its development and publication in order to explain long-term influences due to factors of adverse pre-, peri- and postnatal life conditions (Drake, 2007; Fowden et al., 2009; Schleussner & Schneider, 2007; Matthews, 1999; Walberg et al., 2001; Ward et al., 2004). Underlying mechanisms of lifelong persisting effects are based on biological, neuropsychological as well as anatomical structures and functions in an organism, beginning with prenatal uterine conditions in the fetus. Figure 11 illustrates the numerous functional interactions between mother and fetus, showing at the same time the complex natural mechanism of a pregnancy as well as the different possibilities of adverse influences of intrauterine environment on the fetus. It gives rise to the implication of adaptive or maladaptive long-term effects on the newborn, childhood and adolescence (Barker, 2008; Eriksson et al., 2000; Fowden et al., 2009; Knackstedt et al., 2005; Kofman, 2002; Matthews, 1999; Ward et al., 2004).

Figure 11. Schematic graph illustrating the interaction between the mother, placenta and fetus in mediating programming effects of environmental challenges on fetal development (adapted from Fowden et al., 2008)



However, the term programming stands for the action of environmental factors during a sensitive developmental period or "window" to affect the development and organization of specific tissues. Resulting effects may persist throughout life. Which organ system is affected and to what degree is determined by its individual specific vulnerability, based on the timing of exposure and the system developing during that time "window" (see section 2/Figure 4) (Nyirenda & Seckl, in Hodgson & Coe, 2005; Phillips, 2007).

In the following, animal and human research is presented showing possible influences of prenatal stress on bio-psycho-social variables.

Animal studies

Empirical research demonstrates that prenatal stress has a "programming" effect on the brain and HPA axis in animals (Barker, 1991; Burtlet et al., 2005; Watterberg et al., 2004). Animal research allows the development of experimental protocols in which animals are exposed to

acute and/or chronic stress. Experimental manipulations of prenatal stress include administration of synthetic GC to pregnant animals or maternal restriction of nutrition (Lupien et al., 2009). Exposure to a single or repeated exposure of a pregnant female to stress (Gué et al., 2004; McCromick et al., 1995) or to GCsynth (Altonow-schlorke et al., 2003; Weinstock et al, 1992) increases maternal GC secretion and accordingly alterations in the HPA axis and brain structures as well as functioning in the fetus or newborn (Matthews, 1999; Seckl, 2008; Watterberg, 2006).

Fetal exposure to GCsynth in rats (Levitt et al., 1996) during the last gestational week resulted in lower birth weight and, moreover, in increased basal plasma corticosterone levels in adult male rat offspring. This increase was associated with elevated blood pressure in adults. Furthermore, application of GCsynth to pregnant rats delays the maturation of neurons, glia cells, myelination and vasculature in the offspring. Significant alterations were found in neuronal structure and synapse formation, thus inhibiting neurogenesis (Lucassen et al., 2009; Seckl, 2008). Furthermore, there are decreased levels of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the hippocampus, which inhibit the HPA axis activity of juvenile and adult rats. Hence, this reduction can result in increased basal or/and stress-induced GC secretion (Weaver et al., 2004). Gene expression in murine late placenta also seems to be changed by prenatal GCsynth administration (Baisden et al., 2007). Other brain regions seem to be influenced too, such as decreased spine density in the anterior cingulate gyrus, orbifrontal cortex (Murmu et al., 2006) and central nucleus of the amygdale (Weinstock, 2008). The amygdale play an essential role in the regulation of emotions such as fear and anxiety (Cratty et al., 1995; Weinstock, 2008). Furthermore, depending on the prenatal period of occurring impairments of the nervous system, in fetal rats, an influence on nociception can be observed, as well as long-term development of neuropathic pain (Howard

et al., 2005; Rokyta et al., 2008). Prenatal treatment with dexamethasone (GR agonist) in rhesus monkeys leads to a dose-dependent degeneration of hippocampal neurons and accordingly to a reduced volume at 20 months of age (Uno et al., 1999). Rudolph and coworkers (1999) examined experimentally the effect of very measured local exposure to excess of GC in sheep. They infused cortisone (the active GC in the sheep) into the left coronary artery of the 125th day of fetal sheep gestation (about 2/3s of gestation) at a rate just high enough to mimic term concentration. Three days after the infusion, there were indicators of suppression of cellular proliferation and a shift to cellular hypertrophy, which is normally seen in postnatal life. Furthermore, exposure to prenatal stress has effects on adult behavior such as learning impairments in rats (Vallet et al., 1999; Weinstock, 2008), enhanced sensitivity to drug abuse (Deminere et al., 1992) and increased anxiety- and depression-related behaviors (Vallet et al., 1997; Weinstock, 2008).

To summarize, animal studies provide sufficient empirical evidence for long-lasting programming effects during sensitive prenatal phases of the animal fetus. Influences can be seen on alterations in brain structures and functions as well as on the HPA axis. Furthermore, there are influences on behavior alterations, such as drug abuse, depressive and anxiety-related behavior as well as on somatic complaints, such as elevated blood pressure, nociception and chronic neuropathic pain.

Human studies

In line with animal data, findings from retrospective studies on children whose mothers were exposed to adverse life events, psychological stress or exogenous GC application during their pregnancy suggest long-term neurodevelopmental influences (Cottrell & Seckl, 2009; Glover et al., 2002; 2004; Gluckmann & Hanson, 2004; 2006; Gluckmann et al, 2005; Kapoor et al.,

2008; Seckl & Holmes, 2007). Nyirenda and Seckl (2005) suggested that fetal exposure to endogenous (in response to maternal stress during pregnancy) or to exogenous glucocorticoids may lead to adverse adult cardiovascular, metabolic, neuroendocrine and behavioral phenotype (in Hodgson & Coe, 2005; Nuyt & Alexander, 2009; Phillips & Barker, 1997; Poggi Davis et al., 2004; Woods et al., 2005; 2006). In pregnant women who had a premature birth (between 28th and 37th GW), McLean et al. (1995) found higher CRH levels in plasma already between the 15th and 18th GW as compared to women with a birth up to the 37th GW or post-term.

Generally, GC are important for normal maturation in most regions of the developing central nervous system (CNS). They are involved in initiating terminal maturation, remodeling axons and dendrites, and ensuring cell survival (Meany et al., 1988). Furthermore, there is a high expression of 11-β-HSD2 in the CNS at mid gestation, which protects vulnerable developing cells from excessive GC exposure (Brown et al., 1996). Prenatal corticosteroid therapy seems to be associated with increased placental adrenomedullin (Marionini et al., 2006) reduced placental hormone production and maternal bone formation, impaired glucose tolerance as well as altered function of the HPA axis (Ogueh & Johnson, 2000). In utero exposure to GC might have widespread acute effects on neuronal structure and synapse formation, which can result in permanent alterations in brain structures and functions (Lupien et al., 2009; van den Berg et al., 2009; Wellberg & Seckl, 2001).

Human studies provide an inconsistent picture. Some studies found altered physiological or psychological differences in children/adults exposed to glucocorticoids prenatally as compared to their control groups (Doyle et al., 2000, French et al., 2004; Kajantie et al., 2006; Mulder et al., 2004; O'Conner et al., 2002; 2003; 2009; Trautman et al., 1995). However,

other studies did not find significant intergroup differences (Dalziel et al., 2004; 2005a, b; 2006; Davis et al., 2007; Dessens et al., 2000; diPietro et al., 2006; Hasbargen et al., 2001, Schmand et al., 1990; Throp et al., 2003).

Maternal exposure to stress, anxiety, depression or GC application during pregnancy is linked to lower weight or a relatively smaller size of the newborn with regard to gestational age (Kapoor et al., 2000; NIH, 1995; 2001; Nyut & Alexander, 2009; Pedersen et al., 2007). Alterations in HPA axis activity are found in children at different ages, including 6 months (Lyons-Ruth et al., 2000), 5 years (Gutteling et al., 2000) and 10 years (O'Conner et al., 2005). Furthermore, Kajantje et al. (2006) found a higher circulating glucocorticoid bioactivity in preterm newborns after prenatal betamethasone treatment. The level was highly dependent on the time between the last betamethasone dose application and the birth of the infants. The shorter the time between the last treatment, the higher the circulating GC activity at birth. Mulder and colleagues (2004) investigated pregnant women with a risk of preterm birth, measuring the influence of prenatal betamethasone administration and its influence on fetal heart rate (HR) and behavior depending on gestational age. At the gestational age of 29-34 weeks, they found a decrease in fetal HR on day 1 of a 5-day period (0-4). Furthermore, on days 1 and 2 they observed reduced breathing activity and prolonged episodes of quiescence with a concomitant decrease in body movements. These changes were not found if betamethasone occurred at 26-28 weeks of gestational age.

Moreover, there appear to be influences on cognitive and behavioral development (Glover et al., 1997; Matthwes, 1999; Seckl & Holmes, 2009). Psycho-social behavior alterations seem to occur, including social behavior and deficit hyperactivity disorder (French et al., 2004, Rodriguez & Bohlin, 2005, van den Berg & Marcoien, 2004), sleep disturbances as well as

psychiatric anomalies including depressive symptoms, drug abuse, mood and anxiety disorders (Glover et al., 2009; Lupien et al., 2009; Seckl & Holmes, 2009; van den Berg & Marcoen, 2004). Trautman and colleagues (1995) assessed children exposed prenatally to dexamethasone during the first trimester of the pregnancy. The treatment was carried out due to their prenatal diagnosis of congenital adrenal hyperplasia owing to 21-dehydroxylase deficiency. The children were aged between 6 months and 5 ½ years. The researchers found that children exposed to dexamethasone showed more shyness, greater emotionality, less sociability and a trend for greater avoidance. Furthermore, exposed children also had significantly higher internalizing values at age 2-3 years as compared to children without prenatal dexamethasone exposure. Hirvikosky et al. (2008) investigated subjects aged 7-17 years with a prenatal diagnosis of congenital adrenal hyperplasia, who had also been treated with dexamethasone. No significant differences were found for the most psychopathological measurements. They found only a difference for the sociability scale, which was higher for the dexamethasone-exposed group as compared to the control group. In an earlier study, dexamethasone treatment were associated with long-term effects on verbal working memory and on certain aspects of self-perception that might be related to poorer verbal working memory (Hirvikosky et al., 2007). An association between prenatal stress and childrens temperament showed Huzig and colleagues (2002) and Davis and colleagues (2007). Van den Berg and colleagues (2008) found a positive association between mother's prenatal anxiety and HPA axis disregulation as well as self-repeorted depressive symptoms in adolescence.

In babies exposed to betamethasone 3-6 days after delivery, Davis and coworkers (2004) found a difference in their cortisol release as compared to babies without prenatal exposure to betamethasone. Babies exposed to betamethasone prenatally failed to exhibit increases in cortisol to either stressor. All babies were born preterm at 33-34 weeks gestation. Stressors

were a heel-stick blood draw and a physical exam. These findings suggest that prenatal corticosteroids might suppress infants' HPA responses to stressors, including heel-stick blood draw, which is a stressor typically encountered in a neonatal intensive care situations. Furthermore, prenatal application of synthetic GC (betamethasone/dexamethasone) is assumed to have resistant effects on birth outcome, childhood cognition and long-term behavior (Sloboda et al., 2005). No significant differences were found between 6-year-old children whose mothers were treated prenatally with betamethasone compared to control children for the variables school progress and cognitive development (1982). In 7-year-old children who were treated prenatally with corticosteroids to prevent respiratory distress syndrome in premature newborns, Throp et al. (2003) found no significant differences as compared to a group of children treated with phenobarbital. Smolders and colleagues (1990) found, in 10-12-year-old children, significantly more hospital admission between the group prenatally exposed to corticosteroids as compared to the group without prenatal corticosteroid exposure. Furthermore, they measured children's height, weight and head circumference as well as neurological variables such as motor functions and reflexes. They also conducted an ophthalmological examination (e.g. defects of visual activity, myopia) and assessed sleep disturbances and onset of puberty. No significant group differences were found in these variables. Laplante and colleagues (2000) fund a significant association of prenatal maternal stress and cognitive as well as linguistic functioning in 5 ½-year-old children.

Moreover, in a twenty-year follow-up study Dessens and colleagues (2000) investigated in a randomized, double-blind placebo trial the association between prenatal betamethasone application and bio-psycho-social variables. Subjects were 20-22 years old. The corticosteroid group received 12 mg betamethasone twice within a 24-hour interval. No differences as compared to the placebo group were found in medical or psychological variables. In general, all subjects were healthy and had normal intellectual capacities. Furthermore, the groups did

not differ in any of the following variables: gender development, sexual orientation, sex-specific cognitive functioning and psychoneuroticism. They found exceptionally significant lower systolic blood pressure for the corticosteroid group as compared to the placebo group. However, the groups did not differ in their diastolic blood pressure. Moreover, Dalziel and colleagues (2005; 2006) investigated the influence of prenatal application of betamethasone in a follow-up study of over 30 years, assessing 482 subjects aged 30 years. The corticosteroid group was prenatally treated with 12 mg betamethasone within a 24-hour interval. The mothers of 181 of these were prenatally exposed to a single dose of betamethasone between the 24th and 36th week of gestation. They found no significant differences in the lung function, in the prevalence of wheezing and asthma, or in weight, height and BMI (Dalziel et al., 2006). Furthermore, no significant group differences were found in 87 subjects aged 31 years, who had been prenatally exposed to corticosteroids as compared to 105 placebo subjects for the following variables: cognitive functioning, working memory and attention, psychiatric morbidity, handedness or health-related quality of life (Dalziel et al., 2005). Furthermore, Dalziel et al. (2005) found in 30 years aged subjects exposed to betamethasone as compared to subjects of the placebo group no differences in body size, blood pressure, plasma cortisol, prevalence of diabetes, or history of cardiovascular disease.

To summarize, there are effects of prenatal stress operationalized as exogenous GC exposure or maternal psychological stress, depression or anxiety and numerous neurodevelopmental, cognitive and behavior variables in children and adolescents. A general problem in previous investigation seems to be the confounding with other variables such as the occurrence of a diagnosis of a risk of preterm birth, congenital adrenal hyperplasia, preterm birth or lower birth weight for gestational age.

4.3 Perinatal Adverse Conditions and their Influence on Psychosomatic Health

Perinatal adverse life conditions can be defined as health-threatening conditions during the first 7 or 28 days after birth. Investigating perinatal effects in humans separately represents a methodological and ethical challenge. Perinatal adverse conditions are mostly confounded with prenatal adverse factors such as malnutrition or psycho-social stress of the mother. Furthermore, experimental studies that would experimentally induce adverse conditions are considered unethical (Lupien et al., 2009; Helsinki Principles, 2004). The consequences of maternal stress that are most observable are those on gestational length and birth weight because they are not influenced by postnatal environmental events. Numerous studies have reported a high incidence of preterm birth (before completion of the 37th gestational week) and lower birth weight (less than 2500 grams) (Forsass et al., 1999; Weinstock, 2001). Furthermore, an early start in life (preterm birth or extreme preterm birth) is associated with low birth weight and birth size for gestational age (Chen et al., 1999; Basso et al., 2005; Pedersen et al., 2007; Poggi Davis et al., 2004; Wadhwa et al., 1993). Low birth weight seems to be associated with alterations in the HPA axis activity (Kajantje et al, 2002; Phillips, 2004) and increased rates of metabolic syndrome and hypertension (Curhan et al., 1996; Phillips, 1997; 2004). Most of the studies presented above in section 4.2 with prematurely born children also reported lower birth weight in the sample descriptions. Consequently, it might be suggested that birth weight could also be involved in these effects. However, the amount of this involvement cannot be evaluated.

Animal studies show that drug application in mice during the perinatal period can interfere with gene expression during the determined program of developmental processes. Accordingly there is a disturbance of perinatal ontogenesis, which is characterized by an intensive cell differentiation and receptor formation in already shaped organs such as the brain, immune and endocrine organs (Rokyta et al., 2008). In rats, the last week of embryonic life and the first two postnatal weeks are critical phases in the development of the dopaminergic and serotoninergic systems, at which time they could be particularly vulnerable to injury (Galineau et al., 2004). Combined stress (forced swim and sound

noise) in mice were strong enough to cause an adjustment disorder to a new environment, compared to the application of a unique stressor. Furthermore, mice that experienced the forced swim during the perinatal lactation period showed an increase in the locomotor activity following the stimulation by the sound noise applied 15 min after the measurement. Subsequently, it was found that the stress administrated during the perinatal lactation period, which is assumed to be a critical period for the brain development of the mouse, can have a negative influence on its developmental process (Tokumo et al., 2006).

Gestational stress might lead to emotional problems in offspring (Rice et al., 2006). In mothers with antenatal or postpartum depression, selective serotonin reuptake inhibitor (SSRI) treatment is widely applied. Two months after birth, infants with prenatal and postnatal SSRI exposure showed diminished facial and cardiac autonomic responses to the pain of a heel-lance (Oberlander et al., 2005). Salem et al. (2007) found that some early perinatal risk factors such as cesarean section, hospital delivery, prolonged labor and nuchal cord entanglement, are associated with obsessive-compulsive disorders.

Moreover, lower birth weight and birth size seem to be associated with adult hypertension (Doyle et al., 2000; Huxley et al., 2000; Sabet et al., 2009). Huxley and colleagues (2000) found that birth weight and size are inversely correlated with blood pressure. A recent neuroimaging study showed that low birth combined with lower maternal care was associated with reduced hippocampal volume in adulthood (Buss et al., 2007).

Following the description of pre- and perinatal adverse conditions and their influences on bio-psycho-social development and behavior, the focus will now be on postnatal adverse conditions.

4.4 Postnatal Adverse Life Conditions – Life Events and their Influence on Psychosomatic Heath

Postnatal adverse conditions can be defined as postnatal life-threatening or psychosomatic health-threatening events such as exposure to toxic substances, natural disasters as well as stress. In animals, postnatal stress manipulations include depriving the offspring of maternal contact, modifying maternal behavior and exposing the offspring to synthetic glucocorticoids. The cause-and-effect relationship between stress exposure and its effect on the brain or other relevant variables can be clearly demonstrated (Lupien et al., 2009). Non human primate models show that adverse postnatal care can have a negative impact on the HPA axis (Sanchez et al., 2006; Van den Berg et al., 2005) and behavioral abnormalities (Lupien et al., 2009; Van den Bert et al., 2005). For ethical reasons, the cause-and-effect relationship between stress exposure and its influences on the brain or other bio-psycho-social variables cannot be assessed in humans.

Furthermore, postnatal adverse conditions in humans can be of a different nature, including not only malnutrition, physical and psychological maltreatment or violence (Lupien et al., 2009), but also low socioeconomic status (Braveman, 2009; Danham et al., 2001; Laitinen et al., 2001; Zielinski, 2009), parental divorce (Cartwright, 2006; Herland et al., 2002; O'Conner et al., 1999), psychiatric disorders of the mother / the father (Waylen & Stewart-Brown, 2009), loss of an attachment person or loss of a domestic pet, inadequate education or permanent excessive demands within the family or at school etc.. Postnatal adverse conditions seems to have an influence on mental health in pre-school children (Robinson et al., 2008). The shared element of all of these adversities is their threatening effect for the development and the psychosomatic health of a child as well as his self-esteem. Adverse life conditions

might lead to a disruption of the homeostasis and allostatic load (Goldstein & Kopin, 2007; McEwen & Stellar, 1993). Involved mechanisms are the SAM axis, HPA axis as well as brain structures such as hippocampus, amygdale and prefrontal cortex (Dettling et al., 1999; Herman et al., 2005; McEwen, 2007), resulting in cognitive and emotional evaluation of life-threatening events and the bio-psycho-social competencies to cope with them (Lazarus & Folkman, 1984; Folkman, 1997).

A human equivalent to the animal separation paradigm might be studies with children who attend full-day or out-of-home daycare institutions. Such children seem to have rising glucocorticoid levels over the day as compared to children who are cared for at home, and these levels higher for toddlers than in older preschool-aged children (Geoffroy et al., 2006, Gunnar et al., 2002). Furthermore, there seems to be an association of elevated GC levels depending on the quality of care during the day. However, children who are exposed to poor care for long time during the day early in development seem to have an increased risk of behavior problems later in development (Grant et al., 2006; Gunnar et al., 2006; NICHD. Early Child Care Research Network, 2002).

Moreover, parent-child interactions also influence the child's HPA axis activity. Poorer parenting seems to be associated with either smaller increases in or less prolonged activations of HPA axis to everyday perturbations (Albers et al., 2008). Maternal depression is considered to interfere with sensitive and supportive child care. There is increasing evidence of an association between the mother's severe depression in the child's early years and the child's heightened activity of the HPA axis or development of depression during adolescence (Helligan et al., 2000). Furthermore, preschool-aged children of mothers with depression

show more electroencephalographic alterations in frontal lobe activity, which are associated with diminished empathy and other behavioral problems (Jones, 2000).

Furthermore, life events can be defined as discrete observable experiences that lead to significant changes and have an explicit beginning, a short duration and a definite ending, e.g. divorce, dismissal from a job, loss of a family member (Ehlert, 2003). Such experiences are dependent on coping strategies and personal resources and can develop into chronic stressors. Chronic stressors do not always begin with a single event or incidence, but often have a sneaking and gradual commencement. They are of long-lasting duration and of continuous existence in individual daily routines, e.g. job / professional requests, role expectations in the social and professional environment, insecurity or interactional conflicts (Ehlert, 2003). Research into potential stressors distinguishes between acute traumatic events, chronic strains or adversities, and stressful life events (Grant et al., 2003; Michels, 2003). Studies investigating childhood maltreatment has consistently found that early victimization is associated with later deficits in mental health (Bouma et al., 2008; Fumagalli et al., 2007; Heim et al., 1998; Lupien et al., 2009) and physical health (Felitti et al., 1998; Grant et al., 2006; Heim & Nemeroff, 1999; Kaufman et al., 2000; Salem et al., 2007). In his review including 270,000 subjects from 587 studies, Maniglio (2009) found evidence that survivors of childhood sexual abuse are significantly at risk of a wide range of medical, psychological, sexual and behavioral disorders. Critical life events might have an impact on the onset of depression, higher rates of depression in older age (Caspi et al., 2003; Comijs et al., 2007; Horesch et al., 2008) as well as generally on mental well-being (Bouma et al., 2008; Furniss et al., 2009) and somatic symptoms (Furniss et al., 2009; Liakopoulou-Kairis, 2002; Robinson et al., 1989; Walker et al., 1994).

To conclude, pre-, peri- and postnatal adverse life events seem to have a disturbing effect on neuro-developmental processes and subsequently on physiological, psychological and social behavior in children and adolescents. In the following, general methodological aspects of this issue will be described.

5. Conclusion, Study Idea, Questions and Hypotheses

In summary, the theoretical background section discussed issues showing the importance of pre-, peri- and postnatal development periods including sensitive windows. Sensitive developmental windows are crucial due to their vulnerability for exogenous or endogenous psycho-physiological disturbances. Such neurodevelopmental disturbances might lead to long-term influences on mental and/or somatic health in children and adolescents (Cottrell and Seckl, 2007; Doyle, 2000; Glover et al., 2009; Lupien et al., 2009; Van den Berg et al., 2009). This leads us to the highly interesting research question of whether pre-, peri- and postnatal adverse factors might have a direct and/or interacting impact on mental and somatic health in children from birth up to the age of ten years.

***Hence, we hypothesized that*:**

a) Prenatal, perinatal and postnatal adverse conditions lead to psychological abnormalities and alterations in the psychosocial functioning level in ten-year-old children
b) Prenatal stress has an adverse influence on physiological outcomes at birth as well as on physiological and subjective health variables form birth up to the age of ten years
c) There is an interaction between pre-, peri- and postnatal adverse conditions in predicting health psychosomatic outcomes

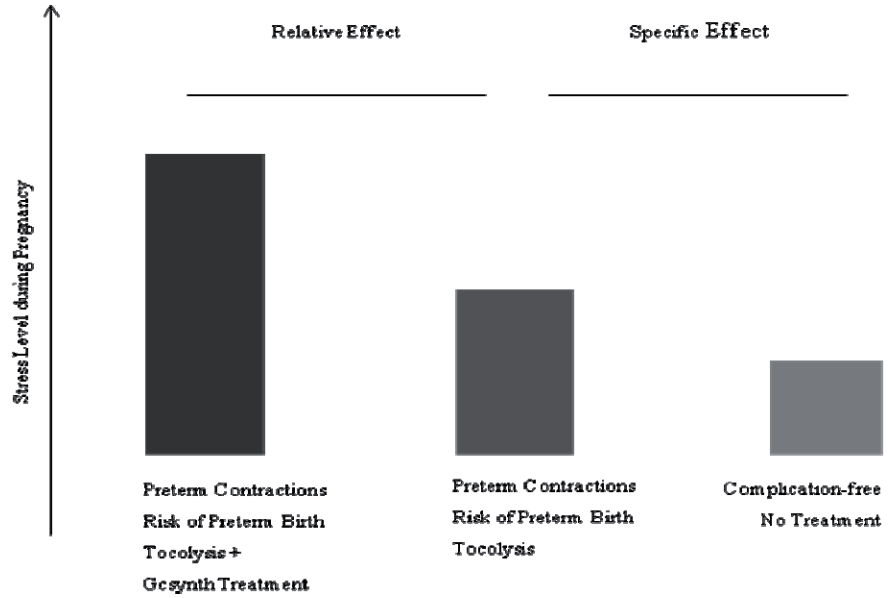
On this account, a study setting with three groups of children, who had experienced different levels of prenatal stress, was planned. Retrospective data on the course of pregnancy, perinatal outcomes, developmental and health physiological and psychometric information were collected.

6. Methods and Ethics

6.1 Operationalization and Study Design

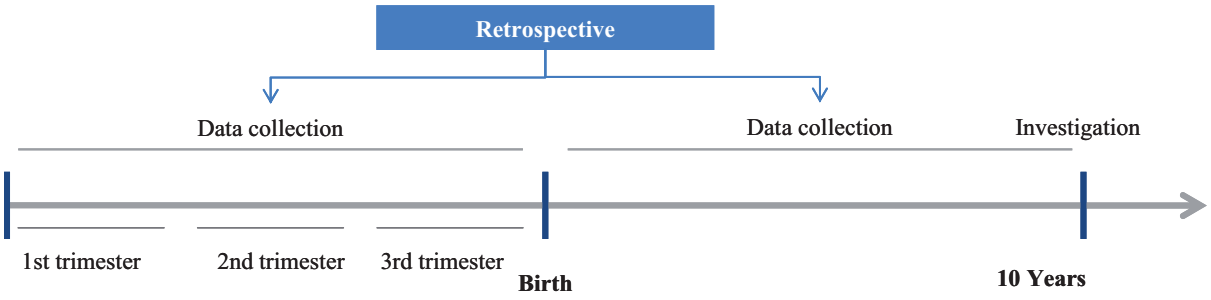
The present study aimed to investigate the influence of pre-, peri- and postnatal stress on psycho-bio-social behavior in children from birth up to the age of ten years. Therefore, we operationalized prenatal stress through the application of synthetic glucocorticoids (GC) that had been administered in order to prevent respiratory distress syndrome in the case of the occurrence of preterm contractions and accordingly a risk of premature delivery before the 34^{th} gestational week in pregnant women. The administration of GC leads to faster maturation of fetal pulmonary alveoli and brings about a lower neonatal and perinatal morbidity and mortality. Due to methodological considerations, we decided on a progressive group comparison design in order to eliminate the confounding factor of the risk of preterm delivery, because this is also expected to be a stressor for pregnant women. Consequently, the high prenatal stress group (H-PNS) included children whose mothers had preterm contractions and accordingly a risk of preterm birth and were consequently treated with synthetic glucocorticoids. The medium prenatal stress group consisted of children whose mothers had preterm contractions and also a risk of preterm birth but who had been alternatively treated, i.e. bed rest and application of magnesium. Moreover, a low prenatal stress group was formed which included children whose mothers had a complication-free pregnancy. (Figure 12).

Figure 12. Methodological formation of the three investigated groups



The graduation of adverse prenatal conditions allows a differentiated examination and comparison of the three groups in order to identify long-term influences of prenatal stress. The complete study design is retrospectively matched and cross-sectional (Figure 13). To prevent possible bias, we consulted medical data about each child and the mother's pregnancy to assess as much physiological data as possible.

Figure 13. Study design

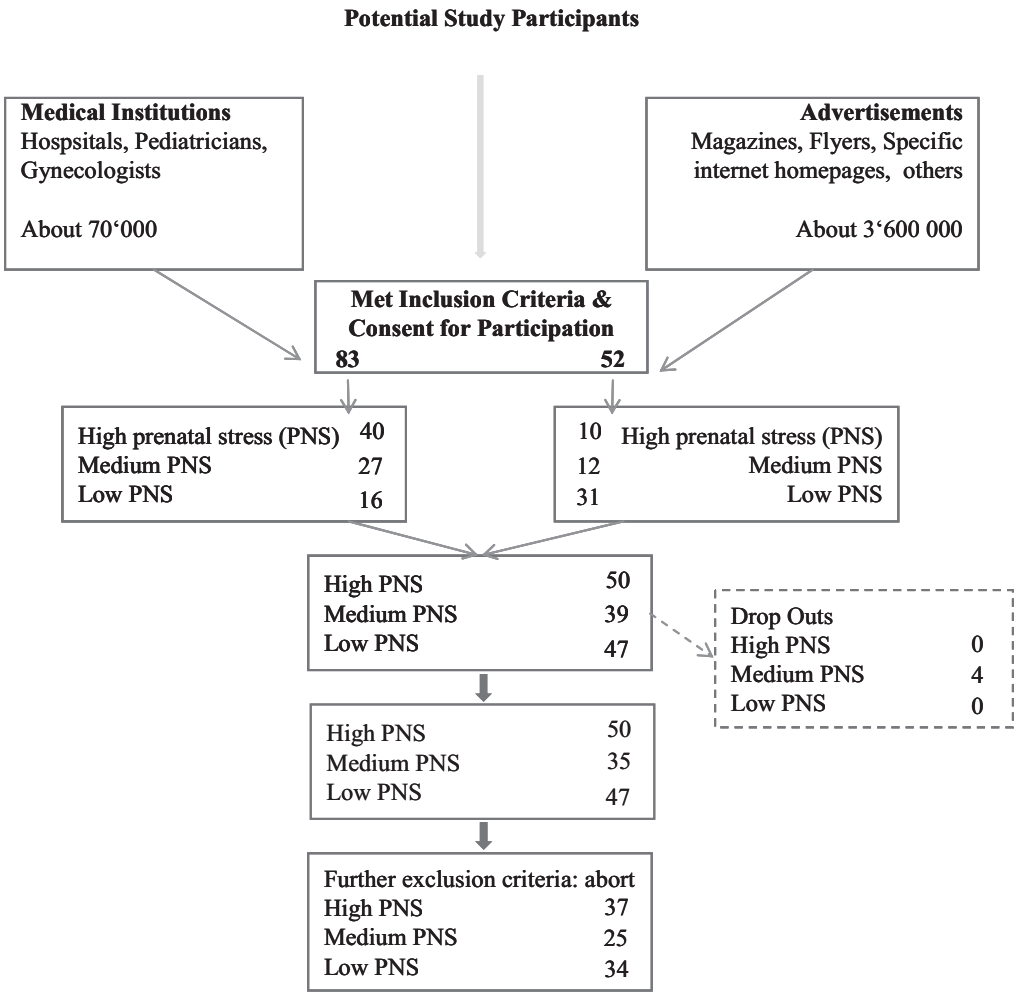


6.2 Subjects and Recruitment

The study sample consists of 136 ten-year-old healthy and non-medicated children. Due to abortion /miscarriage as a further exclusion criterion the data analysis of this dissertation are

based on reduced sample of N=96 (Figure 14) children, who are divided into three groups. The investigated groups are matched for age, sex and APGAR groups. Figure 17 presents the flow chart showing the recruitment process and the composition of the study sample.

Figure 14. Flow Chart



6.3 Ethics for studies with children

There are internationally accepted objectives for experimental studies on human beings (Helsinki Principles, 2004). Special guidelines are elaborated and implicated in the case of investigation on children and generally not yet autonomous subjects. The benefits of the research for the children assessed and for other children should be unequivocally proven.Our

study protocol was approved by the ethics committee of the state of Zurich (Ethikkommission des Kantons Zürich, SPUK) in February 2007. Additionally, all study documents, i.e. written information for subjects and written consent were prepared and adapted for 10-year-old children. Finally, all children were accompanied by a study member during the entire assessment time. All children were reimbursed with a voucher for CHF 60 and their parents obtained CHF 50 for their travel costs to the locations of the University of Zurich, where the investigation took place.

Part II – Empirical Studies

7. Pre-Analysis –Mother's Perception of Preterm Contractions and the Risk of Preterm Birth

7.1 Introduction

Preterm contractions has the highest prevalence rate among pregnancy complications (Breckwoldt & Pfleiderer, 2008) and are due to their risk for preterm birth a major problem in perinatal health care (Tucker & McGuire, 2006). Preterm birth is associated with high rates of neonatal morbidity and mortality (Iannuci et al., 1996; Krähenmann et al., 2005). The underlying mechanisms of preterm contractions are still unclear (Lopez Bernal, 2007; Tyson et al., 2009; Wenab et al., 2004). King et al. (2010) found that medical complications during pregnancy are associated with higher anxiety and depression in pregnant women. A literature analysis shows that there is a lack of research about how the pregnant women perceive themselves being confronted with the risk of preterm birth and consequently the implication of losing their child.

Generally, preterm contractions are considered to be stressful for the pregnant woman. For this reason, the occurrence of preterm contractions and accordingly the risk of preterm birth is often used for operationalizing prenatal stress in studies investigating the influence of prenatal stress and various variables in children, such as mental or somatic disorders (de Vries et al., 2008; Doyle et al., 2000; Schmand et al., 1990). Furthermore, the perception of the mother seems to play a crucial role in terms of psychological stress or social disadvantage (Ehlert et al., 2004; Heim et al., 2000; Zambrana et al., 1997). The perception of stress by the mother might lead to activation of the maternal stress axis SAM and HPA (Ogueh & Johnson, 2000, van den Berg et al., 2009) and accordingly to an activation of fetal SAM axis and HPA axis

(Kajantie et al., 2006). The experience of the mother's prenatal psychological stress can form part of the explanatory factors of prenatal stress and accordingly the occurrence of the risk of preterm birth (Dunkel-Schetter, 1998; Dole et al., 2003; Ehlert, 2004).

The aim of this pre-analysis was to investigate the specific effect of mothers' perception of the risk of preterm contractions and thus the risk of preterm birth.

7.2 Methods and Material

7.2.1 Subjects and Recruitment Criteria

Therefore, retrospectively collected data of ninety-six mothers were analyzed. The mothers were participating in a study about **"**Prenatal stress and the psychosocial and psychobiological development of children**"** and accordingly both the mothers and the children were divided into three groups. The high prenatal stress groups consisted of mothers with an occurrence of preterm contractions and had accordingly a risk of preterm delivery, who were treated with synthetic glucocorticoids. The medium prenatal stress group was formed by mothers with preterm contractions and also a risk of preterm delivery but without a treatment with synthetic glucocorticoids. Finally, the low prenatal stress group consisted of mothers with a complication-free pregnancy. Exclusion criteria were: childbirth before 34th week of gestation, incidence of hypertension, diabetes mellitus or severe anomalies during pregnancy, and insufficient German language skills of parents and children.

All study participants provided written informed consent. The study design followed the ethical criteria of the Declaration of Helsinki (2004) and was approved by the Human Ethics Committee of the state of Zurich.

7.2.3 Procedure and Measurements

The assessments were conducted in the laboratories of the University of Zurich, Psychological Institute, and include two sessions in which interviews were conducted and questionnaires

filled in by parents and their children. Initial written informed consent to participate in the study was obtained from all mothers and their children. Demographic variables were assessed and psychometric instruments applied.

The instrument was applied to assess overall stress index during the pregnancy. Furthermore, demographic and anamnestic data were recorded.

Medical Records of mother's pregnancy and birth records of children: Standardized medical records from different hospitals were used for collecting pre- and perinatal data. Prenatally recorded medical data about the course and consequently possible occurrence of a diagnosed risk of preterm delivery, as well as the nature of the following medical treatment, were collected. Potential participants were selected for the high, medium or low prenatal stress group.

Evaluation of the pregnancy course (Schwangerschafts-Verlaufs-Fragebogen SVF, Meier-Schick & Schöbi, 2004): The SVA is a standardized semi-structured interview and was developed to assess the course of the pregnancy. It was generated based on pre-existing literature and used primarily for a prospective study with pregnant women. The inventory consists of 20 items, including an overall estimation of the stress index of the pregnancy. This overall impact was applied for the study question of this pre-analysis.

We used SPSS 17.0 (SPSS Inc., 2008) for our data analysis. ANOVAs and nonparametric statistical tests were conducted for analyzing intergroup effects.

7.3 Results

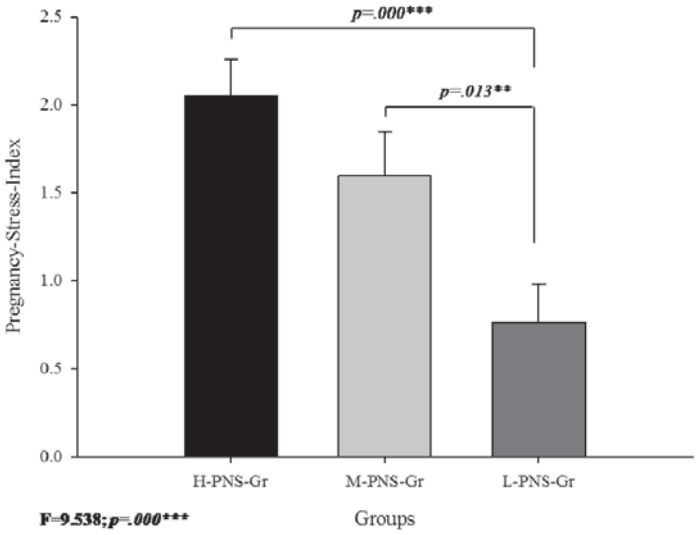
Retrospective subject characteristics of mothers

Mothers of the three investigated groups did not differ in their age of pregnancy (H-PNS-Gr = 30.31±.76; M-PNS-Gr = 29±.74 and L-PNS-Gr = 30.5±.58; values given in years, means and SEM) as well as in their socioeconomic status, ethnicity and civil status. None of them had previously had an abortion/miscarriage.

Mother's perception of the risk of prenatal delivery

There are significant differences in the stress index during pregnancy between the mothers classified as belonging to the high and medium prenatal stress group and mothers with a complication-free pregnancy, with the index being highest for mothers with high prenatal stress levels (Figure 15).

Figure 15. Stress index during pregnancy. (H / M / L-PNS-Gr = High / Medium / Low Prenatal stress groups). Values given are means and standard error of means (SEM)



7.4 Discussion

This data analysis addressed the gap in the research concerning mothers' perception of the occurrence of the risk of preterm contractions and accordingly preterm birth.

Significant group differences were revealed for the mothers' stress index during their pregnancy ten years previously with regard to their perception of the pregnancy and the occurrence of the risk of preterm delivery. Mothers with preterm contractions and thus the risk of preterm birth who were treated with synthetic glucocorticoids show the highest levels of stress, followed by mothers who also experienced preterm contractions and consequently a risk of preterm delivery but were alternatively medicated. Both showed higher levels compared to the mothers with a complication-free pregnancy. This result is in line with the most recent findings from King and colleagues (2010), who found that mothers with a medical diagnosis such as gestational hypertension, gestational diabetes or pre-eclampsia are more depressed and anxious than mothers with a complication-free pregnancy. The findings of this pre-analysis are, to the best of our knowledge, the first to date to investigate mothers' perception and association of related stress experience of the occurrence of preterm contractions and thus the risk of premature birth. Mothers' perception of given psychological stress or the occurrence of preterm contractions and thus the risk of premature birth could also play a crucial role in further physiological stress reactions and accordingly result in an increased duration of the stress period (Ehlert et al., 2003; Ehlert, 2004; Heim et al., 2000; Zambrana et al., 1997). Consequently, there might be increased levels of fetal GC, with possible programming effects resulting in heightened risk conditions for psychosomatic health in children and adolescents (Cottrell & Seckl, 2009; Lupien et al., 2009, Seckl & Holmes, 2007; Van den Berg et al., 2005).

However, this study has one main methodological limitation. The results, and accordingly the interpretations, are based on a retrospective data which date back 10 years in the subjects' lives. Thus, time and memory biases might have arisen.

Conclusions

In summary, our data demonstrate an important association in the emotional state of mothers who experienced preterm contractions and accordingly a risk of preterm delivery during their pregnancy. The findings suggest clinical implications for stress prevention and management in pregnant woman who have preterm contractions, including professional medical and psychological intervention during this difficult phase in their pregnancy.

The consequences derived for the further data analysis I and II concern methodological confirmation of the study operationalization process. This finding supports the graduation of the stress levels into high, medium and low prenatal stress levels. In the following, the main findings of the empirical data analysis are described.

8. Data Analysis I – Adverse Prenatal, Perinatal and Postnatal Conditions and Mental Health in Children

8.1 Introduction

Recent research identifies the extensive dysfunctional implications of prenatal, perinatal and postnatal adverse conditions for the bio-psycho-social development, mental health and psychosocial functioning in children and adolescents (Lupien et al., 2009; Rokyta et al., 2008; Schwab et al., 2007; Talge et al., 2007). Animal and human research indicates lifelong

persisting changes in the endocrine, vegetative and central nervous systems of the fetus. Furthermore, physiological, cognitive, emotional and behavioral functioning in childhood and adolescence are based on prenatal stress neuroendocrine alterations (Barker, 1991; Cottrell & Seckl, 2009; Lupien et al., 2009; Seckl, 2004, Van den Bergh et al., 2005). In the following, basic empirical findings about pre-, peri- and postnatal adverse conditions are described.

Animal studies consistently show that exposure to stress in early life has programming effects on the hypothalamus-pituitary-adrenal axis (HPA) and the brain itself (Barker 1991; Cottrell & Seckl, 2009). A single or repeated exposure of a pregnant female to stress (Cadet et al., 1986) or to glucocorticoids (GC) (Dean & Matthews, 1999) increases maternal GC secretion. A part of the maternal GC passes through the placenta and reaches the fetus, resulting in increasing fetal HPA axis activity and modifying brain development (Fowden et al., 2009; Seckl, 2008; Cottrell & Seckle, 2009). GC are important for the maturation of the brain. They initiate terminal maturation, remodel axons and dendrites and influence cell survival. During the late gestational stage of pregnancy, GC are crucial to stimulate surfactant production by the lungs and improve survival (Meyer, 1983; Roberts & Dalziel, 2006). Both elevated and suppressed levels of GC may have impairing effects of brain development as well as brain functioning. Long-term consequences of these changes seem to result in altered physiological, emotional and behavioral states (Lupien et al., 2009; Van den Berg et al., 2005). Juvenile and adult rats exposed to prenatal stress show decreased numbers of mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) in the hippocampus, which inhibits HPA axis activity (Weaver et al., 2004). In rhesus monkeys, prenatal application of the synthetic glucocorticoid (GCsynth) agonist dexamethasone causes a dose-dependent degeneration of hippocampal neurons and leads to a reduced hippocampal volume at 20 months of age (Uno et al., 1990). Furthermore, other brain regions are affected. Rats exposed to stress during the last week of gestation show significantly decreased dendritic spine density in the anterior

cingulate gyrus and the orbifrontal cortex (Murmu et al., 2006). Moreover, the levels of the corticotrophin-releasing hormone (CRH) in the central nucleus of the amygdala are increased. The amygdala has a central function in regulating fear and anxiety (Cotterell & Seckl, 2009). Furthermore, major effects of exposure to prenatal stress on adult behavior seem to be learning impairments, enhanced sensitivity to drug abuse, increased depression- and anxiety-related behavior, maladaptive coping with new situations and exploring behavior (Lupien et al, 2009; Van den Berg et al., 2005).

Concerning long-term neurodevelopmental effects, the results of human studies on children whose mothers experienced psychological stress, adverse events or exogenous GC administration during pregnancy are consistent with the findings of animal research (Lupien et al, 2009; Cottrell & Seckl, 2009). Maternal stress exposure, anxiety, depression and GC treatment during pregnancy are linked to lower birth weight or a relatively smaller size of the baby concerning gestational age (Kapoor et al., 2008; Nuyt & Alexander, 2009; Pedersen et al., 2007). Children at different stages of life, including 6 months (Lyons-Ruth et al., 2000), 5 years (Gutteling et al., 2000) and 10 years (O'Conner et al., 2005), who were exposed to prenatal stress, show an increased basal HPA axis activity. Furthermore, there are disturbances in the neurological and cognitive development and behavior (Glover et al., 1997; Matthews, 1999; Seckl & Holmes, 2009; Stott et al., 1973). The behavioral alterations include un-/anti-sociability, attention deficit / hyperactivity disorder (Rodriguez & Bohlin, 2005; Van den Berg & Marcoien, 2004) and sleep disturbances as well as some psychiatric anomalies, including depressive symptoms, drug abuse as well as mood and anxiety disorders (Glover et al, 2009; Lupien et al., 2009; Seckl & Holmes, 2009; Van den Berg & Marcoen, 2004). Other studies found little or no significant effect of prenatally administrated synthetic glucocorticoids such as dexamethasone (Hirvikoski et al., 2008). Schmand and colleagues

(1990) investigated the association of potential side effects of prenatal administration of corticosteroids. They investigated 10-12-year-old children in a randomized, double-blind, placebo-controlled study and found no significant differences between the corticoid group and the placebo group in the children's socio-emotional functioning, as well as in other variables such as school achievement, learning difficulties or behavioral disturbances.

Moreover, perinatal adverse outcomes such as low gestational age, low birth weight and small birth size can be a result of a disadvantageous prenatal environment (Pedersen et al., 2007; Wadhwa et al., 1993). Low birth weight has been shown to be associated with alterations in the HPA axis activity and increased rates of metabolic syndrome (Phillips, 2004). Follow-up studies in children with low birth weight and small size for gestation reveal a considerable variability in outcome measures (Berker et al., 2002), suggesting that perinatal factors might interact with prenatal adverse conditions. Due to ongoing maturation processes in the perinatal and postnatal period, sensitive phases for negative effects of adverse events can be found in all periods of time (Lupien et al., 2009). The complexity and variability of the findings suggest a multi-factorial interaction of various factors in the etiology and the maintenance of bio-socio-psychological disorders in children and adolescents, also considering protective factors such as optimal care of parents. A recent neuroimaging study showed that low birth combined with lower levels of maternal care was associated with reduced hippocampal volume in adulthood (Buss et al., 2007).

No less important than both the pre- and the perinatal period for the development and successful coping with life-related challenges is the postnatal period (McEwen, 2008; Rokyta et al., 2008; Vasconcelos et al., 2007). Animal experiments and human retrospective and single case study data are consistent in their findings regarding the exposure to stress and its impacts on the brain (Lupien et al., 2007). Postnatal manipulations include depriving the

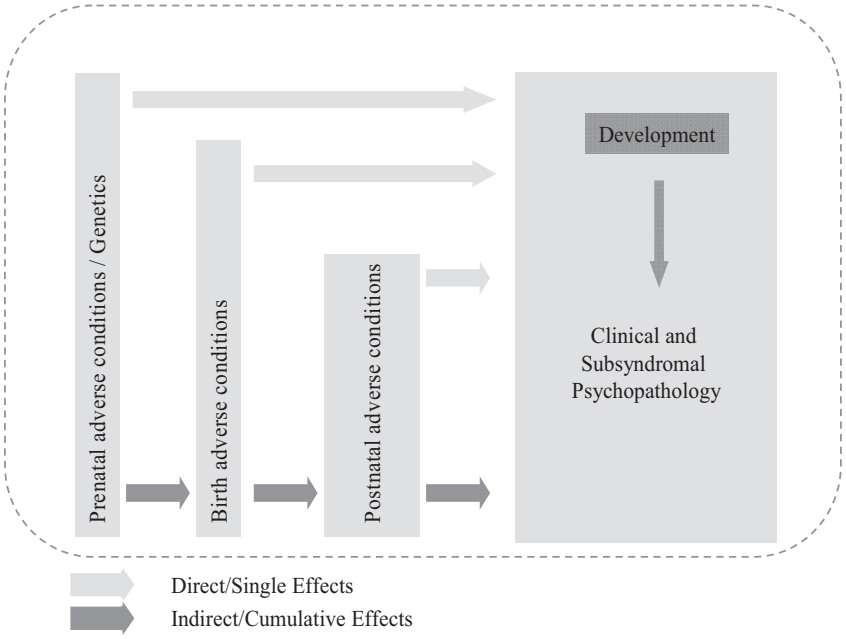
animal of maternal contact, modifying maternal behavior and exposing the animal to stressful situations or to exogenous GC. Prolonged separation of rats from their mothers during post-infancy increases the density of CRH binding sites in the prefrontal cortex, amygdala, hypothalamus, hippocampus and cerebellum (Anisman et al., 1998; Liu et al., 1997). The long-term effects of prolonged stress, such as separation, depend on the age of the pup and the duration of the deprivation (de Kloet et al., 2003). Generally, the negative effect increases when the separation occurs earlier in infancy and lasts for longer. Studies on monkeys have shown that repeated, unpredictable separation from the mother, unpredictable maternal feeding or spontaneous maternal abusive behavior alters the diurnal activity of the HPA and increases CRH levels in the cerebrospinal fluid axis for months or even years after the adverse period (Sanchez, 2006). In rodents, brain regions are also affected and the alterations include heightened fear behavior, exaggerated startle responses, hippocampal changes and atypical development of prefrontal cortex regions, which are involved in emotional and behavioral control (Rosenblum et al., 2002; Sanchez et al., 2002; Sanchez et al., 2005).

Due to ethical issues, the cause-and-effect impact of stress on the brain of adverse conditions cannot be studied in humans (Helsinki, 2004). Physical, sexual or emotional child abuse and maltreatment are strongly associated with different somatic and psychiatric disorders (Maniglio, 2009; Zielinski, 2010). Adverse postnatal conditions such as low socioeconomic status (Braveman, 2009; Waylen & Stewart-Brown, 2009; Zielinski, 2009), parental divorce (Cartwright, 2006; Herland et al., 2002; O'Conner et al., 1999), psychiatric disorders of mother and/or father (Waylen & Stewart-Brown, 2009), birth of a sibling, child psychiatric and/or somatic disorder, natural disasters and transitional events are considered as critical life events and are related to physiological, social and psychological preconditions. Critical life events have an impact on the onset of depression, higher rates of depression in older age (Comijs et al., 2007; Horsch et al., 2008), and generally on mental well-being (Bouma, et al.,

2008, Furniss et al., 2009) and somatic symptoms (Furniss et al., 2009; Liakopoulou-Kairis, 2002; Robinson et al., 1989, Walker et al., 1994)

In summary, there seems to be an increased physiological, emotional and behavioral vulnerability for dysfunctional coping with stress and adverse life events as a consequence of pre-, peri- and postnatal adverse conditions. This can result in a higher emotional vulnerability for psychiatric disorders and generally in a lower level of psychosocial functioning (Figure 16).

Figure 16. Model – Prenatal, perinatal and postnatal adverse conditions and their influence on mental health and the psychosocial level of function



The aim of this study was primarily to investigate the effect of prenatal stress and furthermore to elucidate the impact of perinatal and postnatal adverse conditions on mental health and psycho-social functioning.

8.2 Methods and Material

8.2.1 Subjects and Recruitment Criteria

The study sample consisted of N=97 healthy, non-medicated ten-year-old children. Prenatal stress was operationalized by the administration of a synthetic glucocorticoid as medical treatment before the 34th week of gestation in order to prevent respiratory distress syndrome in newborns and accordingly their morbidity and mortality. The high prenatal stress investigation (H-PNS) group (n=37) is characterized by children whose mothers had preterm contractions and accordingly a risk of preterm delivery before the 34th week of gestation during their pregnancy and were subsequently treated with GCsynth. The medium prenatal (M-PNS) stress group (n=25) also consisted of children with a history of preterm contractions and thus a risk of preterm birth but without application of GC. In the low prenatal stress (L-PNS) group (n=34), there were children with a medical history of a complication-free pregnancy. The recruitment was carried out in cooperation with hospitals, pediatricians, physicians and obstetricians in the greater area of Zurich and through advertisements in various magazines (Figure 14). Potential participants were screened for the study inclusion and exclusion criteria by checking the mother's pregnancy medical histories and the birth records of the children, and additionally by an extensive telephone interview with the mothers for current data. Exclusion criteria were: childbirth before 34 weeks of gestation; APGAR score below a value of 7; severe postnatal complications and treatment with GC; current treatment with GC medication or psychiatric medication/medication with psychoactive drugs; hypertension, diabetes mellitus or severe aberrations during pregnancy, and insufficient German language skills of parents and children.

The study was approved by the Human Ethics Committee of the canton of Zurich, Switzerland. Special attention was paid to the partial autonomy of the ten-year-old children by

providing study information material as well as the informed consent in a manner that could be understood by children aged ten years.

8.2.3 Procedure and Measurements

Written informed consent to participate in the study was obtained both from the parents and the children themselves. The assessments were conducted in the laboratories of the University of Zurich, Institute of Psychology, and included two sessions during which interviews were conducted and questionnaires filled in by parents and their children.

For the examination of the explanatory variables about prenatal, perinatal and postnatal conditions, the following instruments were used:

Medical Records of the mother's pregnancy and birth of the children: Standardized medical records of the cooperating hospitals were used to collect prenatal and perinatal data. Considering prenatal information about complications during each pregnancy and about subsequent treatment due to risk of preterm delivery, the children were included in the study and assigned to either the high, medium or low prenatal stress group. The birth records were important for the following perinatal variables: *week of gestation at birth*, *birth weight* and *size*, *APGAR scores* and the *occurrence of perinatal complications* right after birth. As control variable, children's *General Intelligence level* was measured with the Coloured Progressive Matrices (CPM), Bulheller & Häcker, 2002).

Semi-structured standardized anamnestic interview for children and parents (Child Life-Stage Inventory): The Child Life-Stage Inventory was applied to collect anamnestic, demographic, postnatal developmental, socioeconomic and health-related data about the study participants. It consists of a version for the child and one for the parents. Health-related data were

additionally required of the mothers by consulting their pediatricians or the children's health card. Based on pre-existing literature, the following ten items were identified as possible adverse postnatal life conditions: *1. divorce of parents; 2. birth of sibling(s); 3. psychological health diseases of the child himself; 4. medical health problems of the child; 5. accidents and hospitalizations of the child; 6. fears and difficulties at the beginning of schooling; 7. psychiatric diseases of the child's mother; 8. somatic diseases of the child's mother; 9. psychiatric diseases of the child's father, and 10. somatic diseases of the child's father.* Additionally, the ethnicity of the mother and father and the family socioeconomic status were assessed, as these variables were considered as potential covariates.

Diagnostic Interview for Psychiatric Disorders for Children (Kinder-DIPS, Schneider et al. 09): The "DIPS-Child" was developed for the assessment of psychiatric disorders in children and adolescents between the ages of six and eighteen. The structured interview includes an adapted version of the DIPS for direct questioning of the child or adolescent, and a parallel version for the parents. It is divided into a first section consisting of a screening to detect the mean problems and stressful life events during the past 6 months, a special section for the detection of specific mental disorders, and a section for the assessment of the psychiatric history of the child and the family anamnesis of mental disorders. The questions and the resulting clinical diagnosis follow the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) and the International Classification of Diseases (ICD-10) and allow psychiatric diagnoses. The study doctoral students conducting the interviews were specifically trained for the professional implementation, evaluation and interpretation of the DIPS for children. If the children showed some but not all necessary symptoms of a certain psychiatric disorder (according to DSM-IV and/or ICD-10), subclinical abnormalities or

psychological maladjustment were diagnosed only if the explored symptoms were relevant for the children's health and were impairing their daily life. All diagnoses were inter-rated twice.

Life Event Scale (LES), Steinhausen & Winkler Metzke, 2001: This questionnaire can be used for the assessment of critical live events in childhood and adolescence. It is a self-assessment instrument that contains the domains *school*, *family*, *friendships*, *illness*, *accidents* and *losses*. The items can be rated on a five-point Likert-type scale with options from (-2) *very unpleasant* to (+2) *very pleasant*. The LES was evaluated in an epidemiological study with a representative sample of 1188 children and adolescents. Reliability and validity of the LES are reported as good. The number of experienced life events and the impact score increase with age. These two scores seem to be higher among girls, urban and migrant children and adolescents compared to boys, rural and indigenous individuals. Furthermore, they correlate significantly with indicators of behavioral and emotional abnormalities in children and adolescents (Steinhausen & Winkler Metzke, 2001; Steinhausen, Eschmann & Winkler Metzke, 2007).

8.2.4 Statistics

SPSS 17.0 (SPSS Inc., 2008) was used for the data analysis. Data were tested for normal distribution and homogeneity of variance using Kolmogorov-Smirnov and Levene's tests before statistical procedures were applied. ANOVAs and nonparametric statistical tests were conducted for the analysis of intergroup effects. Odds ratios (2x2 comparisons with risk calculation on the X^2 test) were applied to analyze the impact of pre-, peri- and postnatal adverse conditions on the dependent variables of children's mental health. A multivariate linear regression analysis was conducted to detect their predictive values for mental health

and psychosocial functioning of the ten-year-old children. All presented results are means and standard errors of means (SEM) unless otherwise indicated.

8.3 Results

Sample characteristics

Table 5 provides an overview of the characteristics of the study sample. Significant differences were found between the children of the H-PNS group and L-PNS for the variables *gestational week*, *birth weight* and *birth size*. Based on the matching at the recruitment, there was no group difference between *APGAR-score values*. Moreover, no significant group differences were found for the variables *gender*, *intelligence values*, *ethnicity of the mother*, *socioeconomic status* and *mother's age at pregnancy*.

Table 5. Sample characteristics and control variables

	H-PNS-Gr (n=37)	M-PNS-Gr (n=25)	L-PNS-Gr (n=34)	*p*
Day of gestation	264.00±2.41	264.83±2.79	276.26±1.80	*.000***
APGAR 1	8.00±0.18	8.24±0.18	8.44±0.15	*n.s.*
APGAR 2	9.11±0.13	9.20±0.15	9.41±0.13	*n.s.*
APGAR 3	9.43±0.13	9.40±0.15	9.76±0.74	*n.s.*
Weight (gram)	3091.81±83.31	2964.77±106±18	3417±73.80	*.001***
Length (cm)	47.75±0.36	47.75±0.55	49.59±0.35	*.001***
Sex (m/w)	22 / 15	9 / 16	12 / 22	*0.75*
CPM	102.57±3.08	103.25±3.51	100.62±2.83	*(X^2)*
Control Var.				*n. s.*
Age of mother by gestation	30.71±.76	29.25±.74	30.5±.58	*n.s.*
Socioeconomic status	4.95±.33	4.92±.36	5.21±.19	*n.s.*

Prenatal adverse conditions – Prenatal Stress

First, ANOVAS were conducted in order to analyze group effects between the experimental group and the two control groups. Significant differences in psychosocial functioning and psychological deficits between children of the H-PNS group and the L-PNS group as well as between the M-PNS and the L-PNS group are shown in Table 6 and Figures 17 and 18. Furthermore, significant differences were found between the M-PNS group and the L-PNS group. Children with high levels of prenatal stress experiences seem to have a lower level of

psychosocial functioning and, moreover, higher psychological subclinical abnormalities in comparison to children with low levels of prenatal stress.

Table 6. Mental health characteristics – Differences between the children with high, medium and low levels of prenatal stress (H/M/L – PNS-Gr)

	H-PNS-Gr (n=37)	M-PNS-Gr (n=25)	L-PNS-Gr (n=34)	*p*	*Post Hoc Tests*
Level of Psychosocial Functioning	92.84±1.69	96.60±1.18	98.82±0.56	*.003***	*H-PNS to M-PNS: p=.001*** *H-PNS to L-PNS: p=n.s.* *M-PNS to L-PNS: p=0.5**
Subclinical Symptoms	1.35±0.29	1.00±.31	0.21±0.12	*.004****	*H-PNS to M-PNS: p=.001*** *H-PNS to L-PNS: p=n.s.* *M-PNS to L-PNS: p=0.36**

Values shown are mean ± SEM. Significance levels are computed by ANOVAs. H-PNS-Gr =High prenatal stress group; M-PNS-Gr=Medium prenatal stress group; L-PNS-Gr=Low prenatal stress group. * $p < .05$, * *$p < .01$, ***$p < .001$

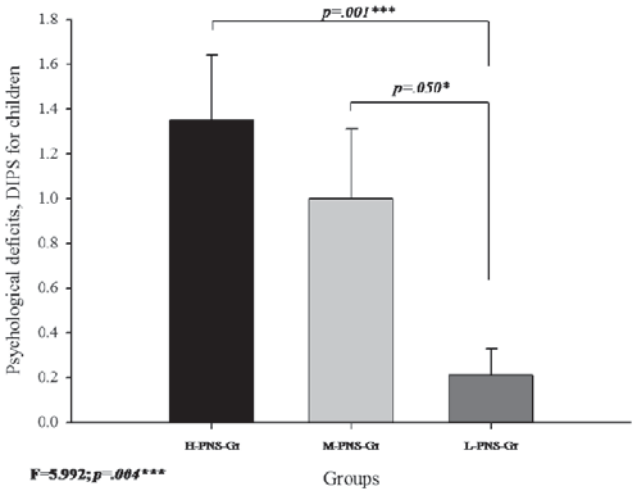


Figure 17. Group differences for psychological deficits in ten-year-old children (H/M/L-PNS-Gr. = High/Medium/Low Prenatal Stress Group)

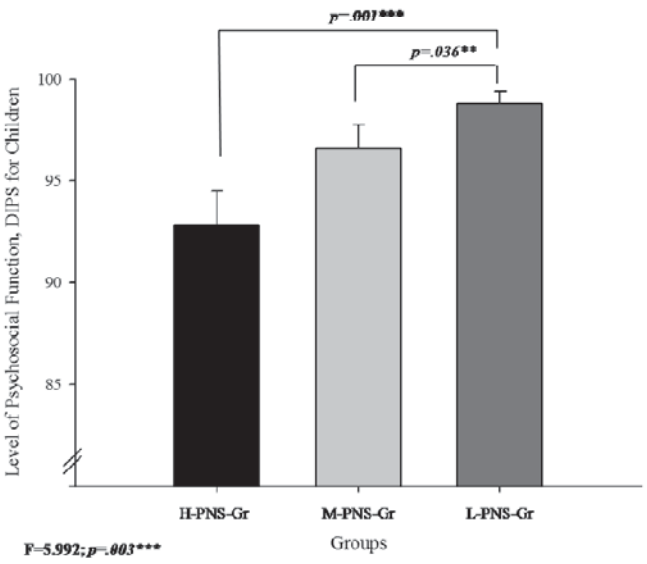


Figure 18. Group differences in the levels of psycho-social functioning (H/M/L-PNS-Gr. = High/Medium/Low Prenatal Stress Group)

Moreover, odds ratios were calculated to investigate the importance of prenatal stress as a risk factor for mental health and functioning in children. Table 3 shows a 7.87 times higher risk of psychological abnormalities in children whose mothers received GCsynth as treatment because of their risk of preterm delivery. This risk score was 4.86 times higher in children whose mothers also had a risk of preterm delivery but were not treated with GC in comparison to the children whose mothers had a complication-free pregnancy.

Furthermore, linear regression analysis was performed to measure the extent to which the prenatal stress levels predict the state of mental health in ten-year-old children. Table 7 shows a significant predictive value of the variable prenatal stress for the level of psychosocial functioning in 10-year-old children. This effect can also be shown after controlling for confounding effects of the variables week of gestation at birth, birth weight and size and gender.

Table 7. Odds ratios and relative ratios for pre- and perinatal stress as risk factors for psychological abnormalities

	Odds ratio	CI (95%)	*Chi-Square (df)*
Prenatal Adverse Conditions			
H-PNS vs. M-PNS	7.873	2.037 – 30.425	*0.001 *** (1)*
H-PNS. vs. L-PNS	1.619	0.559 – 4.685	*n.s.*
M-PNS vs. L-PNS	4.863	1.137 – 20.788	*0.024** (1)*
Perinatal Adverse Conditions			
Week of gestation	1.095	0.447 – 9.814	*n.s.*
Birth Weight (in gram)	1.175	0.482 – 2.862	*n.s.*
Birth Size	1.500	0.437 – 5.145	*n.s.*

Perinatal adverse conditions

Nonparametric tests for independent samples and subgroup analysis (median split; extreme groups) were conducted to test the effect of a gestational age at birth of less than 37 weeks, low birth weight and low birth size on mental well-being in children. There were no significant differences between the groups.

Postnatal adverse conditions

To test the impact of adverse postnatal conditions, odds ratios were used to detect possible risk factors for mental health and functioning of the children. For the following variables, no significant results were found: divorce of parents (OR 1.026; CI 95%: .292 – 3.602); birth of sibling(s) (OR 0.333; CI 95%: .097 – 1.146); somatic diseases of the children (OR 0.978; CI 95%: .886 – 1.079); accidents or hospitalization of the children (OR 1.026; CI 95%: .292 –

3.602); psychiatric health/illness of the mother (OR 2.571; CI 95%: .773 – 8.556) and somatic health/illness of the father (OR 0.865; CI 95%: .345 – 2.170). High and significant odds ratios were observed for the following adverse postnatal conditions: somatic illness of the mother (OR 3.748; CI 95%: 1.015 – 13.846; X^2 = 0.038*); psychiatric diseases of the father (OR 5.079; CI 95%: 1.118 – 23.082; X^2 = 0.023**) and fear or difficulties of the children at the onset of the school period (OR 11.550; CI 95%: 2.220 – 60.091; X^2 = 0.001***).

Prenatal, perinatal and postnatal adverse conditions

The multilevel linear regression analysis presented in Table 8 shows significant predictive values of the variables prenatal stress and the total (quantity) of postnatal critical life events. Model II explains 8.6% of the variance of the psycho-social functioning of children. Model III explains 9.4% and Model IV 13.10 of the total variance.

Table 8. Regression analysis predicting the level of psychosocial function (R^2 = 8.6 % for Model II, R^2 = 9.4 % for Model III and R^2 = 13.10 for Model IV)

	Model I B / SEB / β / p	Model II B / SEB / β / p	Model III B / SEB / β / p	Model IV B / SEB / β / p
Gestation week	.11 / .079 / .197 / n.s.	.058 / .084 / .10 / n.s	.030/ .082 / .055 / n.s.	.027/ .081 / .048 / n.s.
Weight (in grams)	.001 / .003 / .061 / n.s.	.001 / .003 / .089 / n.s	.002 / .003 / .101 / n.s.	.001 / .003 / .086 / n.s.
Length (in cm)	-.028 / .57 / -.007 / n.s.	.191 / .577 / .058 / n.s.	.059 / .571 / -.018 / n.s.	-.087 / .559 / -.026 / n.s.
Sex		2.87 /1.69 / .186 / n.s.	.98/ 1.68 / .128 / n.s.	1.90/ 1.65 / .123 / n.s.
Prenatal Stress			.19 / .49 / .267 / .017*	1.38 / .48 / .309 / .006**
LES (total)				.413 / .188 / .214 / .031*

* $p < .05$, ** $p < .01$, *** $p < .001$

8.4 Discussion

Children with high prenatal stress show significantly higher levels of psychological symptoms such as specific phobia, separation anxiety, enuresis/encopresis and sleep disorders than children with low prenatal stress levels. Moreover, a lower grade of psycho-social functioning can be found in children in the high prenatal stress group than in children both of the medium and the low prenatal stress group. Furthermore, significantly higher psychological abnormalities are reported in children with medium antenatal stress levels compared to children with low prenatal stress. There was no significant difference between the medium and the low prenatal stress groups in the level of their psychosocial functioning. These findings may reflect a higher vulnerability for psychiatric disorders of the children exposed to adverse conditions - such as stress - in their prenatal period.

The three groups differed in various perinatal variables. The children with high prenatal stress and children with medium prenatal stress levels were born significantly earlier concerning their gestational age and with lower birth weight and lower birth size compared to children with low prenatal stress levels. These results suggest that mothers who have a risk of preterm birth experience high levels of stress, which can consequently lead to preterm delivery and negative influences on both birth weight and size. Interestingly, children with high and medium prenatal stress do not differ significantly in most of the assessed variables. This might reflect the fact that the experienced stress of the two groups might be comparable. The difference might lie in the duration and intensity of the prenatal stress. The administration of synthetic GC to the mothers of the high prenatal stress group children could additionally enhance the stress level. Accordingly, an activation of the maternal and fetal HPA axis might ensue to a higher degree compared to the children of the medium prenatal stress group. Our findings support the programming hypothesis (Barker, 1991; Cottrell & Barker, 2009). Due to the increased maternal glucocorticoid concentrations, it is partially able to pass the placenta

barrier and reach the fetus, resulting in an increasing fetal HPA axis activity and the possibility of modified brain development and altered programming of biological patterns of both endocrine and nervous activation and reactivity (Seckl, 2008; Cottrell & Seckl, 2009). These changes can implicate altered physiological, emotional and behavioral functionality in children and adolescents (Barker, 1995; Lupien et al., 2009; Seckl, 2008; Van den Berg et al., 2005).

Furthermore, prenatal stress and the amount of postnatal critical life events seem to be risk factors for a lower level of psychosocial functioning in ten-year-old children. The explained variance is between 9.6% and 13.10% after controlling for main effects of perinatal factors and gender. These results support the programming hypothesis and the importance of the impact of prenatal exposure to adverse conditions. The effect seems to be long-lasting and, moreover, independent of the gestational age at birth, birth weight and size (Barker et al., 2002; Pedersen et al., 2007).

Our findings also suggest a strong effect of postnatal critical life events. Interestingly, variables such as divorce of parents, birth of sibling(s), accidents or hospitalization of children, somatic illness of father and psychiatric disorders of mothers did not significantly augment the risk of psychological symptoms in ten-year-old children. Significantly associated with heightened risk of psychological abnormalities were somatic illness of the mother, psychiatric disorder of the father and fear or difficulties of the children at the beginning of the school time. The risk of psychological symptoms in children was, in the case of somatic illness of the mother, nearly four times higher than it was in children with healthy mothers. Children whose fathers had a psychiatric disorder showed an 8.6-fold higher risk, and those with fear and difficulties at the onset of the school time showed an 11.5 times higher risk of psychological abnormalities. These findings point to important risk and predictive factors for children's psychological abnormalities. They might reflect the importance of a healthy and

supportive environment for an adaptive development and successful coping with life challenges such as the beginning of the school time or other transitional life events. Additionally, they support the hypothesis that sensitive phases for maladaptive alterations may occur in all periods of life (Braveman & Barclay, 2009; Lupien et al., 2009; Poggi Davis et al., 1999; Shonkoff et al., 2009). The reasoning might be of clinical importance, since the role of fetal programming and its long-term effects has been previously discussed as a potential causal factor for the etiology and maintenance of psychopathological disorders (Barker, 1991; Cottrell & Seckl, 2008; McEwen, 2008, Lupien et al., 2009; O'Conner et al., 1999; Rosenblum et al., 2002; Sanchez et al., 2005; Sanchez, 2006; Van den Berg et al., 2005; Zielinski 2009). Confrontation with adverse life conditions in sensitive developmental and vulnerable phases might have lifelong negative effects and induce higher emotional vulnerability.

The present study has several strengths. The study design is built on a stepwise graduation of prenatal stress in order to avoid confounding with the risk of preterm birth and the exposure to exogenous glucocorticoids. To the best of our knowledge, it is the first study to investigate prenatal stress without confounding of pregnancy complications such as medical diagnosis of the mother or the fetus. Furthermore, the sessions of the investigation were highly standardized and fulfill all required ethical criteria.

However, the present study also has several limitations. Our data were assessed retrospectively, meaning that the causal interpretations and generalization of the observed effects should only be carried out with respect to these methodological constrictions. Furthermore, our assessment procedure could be biased by subjectivity and social desirability as a consequence of using questionnaires. For future research on prenatal, perinatal and

postnatal adverse conditions and their direct and dependent influences on psychological health, a prospective study design with a hierarchical adjustment of groups with single and combined adverse prenatal, perinatal and postnatal conditions should be preferred.

Conclusions

To summarize, our data demonstrate an important and predictive role of adverse prenatal, perinatal and postnatal conditions for the etiology and maintenance of psychological abnormalities, and accordingly, the onset of psychiatric disorders, and generally the adequate functioning and challenge from different life conditions of children on psychological, social, biological and behavioral levels. Our findings suggest a possible clinical implication with an initial focus on an optimal medical and social support of pregnant women, followed by prevention activities with children identified as groups at heightened risk of psychobiosocial developmental diseases.

9. Data Analysis II – Prenatal Stress and Somatic Health

9.1 Introduction

Prenatal stress might have far-reaching consequences as a risk factor for developmental disturbances, and accordingly the development and maintenance of various somatic health complaints (Cottrell & Seckl, 2009, Gluckmann, 2004; Lupien et al., 2009; Nuyt & Alexander, 2009; van den Berg et al., 2005). Animal and human studies provide substantial support that prenatal stress can lead to lower gestational age, lower birth weight and lower birth size for gestational age (Brett et al, 1997; Copper et al., 1996; Cottrell & Seckl, 2009; Lou et al., 1994; Wadhwa et al, 1993). Furthermore, epidemiological research suggests that

prenatal adverse conditions (Barker, 2002; Gluckmann, 2004; Osmond, 2000; Terry & Susser, 2001) and low birth weight and birth size can be considerable risk factors for psychological and somatic health in adult life, including hypertension, coronary heart disease and type 2 diabetes mellitus (Barker, 1995; Cottrell & Seckl, 2009; Gluckman, 2004; Michel, 2003; Sallout & Walker, 2003). Underlying mechanisms can be explained through the "fetal programming" hypothesis (Barker, 1989; Barker, 1991; Barker, 2002; Cottrell & Seckl, 2009; Lupien et al, 2009; Van den Berg et al., 2005). Fetal programming implies long-lasting neuro-developmental structural as well as functional alterations in the fetus (Cottrell & Seckl, 2009; Fowden et al., 2009; Lupien et al, 2009; Van den Berg et al., 2005). These effects are due to genetic and adverse environmental conditions as well as the interactions of the of maternal-placental-fetal entity. Especially involved is the maternal hypothalamus-pituitary-adrenal axis (HPA), placenta and fetal HPA (Cottrell & Seckl, 2009; Fowden et al., 2009) and the entity of the sympathetic-adrenal axis (SAM) (Juster et al., 2009; Mc'Ewen & Wingfield, 2009).

Prenatal stress as well as low birth weight and size are considered as risk factors for somatic diseases in childhood and adult life such as cardiovascular diseases and hypertension (Barker, 1989; Barker, 1993; Curhan et al., 1996; Gluckman et al., 2005; Nuyt, 2008; Seckl, 2004). Elevated blood pressure in animal offspring also seems to be triggered by antenatal administration of glucocorticoids (GC) during pregnancy (Anderson, 2005; Nuyt & Alexander, 2009). Epidemiological studies provide evidence for an association of low birth weight and its relation to an increased risk of neonatal and infant mortality (Forssas et al., 1999; Pedersen et al., 2007), to adult blood pressure and to the incidence of cardiovascular morbidity and mortality (Loos et al., 2001; Nuyt & Alexander, 2009; Seckl, 2004; Seckl & Holmes, 2007). Birth weight and size are inversely correlated with blood pressure (Huxley et al., 2000). Sabet et al. (2009) found a two-fold heightened odds ratio for children with a birth

weight under 2500 grams for somatic complaints at the age 12 years, which in a subgroup analysis was found to be greatest among girls. Doyle and coworkers (2000) investigated the association between 14-year-old children. All children were born in the gestational age range of 24 to 36 completed weeks and of lower than 1500 grams birth weight. Pregnant women received one course of GC (betamethasone), administered over 48 hours in two divided doses of a total of 24 mg. None of the children received GC in the neonatal period. They found that children exposed to prenatal GC had higher systolic and diastolic blood pressure. Moreover, several had blood pressure in the hypertensive range (Doyle et al., 2000). De Vries and colleagues found no significant group differences in children exposed to prenatal or neonatal GC for blood pressure or any other biometric variable. All children were born preterm before completion of the 32nd gestational week and of low birth weight below 1500 grams. The study did not include a group of children who were born at term and weighed a minimum of 2500 grams. Furthermore, no significant differences in blood pressure and other biometric variables were found by Chen and colleagues (2008) in their study with 6-10-year-old children. All mothers received two or more courses of prenatal GC (bethamethasone or dexamethasone) and were born at 35 to 42 weeks of gestation. All children had a birth weight above 2000 grams. Other studies with children exposed to prenatal GC also found no significant associations (Crowther et al., 2008). Although no differences were found, the authors did not rule out an adverse effect of prenatal stress (Chen et al., 2008; de Vries et al., 2008). O'Regan et colleagues (2008) investigated the nature of hypertension with the aim of elucidating its origins considering the hypothesis that fetal programming as well as low birth weight are predictive for hypertension in adult life. They were able to show that prenatal dexamethasone administration during the last gestational week in offspring with low birth weight (14% reduction) leads to basal hypotension (approx. 4-8 mmHg lower), with the commonly expected hypertensive reaction only being recorded when these offspring are subjected to

even mild stressors or more severe stressors (up to 30 mmHg higher than controls). In a twenty-year follow-up study, Dassens and colleagues (2000) found significantly lower systolic blood pressure in 20-22-year-old subjects who were prenatally treated with GC. No intergroup differences were found for the diastolic blood pressure. This group was compared to placebo subjects. The mothers of both groups had a risk of preterm birth and were double-blind randomized for the GC or placebo group. The inconsistency in the previous data still remains. Further research without confounding of the risk of preterm birth and birth weight are needed.

Additionally, two further common health problems in pediatric institutions are children's headache and abdominal pain (Dorn et al., 2003; Metsahoncala et al., 1998; Rhee, 2001; von Baeyer, 2007). Fifty to ninety percent of children and adolescents experience some type of headache of varying severity and duration at least once a year (Barea et al., 1996; Rhee, 2000; Rhee, 2001). Frequent headaches occurring once a week or more have been reported among 20% to 30% of schoolchildren (King & Sharpley, 1990; Rhee, 2000). Experience of chronic headaches in children affects their development and might have influences in terms of school impairments and in their adult life (Bille, 1997;Metsahoncala et al., 1998). Bille (1997) reported the findings of a 40-year longitudinal study investigating a prolonged disease of recurrent headaches in a subgroup of children aged 7 to 13 years old who were diagnosed with migraine. This subgroup of children showed a failure to outgrow their headaches and consequently influences on their adult life, encompassing physical and psychosocial functioning. Eight-nine-year-old children with recurring headaches reported in a follow-up study conducted by Metsahoncala and colleagues (1998) being negatively influenced in school and in terms of their social interactions with peers. There was also an association reported of stress in school and headache, which was greater in girls. Furthermore, between

4% and 25% of school-aged children complain of stomach aches/recurrent abdominal pain, which are severe enough to interfere negatively with their daily activities. They can occur from the age of two years (Ramchandani et al., 2005) and account for approximately 2% to 4% of all pediatric visits (American Academy of Pediatrics, 2005). Schulte et al. (2010) suggest in their review that those children with functional abdominal pain who cannot adapt to the pain are at risk of negative long-term effects such as development of a somatoform adjustment disorder. To date, the etiopathogenesis of headaches and abdominal pain has not been fully understood (Alfen et al., 2003; Schulte et al., 2010). There is a proposal of a multi-causal etiology model (Cicchetti, 2006). Besides genetic, organic, family-related, socioeconomic and child-related factors, there is also a developmental pathology perspective as well as the hypothesis of a trigger effect of life events (Heim et al., 2000; Walker et al, 2001; Schulte et al., 2010) and stressors (Walker et al., 2001). Alfven and colleagues (2003) found in their study that in 48% of the children with abdominal pain, negative stress might play a major role in the pathogenesis and maintenance of the somatic complaints. These children rated their stressors as more severe than healthy children (Alfven et al., 2003).

To conclude, studies that investigate the effect of prenatal stress on somatic complaints in ten-year-old children remain scarce. Furthermore, a link between adverse influences of prenatal stress and headaches / abdominal complaints conditions has yet to be established.

Considering the fetal programming hypothesis and subsequent influences on the HPA, vegetative and central nervous system as well as immune system (Cottrell and Seckl, 2009; Devreux et al., 2001; Lupien et al., 2009; Noakes et al., 2003; Van den Berg et al., 2005; Wadhwa et al., 2001), there might also be an impact of prenatal stress explaining a part of the etiological variance of occurring headaches and abdominal pains in children and adolescents.

The aim of this study was to assess in a retrospective design the influence of prenatal stress on physiological and subjective indicators of health in children from birth up to the age of ten.

9.2 Methods and Material

9.2.1 Subjects and Recruitment Criteria

The sample of this study is a subgroup of a larger study sample of 10-year-old Swiss children (see Ehlert et al., submitted). The final study sample consisted of N=94 ten-year-old subjects. Prenatal stress was operationalized by the occurrence of preterm delivery risk and accordingly the medical treatment. The high stress group (H-PNS-Gr: n=37) consisted of children whose mothers had preterm contractions and accordingly a risk of preterm delivery during their pregnancy and were treated with synthetic glucocorticoids. GCsynth had been applied in order to prevent respiratory distress syndrome and therefore also newborn morbidity and mortality in the case of birth before completed 34th week of gestation. The medium stress group (M-PNS-Gr: n=24) contained children with a history of preterm contractions and the risk of premature delivery and without administration of GCsynth. Finally, the low stress group (L-PNS-Gr: n=33) was composed of children whose mothers had a complication-free pregnancy. The recruitment was carried out in cooperation with hospitals, pediatricians, physicians and obstetricians from around Zurich as well as through advertisements in different magazines. Inclusion and exclusion criteria were checked by screening of the mother's pregnancy and medical histories and birth records of children. Furthermore, current data were gathered through a telephone interview with the mothers. Exclusion criteria were: childbirth before completed 34th gestational week; APGAR under a value of 7; severe postnatal complications and treatment with GCs; current treatment with GC medication or psychotropic drugs; severe fetal anomalies, mother's incidence of hypertension, diabetes mellitus and insufficient German language skills of parents and children.

The study was approved by the Human Ethics Committee of the canton of Zurich, Switzerland. Written informed consent was obtained from all participating children and their parents.

9.2.3 Procedure and Measurements

The investigations were conducted in the laboratories of the University of Zurich, Institute of Psychology and included two sessions in which interviews were conducted and questionnaires completed by children and their parents. Physiological health indicators were measured by the study team during the sessions. The reimbursement for all children was a voucher to the value of CHF 60. Parents were reimbursed for their travel costs.

Prenatal stress, and somatic and subjective health for the time between birth and ten years were assessed by the following instruments.

Medical records of mother's pregnancy and birth records of children: Standardized medical records from different hospitals were used for collecting pre- and perinatal data. Data were assessed regarding the course and accordingly possible occurrence of a diagnosed risk of preterm delivery as well as the nature of the following medical treatment. Accordingly, potential participants were selected for the high, medium or low prenatal stress group. The birth records were used for the perinatal variables *week of gestation*, *birth weight* and *size* as well as the *APGAR-score*.

Semi-structured standardized anamnestic and demographic interview for children and parents (Children's Life-Stage Inventory): Based on pre-existing literature as well as semi-structured standardized interviews, the Children's Life-Stage Inventory was generated. The inventory

contains standardized items for collecting demographic, peri- and postnatal developmental data, and socioeconomic and health-related information about parents and their children. The objectivity of health-related data was also supported by medical developmental cards or mothers' inquiries to their pediatricians. The following items were defined as potential somatic complaints in children: 1. Children's diseases as babies, during, infancy and toddlerhood (early medical diseases); 2. cardiovascular complaints; 3. abdominal pain and headache; 4 . skin diseases; 5. allergies; 6. asthma; 7. accidents and hospitalizations of the child. Further health indicators were whether children needed some health utilities such as eyeglasses as well as therapies such as logopedics, ergotherapy, psychomotor therapy, educational counseling or psychotherapy. Possible confounding variables were the mother's age at gestation, the ethnicity of the mother as well as the socioeconomic status of the family. Furthermore, the general intelligence of the ten-year-old children was assessed with Colored Progressive Matrices (CPM) (Bulheller & Häcker, 2002).

Giessen Subjective Complaints List for children and adolescents (Giessener Beschwerde Fragebogen für Kinder und Jugendliche (GBB-KJ, Brähler, 1992):

This questionnaire was designed to assess children's subjective somatic complaints. It contains 59 items on a 5-point Likert scale ranging from 0 (never suffering from this symptom) to 4 (constantly suffering from this symptom). Data from representative samples of a German population have shown good reliability and validity. There are 5 subscales: 1. *cardiac complaints*; 2. *gastric complaints*; 3. *limb pain*; 4. *fatigue tendency*; 5. *cold symptoms* and an *overall subscale of total complaints* (Brähler, 1992; Hetzer et al., 1997). Data analysis is possible on three levels: Single complaints, principle symptom groups and the overall complaints index.

Physiological measurements: Blood pressure (BP) and pulse pressure (PP) were assessed with a sphygmomanometer, OMRON R4 Plus (OMRON Medical Technology, Germany). Blood pressure was measured three times on different days and times in a sitting position after a minimum of 5 minutes resting time (Barath et al., 2009; Pickering et al., 2005; Turi et al., 2008).

9.2.4 Statistics

SPSS 17.0 (SPSS Inc., 2008, Chicago Illinois) was used for our data analysis. α- and β- error adjustments were applied with the Bonferroni procedure. The significance level was set at α = 5% and β = 20% (two-tailed). Data were tested for normal distribution and homogeneity of variance using Kolmogorov-Smirnov and Levene's tests before statistical procedures were applied. Univariate and nonparametric statistical tests were conducted for analyzing intergroup effects. Furthermore, univariate and multivariate regression analyses were used to detect predicting values of the prenatal stress, and perinatal factors, for somatic health as criterion variables.

9.3 Results

Sample characteristics

A total sample of N=94 of ten-year-old children was analyzed. The high prenatal stress group (H-PNS) included n=37 children, the medium prenatal stress group (M-PNS) included n=24 and the low prenatal stress group (L-PNS) included n=33 children (Table 9). The groups did not differ significantly from each other in their *APGAR-scores*, *sex* and *child general intelligence level*. Furthermore, no significant differences were found for the variables *mother's age at pregnancy*, *mother's ethnicity* and *socioeconomic status*.

Table 9. Sample characteristics and control variables (Means and SEM)

	H-PNS-Gr (n=37)	M-PNS-Gr (n=24)	L-PNS-Gr (n=33)	*p*
Week of gestation	264.00±2.41	264.83±2.79	276.26±1.80	*.000****
Birth weight (in grams)	3091.81±83.31	2964.77±106±18	3417±73.80	*.001****
Birth size (in cm)	47.75±0.36	47.75±0.55	49.59±0.35	*.001****
APGAR 1	8.00±0.18	8.20±0.18	8.42±0.16	*n.s.*
APGAR 2	9.11±0.13	9.20±0.16	9.39±0.13	*n.s.*
APGAR 3	9.43±0.13	9.41±0.16	9.76±0.76	*n.s.*
Sex (m/w)	22 / 15	9 / 15	12 / 21	*n.s.*
CPM	102.57±3.08	103.26±3.66	100.55±2.92	*n.s.*
Control Variables				
Age of mother by gestation	30.50±.76	29.03±.77	30.9±.61	*n.s.*
Socioeconomic Status	4.95±.33	4.88±.37	5.15±.19	*n.s.*

n = valid cases, SEM = standard error of means. H-PNS-Gr =High prenatal stress group; M-PNS-Gr=Medium prenatal stress group; L-PNS-Gr=Low prenatal stress group. * $p < .05$, * *$p < .01$, ***$p < .001$

Physiological somatic health variables

The groups differed significantly in the variables week of gestation, birth weight and birth size, with both H-PNS and M-PNS having the lowest values as compared to the L-PNS group. No significant differences were found between the H-PNS and M-PNS group. There was a weight difference of 9.51% between the H-PNS group and the L-PNS and 4.1% between the H-PNS group and the M-PNS group. The weight difference between the M-PNS group and the L-PNS group was 13.23% (Table1).

Moreover, significant differences between the groups were revealed for the diastolic blood pressure (BP), lowest for the H-PNS group compared to the L-PNS group. There was a group difference of 2.78% mmHg between the H-PNS group and the L-PNS group. The difference between the M-PNS group and the L-PNS group was 1.45 mmHg. No significant group differences were obtained for the variables systolic BP and pulse pressure (Table 10).

Table 10. Somatic variables at the age of ten (Means and SEM)

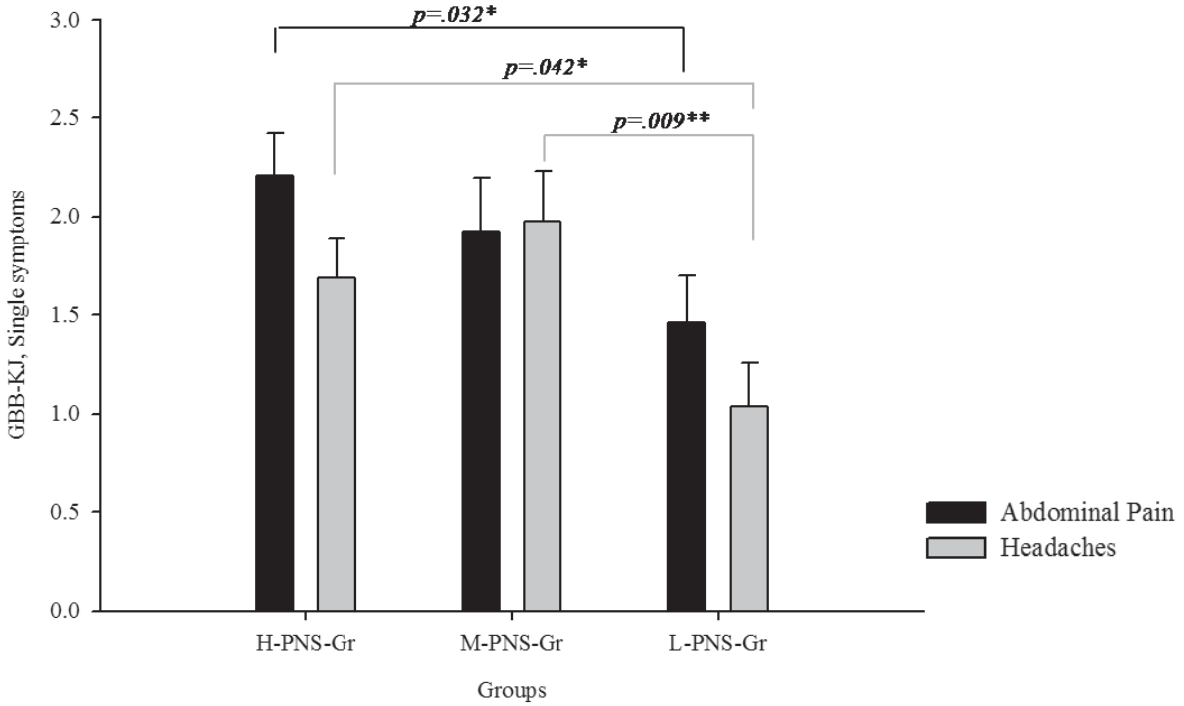
	H-PNS-Gr (n=37)	M-PNS-GR (n=24)	L-PNS-Gr (n=33)	*p*
BMI	16.64±0.39	16.65±0.55	17.12±0.32	*n.s.*
BP systolic (mmHg)	97.20±1.14	96.03±1.30	96.58±1.22	*n.s.*
BP diastolic (mmHg)	56.32±1.16	57.65±0.71	59.10±1.25	*0.033** *H vs. L*
Pulse Pressure (PP)	78.77±1.78	82.06±2.17	80.02±1.27	*n.s.*

n = valid cases, SEM = standard error of means. H-PNS-Gr =High prenatal stress group; M-PNS-Gr=Medium prenatal stress group; L-PNS-Gr=Low prenatal stress group. * $p < .05$, * *$p < .01$, ***$p < .001$

Subjective somatic health variables

Significant group differences were found for the single variables abdominal pain and headaches. The H-PNS group showed significantly higher levels in abdominal pain and headache compared to the L-PNS group. Furthermore, The M-PNS showed significantly higher levels of headaches as compared to the L-PNS group (Figure 1).

Figure 19. Univariate group comparisons for the individual symptoms of headaches and abdominal pain of the Giessen Subjective Complaints Scale for children (GBB-KJ) after controlling for mother's age at pregnancy, socioeconomic status, gender, gestation week, birth weight and birth size



Furthermore, table 11 provides an overview of somatic health variables provided. No other significant group differences were revealed, but there was a higher tendency for the most measured somatic complaints in the H-PNS group and the M-PNS group as compared to the L-PNS group.

Table 11. Subjective somatic health variables (in absolute cases and percent)

.	H-PNS-Gr (n=37)	M-PNS-Gr (n=24)	L-PNS-Gr (n=33)
Somatic complaints	**Absolute cases / percent (%)**		
Children's Life-Stage Inventory			
Early med. diseases	28 / 75.7	23 / 95.8	28 / 84.8
Vomitus (7 days perinatal)	2 / 5.4	0	0
Cardiovascular complaints	1 / 2.7	0	0
Abdominal pain/Headaches	9 / 24.3	8 / 33.3	7 / 21.2
Skin Diseases	4 / 10.8	1 / 4.2	1 / 3.0
Allergies/Asthma	18 (15/3) / 48.6	11 (8/3) / 45.8	11 (10/1) / 33.3
Total of somatic complaints	32	20	19
Accidents/Hospitalizations	22 / 59.5	13 / 54.2	11 / 33.3
Eyeglasses	9 / 24.3	5 / 20.8	5 / 15.2
Therapies	10 / 27.0	9 / 37.5	9 / 27.3
GBB-KJ			
Cardiac complaints	15 / 40.5	6 / 25	8 / 24.2
Gastric complaints	13 / 35.1	6 / 25	13 / 39.4
Limb pain	16 / 43.2	7 / 29.2	9 / 27.3
Fatigue tendency	16 / 43.2	11 / 45.8	17 / 51.5
Cold symptoms	6 / 16.2	10 / 41.7	11 / 33.3
Headaches	19 / 51.4	15 / 62.5	9 / 27.3
Abdominal pain	16 / 43.2	9 / 37.5	5 / 15.2
Upset stomach	9 / 24.3	2 / 8.33	5 / 15.2

Associations between prenatal stress, perinatal outcomes and somatic health variables at the age of ten

Significant predictive scores were found for prenatal stress and the dependent variables of prenatal adverse conditions. Prenatal stress was able to explain 14.4% of the total variance for gestational week, 7.9% for birth weight and 11.5% for birth size (Table 12).

Table 12. Univariate linear regression analysis - prediction role of prenatal stress for the perinatal adverse conditions: gestation week, birth weight and size

	Prenatal Stress – Predictor Variable
Dependent Variables	Rsquare / B / SEB / β / p
Week of gestation	**.144** / 3.077 / .078 / .38 / 0.000***
Weight (in grams)	**.079** / 80.32 / 28.52 / .28 / 0.006***
Size (in cm)	**.115** / .460 / .134 / .34 / 0.001***

H-PNS-Gr =High prenatal stress group; M-PNS-Gr=Medium prenatal stress group; L-PNS-Gr=Low prenatal stress group. * $p < .05$, * *$p < .01$, ***$p < .001$

Moreover, significant predictive scores were revealed for prenatal stress and the dependent variable diastolic BP. The regression model including prenatal stress explained a variance of R^2=13.2% of the total variance in diastolic BP. This was the case after the stepwise entry into the regression model of the following variables: mother's age at pregnancy, socioeconomic status, sex, gestational week, birth weight and birth size (Table. 13).

Furthermore, significant predictive scores were found for the variable birth weight and the dependent variable systolic BP. Birth weight was able to explain a variance of R^2=12.2% of the total variance in systolic BP. This was the case of the stepwise entry in the regression model of the following variables: mother's age at pregnancy, socioeconomic status, sex, gestational week, birth size and the variable prenatal stress (Table 13).

Table 13. Stepwise multiple regression analysis predicting systolic blood pressure (R^2 = 5.2 % for Model III, R^2 = 12.2 % for Model IV) as well as for diastolic blood pressure (R^2 = 8.4 % for Model III and R^2 = 13.2 for Model IV)

Predicted Variable	Model I	Model II	Model III	Model IV
Systolic BP	B / SEB / β / p	B / SEB / β / p	B / SEB / β / p	B / SEB / β / p
MAP	-.213 / .185 /-.128 / n.s.	-.255 / .184 / -.154 / n.s	-.278/ .182 /- .167 / n.s.	-.280/ .148 / -.169 / n.s.
SES	.068 / .447 / .017 / n.s.	.090 / .442 / .022 / n.s	.050 / .440 / .012 / n.s.	.046 / .443 / .011 / n.s.
Sex		-2.500 /1 .411 /- .185 / *.080 n.s.*	-2.641 / 1.508 / -.195 / *.083 n.s.*	-2.685 / 1.554 / -.199 / *.088 n.s.*
GW			.028/ .074 / .059 / n.s.	.027/ .076 / .056 / n.s.
Birth Size (in cm)			.810 / .509 / .282 / n.s	.797 / .521 / .278 / n.s.
Birth Weight (in grams)			-.006 / .002 / -.451 / **.013****	-.006 / .002 / -.450 / **.014****
Prenatal Stress				.058 / .443 / .015 / n.s.
Predicted Variable				
Diastolic BP				
MAP	-.257 / .176 /-.162 / n.s.	-.282 / .177 / -.178 / n.s	-.316/ .177 /- .200 / n.s.	-.350/ .147 / -.221 / ***.048****
SES	-.090 / .425 / -.023 / n.s.	-.077 / .425 / -.020 / n.s	-.16 / .429 / -.042 / n.s.	-.222 / .421 / -.058 / n.s.
Sex		-1.475 /1 .357 /- .114 / n.s.	-1.97 / 1.47 / -.153 / n.s.	-2.665 / 1.475 / -.207 / *.074 n.s.*
GW			.085/ .073 / .185 / n.s.	.065/ .072 / .141 / n.s.
Birth Size (in cm)			.522 / .496 / .191 / n.s	.320 / .494 / .117 / n.s.
Birth Weight (in grams)			.005 / .002 / -.365 / **.047***	-.005 / .002 / -.352 / **.050***
Prenatal Stress				.911 / .421 / .246 / **.033***

MGA = Mother's age at pregnancy; SES = Socioeconomic Status; GW = Gestational age of the child; * $p < .05$, * *$p < .01$, ***$p < .001$

9.4 Discussion

The present study investigated the influence of prenatal stress on perinatal and somatic health variables in children from birth until the age of ten. The assessments were based on a bio-psycho-social model including physiological and psychometric health variables. To our knowledge, this is the first study to investigate prenatal stress and physiological as well as subjective health complaints such as headaches and abdominal pain during the life period from birth up to ten years.

Ten-year-old children with experience of high and medium prenatal stress levels show significantly lower gestational age, birth weight and size than children with low prenatal stress levels. Compared to children with low prenatal stress, there was a weight difference of 9.51% lower for children with high prenatal stress and 13.23% lower for children with medium prenatal stress, considering that all children was above the weight range of 2,500 gram due to the specific exclusion criteria to avoid confounding. Furthermore, prenatal stress is a significant predictor for the perinatal outcomes week of gestation, explaining 14.4 percent (%) of the variance, and birth weight and size, explaining 7.9% and 11.5% of the variance, respectively. Our findings are in line with previous literature and confirm the influence or prenatal stress on perinatal outcomes at birth (Copper et al., 1996; Cottrell and Seckl, 2009; Lupien et al., 2009; Rondo et al., 2003; Seckl & Holmes, 2007; Wadhwa et al., 1993; Van den Berg et al., 2007). Lower perinatal health outcomes seem to be associated with higher neonatal morbidity and mortality (Fossas et al., 1999; Pedersen et al., 2007), an increased risk of cardiovascular disorders, arteriosclerosis and type 2 diabetes mellitus (Barker, 2005; Drake et al., 2007; Gluckmann, 2004; Cottrell & Seckl, 2009; Seckl & Holmes, 2007), as well as elevated blood pressure (Anderson, 2005; Nuyt, 2008; Nuyt & Alexander., 2009; Seckl, 2004) indicating that the high prenatal stress group is a risk group for adverse health disparities

compared to children without prenatal stress (Bravemann & Barclay, 2009; Shonkoff et al., 2009; Seckl, 2004).

An important finding of this study is that children with high prenatal stress show lower diastolic blood pressure values as compared to children with medium or low prenatal stress. Interestingly, the intergroup significance does not appear until mother's gestational age, socioeconomic status, sex and perinatal outcomes are controlled for. This may reflect an effect of prenatal stress independent from other variables as mentioned above. Between the children with high prenatal stress and children with low prenatal stress, there was a blood pressure difference of 2.78 mmHg and compared to the children with medium prenatal stress, a difference of 1.45 mmHg. In addition, prenatal stress seems to a significant predictor (R^2 = 13.2%, β=.246, *p=.033**) of diastolic blood pressure after controlling for confounding variables. For systolic blood pressure, birth weight seems to be the better predicting factor (R^2 = 12.2%, β=-.450, *p=.014**). Our findings are not in line with the results of Doyle and colleagues (2000) and Chen and colleagues (2008) as well as Woods (2005). However, they are in accordance with the findings of Dassens et l. (2000), who reported significantly lower systolic blood pressure in 20-22-year-old subjects who were prenatally exposed to GC. Furthermore, the findings of this study are in line with results of O'Regan and colleagues (2008), suggesting basal hypotension and stress-related hypertension in experimental rats exposed to prenatal synthetic GC compared to controls. In humans, elevated basal blood pressure and increased stress reactivity in systolic and diastolic blood pressure can lead to long-term clinically relevant essential hypertension, which is a powerful, consistent, and independent risk factor for cardiovascular and renal diseases (Pickering et al., 2005; Wirtz et al., 2006; Wuhl et al., 2003).

Additionally, significant intergroup differences were found for single symptoms of abdominal pain and headaches in children with high and medium levels of prenatal stress compared to children with low prenatal stress. Children exposed to high prenatal stress reported more headaches and abdominal pain as compared to the children exposed to low prenatal stress. Furthermore, children exposed to medium prenatal stress also reported more headaches as compared to the children exposed to low prenatal stress. Epidemiological studies have shown that headache and abdominal pain are common pediatric problems, indicating headache complaints (Dorn et al., 2003; Liakopoulou-Kairis, 2002; Metsahoncala et al., 1998; Rhee, 2001) and abdominal pain complaints for the adolescence and adult life. They even suggest an etiological factor for the development of somatoform disorders in adult life (Hodges et al., 1984; Liakopoulou-Kairis, 2002; Schulte et al. 2010, von Baeyer, 2007). Headaches are experienced by a large proportion of the general population (Barea et al., 1996; Rhee, 2000/2001). In their chronic occurrence, they can have influences on the current life until adulthood, encompassing physical and psychosocial functioning of the affected children (Bille et al, 1997; Metsahoncala et al., 1998). Abdominal complaints can occurred from a very early age (Ramchandani et al., 2005) and can influence the children's well-being and accordingly their school performances and social interactions in their family and with peers (Liakopoulou-Kairis, 2002; Schulte et al., 2010). Children who often experience headaches and/or abdominal pain might perceive their daily life challenges as more demanding than children without somatic complaints. This could result in their additionally being more stressed besides daily school demands (Walket et al., 1994; von Baeyer et al, 2007; Schulte et al., 2010). This might result subsequently in higher emotional and physiological stress conditions, activating corresponding sympathetic and endocrine axis (von Baeyer et al, 2007; Schulte et al., 2010; Shonkoff et al., 2009). Consequently, our findings might suggest an etiological and

maintaining factor for clarifying the underlying mechanisms of headaches and abdominal complaints.

The present study has several strengths, such as the stepwise controlled operationalization of high, medium and prenatal stress, and the high standardized investigation procedure including comparable study setting conditions following the study protocol for each subject. Compared to previous studies, the present study is free of confounding with the occurrence of the risk of preterm birth and birth weight under the minimum of 2500 grams ,and babies born after completion of the 34th gestational week.

However, the present study also comprises limitations. Our findings and implications might not be generalized to all children with prenatal stress. First, this is the case because our study design is retrospective, meaning that causal interpretations of the observed effects should only be made with caution. Second the study sample was overall of medium or high socioeconomic status. Thus, there might be a bias in the study sample self-selection. Third, the questionnaires used for assessing subjective health complaints in ten-year-old children might have validity limitations. For future research, a prospective study design including standardized objective health monitoring instruments would be preferable.

Conclusion

The main findings of this study are the lower diastolic blood pressure and the increased reported values for headaches and abdominal pain in children with prenatal stress, as well as the predictive value of prenatal stress for diastolic blood pressure and the predictive value of birth weight for systolic blood pressure. Empirical findings demonstrate that intrauterine exposure to GCsynth as well as psychological stress can have clinically relevant influences on

organs other than the lung, including structural and functional alterations in kidney and brain, HPA axis function as well as long-term effects on cognitive, psychological or behavioral development (Cattarelli et al., 2002; Owen et al., 2005; O'Shea & Doyle, 2001, Seckl, 2004, Sloboda et al., 2005; Tegethoff et al., 2009). In summary, our findings show that prenatal stress might be a risk factor for developing somatic complaints including alterations in blood pressure and further elevated complaints of headaches and abdominal pain. This might be an indication that children with prenatal stress could belong to a risk group for hypertension, cardiovascular diseases as well as somatoform diseases in adolescence and adult life.

Part III – General Discussion

10. General Considerations and Summary of the Study Results

From the beginning of a new human life, there exist periods of pre-, peri- and postnatal development as well as assigned sensitive phases for health-threatening influences (Häcker et al., 2005;Petermann et al., 2004). Pre-, peri- and postnatal adverse conditions has been suggested as central risk factors for the development and maintenance of psychosomatic health diseases (Chen et al., 2008; Cottrell & Seckl, 2009; Glover et al., 2009; Doyle et al., 2000; Lupien et al., 2009; Nyut & Alexander, 2009; Petermann et al., 2004; van den Berg et al., 2009). The existing data are not consistent. However, several studies found no significant associations between prenatal adverse conditions and health in children (de Vries et al., 2008; Hirvikoski et al., 2008) and adolescents (Dalziel et al., 2004). The main problem for such inconsistency might be of a methodological nature (Lupien et al., 2009). In human pre-, and perinatal research, experimental study designs are not realizable for ethical reasons (Lupien et al., 2009). Therefore, confounding might be a general problem. Nevertheless, underlying mechanisms of psychosomatic health in children are of high social and health relevance worldwide (WHO). The present study aimed to contribute to the elucidating process of underlying mechanisms of psychosomatic health in children.

The main hypothesis of this study were was that considering empirical research of development sciences and animal and human research, adverse pre-, peri- and postnatal conditions might have negative impacts on children's psychological and somatic health.. Many negative effects in single sensitive developmental periods may lead to higher vulnerability. However, the literature shows that reversibility through resilience factors as

well as brain plasticity is possible. Nevertheless, there is also an increased risk of psychological and somatic health if prenatal stress is followed by peri- and /or postnatal adverse conditions.

10.1 Pre-Analysis - Retrospective Mothers' Perception of Preterm Contractions and the Risk of Premature Birth

We measured the perception of the pregnant women and mothers of the 10-year-old study subjects of having been stressed during the pregnancy 10 years before. Significant differences were found for the prenatal stress index in mothers belonging to the high prenatal stress (H-PNS) group as compared to the low prenatal stress (L-PNS) group. Furthermore, significant differences were found for the mothers belonging to the medium prenatal stress (M-PNS) group as compared to the mothers of the low prenatal stress group. No significant differences were found between the high and medium prenatal stress group. The effects are controlled for the age of the mother at pregnancy, socioeconomic status, civil status as well as for their ethnicity.

In the following, these findings will be integrated in pre-existing literature in this section due to their pre-analysis role.

To the best of our knowledge, no previous study has assessed the mother's perception in terms of the occurrence of preterm contractions and accordingly preterm birth, which is of the highest prevalence among pregnancy complications (Iannuci et al., 1996; Breckwoldt & Pfleiderer, 2008; Krähenmann et al., 2005). Preterm birth is responsible for a high neonatal morbidity and mortality (Beinder & Vetter, 2007; Lopez Bernal, 2007; Wenab et al., 2004). Commonly, there exists the hypothesis that the occurrence of preterm contractions and thus

the risk of preterm birth is associated with heightened anxiety and stressful experiences of the pregnant women. The finding of this study is in line with our hypothesis and the findings of King et al. (2009), who showed that pregnant women with a medical diagnosis such as hypertension, pre-eclampsia or hematological disorders were more anxious and depressed than pregnant women with a complication-free pregnancy.

10.2 Data Analysis I - Adverse Pre-, Peri- and Postnatal Conditions and Mental Health in Children

Ninety-six healthy ten-year-old children, who were divided into three groups of different prenatal stress levels were investigated. Pre-, peri- and postnatal adverse conditions were assessed through the following instruments: mother's medical history during the pregnancy, birth reports of the newborns and Children's Life-Stage Inventory. For the examination of children's psychological health, the standardized Diagnostic Interview for Psychiatric Disorders for Children was applied (Child DIPS, Schneider et al., 2009). Furthermore, the Life Event Scale (LES, Steinhausen et al., 2001) for assessing life events in children was applied.

Significant differences between the groups were found for psychological abnormalities and psycho-social functioning in ten-year-old children, which were highest and lowest respectively for the H-PNS group as compared to the L-PNS group. Furthermore, the children of the H-PNS group have a near nine times higher risk and those of the M-PNS group a near five times higher risk of psychological abnormalities as compared to the children of the L-PNS group. Prenatal stress is, moreover, a significant predictive factor for psychosocial functioning of ten-year-old children.

Additionally, the account of postnatal life events is a significant predictor for the psychosocial functioning of the investigated children. Moreover, postnatal life events increased the risk by between nearly 5 times and 12 times for a lower psychosocial functioning in ten-year-old children. No significant differences were found in association with adverse perinatal outcomes and psychological adjustment in ten-year-old children. This could result due to the minimum weight of the investigated children of 2500 grams.

These findings may reflect a higher vulnerability to psychiatric disorders of the children exposed in their prenatal period to prenatal stress.

10.3 Data Analysis II - Influence of Prenatal Stress on Perinatal Outcomes and Somatic Health in Children

For the present study, data of 94 healthy ten-year-old children, who were exposed to high, medium or low prenatal stress, were investigated. Physiological data were assessed through mothers' medical history during the pregnancy, birth reports of the newborns and Children's Life-Stage Inventory. Psychometric data were collected through the Giessen Subjective Complaints List (GBB-KJ, Brähler, 1992).

Data analysis shows that children with high and medium prenatal stress levels have lower values for gestational week, birth weight and birth size compared to children with low prenatal stress. No significant differences were found for somatic health indicators between birth and the age of ten years. Significant differences between the groups were revealed for diastolic blood pressure, which was lowest for the H-PNS group as compared to children of the L-PNS group. No significant differences were found in systolic blood pressure and pulse pressure. Prenatal stress and lower birth weight seem to have significant predictive value for

blood pressure. Moreover, the groups differed significantly in their reporting of headaches and abdominal pain. Children with high prenatal stress reported experiencing significantly more headaches and abdominal pain as compared to children exposed to low prenatal stress levels. Furthermore, children exposed to medium prenatal stress reported experiencing more headaches as compared to children exposed to low prenatal stress.

11. Methodological Considerations and Limitations

The present study has several strengths. The study groups were built in a stepwise manner considering the level of prenatal stress. In this way, it was possible to separately control for the effects of the occurrence of preterm birth and thus risk of preterm birth as a stress variable as well as the additionally administered synthetic glucocorticoids. As far as we are aware, this is the first study without confounding of the two mentioned variables or without confounding with other variables such as other medical diagnoses or very low gestational age as well as very low birth weight at birth. Furthermore, physiological and psychometric variables were included as well as physiological data from the prenatal time until the age of ten years. The investigation sessions were highly standardized in order to avoid confounding and fulfilled all required ethical criteria concerning research in non-autonomous subjects.

However, the present study also has several limitations. First, the design of the present study is retrospective and cross-sectional. Therefore, generalization and data interpretation should be carried out with respect to these methodological restrictions (Sedlmeier & Renkewitz, 2008). Furthermore, questionnaires for assessing psychometric variables were used.

Accordingly, there might be a bias due to social desirability or response bias (e.g. tendency towards giving the middle answer).

12. Integration of the current findings

In this section, the main findings of the current thesis will be embedded into the previous literature taking into account the theoretical background presented above (chapters 2-4).

The main finding of the first data analysis was the establishment of significant group differences for psychological abnormalities and psycho-social functioning in ten-year-old children exposed to high prenatal stress as compared to children with low prenatal stress. Psychological abnormalities were reflected in increased symptoms of specific phobia, separation anxiety, enuresis/encopresis and symptoms of sleep disorders. These findings are in line with previous studies investigating the influence of prenatal stress on psychological abnormalities or psychiatric disorders in children or adolescents (DiPietro et al., 2004; Glover et al., 2004; Hirvikoski et al., 2008, Obel et al., 2003a; van den Berg et al., 2005). They might be of clinical relevance due to the fact that clinical symptoms are a risk factor for developing and maintaining psychiatric disorders.

Furthermore, prenatal stress and the quantity of postnatal critical life events seem to be risk factors for a lower psycho-social level of functioning in ten-year-old children. The explained variance is between 9.6% and 13.10% after controlling for main effects of perinatal factors and gender, which lends support to the programming hypothesis and the importance of prenatal exposure to adverse conditions. The effect seems to be long-lasting and, moreover, independent of the week of gestation, birth weight and size, a finding which is in line with

previous research (Barker et al., 2002; Pedersen et al., 2007; Seckl & Holmes, 2007; Talge et al., 2007; Ward et al., 2004).

Moreover, the findings of this study also suggest a strong effect of postnatal critical life events. Interestingly, variables such as “divorce of parents”, “birth of sibling(s)”, “accidents or hospitalization of children”, “somatic illness of father and psychiatric disorders of mothers” were not significant in augmenting the risk of psychological symptoms in ten-year-old children. These findings are inconsistent with previous literature, which suggests an adverse effect of parents’ divorce as well as of psychiatric diseases of mothers or somatic diseases of parents (Cartwright, 2006; Herland et al., 2002; O’Conner et al., 1999).

Furthermore, significantly associated with heightened risk of psychological abnormalities were the variables “somatic illness of the mother”, “psychiatric disorder of the father” and “children’s fear or difficulties at the beginning of the school time”. The risk of psychological symptoms in children was, in the case of the mother’s somatic illness, nearly four times higher than in children of healthy mothers. Children whose fathers had a psychiatric disorder had an 8.6-fold higher risk, and those who had fears and difficulties at the onset of the school time had an 11.5-times higher risk of psychological abnormalities.

Moreover, in the second data analysis, ten-year-old children with experiences of high levels of prenatal stress showed significantly lower gestational age, birth weight and size followed by children with medium levels of prenatal stress, both as compared to children with low levels of prenatal stress. These findings are consistent with previous literature and confirm the influence of prenatal stress for perinatal outcomes at birth (Copper et al., 1996; Cottrell and

Seckl, 2009; Lupien et al., 2009; Rondo et al., 2003; Wadhwa et al., 1993; Van den Berg et al., 2007).

Furthermore, children exposed to high prenatal stress levels show lower diastolic blood as compared to children exposed to low prenatal stress levels. Additionally, prenatal stress and birth weight have a significant predictive value for diastolic and systolic blood pressure, respectively. Various lines of research showed significant correlations between prenatal stress and hypertension and the risk of developing other cardiovascular and artheriosclerotic disease (Drake et al., 2007; Nuyt & Alexander, 2009; Woods, 2006). These findings are not in line with empirical research showing that children who were exposed to prenatal stress had higher systolic and diastolic blood pressure (Doyle et al., 2000). They are also inconsistent with studies, which found no effect of prenatal stress on children's blood pressure (Chen et al., 2008; de Vries et al., 2008; Woods & Weeks, 2005; Woods, 2006). The present findings are in accordance with the results of O'Regan and coworkers (2008), who found basal hypotension in rat offspring exposed to prenatal stress and a hypertensive reactivity even to mild stressors. Accordingly, considering the limitations of animal models for humans, there might be indications for basal hypertension and hypertensive stress reactivity in children exposed to high prenatal stress as compared to children exposed to low prenatal stress.

Moreover, significant intergroup differences were found for headaches and abdominal pain. Children exposed to high prenatal stress seem to experience more headaches and abdominal pain as compared to children exposed to low prenatal stress. Furthermore, children exposed to medium prenatal stress seem to have more headaches compared to children exposed to low prenatal stress. To our knowledge, no previous study has investigated the association of prenatal stress with headaches or with abdominal pain. Empirical research demonstrates a link

between headaches (Liakopoulou-Kairis et al., 2002; Ramchandani et al., 2005; Rhee, 2000) as well as abdominal pain (Alven et al., 2003; Schulte et al., 2010) and postnatal adverse life events. It seems that negative life events play a crucial etiological and maintaining role in children with headaches or abdominal pain. Negative life events might lead to allostatic load and might have lifelong negative effects (McEwen, 2000; Goldstein & Kopin, 2007). Prenatal stress can also be considered as a prenatal critical life event, due to the connection with the maternal-placental-fetal endocrine entity and function, which might result in fetal programming effects for the HPA axis, the vegetative as well as the central nervous system (Barker, 2002; Fowden et al., 2008; Glover et al, 2009; Lupien et al., 2009; Matthews, 1999; Van den Berg, 2007). Lifelong negative effects of fetal programming can result in emotional, cognitive and behavioral deficits in children and adolescents (Lupien et al., 2009; Seckl & Holmes, 2007).

To summarize, our findings present significant group differences and important risk and predictive factors for children's psychological abnormalities and somatic complaints. They might reflect the importance of a healthy and supportive environment for an adaptive development and successful coping with life challenges such as the beginning of the school time or other transitional life events. Additionally, they supports the hypothesis that in all periods of life, there can be sensitive phases for maladaptive alterations (Cottrell & Seckl, 2009; Fowden et al., 2008; Lupien et al., 2009; Newman & Newman, 2009; Petermann et al., 2004). The reasoning might be of clinical importance since the roles of fetal programming and their long-term effects have been previously discussed as potential causal factors for the etiology and maintenance of psychopathological disorders (Barker, 1991; Cottrell & Seckl, 2009; McEwen, 2008, Lupien et al., 2009; O'Conner et al., 1999; Rosenblum et al., 2002; Sanchez et al., 2005; Sanchez, 2006; Van den Berg et al., 2005; Ward et al., 2010; Zielinski

2009). Confrontation with adverse life conditions in sensitive developmental and vulnerable phases can have long-term negative effects and induce lower physiological as well as emotional vulnerability in children and adolescents. The results allow the conclusion that prenatal stress per se does not lead to psychological, emotional and behavioral abnormalities in children and adolescence. Presumably, the co-occurrence of pre-, peri- and postnatal adverse life conditions can end in psycho-social maladjustment in children and adolescence.

13. Implications for Prevention and Clinical Interventions

As described in the theoretical background, pre-, peri- and postnatal age-specific development without endogenous or exogenous disturbances is crucial for the psychosomatic health of children. The findings of the present data analysis might reflect a higher vulnerability of children exposed to prenatal stress as well as to perinatal and postnatal adverse conditions for psychological abnormalities and somatic complaints.

Accordingly, implications can be derived for prevention and clinical implications on two main points.

1.) Prevention and clinical interventions in pregnant women
2.) Prevention and clinical interventions in children

First, due to the naturally given fact that the primary developmental period is during the pregnancy, in the body of the pregnant women, prevention possibilities for complications during a pregnancy can be realized (Trunbull et al., 2004; Urizar et al., 2004; Van den Berg et al., 2008). Primarily, a professional evaluation of the individual risk profile of the pregnant women is needed. This might be realizable through a close bio-psycho-social monitoring and

supervision by the gynecologist during the whole pregnancy. The individual risk profile might be developed under consideration of factors such as lifestyle of the mother and her partner, social support possibilities, professional situation of the mother, socioeconomic status, ethnicity and important health anamnesis. This could lead to an individual prevention plan of complications during the pregnancy. In the case of pregnancy complications that have already arisen, there could be medicinal care and treatment as well as other individual supporting possibilities, depending on what is considered as helpful and supportive by the pregnant women, e.g. contact with other mothers in similar situations (similar to self-help groups) or psychological support. If hospitalization or bed rest are needed, there could be also modern communications such as wireless internet access or home visits, and concrete supportive as well as practicable intervention possibilities.

Second, prevention and clinical intervention in children themselves is also possible, as helpful, practicable and economic prevention in children is crucial in order to gain good knowledge about predictive and risk factors with long-term effects on children, adolescents and adults. A crucial factor is the empowerment of the concerned parents, supplemented by individual medical and/or psycho-social support and interventions. The parents play an important role in the case of medical or psychological abnormalities that have already occurred and should be considered as an indispensable partner during the clinical interventions. Clinical interventions depend on the profile of disease and resources of the concerned newborn, child or adolescent himself as well as resources of his parents and/or other important attachment subjects.

For successful and optimal prevention and clinical interventions, interdisciplinary cooperation, including children as well as their parents and close environment, is crucial and recommendable.

14. Directions for Future Research

For future research, there are several methodological points that might be considered.

Longitudinal / prospective study design

Composition of the study sample analogous to the general population

Enlargement of the study sample to investigate possible gender effects

Consideration of salutogenic factors

First, the longitudinal design offers the possibility of current data collection, avoiding the time effect. There might be causal interpretations possible. Second, a representative study sample, analogous to the general population, would make the generalization broader and would be close to the natural reality. Furthermore, there would be investigation of possible gender effects in order to adjust prevention and/or clinical interventions, also to the children's gender if required. Moreover, there are always subjects who stay healthy despite extreme adverse conditions (McEwen, 1979; Goldstein & McEwen, 2002; Juster et al., 2009). It would be very helpful and beneficial for all children and adolescents to identify resilience factors, which account for retaining mental and psychological health.

Moreover, prenatal psycho-social stress is considered as a main etiological factor for the incidence of preterm birth in pregnant women. Preterm birth has the highest prevalence rate among pregnancy complications. Furthermore, it seems to be a crucial cause for a decreased

gestational period and accordingly also adverse perinatal outcomes. Moreover, clinical epidemiological research shows that prenatal birth is a crucial cause for higher morbidity and mortality in newborns (Breckwoldt & Pfleiderer, 2008;Iannucci et al., 1995; Krähenmann et al., 2005; StatSanté, 2007).

Considering the findings of this study and the high value of longitudinal prospective studies, it would be of great empirical and clinical worth to investigate all children who participated in this present investigation in a follow-up after they have reached puberty, and to accompany them for as long as possible throughout their lives. Such a study design would allow deeper conclusions to be drawn about long-term effects of pre-, peri- and postnatal adverse conditions. Moreover, the focus would also be on resilience or salutogenic factors due to their health relevance.

Furthermore, it would be illuminating to investigate the effect of psychological interventions on mothers with a diagnosis preterm contractions and accordingly of preterm birth during their pregnancy in comparison to pregnant women experiencing risk of preterm birth without a psychological intervention. Particularly beneficial would be a longitudinal as well as randomized clinical trial study design, including an adequate placebo group. Such findings would elucidate three main basic clinical questions: First, the underlying etiological and maintaining processes of preterm contractions, e.g. endocrine and psychosocial variables; second, the possible benefits of a psychological intervention, and third, the influence of prenatal adverse conditions on developmental processes as well as on perinatal outcomes and postnatal adaptation. Furthermore, the influence of pre-, peri-, and postnatal adverse conditions on psychosomatic health in different life stages should be assessed. Moreover, resilience/salutogenic factors should be considered as such a study would be of central

practical application relevance, primarily for the intervention study groups of the pregnant women and, furthermore, for later application of these findings in constructing preterm contractions and thus preterm delivery-specific clinical intervention guidelines. However, such a clinical study remains to be realized.

Part IV – References

15. References

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09. 2006 – 06.2010	Doctoral Student, Department of Psychology, Clinical Psychology and Psychotherapy, University of Zurich, Zurich, Switzerland (Chair: Dr. U. Ehlert)
04. 2008 – 05. 2009	Organization and Coordination of the 6th Congress for Clinical Psychology and Psychotherapy and the 21st Symposium of the German psychological professional group for clinical psychology and psychotherapy (Deutsche Gesellschaft für Psychologie, DGPs)
03. 2005 – 12. 2006	Research Assistant, Sanatorium Kilchberg; Project: Life Quality in patients with bipolar disorders, Kilchberg, Switzerland
06. 2006 – 04. 2008	Research Assistant, Stein Consults; Project: Evaluation of stress coping management in companies, Munich, Germany
12. 2004 – 12. 2005	Project employee and secretary, KomIn – "Kompetenzzentrum für Integration des Kanton Schwyz", Pfäffikon, Switzerland
06. 1992 – 12. 2005	Intercultural Mediator and Translator Albanian-German, Zurich, Switzerland
08. 2004 – 02. 2005	Employee with leadership position in MIGROS, Zurich, Switzerland
01. 1995 – 12. 1999	Dental Assistant, Dr. med. dent Ch. Walther, Volketswil, Switzerland

Research Interests

Prenatal Stress; Development in children and adolescents; Intercultural Psychology and Psychotherapy; Behavioral Medicine

Publications

2010

Gillhoff, K., Gaab, J., Emini, L., Maroni, C., Tholuck, J. & Greil, W. (2008). Effects of a multimodal lifestyle intervention on body mass index in patients with bipolar disorder: A randomized controlled trial. Prim Care Companion Journal of Clinical Psychiatry, 12(5); e1-e8.

2008

Wirtz, P.H., Ehlert, U., Emini, L. & Suter, T. (2008). Higher body mass index (BMI) is associated with reduced glucocorticoid inhibition of inflammatory cytokine production following acute psychosocial stress in men. Psychoneuroendocrinology 33:1102-1110.

2007

Wirtz, P.H., Ehlert, U., Emini, L., Ruedisueli, K., Groessbauer, S. & Von Känel, R. (2007). Procoagulant stress reactivity and recovery in apparently healthy men with systolic and diastolic hypertension. J Psychosom Res 2007;63:51-58.

Wirtz, P.H., Von Känel, R., Emini, L., Suter, T., Fontana, A.,& Ehlert, U. (2007). Variations in anticipatory cognitive stress appraisal and differential proinflammatory cytokine expression in response to acute stress. Brain Behav Immun 21 (2007):851-859.

Wirtz, P.H., Von Känel, R., Emini, L., Ruedisueli, K., Groessbauer, S., Maercker, A.,& Ehlert, U. (2007). Evidence for altered hypothalamus-pituitary-adrenal axis functioning in systemic hypertension: blunted cortisol response to awakening and lower negative feedback sensitivity. Psychoneuroendocrinology 2007;32:430-436.

Wirtz, P.H., Elsenbruch, S., Emini, L., Ruedisueli, K., Groessbauer, S. & Ehlert, U. (2007). Perfectionism and the Cortisol Response to Psychosocial Stress in Men. Psychosom Med 2007;69:249-255.

2006

Wirtz, P.H., Ehlert, U., Emini, L., Ruedisueli, K., Groessbauer, S. & Von Känel, R. (2006). The role of stress hormones in the relationship between systemic hypertension and the hypercoagulable state. J Hypertens 2006;24(12):2409-16.

Wirtz, P.H., Ehlert, U., Emini, L., Ruedisueli, K., Groessbauer, S., Gaab, J., Elsenbruch, S. & Von Känel, R. (2006). Anticipatory cognitive stress appraisal and the acute procoagulant stress response. Psychosom Med 2006;68:851-8.

Wirtz, P.H., Von Känel, R., Mohiyeddini, C., Emini, L., Ruedisueli, K., Groessbauer, S. & Ehlert, U. (2006). Low social support and poor emotional regulation are associated with increased stress hormone reactivity to mental stress in systemic hypertension. J Clin Endocrinol and Metab 2006; 91(10):3857-3865.

Books

Ehlert, U., Emini, L. & Erni, K. (2008). Emotions / Motivation, Modul 9. Universitäre Fernstudien Schweiz, Studienzentrum Brig. INTEGRATE.

Shaqiri-Emini, L., Lupke, U. & Ehlert, U. (2011.). Verhaltensmedizin (Behavioral Medicine). In Meinlschmidt, G., Schneider, S. & Margraf, J. (Hrsg.). Lehrbuch der Verhaltenstherapie: Materialien für die Psychotherapie (Bd. 4). Berlin Heidelberg New York Tokio: Springer.

Honors & Funding Support

Awards and Prizes

2009	Poster Award, Prenatal Stress (PNS) - Association with emotional regulation, subjective health well-being and quality of life in children. 20th World Congress on Psychosomatic Medicine, Torino, Italy.

Continuing Education

2006-present	Postgraduate Student of Psychotherapy – Cognitive Behavioral Psychotherapy and Behavioral Medicine
2008	Writing scientific English, University of Zurich, Switzerland
2007	Teaching Methods, University of Zurich, Switzerland

Teaching Experience

IPT Zurich	
01.2011 – present	Adult education: Psychological strategies in coping with critical life events
University of Zurich	
Fall semester 2008	Symptomatology, Etiology, and Treatment of Mental Disorders
Spring semester 2008	Problem Analysis in Psychotherapy

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Fall semester 2007	Evaluation of Techniques of Clinical Psychology and Psychotherapy
Spring semester 2007	Methods in Clinical Psychology and Psychotherapy

Clinical Experience:

01. 2011 – present	Clinical Psychologist, Adult Education, Intervision and Supervision for coaches/conselors and other staff members, IPT Integration pour tous, Altstetten, Zurich, Switzerland
02. 2012 – present	Psychotherapist (Cognitive Behavioral Therapy and Behavioral Medicine) at a doctor's office for psychiatry, Wetzikon, Zurich (Medical pracititionar: Dr. E. Gutte)
09. 2006 – 02.2012	Psychotherapist (Cognitive Behavioral Therapy) in the Outpatient Clinic and Research Unit for Behavioral Medicine at the University of Zurich (Chair: Dr. U. Ehlert)
11. 2009 – 12.2009	Psychotherapist (Cognitive Behavioral Therapy and Behavioral Medicine) in the Clinic for sleep disorders in Zurzach (KSM)
03. 2005 – 12. 2006	Research Assistant, Sanatorium Kilchberg; Project: Life Quality in patients with bipolar disorders, Kilchberg, Switzerland

Research Experience

2006 - 2010	*Prenatal Stress – Impact on the psycho-bio-social development in 10-year-old children.* PI: Prof. Dr. Ulrike Ehlert, University of Zurich, Zurich, Switzerland
2006 – 2008	*Evaluation of stress management training in companies.* PI: Prof. Dr. Ulrike Ehlert, M.S. Frank Stein, University of Zurich, Zurich, Switzerland
2005 – 2006	*Life Quality in patients with bipolar disorders.* PI: Prof. Dr. Ulrike Ehlert, M.S. Kornelia Gillhoff, University of Zurich, Zurich, Switzerland
2003 – 2005	*Psycho-socio-biological activity and reactivity in essential hypertension.* PI: Prof. Dr. Ulrike Ehlert, Ph.D. Petra Wirtz, University of Zurich, Zurich, Switzerland

Professional Memberships

Swiss Psychological Society (Fachverein der Schweizer Psychologinnen und Psychologen, FSP)