Epidemiological studies of

Stress during pregnancy and fetal brain development

PhD thesis
Carsten Obel

Faculty of Health Sciences, University of Aarhus 2003

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This thesis is based on the following five papers, which will be referred to by roman numerals


**List of abbreviations often used in this thesis**

11 β-HSD        11 β-hydro steroid dehydrogenase  
ABCohort        The Aarhus birth cohort  
ACTH            Adrenocorticotropic hormone  
ADHD            Attention deficit hyperactivity disorders  
CBCL            Child behaviour checklist  
CI              Confidence interval  
CNS             Central nervous system  
CPR number      Civil registration number  
CRH             Corticotrophin releasing hormone  
HKD             Hyperkinetic disorder  
LHPA            Limbic hypothalamic pituitary adrenal  
SDQ             Strengths and difficulties questionnaire  
OR              Odds ratio
Preface

Five hundred years ago the well-known painter, scientist and mirror-writer Leonardo da Vinci commented on the pregnancy situation ‘*The same soul governs the two bodies and the desires and fears and sorrows are common...*’ It remains unknown if he himself had experienced stress in intrauterine life but it seems likely that he had an atypical brain lateralisation. In any case his example illustrates that atypical brain lateralisation is not necessarily a disadvantage.

The overall aim of this thesis is to study maternal stress in relation to fetal brain development in an epidemiological setting. The thesis is based on data from the Aarhus Birth Cohort (ABCohort), which was established in 1989. After being involved in the postnatal follow up programme of part of this cohort since 1992, my first impetus for the current thesis was the concurrent observations in humans linking the prenatal environment to handedness in the offspring and the animal experiments linking prenatal stress to lateralisation of the brain. Subsequently handedness was added to our follow up programme from 1995 of attention problems and language development of the child.

A number of studies have found an association between antenatal stress and preterm delivery and recently associations between severe stress and certain malformations and a change in sex ratio have been reported. There is also some evidence of immediate fetal reactions to maternal stress. These reports provide some evidence of the possibility, that the maternal stress response can be transferred to the fetus and interfere with fetal development, but in 1999 when this project was planned the good epidemiological studies of long term consequences of stress for the offspring were few.

A detailed description of the data collection has been given priority for a number of reasons. First, one of the central methodological processes of this thesis was the identification of valid measures of child behaviours. Second, only a small part of the data collection is presented in the papers. The presented documentation is of importance, given the potential future possibilities of using the collected data. At present projects are being carried out, that use parts of these data including child behaviour, Tourettes syndrome, learning problems and otitis media.

I am grateful to those who contributed to the data collection; the more than 7000 parents and the 2000 teachers who provided data and to my co-workers, who contributed with knowledge, conscientious work and mental support. The list of contributors is too long for a preface, and can be found in the acknowledgement.

Carsten Obel, April 2003
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Introduction

The idea that maternal emotional factors may play a role in fetal life is ancient and has been expressed in almost all known cultural settings\(^1\). As early as in 1867, Whitehead described more fetal movements in mothers undergoing severe emotional stress\(^1\), but Sontag was probably the first to describe this phenomenon in scientific papers\(^2,3\). Stress-exposed fetuses were later described as ‘hyperactive, irritable, fussy and easy crying’ during the first 2½ years of their life\(^1\).

The first animal models to support the idea that the early environment in particular may influence behaviour\(^4\) and modify the stress system\(^5\), were published almost half a decade ago. In 1973, Stott was probably the first to report exploratory findings from a follow up study, suggesting that antenatal stressed mothers were more likely to have hyperactive children\(^6\).

The central nervous system (CNS) plays an important role in the response to psychological stress. The stress response has often been described as a ‘double edged sword’\(^7\), a certain amount is beneficial whereas if the stress response does not ‘shut off’ the excess exposure of cortisol is damaging for the organism including the central nervous system (CNS)\(^8\). Recent findings that excess amounts of stress may permanently impair certain functions of the developed adult brain, support this view\(^9\). The underlying mechanism is thought to be an influence on the production of neurons in the dentate gyrus of the hippocampus, which is a group of cells uniquely characterised by production throughout adult life.

The brain of the developing fetus, which is characterised by cell production, migration and organisation, would be expected to be far more sensitive to these exposures than the adult brain, but little is known about the role of maternal psychological stress during pregnancy for the development of the fetal CNS in humans.

The epigenetic view on brain development suggest, that interaction between genes and environment can influence the developmental trajectory and that events at one point in time have consequences that are manifested later in the developmental process\(^10\).

The hypothesis of the current thesis is an epigenetic role of chronic antenatal stress i.e. that psychological stress during pregnancy can influence the development of the fetal brain as reflected in measures of brain size and brain function during childhood.
1. Background

1.1. The definition of maternal stress from a fetus’ point of view

Stress is an ambiguous term\textsuperscript{11}. A variety of broad and narrow definitions have been suggested within the fields of psychology, behavioural sciences and physiology. One definition is provided by Lazarus, who has defined stress as ‘A particular kind of relationship between person and environment’\textsuperscript{12}. Another, by Levine suggested that stress is ‘anything, that induces increased secretion of glucorticoids’\textsuperscript{13}. A third definition by McEwen restricted the term to refer to ‘events, that are threatening to an individual, and which elicit physiological and behavioural responses…’\textsuperscript{14}.

The choice of definition is dependent on the psychosocial or psychobiological aspects of stress in focus. The pregnancy situation is unique in this respect because the stress of the mother may not only influence herself, but also her fetus. The fetoplacental unit connects the two individuals biologically and the hormonal response to stress may be transferred to the child. Even though other elements of the physiological stress response may be of importance the definition of \textit{maternal stress used in the current setting is restricted to the direct activation of the limbic hypothalamic pituitary adrenal (LHPA) axis by psychological factors}. Maternal stress will in the following refer to this definition.

In fact little is known about the physiological response to psychological stress during pregnancy and to study the effects of maternal stress on the fetal development is complicated by the fact that this exposure is connected to a number of factors that can also be related to fetal brain development. First, maternal stress may be influenced by a number of genetic and social factors, including personality, ability to cope with the stressor, and social support and unreported sources of stress, which may be of importance for the risk of the child to develop psychopathology. Secondly, in contrast to the classical animal ‘fight and flight’ response to stress, stressed humans are more likely to change lifestyle i.e. smoke more cigarettes\textsuperscript{15}, change their diet\textsuperscript{16} and increase their alcohol intake and coffee consumption. These changes may all have the potential to influence fetal brain development\textsuperscript{17-21}. This influence may be caused by the passage of the constituents over the placenta or by stimulation of the stress hormones through the maternal LHPA axis or the placenta.

Thirdly, the psychological well being of the mother in and after pregnancy is associated\textsuperscript{22,23} and this may influence the psychological environment of the newborn child. The early postnatal environment modulates the stress response and emotional behaviour in primate infants\textsuperscript{24}, and may also influence the early human development\textsuperscript{25}. Severe maltreatment and abuse in early childhood enhances the risk of major depression\textsuperscript{26-28}, and even less extreme exposures related to maternal anxiety and depression are associated to a higher risk of emotional and conduct disorders in the child\textsuperscript{29}. The possible ways stress may be associated to fetal brain development are summarised in figure 1.1.
Ideally the effect of maternal stress would include collection of data on the factors mentioned above and a continuous monitoring of the activity of the LHPA axis through pregnancy, which seems unrealistic in a large scale epidemiological setting. In epidemiological studies have used different measures reflecting various aspects of stress with registration of potential stressors such as life events, war and nature catastrophes, and self report of perceived stress related to the stressor or psychological distress such as anxiety and depression.

Given the many unknown factors, it seems unlikely that any of these measures alone will be a good indicator of psychologically induced activity of the LHPA axis. An association between stressful events and cortisol has been found at least in non-pregnant women \(^{30\text{-}32}\). Patients with endogenous depression generally display the same alterations in the LHPA axis as the chronically stressed\(^ {33}\), but the LHPA activity in less pathological levels of psychological distress such as anxiety, are not entirely clear\(^ {32\text{-}34}\).

To distinguish between the many ways, by which antenatal stress may influence the development of the child, it is of major importance to take these factors into account in the design of epidemiological studies.

### 1.2 The physiological response to psychological stress during pregnancy

It is essential for the individual to adjust not only to life-threatening stressors, but to the challenge of life at all levels including the daily life cycle of rest and activity. The principal
mechanisms of adjustment are under the control of the sympathetic nervous system (SNS) and the LHPA axis. The activation of the SNS is especially prominent during exposure to cold, orthostasis, and mild exercise whereas LHPA axis activation is especially prominent when the individual is exposed to hypoglycaemia and psychological stress. SNS only plays a minor role in chronic psychological stress and short adrenal SNS stress response is less likely to have serious impact on the fetal brain development. The SNS reaction will not be discussed further in this thesis.

The normal activity of the LHPA system displays a diurnal rhythm with high activity in the morning, which decreases over the day reaching the lowest level in the evening. The involvement of the limbic system is unique to mammals, and comprises a circuit of grey matter structures around the brain stem on the medial surface of the brain. The hippocampus and amygdala are part of this system, and both structures and are central components in the physiological response to stress. Physical and psychological stress activates the LHPA axis at different levels. The prefrontal cortex and the limbic system are central in the response to ‘processive stressors’ such as psychological stress. In contrast ‘systemic stressors’ such as physical stress do not involve these higher centres, but activates the LHPA axis at the hypothalamic level.

When confronted with psychological stress neural stimulation from the prefrontal cortex and limbic system stimulate the hypothalamus to release corticotrophin releasing hormone (CRH) into the hypophysial portal system causing a release of adrenocorticotropic hormone (ACTH) into the peripheral blood circulation. ACTH stimulates secretion of cortisol from the adrenal glands. The increased levels of glucocorticoid serve to down regulate the secretion of hypothalamic CRH and this negative feedback loop shuts off the hormonal stress response and restores steady state.

In chronic psychological stress this negative feedback mechanism is compromised by an increased central drive of the LHPA axis. A larger production hypothalamic production of CRH and a reduction in the number of cortisol receptors in the limbic system. This hormonal situation has some similarity with the conditions in late pregnancy. Third trimester is characterised by a higher cortisol and CRH production and possibly a blunted negative feedback mechanism of the LHPA axis.

In pregnancies of some primates including humans, gorillas, chimpanzees and rhesus monkeys, a considerable amount of CRH is produced by the syncytiotrophoblasts releasing hormone into the hypophysial portal system causing a release of adrenocorticotropic hormone into the peripheral blood circulation. ACTH stimulates secretion of cortisol from the adrenal glands. The increased levels of glucocorticoid serve to down regulate the secretion of hypothalamic CRH and this negative feedback loop shuts off the hormonal stress response and restores steady state.

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growth retardation, bacterial infectious disease, pre-eclampsia, diabetes and twin pregnancies.

Third trimester of pregnancy is usually characterised by elevated cortisol levels, and since CRH is also elevated a causal link has been proposed. It is not known exactly how CRH interfere with the LHPA axis and a number of other factors may play a role in the regulation. Injection of CRH in seven pregnant women did not cause a rise in cortisol, except for one woman who was very stressed by the procedure and an alternative explanation of the higher cortisol levels may be a pregnancy related change in the set point of the usual LHPA feedback mechanism.

It has been suggested that this up-regulation of stress hormones in maternal plasma may blunt the hormonal reaction to stress, and thereby protect the fetus against maternal stress in the third trimester, but others seem to reach the opposite conclusion based on the same evidence. A recent study found a statistically significant weaker cortisol response to cold water in ten pregnant women around 36 weeks of gestation compared to the response in ten non-pregnant students of mid-wifery. These results indicate a blunted LHPA response just before term at least to physical stressors. The studies of the role of psychological and other environmental stress for the stress response in late pregnancy are small and methodologically weak. One study found no association between psychosocial stress and cortisol/CRH in third trimester of pregnancy, whereas others found associations with some measures of stress. None of the studies used prospectively collected data, and it is unknown if the stress exposure would have elicited a hormonal response in early pregnancy or in non-pregnant women.

Experiments in ewes suggest that the explanation of the higher levels of cortisol in third trimester could be a reduction in the central feedback loop of the HPA axis. If a similar mechanism exists in humans a hyper reactivity to stress instead of a blunting of the physiological response would be expected.

The fetal LHPA axis is important for the normal development early in gestation. ACTH as well as cortisol is probably produced by the fetus from the end of the first trimester. The development and function of the human fetal adrenal cortex differ from other species. The adrenal glands are disproportionately large and exhibit extraordinary growth and production of steroids in the second and third trimester. Adrenal glands also develop in anencephalic fetuses which makes a supplementary regulatory role of placental and maternal hormones very likely.

The cortisol produced by the fetus contributes to maturation of fetal organs but maternal production also seems to play an important role in this process. Even though the fetus can elicit an independent cortisol response to stress from midgestation the strength of this response increases by gestational age and the maternal LHPA axis may play a role in regulation of basic and stress mediated levels of these hormones in the fetal circulation throughout intrauterine life.

1.3 Transfer of maternal stress to the fetus
Maternal stress may influence the fetal development by reduction of the vascular transport of oxygen and nutrition’s to the fetus or by influence of the hormonal environment transferred to the fetus.
Two studies have evaluated the blood flow to the fetus in anxious pregnant women. In both the Spielberg state and trait anxiety questionnaire (STAI) was used. Teixera studied 100 pregnant women and observed an association between high uterine artery resistance index, i.e., a decreased blood flow and high state and trait anxiety scores. The strongest association was found to state anxiety. Sjostrom studied the blood flow in the umbilicus and the middle cerebral arteries of the fetus in 37 women. A higher resistance index was found in the umbilicus in the fetus among women with a high trait anxiety score while a lower resistance was found in the middle cerebral arteries of the fetus. In contrast to the study by Teixeira there was no sign of decreased blood flow in women with a high state anxiety score. The differences in their findings could be due to small sample size, different anxiety profiles in the two samples or possibly that the differentiation of state and trait anxiety by STAI is unreliable in pregnancy.

A decreased blood supply may restrict the supply of oxygen and nutrition and hypoxic damages to the developing brain, which may in itself be damaging. Still, the ‘brain sparing mechanism’ seems to favour the brain except in extreme situations, and protect the brain from damage. A decreased blood supply is therefore not the most likely way, that the maternal stress response is transferred to the fetus, but a compromised supply to other organ systems may result in a hormonal stress response that may accelerate brain maturation resulting in slightly poorer cognitive outcome.

In humans fetal cortisol levels in pregnancy are related to maternal concentrations. The placental enzyme 11β-hydro steroid dehydrogenase (11β-HSD) converts cortisol to the biological inactive cortisone, but some cortisol pass over the placenta, exceeding the capacity of 11β-HSD. One study where radioactivity labelled cortisol was injected immediately before induced abortion suggested that 15% of the cortisol pass the placenta unmetabolised. Because fetal levels of cortisol are much lower than maternal levels a rise of 10-20% in the mother could still double fetal concentrations.

Placental CRH may be important for the communication between the maternal and fetal LHPA axes. Placental CRH is thought to be secreted into the fetal circulation throughout pregnancy and has been identified in preterm children down to 24 gestational weeks. Maternal cortisol stimulates placental CRH which in turn stimulates local placental ACTH production. CRH can also penetrate the blood-brain barrier to stimulate the fetal production of ACTH. Administration of the synthetic glucocorticoid dexamethasone after week 30 of gestation stimulates CRH release in fetal as well as maternal blood, but this hormone is not metabolised by 11β-HSD and cortisol may therefore not have the same capability as dexamethasone to stimulate CRH.

1.4 Stress hormones and fetal brain development
The epigenetic view on brain development suggest that influences in certain time windows in the organisation of the developing brain not only influence the present stage of the development but also the proceeding processes. Neurons are produced and organised in discrete periods of embryonic development and hyperplasia, ectopia and dysplasia may be the result of exposure interfering with neurogenesis, migration and differentiation respectively. Severe stress may have the potential to influence these early processes in the brain.
development resulting in malformations or fetal death as suggested by recent epidemiological reports\textsuperscript{89,90}. In later stages of development the exposure may be programming cellular function on receptor level which may cause permanent changes in cell function\textsuperscript{87}. Interference with specific receptors within the synaptogenesis period in the last trimester of pregnancy may influence the regulation of apoptosis (programmed cell death)\textsuperscript{91}.

Animal studies suggest that stress hormones have a number of dose dependent and general modulating effects on brain development including a reduction of brain growth\textsuperscript{92,93}, a delay in axon myelisation and a sustained effect on the formation of polyamines, which are major regulators of neural cell replication and differentiation\textsuperscript{94,95}. Cortisol also has a regulating effect on the synthesis of neural cell adhesion molecules\textsuperscript{96} microtubule associated proteins\textsuperscript{97} and neurothrophic factors, which are important in neuron maturation and synaptic stabilisation.

CRH and cortisol in fetal blood can cross the blood-brain barrier but the exposure is dependent of local enzymatic factors and the interaction with other hormones. Corticosterone, the rat cortisol, can pass the blood brain barrier\textsuperscript{98}, but the brain is partially protected by local enzymes (11\textbeta\textsubscript{HSD}). Animal studies suggest, that in the last part of pregnancy the enzymatic activity goes down\textsuperscript{99} allowing higher levels of cortisol to interact with the specific receptors\textsuperscript{100-102}.

Cortisol and CRH receptors are found in various parts of the brain\textsuperscript{103-106}. The hippocampus and parahippocampal areas have the largest concentrations of cortisol and CRH receptors\textsuperscript{107} and are the most vulnerable CNS sites to stress\textsuperscript{108}. Excess prenatal stress may reduce the number of glucocorticoid receptors in the hippocampus\textsuperscript{109,110} with a long term impairment of the negative feed-back mechanism as a consequence.

Administration of CRH\textsuperscript{111} as well as cortisol\textsuperscript{112} to fetal rat brains caused a loss of pyramidal hippocampal neurons. Prenatal stress applied to pregnant rats during day 15-21 (imitating the beginning of second trimester exposure in humans) resulted in a 30\% reduction in hippocampal synaptic density\textsuperscript{113}. The same kind of effect was found in rhesus monkeys after a single injection of glucocorticoid, which caused a dose-dependent neural degeneration on hippocampal pyramidal cells\textsuperscript{114}. Hippocampal volume was analysed 20 months postpartum by magnetic resonance imaging and a reduction of 30\% in hippocampal volume was found\textsuperscript{115}. These findings are in line with the change in function of the LHPA axis in animals prenatal stressed rats\textsuperscript{116,117-119} as well as rhesus monkeys\textsuperscript{120}.

The sex of the offspring may be important for the vulnerability to stress because sex hormones interfere with CRH and cortisol\textsuperscript{121}. The hippocampus is sensitive to gonadal hormones and express both intracellular androgen and estrogenic receptors\textsuperscript{122,123} and estrogenic receptors are present in neonatal rat brains\textsuperscript{124,125}. This may be the explanation behind the gender differences in vulnerability to prenatal stress observed in some animal experiments\textsuperscript{126,127,129}.

1.5 A model of fetal allostasis
The biological terminology of stress dates back to the mid-nineteenth century where Claude Bernard introduced the term homeostasis as the body’s need to keep a constant internal environment in situations of stress\textsuperscript{130}.
The advances in understanding the biological effect of psychological stress from the middle of the 1950’s has led to the use of the terminology of allostasis, to characterise systems in which the physiological set point is fluid and changing. This concept has further been developed by McEwen and coworkers.

Allostasis is achieving stability through change and the term emphasizes that the stress systems are able to keep the body stable by being able to change themselves. Allostatic load refers to the price the body has to pay for these adjustments, and this may be a problem if exposure to stress is prolonged, the stress reaction does not “shut off” (as in anxiety and depression) or if the stress response is inadequate. Allostatic overload denotes situations with in which the organism is unable to escape the stressful situation. In type I allostatic overload the organism tends to find alternative ways to adjust to the situation in order to increase the chance of surviving within the stressful environment, whereas type II allostatic overload is characterised by an absence of escape response. Allostatic overload may cause long term changes in organ function.

The foundation of this model is based on the physiological responses to stress. Allostatic load is mediated by a number of factors but the LHPA axis response including cortisol and corticotrophin releasing hormone (CRH) are central in relation to the brain.

The concept of allostasis and the ‘allostatic’ load model may be useful in understanding the biological effects of maternal stress on the fetus. The primary function of the placenta and fetal and maternal LHPA axes is to secure fetal allostasis i.e. to adjust to keep stability through the changes related to the consecutive developmental stages. If challenged by excess stress, an acceleration of the maturation processes in various organ systems may occur for the immediate benefit of child who may be about to meet the extra uterine environment earlier than expected. In the terminology of McEwen et al. this would be an activation of ‘the emergency history stage’ or allostatic overload type I. The ‘escape’ mechanism may be of short term benefit for the child and in some cases even life saving, but the child may have to pay a price reflected in an influence on the normal brain development. Poorer cognitive outcome among children stressed in fetal life by restricted nutritional supply and psychopathology in offspring of prenatal stressed humans and animals fit into this model.

1.6 Animal models of prenatal stress and behaviour of the offspring
A number of behavioural changes have been observed in prenatal stressed rats including reduced learning and memory, deviant reaction to stress, shorter attention span, disturbance of sex-typical behaviour, working memory and lateralised behaviours.

The early stages of fetal brain development in these rodents should be comparable with that of humans. At the end of a normal rat pregnancy, at 22-23 days of gestation, the developmental stage resembles that of a 16-17 weeks human fetus. As a consequence human brain development in the third trimester corresponds to the early postpartum period in the rat. Stress experiments in newborn rat includes daily separation from the mother, with and without its littermates in various periods and these experiments may be of interest in relation to the role of stress exposure in third trimester of human pregnancies, and the early neonatal environment of the rat has been shown to influence LHPA axis functions as well as
behaviour. To extrapolate from stress experienced in the neonatal period to the intrauterine situation in humans may be a problem. The LHPA axis seems to be less responsive to stress in first weeks of the life of a newborn rat and the comparability is dependent of whether this corresponds to a similar situation in the third trimester of human pregnancy. In some primates the state of the HPA axis just after birth is not characterised by this phenomenon and may in fact be hyperresponsive.

In contrast the timing of brain development in relation to birth in primates is closer to that of humans. Rhesus monkeys, the most often used primate model, have a normal gestational length is 165 days, but at birth the brain is already more than half the adult size compared to 25% in humans. Primates are phylogenetically closer to humans and more similar concerning CNS handling of stress and regulation of the LHPA axis. Non-human primate stress paradigms can be made quite similar to those relevant for humans. This is especially relevant because unlike in rodents the LHPA axis reaction to psychological is under strong influence of higher cerebral centres such as the mesocorticolimbic system (processive stress). Furthermore the placental CRH production is also found in the rhesus monkey, which is the species most often used in experiments.

Experiments with primates are few, but show that prenatal stressed rhesus monkeys have a shorter attention span a stronger emotional reaction to stress and lower levels of exploratory behaviour.

1.7 Stress in human pregnancy and behaviour in the offspring—a systematic review

The animal studies suggest that the influence of maternal stress on fetal brain development is a biological possibility, but empirical evidence from human studies is needed to establish knowledge of causation. In the following, a systematic review of the literature of stress related psychological factors to measures of fetal brain development is presented.

1.7.1 Review procedure

In January 2003 searches of PUBMED from 1968 to 2003 and EMBASE from 1974 to 2003 were performed using the combination of the search parameters (‘pregnancy’ or ‘prenatal’) AND (‘stress’ or ‘distress’) with ‘brain’, ‘development’, ‘epilepsy’, ‘schizophrenia’, ‘ADHD’, ‘attention’, ‘behavio (u) r’, ‘handedness’, ‘emotional’, ‘depression’, ‘cerebral palsy’ respectively. A search using the Medical Subject Headings (MESH): ‘pregnancy’, ‘stresses and ‘brain’ was also conducted and similar searches were done in the psychological database PSYCINFO. A number of studies were identified by examining the reference lists of the identified studies and through a search in the Science Citation Index from 1986 to 2003 on the citation of the first studies in the area.

1.7.2 Comparability of studies

Peer reviewed papers in English, that examined the association between prenatal stress and indicators of fetal brain development were included in the review. Congress abstracts were excluded, even though they were published in a peer-reviewed journal, since they did not provide sufficient data to make a critical evaluation. Studies of immediate autonomic fetal reactions to prenatal stress such as change in heart rate and activity were not included. A
number of studies were methodologically weak, but were included because they had been widely cited.

The characteristics of the reviewed studies are presented in table 1.1 (Appendix A1). In some of the studies no risk estimates were provided. If the information was available odds ratios and 95% confidence intervals were calculated. The comparison of the identified studies was complicated by the use of quite different measures of exposure. The exposures can be categorised in three groups:

- Ecological designs with information on external events. This information was not specific for the pregnant women, but was assumed to have stressed the whole population. The events included the 1976 earthquake in Tang Shan, China, the end of the second world war in Germany and in the Netherlands the invasion in 1944 and the Flood disaster in 1953.

- Life events, that occurred just before or during pregnancy. In a single study the effect of the death of spouse during pregnancy was evaluated by use of registers. In other studies information on stressful life events were collected prospectively by questionnaires or retrospectively by interviews and in some cases with the possibility to register the experience of events as well as perceived stress by the event.

- Information on mental well-being or psychological distress was collected prospectively by questionnaires or retrospectively by interviews or questionnaires.

There was some consistency in the choice of endpoints related to fetal brain development. In the seventies three studies were published reporting associations between psychological factors in pregnancy and behavioural problems in childhood, schizophrenia and homosexuality respectively and most of the later studies also used these endpoints.

1.7.3 Schizophrenia

Schizophrenia is the most serious adult psychiatric disease with a lifetime cumulative incidence of about 8-15 per thousand in most populations. The hippocampus seems to play a central role in schizophrenia. In schizophrenic patients this structure is smaller, has fewer glucocorticoid receptors and a reduced negative feedback regulation of the HPA axis. Although genetic factors play a role in the aetiology, a number of prenatal environmental factors such as infections, obstetrical complications and under nourishment have been associated with a higher risk of schizophrenia.

Four studies were identified that directly aimed to test the hypothesis that prenatal stress increases the risk of schizophrenia in the offspring. All studies used the DSM diagnosis as endpoint.

Huttunen linked 167 children, who during their intrauterine life lost their father in the Second World War, with 168 who lost a father within the first year of life to the national register of psychiatric diseases. In both groups the mortality as well as the psychiatric morbidity was unexpectedly high. Those who lost their father in intrauterine life tended to have a higher mortality. Thirteen (8%) and 8 (5%) respectively died before the age of 15. Among those who experienced their 15th birthday, six in the prenatal stressed group compared
to one had a diagnosis of schizophrenia. There were no statistically significant differences between any other single disorder, but overall the prenatal stressed were more likely to have a psychiatric diagnosis. It was a particular strength of this study that the control group were children with the same kind of exposure just after birth even though the role of the early postpartum environment seems less crucial that previously believed\textsuperscript{175}

In another Finnish study of children born about 20 years later Myhrman used ‘unwanted ness of pregnancy’ as an indicator of prenatal stress and found that unwanted children had more than twice the risk of developing schizophrenia\textsuperscript{176}. Unwanted children where the mother was depressed in pregnancy had three times the risk of schizophrenia compared to wanted children. Depression alone was associated with schizophrenia in the offspring also after control for potential confounders as reported in a later paper\textsuperscript{177}. These associations might as well be due to genetic factors as to stress.

Two recent studies from the Netherlands aimed at testing the hypothesis in an ecological design and used the May 1940 invasion\textsuperscript{156} and the 1953 flood disaster respectively, as indicators of potential stress in pregnancy\textsuperscript{157}.

Women, who were pregnant during the four day invasion in May 1940, were compared with women, who were pregnant in 1939, 1941 and 1942 and a small, but statistically significant difference was found between unexposed and exposed women. The offspring of women exposed to the invasion in first trimester had the highest risk and were 28 \% (95\% CI: 7-53\%) more likely to develop schizophrenia. Exposure in the second trimester was also associated to a higher risk of schizophrenia in the offspring, but only in men.

In a smaller study which used the same kind of design, women who experienced the 1953 flood disaster were compared to women with pregnancies during the two previous and two following years in the same region of the Netherlands\textsuperscript{157}. Even though there was about twice as many patients with schizophrenia among the offspring of the exposed, this difference did not reach statistical significance.

The strength of these studies were the comparability of endpoints and to some degree of exposure\textsuperscript{151;156;157} and together they suggest an association between prenatal stress and schizophrenia in the offspring. The risk estimates varied but seemed to be related to the level of stress used as exposure. A very strong association (OR=6.4) was found among the pregnant woman, who lost their husband\textsuperscript{151}, an event that is rated as one of the most stressful life event in pregnancy\textsuperscript{178}. An intermediate risk estimate was found among women who experienced the Dutch flood disaster in 1953 and all living close to the event (OR=1.9)\textsuperscript{157}. The smallest effect was found in women exposed to the probably less distinct exposure, which was the German invasion of the Netherlands (OR=1.3)\textsuperscript{156}.

The findings from other ecological studies may reflect a causal role of prenatal stress in the aetiology of schizophrenia, as recently pointed out by Koenig et al.\textsuperscript{137}. Exposure during pregnancy to famine\textsuperscript{179;180} and different kinds of infections\textsuperscript{181-183} have been linked to a higher risk of schizophrenia. Infection\textsuperscript{184} as well as starvation\textsuperscript{185} induce a hormonal stress response and could be the common factor which link these findings etiologically\textsuperscript{186;187}.

1.7.4 Homosexuality and gender role behaviour

Homosexuality has a prevalence between 1 and 5 \%\textsuperscript{188}. Recent studies suggest that mental illness is more often found among homosexuals\textsuperscript{189;190}. A specific group of cells in the medial
zone of the anterior hypothalamus may possibly play a role in male typical sexual behaviour. This hypothalamic area is smaller in homosexual in comparison to heterosexual men and resembles women in size. Six studies were identified, linking prenatal stress with offspring sexuality and one with gender role behaviour in childhood.

In an ecological design Dörner et al. studied 865 homosexual men born between 1932 and 1953, who attended his clinic in East Germany. He related the number of homosexual men born each year to the total numbers of births that year and found that this ‘prevalence’ was higher among men born in the period 1941-47 with a peak in 1944-1945. Prenatal stress factors related to the end of the war was hypothesised to be the cause, but the selection of cases is a weak spot in this kind of study design. Dörner et al. later conducted a case-control study of 60 homosexual men, 40 bisexual and 100 heterosexual men. These men were interviewed about life events during their prenatal period, a design that would tend to maximize the risk of information bias. Of the homosexual men, one third reported moderate, and one third severe prenatal stress compared to the only 6% who reported moderate prenatal stress among heterosexuals. How the men were recruited was not described.

The first findings by Dörner et al. were tested in a West German study and used the same ‘end of war’ exposure but the knowledge of sexual orientation in this study came from posted questionnaires to 21-30 year old men born between 1936 and 1960. The way the participants were recruited was not described, but a surprisingly high proportion (20%) of the sample had practiced homosexual behaviour before the age of 20 years. No difference between men born during the war and after was found. They also investigated whether the homosexuals were more likely to have been born in the cities that suffered the most severe bombing during World War II, but did not find any indication of such a tendency.

In an American study, Bailey recruited 143 male and 72 female psychology students and their mothers. Sexual orientation was evaluated using the Kinsey Fantasy Rating and self rated childhood gender non-conformity, and the mothers were asked to remember life events during pregnancy. No correlation was found between the number of events and these ratings in males, but a significant correlation was identified between the number of second trimester life events and a lesbian like Fantasy Rating in women. This study was probably well performed, but may not have had enough statistical power to detect a possible association.

In another American study Ellis et al. identified 283 mothers aged 36-77 years and asked them to remember stressful experiences in each trimester of pregnancy. The offspring of these women were asked to report the percentage of time they imagined having a sexual relationship with their own sex. A higher ‘stress severity’ score in second trimester was reported in male homosexuals.

This design was repeated in a new sample of 7605 students more than 10 years after. The mothers were apparently about the same age as in the previous study and were asked to remember stressful events, amount of overall stress and lack of control in different periods around and during pregnancy. In second trimester the stress rating, which included a combination of the collected information, was associated with homosexuality in the male offspring. No association was found in girls. The computation of the stress score was probably not decided a priori and included combinations of different elements of stress. The procedure was not described and will be impossible to replicate.
Homosexuality in adulthood seems related to early gender roles\textsuperscript{195}. In British ALSPAC study\textsuperscript{196}, Hines et al. studied the association between life events experienced in pregnancy and the score on the Preschool Activities Inventory (PSAI)\textsuperscript{197} when the children were about four years old. PSAI is a 24 items parental questionnaire of child preference for toys, activities and characteristics related to gender role behaviour. They tested the association between number of life events and the PSAI score using correlation analysis. A small, but statistically significant association was found among girls but no association was found among boys. The weak correlations found between number of life events and the gender role score may have hidden the role of the higher levels of stress that are less common in an unselected population of pregnant women.

The studies of using sexual orientation as endpoints had conflicting results and did not provide much evidence of an association between antenatal stress and sexual behaviour in the offspring. It has not been possible to replicate the strong associations initially reported. All studies were retrospective and the mothers or the participants had to recall 20 to 60 years back. They mothers had the knowledge of the sexuality of the participant, knew the hypothesis under investigation and were asked to report details of stress concerning timing, nature, lack of control. The recruitment of participants was poorly described and the measures of stress was not reproducible\textsuperscript{198}.

The better studies found a weak association between number of life events during pregnancy and gender role and lesbian fantasies respectively\textsuperscript{160,163}. Further analysis of the data presented by Hines et al. will probably be the best opportunity to explore this finding further. Since early environmental influence on gender role in childhood may be weaker than for sexual behaviour in adolescence\textsuperscript{199} data from this cohort when the offspring grows up will provide the best possibility to test the hypothesis.

\textit{1.7.5 Depression/emotional symptoms}
Depression is characterised by reduced interest in other people or surroundings, anhedonia, and a decrease in appetite and sexual activity. About 10\% of the population will experience one or more periods of depression, and the age specific prevalence is between 1 and 4 \%. Depression is thought to be related functionally to disturbances in the HPA axis and to structural changes in the amygdala, a critical brain structure for mediation of fear, anxiety and mood regulation\textsuperscript{200}.

In the above mentioned study by Huttunen, where data on manic depression and severe depressive disorders was also collected\textsuperscript{151}, there was an statistically insignificant tendency for children who lost their fathers in the prenatal period to have these diagnoses.

In another study 611 Chinese 18 year olds who were born just after the 1976 earthquake in Tang Shan, China were compared to 604 who were not exposed to the earthquake in pregnancy\textsuperscript{154}. On the Hamilton depression scale (HAMD), the exposed were more likely to have a high score, defined as the upper 10\% of the sample. There was a tendency among boys to a larger effect of the exposure in the second trimester. A larger proportion of males than females were depressed.

In a group of 58 emotionally disturbed 4-19 year olds, Ward found one third of the mothers reporting stressful events during pregnancy\textsuperscript{201}. This finding suggested a role of prenatal stress but the linkage was first critically tested more than ten years later in a proper
epidemiological design\textsuperscript{23}. Using data from the ALSPAC study\textsuperscript{196} an association of equal size was found between anxiety before birth and in the postpartum period to emotional problems in the offspring at about four years of age. The maternal scores of distress correlated strongly (Spearman \( r = 0.50 \)) which made it difficult to distinguish between genetic, prenatal and postnatal effects based on the presented analysis.

The early environment is thought to play a role for the development of a depressive personality\textsuperscript{25,27}. The report by O’Conner et al.\textsuperscript{23} and Hines et al. presented above\textsuperscript{160} are both based on the ALSPAC study\textsuperscript{196}. The strength of this study is that they have information about life events as well as psychological distress. The combination of these data may be informative in deciphering the possible causal factors. A high level of cortisol is found in some depressive women\textsuperscript{202,203} but depressed women may only have high levels of stress hormones when stressed by life events\textsuperscript{32}. The unique possibility to include the postpartum mental state of the mother in the analysis of the association between stress in pregnancy and emotional problems in the offspring is a prerequisite for the further investigation of this association.

1.7.6 Behavioural problems in childhood

The findings of Stott of an association between prenatal stress and child behaviours in the offspring is one of the most widely cited in the animal literature\textsuperscript{6}. He observed 153 children during the first four years of their life. Data on different aspects of the pregnancies were collected by interview within the first six month of life. In this sample, Stott identified 14 women, who suffered from ‘personal tension’ during pregnancy mainly due to marital discord. In this group 10 or more than twice as many children were described as hyperactive compared to the ‘non-tense mothers’. Since then a number of reports have been published using deviant child behaviour as endpoints, ranging from a distinct diagnosis to broad definitions of deviant behaviour using psychometric instruments.

Infantile autism is an uncommon (cumulative incidence 0.05%) but very severe psychiatric disease recognised in early childhood and characterised by inferior social interaction, communication and stereotopies\textsuperscript{174}. In 1976 Ward reported that in 59 autistic children about one third reported to have had ‘family discord’ during the pregnancy. He later identified 59 controls to test these clinical observations in a case control design\textsuperscript{204}. There were more mothers who reported psychiatric diagnosis and family discord. The strong association between family discord and autism in the offspring was not controlled for the available maternal psychiatric diagnosis.

ADHD is one of the most common disorders in child and adolescent psychiatry. The prevalence is between 7 and 10\%\textsuperscript{205}. Children with ADHD are characterised by symptoms of poor sustained attention, hyperactivity and impulsivity\textsuperscript{174}. Clements matched 24 children with a diagnosis of ADHD with 24 of their non-ADHD siblings and interviewed their mothers about stressful life events during pregnancy\textsuperscript{206}. Apparently the mothers were three times as likely to have experiences at least one stressful life events in the pregnancy of the child with ADHD. The genetic factors were equally distributed in this study but recall bias may have been a serious problem using this design, because the same mother had to remember stressful life events in two pregnancies knowing the hypothesis of the study. An association between prenatal stress and ADHD was also found by McIntosh et al. in a more classical case-control
The authors collected information on a number of pre- and perinatal factors with the aim to identify factors that predicted the diagnosis of ADHD. One of the findings were a small but statistically significant difference between cases and controls concerning stress in pregnancy, but as many exposures were tested and no confounding control was performed this finding could as well have been due to bias or chance.

Two studies used infant temperament as endpoint. It has been suggested that emotional disorders, conduct disorders and attention/hyperactivity disorders are extreme manifestations of ordinary non-pathological behaviours or temperaments.

In a follow-up design of 170 Dutch mothers recruited in early pregnancy the offspring were examined 3 and 8 months postpartum. The development and temperament was evaluated with a Dutch instrument by a psychologist blinded to the data on prenatal stress. A number of temperamental factors were evaluated and she found that anxiety and perceived stress scores in pregnancy were associated with a decrease in ‘attention regulation’ score. At 3 months of age the anxiety score was also correlated to a low attention score and perceived stress was correlated to a high ‘difficult behaviour’ score. Daily hassles, was their third aspect of stress but was not associated to any of the two temperament scales.

Martin et al. also studied child temperament according to prenatal stress in a follow-up design. In each trimester data was collected by questionnaires concerning anxiety, depression and mood liability. The mothers were contacted again when the child was 6 months and 5 years of age to complete a questionnaire concerning child temperament. The number of women included in the analyses varied from 188 to 665, which made the evaluation of the statistical tests difficult. A modest correlation was apparently found between indices of maternal distress and childhood temperament. The strongest correlation was found between prenatal psychological distress and a temperament factor labelled ‘negative emotionality’ in boys at five years of age, but this could easily be due to chance by the numerous associations tested.

In another Finnish study the Edinburgh Post Partum Depression Scale was used to evaluate maternal depressive symptoms in the last trimester of pregnancy. When the children were 8 years old, the mothers and teachers of the child were asked to complete the same questions concerning child behaviour, the Child Behaviour Checklist, CBCL and the Teachers Report Form, TRF, respectively. A strong association was found between depression in pregnancy and deviant childhood behaviour, when evaluated by the mother with CBCL, but this association was much weaker and statistically insignificant, when the teachers answered the same questions. No association was found between high scores on the EPDS in pregnancy, and a high score on the internalisation scale. The findings of the present study support the findings by others that the mental state of the mother systematically influences the report of behavioural problems in her child. Mothers depressed during pregnancy are expected to be more likely that non-depressed to be depressed 8 years later and information bias is a possible explanation of their findings.

In two recently published reports from the ALSPAC study data on maternal anxiety and depression (EPDS) were collected twice during pregnancy and three times within the first year of the child’s life. A high level of anxiety was defined as the upper 15% of the scores on the Crown Crisp index. The first study aimed to evaluate the role of prenatal anxiety and depression for different aspects of childhood behaviour. They defined...
deviant child behaviour separately for each gender as scores 2 SD above the mean on the Strengths and Difficulties Questionnaire (SDQ), and used the total behaviour score, the scale of attention, conduct and emotional problems respectively. They found strong associations between a high anxiety score, antenatal as well as postnatal with a high score on all three subscales among the offspring. There was a strong maternal intra-individual correlation between high anxiety scores at the different times of measurement. As a consequence some of the associations disappeared, when all data were entered into the same multivariate model. The association between a high anxiety score in 32nd gestational week and a high attention problem score in the offspring remained highly statistically significant if the child was a boy. In both genders anxiety in 32nd gestational week as well as 18 weeks postpartum was associated with emotional problems and conduct problems in the offspring; the risk estimates were nearly identical.

In the second study using these data, the authors attempted to distinguish between the role of prenatal and postnatal depression for child behaviour using the same statistical strategy\textsuperscript{23}. Despite the statistical power, no results were presented to test whether women, who were only anxious during pregnancy, had a higher risk than those only anxious after birth, and in none of these studies a possible dose response association was evaluated.

In conclusion, the studies of prenatal stress and clinical diagnosis were characterised by being small and methodological weak. The risk of recall bias in the case-control studies is considerable. Alone these studies provide very little evidence for a link between stress in pregnancy and the risk of a childhood psychiatric diagnosis. Information bias was probably also a serious problem in the follow-up studies that used behavioural problems as endpoints. Many of these studies used depression or anxiety as exposures. As suggested by the study by Luoma et al.\textsuperscript{213} the association may be much stronger, when the behavioural scores were based on maternal report, than when teachers were used as informants. Women with depressive symptoms tend to misclassify their children for behaviour problems\textsuperscript{216} and differentiated misclassification may very well have biased the association towards higher values.

1.7.7 Other endpoints in childhood
A few other studies evaluated the association between stress during pregnancy and other measures that may be associated with fetal brain development. One study evaluated the association between stress in pregnancy and a small head circumference at birth\textsuperscript{158} and found a considerable difference in neonatal head circumference between the offspring of 70 stressed and 50 unstressed controls; larger than the difference between non-smokers and smokers. A high proportion of smokers were found in the control group and the offspring of these women had surprisingly longer gestations, higher birth weight and probably also larger head circumferences than the base population of neonates they were supposed to represent. The difference in head circumference is therefore likely to be due to a biased selection of controls.

Infantile colic is an infant behaviour of persistent crying during the first 4 month of life. In a German case-control study 37 infants referred to the hospital for persistent crying were compared with 49 without this problem recruited through the local newspaper\textsuperscript{218}. Apparently more than ten times as many of the mothers of persistent criers reported conflicts
with their partners during pregnancy. No attempts were made to control for the available pre- and postnatal factors.

One study evaluated the association between stress during pregnancy and handedness in the offspring. In a sample of 270 students mainly homosexuals and bisexuals mentioned earlier165 handedness was evaluated using hand preference of nine tasks166. The mothers were asked to recall life events during pregnancy. A higher ‘stress-score’ was found more often among mothers of the lefthanders but as mentioned earlier this type of data collection is likely to be biased.

1.8 Conclusions leading to the priorities of the thesis
There are suggestions of associations between stress during pregnancy and various measures of brain functions. On the other hand, evidence of a specific role of stress during pregnancy on fetal brain development is weak. The human and animal studies were characterised by a number of methodological problems. Good epidemiological studies have only recently been published.

At present, there is some evidence of an association between stress during pregnancy and schizophrenia in the offspring. Brain imaging studies suggest that schizophrenia is a progressive disorder that starts developing during pregnancy219,220 and the association to disturbance in the function of the LHPA axis and hippocampal lesions speaks in favour for a role of early stress in the development of this disorder137.

In contrast, the evidence of a role of stress during pregnancy for the development of homosexuality is weak. All studies in this area were methodologically flawed. Homosexuality is only found among primates 221;222, and although animal experiments did show a change in sex typical behaviour in prenatal stressed the extrapolation to human conditions may not be straightforward.

That stress during pregnancy may influence specific behavioural phenotypes is suggested in recent well-conducted studies such as the one by O’Connor et al., who found that anxiety in late pregnancy was associated to a high score on the attention scale of the SDQ in boys 23. This report evaluated the possible role of pre- and early postnatal distress on behaviour of the child. It is generally accepted that the pathogenesis of emotional, conduct and attention disorders are different and their findings support that view. Attention problems were the only scale to be independent of maternal emotions postpartum, and this may motivate further testing of this association.

Brain imaging studies suggest that ADHD is a non progressive disorder that is likely to have developed during the last trimesters of pregnancy219.

The strong association between stress during pregnancy and a lower head circumference at birth, reported by Lou et al., has been widely cited as evidence of a considerable impact of stress on fetal brain development. If their findings are causal it has large public health implications, and it was therefore decided to retest their hypothesis in a follow-up design (Paper III).

The controversy of whether the hormonal changes in the third trimester of pregnancy modulate the physiological response to psychological stress motivated the study of the association between stress and salivary cortisol (Paper II).
The data collection of this thesis included information on a number of endpoints with potential relevance for the hypothesis, but a certain priority was given to attention/hyperactivity problems and mixed-handedness. A more detailed motivation is given below to illustrate the principal considerations of the choice of endpoints. These endpoints are used in paper IV and V respectively.

The high priority of phenotypical behaviour of attention deficit and hyperactivity disorder (ADHD) as endpoint was motivated by the following:

- Experimental studies in rats suggest that prenatal stress and exposure to CRH can influence attention in the offspring\(^{138}\) and that this finding is the most consistent in primates\(^{146,147}\).
- Brain imaging studies suggest a non-progressive disturbance of the fetal brain development, most likely to have been developed in the second or third trimester\(^{219}\).
- Attention and hyperactivity problems are the most common psychiatric disorders, and the identification of potential preventable causes is of public health relevance\(^{205}\).

The high priority of mixed-handedness as an endpoint was motivated by the following:

- Mixed-handedness relates to a well-defined developmental process restricted to the intrauterine development, namely the lateralisation of the brain. Degree of handedness is thought to be determined by early environmental factors\(^{223,224}\) and be relatively uninfluenced by the postnatal environment\(^{225}\). Mixed-Hand preference is related to reduced asymmetry in hemispheric motor representation\(^{226}\) and to a more symmetrical cerebral distribution of language control\(^{227}\).
- Mixed-handedness may be a sensitive marker of deviant brain development, It is a common characteristic of schizophrenia, ADHD, autism and homosexuality\(^{228-231}\) and these groups all tend to have more hemispheric symmetry\(^{232-234}\).
- Animal experiments suggest, that stress may influence lateralisation of the fetal brain\(^{140}\).
2. Aims

The aims of the thesis were to study the associations between
- stress and salivary cortisol during pregnancy
- stress in pregnancy and head circumference at birth
- stress in pregnancy and mixed-handedness in the offspring
- stress in pregnancy and phenotypical behaviour of ADHD
3. Material and methods

3.1 Participants
The original observations in this thesis are based on data from the first years of the Aarhus Birth Cohort (ABCohort), a cohort established in Aarhus in 1989 that covers all births at the Birth Department of Aarhus University Hospital in the years from 1990-99.

Register linkages
The mothers’ civil registration numbers (CPR number) were available from the database of the Perinatal Epidemiological Research Unit (PERU) and were linked to the Danish Civil Registration System (Det Danske CPR register). The CPR numbers of the children of these women were compared with the PERU birthdates to secure the linkage between pregnancy and child. After the completion of this procedure the child was given a unique project number.

The cohort was also linked to the national register of psychiatric diseases to identify children with a psychiatric ICD-10 code. Data was available for outpatient contact since their births and for outpatient contacts since 1994.

Defining the cohort
All children born between 1st of January 1990 and 30th June, whose mothers had any contact with the antenatal department during pregnancy, were eligible. The questionnaire was only sent out to if the child and the mother were alive and living in Denmark in March 2001, in all to parents of 10768 children. Only the information on the children, who participated in the analyses of this thesis, is described. These children fulfilled the following criteria:

- Danish-speaking mothers
- Mothers participated in the first antenatal visit around the 16th gestational weeks at the Department of Obstetrics and Gynaecology, Aarhus University Hospital (about 98% of the total eligible population).

A total of 8036 mother-child pairs fulfilled these criteria, but 84 had requested for address protection from the Danish Civil Registration System, and accordingly 7953 questionnaires were sent out to these participants. Participation is described in section 3.3.1.

Ethics
The project was approved by The Danish Central Scientific Ethical Committee, No. C-2000-15, AA 2000094 and the Danish Data Protection Agency was notified.

3.2 Methods to measure stress during pregnancy
The antenatal and perinatal data collection are described in Paper II-V and elsewhere. The aim of the present section is to focus on the measure of stress, which is the primary exposure of interest in the current thesis.
In the first part of the Aarhus Birth Cohort detailed informations on stress during pregnancy was collected twice during pregnancy, around 16 and 30 weeks of gestation. The 30-item version of the General Health Questionnaire (GHQ-30) was used to evaluate psychological distress during pregnancy (Paper IV). The purpose of this instrument was to evaluate changes in psychological condition. Each item compared the present state with the person’s normal state. Possible answers to each question were: not at all/better than usual, same as usual, worse than usual, and much worse than usual.

The women were also asked about their experience of a number of life events selected by Newton for the use in a pregnant population in 1979. His selection was based on the rating of 160 pregnant women, who scored 59 life events according to the amount of ‘worry, disruption or upheaval’, each event would be expected to cause, if it occurred. The women compared each event to the stress involved with getting married. The women rated each event on a scale from 1-100 with the stress of marriage as the reference (at 50). The women selected 28 events by scoring them above 50, and in the following text the ‘Newton score’ refers to the score minus 50.

In a later publication Newton selected 24 of these question to be ‘objective major life events’ – defined as ‘an event, whose occurrence could be confirmed by a disinterested third party’. For the prenatal data collection in the Aarhus Birth Cohort two of these questions were collapsed and the experience of marital divorce and separation was combined to one question. The 23 events could be rated in the following categories: 1) Not experienced 2) experienced, but with no associated feeling of stress 3) experienced and feelings of minor stress and 4) experienced and feelings of major stress.

![Figure 3.1. Proportion feeling very stressed by event according to Newton score](image-url)
3.2.1 Do objective life events cause a feeling of stress in pregnant women?
The scores from the Newton study were compared with the proportion of women who reported to be very stressed after experiencing the event during pregnancy as shown in figure 3.1. If the selection of events is ‘objective’ according to the definition of Newton one would expect a correlation between these two measures. The exact values for each life event are shown in table 3.1 (Appendix A.2). Although this kind of comparison is somehow untraditional the correlation suggests that the events are ‘objectively’ stressful as defined by Newton above. The events that most Danish women found stressful when they were experienced were in most cases also imagined to be the most stressful by the British women. There was no difference in the perceived stress level at 16 weeks and 30 weeks of gestation. At both occasions 16% of the experienced life events were very stressful whereas 57% and 56% were found to be stressful in 16 weeks and 30 weeks of gestation respectively.

3.2.2 Are objective life events associated with a physiological stress response?
Stress is of particular interest during pregnancy since the foetus may be influenced by the mother’s hormonal response to stress. Little is known about the hormonal stress response during pregnancy. We aimed to study the association between stress and salivary cortisol concentrations in second and third trimester of pregnancy.

In a follow up design salivary cortisol was measured morning and evening in 505 consecutively selected pregnant women. Morning and evening salivary samples were collected twice during pregnancy around 14th and 30th gestational week. At the same time the women reported experience of life events, perceived stress and pregnancy complications.

Stress was associated to higher salivary cortisol in third but not in second trimester of pregnancy. Women who reported high levels of stress in the third trimester had higher evening concentrations of cortisol. Women, who were very stressed by more than one life event had 31% higher evening cortisol concentrations (95% CI: 4-65%) and women, who had late pregnancy complications and were worried about their pregnancy had 39% higher evening cortisol concentration (95% CI: 7-82%). Adjusting for smoking attenuated the associations.

Our findings indicate, that there is an enhanced hormonal reaction to chronic stress in late pregnancy. Summary of Paper I

3.3 General methods of the postnatal data collection
The data collection described in details in this section has been planned and completed within the period of this PhD study from 2000 to 2003. It includes four data collection: The child health questionnaire (parents, March 2001), the hand performance questionnaire (parents, February 2002), the teacher’s questionnaire (teachers, May 2002) and the parents’ attention questionnaire (parents, June 2002).

A follow-up programme including a part of the cohort was conducted together with health nurse Elisabeth Skajaa in 1993 and 1995. Part of this data collection is described in Paper IV and further details are described elsewhere. 3.3.1 The child health questionnaire at 9-11 years of age (appendix Q1)
The aim of the child health questionnaire was not only to collect relevant data for this thesis, but in general to collect data on child health and health problems in general. There were a number of reasons for this decision. First of all, it was considered that, the more general design of the questionnaire would shift the focus from deviant child behaviour (hereby
reducing the risk of information bias) and secondly the more far-reaching scientific potential of collecting data on other aspects of child health in this cohort. Nonetheless, measures of attention problems, handedness and other aspects of child development still had the highest priority.

**Conceptual development**

A small present to the family was sending out with the questionnaire. A package of three versions of the 3-dimensional jigsaws called Happy Cubes® ([www.cricro.com](http://www.cricro.com)) was chosen because it was lightweight and therefore relatively cheap to send. The toy was expected to stimulate a common family activity and had been very popular in the late 90’s in Denmark (but unknown to most children between 9 and 11 years of age).

The parents were invited to participate in the investigation in an accompanying letter of information where they were also given the opportunity to answer the questionnaire by phone. A brief account of the investigation was given in this letter. The parents were informed that more detailed information was made available on the internet homepage of the project [www.aarhus-born.dk](http://www.aarhus-born.dk). They were also offered a ‘one-year later’ newsletter and to be included in an email newsletter service.

The parents had the possibility to contact the research group by mail, email or telephone. Within the first two weeks of the distribution of the questionnaires a telephone hotline was offered, and was also open in the weekends. From late afternoon an answering machine was connected to this line.

The general idea was to use the child health questionnaire as a platform for further investigation, including further contact to the parents, the school and the health system. The research group therefore requested special permission to additionally contact the parents. The parents were also asked for signed consent allowing the research group to contact the child’s teachers and to collect existing data from the health authorities and the educational system.

It was decided to focus on phenotypes relevant to particular disorders than on discrete clinical diagnosis.

**Questions on child development and behaviours**

Twelve questions were selected based on a recent Danish study of the Danish version of the Child Behaviour Checklist (CBCL) to evaluate behaviour relevant for attention problems as described in section 3.2.1. The question of hand preference was primarily based on the largest epidemiological study so far using handedness as endpoint and is further described in section 3.1.

Other aspects of child behaviour and cognitive function were included in the questionnaire and including 48 questions. The three response options from the CBCL mentioned above were used for all these questions. The questions were designed to identify children with empathic problems (including Aspergers syndrome), Tourettes syndrome, obsessive compulsive disorder and emotional problems. These questions were developed with inspiration from existing instruments although some of the questions were formulated to balance the negatively loaded wording of the CBCL. The questions of cognitive function included items of memory function, impressive and expressive language. These were also mainly positively-loaded reformulations of questions constructed for clinical populations.
and developed in collaboration with specialists in language development and child psychology.

Questions on physical child health and background factors
Data on atopic symptoms were collected using well established selections of questions. Questions on other aspects of child health were developed with the help of medical doctors with extensive experience in the specific areas of interest. Retrospective information on the first 6 years of the child’s life included breastfeeding, asthmatic bronchitis, speech development, hospitalisation, recurrent otitis media and medication. Actual information included weight, height, leisure activities, physical activity, school performance and problems, handicaps and chronic diseases, hearing, vision, headaches, abdominal pains, enuresis and medication.

The questionnaire also included information on parental history of attention and school problems, allergy, smoking, weekly working hours, education and socio-economic information. Information on day care in infancy and the toddler’s age, infancy exposure to pets and cigarette smoke were also collected.

Preparatory work
The questions were analysed by a language psychologist who had specialised in wording of questionnaires. Specific questions were added to the questionnaire to detect different interpretations of some of the questions of the ADHD problem scale (see section VI). The questionnaire was also sent to two mothers with dyslexia in the main cohort to check if any of the sentences gave them difficulties. The questionnaires were revised based on this work.

A pilot study was conducted with 100 parents during the summer of 2000. These parents all participated in the very first part of the Aarhus Birth cohort, their children having been born in the last months of 1989. The questionnaire was immediately returned by 54 parents. The rest were contacted by telephone after two weeks, and 18 parents subsequently returned the questionnaire after this reminder. The 72 families were contacted by telephone for a semi-structured interview. The questionnaires had been inspected beforehand, and the participants had been requested to comment on any problems with completing the questionnaire. Some of the conclusions of these interviews were as follows:

- The Happy Cubes had been a success in the majority of the families, but none of the parents thought that this ‘present’ had influenced their willingness to participate
- About one third of the parents believed that they would use the project’s homepage to get further information about the project
- The length of the questionnaire was acceptable. The vast majority of the parents stated that it had taken between 15 and 30 minutes to complete the questionnaire (range 10-60 minutes).
- The questions of the ADHD score were specifically evaluated. Five and two mothers were not certain about the interpretation of ‘impulsive’ and ‘hyperactive’, respectively
- One mother preferred to answer the questionnaire by phone
It was decided to establish a homepage and to send the Happy Cubes out with the questionnaire. The questionnaire was revised based on this pilot study and the final version used on the whole cohort can be found as Appendix 1a. The questions in this questionnaire will be referred to as Q1-Q169.

Logistics and participation
The child health questionnaires were packed over a period of a month and sent out in two portions on the 15th of March and the 28th of March 2001. Of the 7953 children, 4355 returned the questionnaires (54 %). The Central Scientific Ethical Committee permitted only one reminder and the non-responders were contacted after 2 weeks by telephone or post. The majority of the families were identified by linking to TDC’s (Danish telecommunication company) register of telephone numbers. Six university students with experience in telephone interviewing were engaged to contact the non-responders by phone. These interviewers had contact with more than 2000 families in April-May 2001. After this procedure was terminated, 5841 had returned the questionnaire (74%), and of those, 4940 also gave us permission to contact their child’s teachers (and to collect existing data from the health care authorities and school educational systems). Eight questionnaires were filled out during a telephone interview.

There were 16%, who actively refused to participate by mail (9%) or in relation to the telephonic contact (7%). When reminded by telephone, 4% promised to return the questionnaire, but never did so and 7% did not react to the mailed reminder.

Data preparation
The questionnaires were self-administered. The ticked reply box contained a printed number and could be directly keyed. A few questions invited a textual reply and some participants also amplified a ticked response with comments. This text was registered and coded. A summary was coded in cases of extensive text after discussion with the author. The basic questionnaire was coded by two experienced members of the staff at the Perinatal Epidemiological Research Unit. The first 200 questionnaires were coded independently twice by the two staff members and errors evaluated. After completion of the coding procedure, 15% of these questionnaires were coded again and we found no serious errors within this sample. All data were range-checked and edited for logical errors.

3.3.2 The hand performance questionnaire (appendix Q2)
In February 2002, a part of the cohort was contacted again and asked to complete a hand performance questionnaire. The aim of this data collection was

- To evaluate the association between the scoring methods of the hand preference questions used in epidemiological studies, and relative hand performance using validated questionnaires and a simple hand performance task.
- to retest the findings from Paper IV using more well-defined indicators of laterality for the child as well as the parents

We identified 3150 families where the parents lived together, and who had responded to both pregnancy questionnaires as well as the child health questionnaire. The hand performance questionnaires were sent to these families (Appendix 1b) and the child and both parents were
asked to complete a short questionnaire. The hand performance was evaluated in two ways. First, they were asked to fill in Annett’s handedness questionnaire, which is probably the most widely used for the evaluation of handedness in adolescents and adults. Children do not normally have any experience with some of these tasks, and it was stressed that the participants should try to carry out the tasks, if they were uncertain as to which hand that best performed the task best. These questions were supplemented with questions on eye and foot preference in different tasks.

The ‘check of squares’ hand performance task was also used. It has previously been used in another large population study. The families received a plastic “hour glass along with the three questionnaires. The sand in the hour glass took approximately one minute to run through. The participants were asked to check as many as the 200 boxes as they could with a pencil in one minute. They were asked to perform two tests with each hand. We also asked the parents and the child to draw an outline of their hand to get an estimate of relative finger lengths. (relative finger length is associated to autism and may reflect prenatal hormonal factors).

We received completed questionnaires from 2334 families (74%). Unfortunately, the ‘sand’ in the hour glasses was affected by the humid weather conditions, thus decreasing their precision. We examined 50 of these glasses and found that they measured about one minute (+/- 10 seconds), but that about 4% had an even higher variation. The questionnaires were coded as described for the basic questionnaire.

3.3.3 The parents’ attention questionnaire (appendix Q3)

Nearly all the parents who returned the child health questionnaire (99%) gave permission to further contact them for collection of supplementary information. A newsletter and a short questionnaire were sent to the families, following a renewed linkage to the central Danish civil personal register in May 2002. The aim of the questionnaire was to collect further information on attention disorder and co-existing behavioural problems, such as conduct disorders, emotional problems and social/peer relation problems. It was decided to use a newly developed instrument, the ‘Strengths and Difficulties Questionnaire (SDQ)’. After translation into Danish (Paper II), the SDQ-Dan was included in the questionnaire. Both parents were also asked the five attention scale questions of this instrument, but retrospectively formulated to cover their primary school period. Approximately 88% of the participants returned this questionnaire after two postal reminders. The parent’s attention questionnaires were entered by scanning at ‘The Danish Epidemiological Science Centre’ in Copenhagen.

3.3.4 The teachers’ questionnaire (appendix Q4)

A questionnaire was sent to the children’s teachers in April 2002. This questionnaire consisted of the teacher’s version of the SDQ-Dan. On a five point scale, the teachers were also asked to compare the school performance of the child with typical pupils of the same age with respect to reading, spelling, maths, biology, English, history and athletics/sport. In the same manner, they were asked to evaluate the child concerning with respect to work effort, behaviour, general learning ability, concentration, mood, formulation ability, gross and fine motor control, social function and activity level. A single item of the diagnostic extension to
the SDQ, the ‘development and well being assessment’ (DAWBA) was also included to evaluate the attention span of the child.

The teachers of children in the schools of the Municipality of Aarhus were identified based on a central register (Kommune data) and the 452 teachers, who participated in the study, were paid for their work with the questionnaires through a supplement to their salary administered by the local school system authorities. Teachers of children outside the Municipality of Aarhus and in private schools could not be identified and remunerated this way. Contact to these teachers was based on a combination of parental information and linkage to the TDC (Danish Telecommunication Company) register. The teachers outside the municipality of Aarhus, who participated in the study, were given a gift voucher for each questionnaire, if they filled out more than three questionnaires (N=126). All participating teachers outside the Municipality of Aarhus (N=1379) participated in a lottery to win a holiday worth 10,000 DKK. After two reminders, we had received completed questionnaires from 4250 i.e. 86% of the children, whose parents had given us their permission to contact the teachers.

The questionnaires were coded as described for the basic questionnaire, but all teachers’ questionnaires were coded twice.
4. Descriptive results: handedness and attention problems

This section presents the specific methods used to evaluate attention problems and handedness of the children in this cohort and selected descriptive results.

4.1 Measurement of handedness in childhood studies

The question of handedness has been the subject of scientific debate and it is thought that genetic as well as early environmental factors may play a role. Recent findings of a higher proportion of mixed handedness in patients with schizophrenia, ADHD and autism have further stimulated this interest. Most hand preference studies in adult populations use the same questionnaires, but there is much less consistency in children. Hand preference questions are convenient and suitable as parts of larger questionnaires used in epidemiological settings, but the categorisation of handedness is largely dependent on the number of items and the scoring method. There is so far no common standard of designating handedness in epidemiological studies of childhood. This was one of the reasons for collection further data on indicators of laterality.

**Preliminary results**

Annett’s classification of handedness (Annett) in seven categories was used. Two of these classes (3 and 4) are labelled strongly mixed handed and 8% of the children were in this group. With this definition as the golden standard, the 5-item scoring method in Paper IV only identified 29% of the strong mixed handed children. When alternatively the 11-item scoring method from the largest of the previous studies linking the prenatal environment and handedness of the child was used, 34% were classified correctly.

![Figure 4.1. Comparison of the three methods to define mixed-handed children. Distribution on 20 groups of equal size based on relative hand performance (N=2328).](image)

The relative hand performance was calculated (right-left/right+left) and these scores were ranked and categorised into 20 equal groups as has been done in previous studies. The distribution of mixed-handed children according to the scoring methods is shown in...
Figure 4.1. The three definitions of mixed-handedness all seemed to be likely to have a relative hand performance around zero, but there was an overrepresentation in the group of children with a slightly better left performance. Of the children classified as mixed handed by Annett, 30% were in this group, whereas the remaining 70% were nearly equally distributed on the remaining groups.

In figure 4.2 the distribution of the relative hand skills as numbers of square checking is shown for those who by the Annett definition were not mixed-handed (N=2149) and those who were (N=179). The mixed-handed children seem to be a more equal mixture of children with right and left dominated hand performance more than a distinct population with equal right and left performance.

Figure 4.2. Relative hand performance in strong handed (N=2149) and mixed-handed (N=179) respectively.

4.2 Measurement of attention and hyperactivity problems in epidemiological studies

The Attention-Deficit Hyperactivity Disorder (ADHD) is one of the most common psychiatric disorders during childhood and adolescent life. ADHD has an estimated prevalence between 4 and 12% in 6-12 year old children in Europe and the United States. This behaviour may start in preschool age, but ADHD is usually not diagnosed before early school age, where the behaviour interferes with learning. Children with ADHD require large resources from the school systems, the health care system and can be a burden to the families. ADHD is a DSM-IV diagnosis and corresponds to the ICD-10 diagnosis hyperkinetic disorder (HKD), although the diagnostic criteria are slightly different. Both diagnoses include the symptoms attention problems, hyperactivity and impulsivity. The ICD-10 system is used in the Danish hospital registers, but ADHD is favoured here because this is the diagnosis most often used in the literature.

Behavioural characteristics relevant for the diagnosis of ADHD were evaluated at three occasions. In the child health questionnaire completed by the parents at 9-11 years of age a selection of questions from the CBCL was used and at 10-12 years the parents as well as the teachers completed the SDQ. In the present section, the uses of these instruments are motivated and the distributions of the scores of the instruments are compared to previous studies.
4.2.1 The Child Behaviour Checklist (CBCL)

By the time the basic questionnaire was developed, the Child Behaviour Checklist (CBCL) appeared to be the only reasonable method of identifying children who fulfilled the diagnostic criteria for ADHD. The questionnaire had recently been translated into Danish\textsuperscript{272}, and used in a population of Danish children. Based on latent trait analysis\textsuperscript{273}, a selection of 12 questions, the ADHD problem scale, had been identified as the most efficient screening questions for ADHD\textsuperscript{249}. A recent study has confirmed this finding\textsuperscript{274}.

The complete CBCL consists of 118 questions concerning different aspects of deviant child behaviour. The large number of questions combined with the negative formulations of the questions made it unsuitable for use in a large questionnaire covering many other health aspects. As a consequence, we only used the 12 questions identified by Bilenberg\textsuperscript{249}, and mixed these questions with 36 more positively formulated questions related to behaviour and development. This scale was chosen instead of the original attention scale\textsuperscript{214}, because the items of CBCL with relevance for an ADHD diagnosis have displayed very different properties in various cultural settings. In a comparison between a Dutch, an American and an Australian sample, only three items overlapped when the best combination of items to identify ADHD was identified in the samples\textsuperscript{275}.

The original formulation of the official Danish version of the CBCL was used\textsuperscript{276}, but the review by a language psychologist as well as the pilot study suggested that some of the questions, at least in Danish, could be conceived as a positive as well as a negative statement. This was especially apparent concerning the terms ‘impulsive’ and ‘hyperactive’ (Q74 and Q92). In collaboration with the language psychologist questions to distinguish between these interpretations were designed.

Two items were included to evaluate the interpretation of the statement: ‘impulsive or acts without thinking’ (Q92): ‘Is spontaneous, has a lot of initiative’ (Q85) and ‘is thoughtless and ‘incautious’ (Q105). Among the 374 who answered ‘very true’ to the statement ‘impulsive or acts without thinking’ (Q92), 142 (38%) at the same time answered ‘very true’ to the statement: ‘Is spontaneous, has a lot of initiative’ (Q85) and ‘not true’ to the statement: ‘is thoughtless and incautious’ (Q105).

Two items were added to evaluate the interpretation of the statement: ’can’t sit still or is hyperactive’ (Q74): ‘Is restless and fidgety’ (Q66) and ‘is in good form and energetic’ (Q104). Among the 142 who answered ‘very true’ to the statement: ‘can’t sit still or is hyperactive’ (Q74), 17 (12%) at the same time answered ‘not true’ to the question: ‘Is restless and fidgety’ (Q66) and ‘very true’ to the statement: ‘is in good form and energetic’ (Q104).

Descriptive results

The full ADHD problem score was available for 70% of the children, and 8% of the children had a score above 5. Of the 22 children with a hyperkinetic syndrome diagnosis (F90.0) 20 had a score above 5. The remaining two had a score of 5, and one was on central stimulation medication (Ritalin®).

In figure 4.3 the distribution of the ADHD problem score is shown for the current sample and the original sample where the score was developed (with permission from Niels Bilenberg) which consisted of 742 children between 4 and 16 years of age\textsuperscript{249},
4.2.2 The Strength and Difficulties Questionnaire (SDQ)

By the time the basic questionnaire was developed the ‘Strength and Difficulties Questionnaire (SDQ)’ there was no acknowledged Danish version. As a consequence the use of this instrument for the teachers’ questionnaire implicated the organisation of a translation acknowledged by Robert Goodman, who developed the original version and the organisation of a supplementary data collection from the parents. The scientific reasons for using SDQ instead of CBCL were found to be strong enough to justify this work. Two recent reports suggested that the SDQ was better to identify ADHD cases than CBCL and was more acceptable to non-clinical populations. The SDQ was shorter, had relevant scales for evaluating co-morbidity in children with attention problems and included a section evaluating the impact of the problems on daily life situations of the child (this information is part of the diagnosis of ADHD and HKD). The details of the translation process are described in Paper II and of the data collection in section 3.3.3 and 3.3.4.

Descriptive results

The scores of the children, where parents’ as well as teachers’ SDQ data were available for 3823 children and were compared with a sample of 1990 children aged 10-12 years from the UK (with permission from Robert Goodman) and is shown in figure 4.3. The British children had generally higher scores than the Danish children, the largest difference was found in the parents’ scores. The algorithm to identify ADHD cases is based on a combination of symptoms and impact evaluated by the teacher and the parents. It classifies children as likely, probable and unlikely to have the disorder (www.sdqinfo.com). In the Danish sample, we found 4% probable and 2% likely ADHD cases compared to 7% and 3% respectively in the UK sample. In the 3823 children in the Danish sample 8 children had a diagnosis of
hyperkinetic syndrome (F90.0). Five of these were classified as likely by this algorithm and 3 as probable.

Figure 4.4. **Comparison of the attention scores of 3823 Danish (squares) and 1990 English 10-12 year old children. Parents’ score is shown in the upper figure and teachers’ in the lower figure.**
5. Analytic results (summaries of Paper III-IV)

5.1 Stressful life events in pregnancy and head circumference at birth
A strong association between stress in pregnancy and a small head circumference in the offspring at birth was reported in 1994. Although this was an important finding, it has never been replicated. In a follow up study of 4225 women with singleton pregnancies, we collected information on life events twice during pregnancy and measured head circumference shortly after birth following standard procedures. We found no association between experienced or perceived stress by life events during pregnancy and head circumference in the offspring. In conclusion stress in pregnancy may influence fetal brain development in many ways, but we found no support for an effect on the size of the brain as measured by head circumference at birth. Summary of Paper III

5.2 Psychological factors in Pregnancy and Mixed-handedness in the offspring
Animal studies suggest that psychological factors may interfere with the development of brain asymmetry during gestation. We evaluated whether psychological exposures in pregnancy was associated with mixed-handedness in the offspring. In a follow up design, 824 Danish-speaking women with singleton pregnancies provided information on psychological distress and the occurrence of life events in early second and third trimester of pregnancy. The handedness of the child was based on the maternal report when the child was 3½ years of age. Among the 419 boys and 405 girls 7% and 5% respectively were mixed-handed, whereas mixed-handedness was found in 3% of the parents.

Psychological distress in the third trimester as well as stressful life events were related to a higher prevalence of mixed-handedness in the offspring in a dose response pattern. About 16% of the women reported more than one life event in third trimester of pregnancy and among the offspring of these women 11% were mixed-handed (OR=2.3; 95% CI: 1.2-4.4). Women, who at the same time reported a high level of distress and stressful life events, had a three to four fold higher prevalence of mixed-handedness in the offspring. Summary of Paper IV

5.3 Stress during pregnancy and attention deficit/hyperactivity problems
Animal studies suggest that stress in pregnancy may cause behavioural problems in the offspring that resemble the Attention Deficit Hyperactivity Disorder (ADHD). The influence of hormonal response to stress on the fetal brain is a biological possibility, but human evidence for such an effect is sparse.

We investigated the association between stress in pregnancy and ADHD-related behaviour in childhood. We conducted a follow-up study of 4031 Danish-speaking women who provided information on life events in the first and second trimester of pregnancy. Information on behaviour relevant for the diagnosis of ADHD was collected when the children were 9 to 11 years of age by questionnaires sent to the parents. We used the ‘ADHD
problem score’ based on questions from the Child Behaviour Checklist Women, who reported stressful life events during pregnancy, gave birth to children with a higher risk of a high ADHD problem score, especially in boys.

The number of life events the mother experienced in the second trimester was associated with a high ADHD score (test for trend, P<0.01). Stressful life events in the first trimester of pregnancy were not associated with a high ADHD score in boys. The mothers of girls who reported more than one life event in the first as well as the second trimester were more likely to have a high ADHD score (OR=2.3; 95% CI: 1.3-4.2).

Stress in pregnancy was associated with attention problems in the offspring.

Summary of Paper V
6. Discussion

The overall idea of this thesis was to test if maternal exposure to stress during pregnancy can influence fetal brain development. The hypothesised biological mechanism was a stress mediated biological influence on fetal brain development. One of the strengths of this study was the follow-up design including the use of the same measures of stress twice during pregnancy. The data collection also included information on potential confounding factors, which made it possible to adjust the analyses for a number of lifestyle factors related to stress.

A possible weakness of the studies was the risk of bias related to the measures of stress, handedness and ADHD like behaviour. A focused discussion is given in the papers about this and other potential sources of bias. In the following section, a more general discussion of the implications of the findings, and the general methodological problems in measuring stress and behaviour is given.

6.1 Stress and cortisol during pregnancy

The principal measure of stress in the studies was the maternal report of life events in the first and second trimester of pregnancy. In Paper I we evaluated the association between the experience of life events and salivary cortisol in a cohort of 505 women at the time, when the questionnaires were completed. We found no association between experience of stressful life events and salivary cortisol in the first part of pregnancy, but this measure of stress was statistically significant related to a higher evening salivary cortisol level in the third trimester of pregnancy. The cortisol reaction to smoking was similar. These findings suggest that the hormonal reaction to stress (and smoking) is enhanced in the third trimester of pregnancy, which may be due to a diminished negative feedback of the maternal LHPA axis or interference with placental production of CRH.

The study added empirical substance to the discussion of how the late pregnancy changes in the regulation of the LHPA axis influence the physiological response to psychological stress. The cortisol response to cold water has been found to be dampened just before birth. This discrepancy in findings may be due to the different levels that regulates this kind of physical stress and psychological stress. The reaction to the latter include the prefrontal cortex and the limbic systems, whereas the reaction to cold water is executed at a hypothalamic level with a stronger involvement of the SNS.

6.2 Stress during pregnancy and childhood behaviours

Papers III-V evaluated the association between stress and measures of brain size and function. We found no association between stress during pregnancy and head circumference at birth, but stress during second trimester of pregnancy was associated to mixed-handedness at 3½ years as well as a high ADHD problem score at 9-11 years of age. These papers contributed to the knowledge of the association between maternal stress during pregnancy and fetal brain development.

The previous documentation of an association between antenatal stress and child behaviour was of variable quality. Those with specific endpoints were small and
methodologically weak\textsuperscript{162,201,204,206} and the methodologically stronger studies used very broad measures of child behaviour\textsuperscript{23,29,210,213} and did not have an a priori expectation as to which phenotypes were the most relevant in relation to a possible role of antenatal stress.

Deviant temperament, emotional problems, conduct disorders and attention and hyperactivity disorders may be influenced by shared genetic factors, but the possible causal role of early environmental factors are unlikely to be common. In one study antenatal and postpartum anxiety was equally associated to conduct as well as emotional problems in the child, which was not the case for attention problems\textsuperscript{23}. They found that maternal anxiety evaluated in week 32 had the strongest association to a high attention problem score on the SDQ\textsuperscript{23}. This suggests a different role of the early environment in these disorders and is compatible with the relatively distinct structural changes in brains of children with ADHD\textsuperscript{219} and more inconsistent findings in patients with anxiety\textsuperscript{281} and depression\textsuperscript{282,283}. The brain imaging findings suggest that ADHD is a non progressive disorder, which probably is established in the second or third trimester of pregnancy\textsuperscript{87,219}.

Our findings corroborate these findings, since the strong association between stress in the second trimester and mixed-handedness as well as ADHD like behaviour was confirmed. In both our studies there was a dose response like association but we were not able to identify a specific threshold for the effect.

Both studies also found the strongest association between stress and ADHD-like behaviour in boys. A higher proportion of high ADHD scores were found in girls, whose mother had experienced life events in early as well as mid pregnancy (Paper V). This may be a random finding, but could reflect the differences in timing of brain development\textsuperscript{284}, interaction with sex hormones in the brain\textsuperscript{285} or more stress vulnerable brains in boys, as suggested by the study of other exposures\textsuperscript{286}.

Apart from specific structural changes in the brain, children with ADHD have slightly smaller brains\textsuperscript{219,287}. We found that children with a high ADHD problem score and those with a diagnosis of hyperkinetic disorder had slightly smaller head circumference at birth than their peers, but this difference disappeared after adjustment for gestational age at birth.

Our findings suggest that children exposed to stress in the second trimester have a higher prevalence of mixed-handed as well as a high ADHD problem score. Non-right handedness has been found to occur more often in children with ADHD\textsuperscript{230}, and the brain of these children has also been found to be more symmetric\textsuperscript{234}.

When the definition by Kieler et al.\textsuperscript{250} were used, 18% of the children with a high ADHD problem score were mixed-handed compared to 11% of those with a lower score (OR=1.9; 95% CI: 1.4-2.5). This may be due to a common genetic factor or to the exposure of stress, which may be ruled out by evaluating this association stratified for parental disposition and stress.

### 6.3 The measurement of stress

In the studies of the current thesis, we used the experience of life events as the main indicator of stress. We used an a priori definition of events based on the life event scale of Holmes and Rahe\textsuperscript{288}, modified in the late 1970’s.\textsuperscript{178} Newton et al. excluded the events irrelevant for the pregnant woman (such as inability to get pregnant). This scale, which was developed more
than 10 years before the use in our studies, may have been somewhat outdated. The importance of events related to death, diseases among close relatives and marital conflicts are probably relatively unchanged over time, whereas the situation of women in relation to work and financial matters is not as it was in the 60-70’s necessarily linked to the husband’s situation. We might therefore have missed some of the life events linked to the working situation of the woman. The scales used in other large cohort studies\textsuperscript{160} have the same problem as they are based on the same scales\textsuperscript{289}

The findings from Paper I and section 3 suggest that this measure of stress do have some psychological as well as biological relevance. Despite the limitation of small numbers the rating of events from the original work of Newton correlated well with the level of stress among the women, who experienced the event during pregnancy. In our study, we did not find support for the findings of Glynn et al that potential stressful events are perceived less stressful in the third trimester (described in section 3.1).

The study presented in Paper I was not designed to evaluate the physiological response to stress and the unknown and variable temporal distance between the experienced events and the single day measurement of salivary cortisol limits the probability of detecting these associations. To identify an indicator of stress that correlates well with the physiological response in most people seems Utopian, but a more specifically designed study to describe the association between the various components of stress is not unrealistic and is needed to develop the methodology.

Even though we were not able to document a biological stress effect, there is reason to believe that life events as measures of stress are relevant for evaluating the hypothesis of the thesis. Depressed women may only have higher serum cortisol concentration when exposed to stressful life events\textsuperscript{32}, and the association between stressful life events and cortisol level is relatively well documented\textsuperscript{30;31}. For future investigations, a weighted score\textsuperscript{290} based on physiological response of an updated list of life events with information of perceived stress may be a more sensitive measure of stress.

6.4 The measurement of handedness
This thesis has introduced mixed-handedness as an endpoint of relevance for fetal brain development. The idea that atypical handedness may reflect an environmental influence is far from new, but the methodology of evaluating handedness in epidemiological studies of children is not well developed. In epidemiological studies, left handedness has been suggested as an indicator of neurotoxic exposure in pregnancy\textsuperscript{291}, and left handedness as well as non-right handedness has been used in this respect.

The question, what determines handedness has been a matter of scientific discussion for the last 50 years. The matter of controversy has primarily been direction of handedness and not so much degree of laterality\textsuperscript{224;292-295}. At present most people with interest in this field agree, that direction of handedness is somehow genetically determined\textsuperscript{224;294}. This may not be the case for degree of handedness and as a consequence the focus on left handedness as ‘pathological’ handedness has changed to more attention on the degree of handedness or mixed-handedness\textsuperscript{223}. 
As mentioned in section 1.8, mixed-handedness is more common among a number of psychiatric patients, who might share other phenotypes. These groups of patients also have more symmetric brains, which is in line with the findings that among mixed-handed the majority have a bilateral cerebral representation of language function, which is unilaterally represented in more than 80% of right and lefthanders.227

The main methodological problem is that there is no established definition of how to define mixed-handedness. Mixed-handedness can be defined broadly and narrowly and based on hand preference in a number of daily tasks or by relative hand performance. Broad and narrow definitions of mixed-handedness relate to different brain pathologies and it is not known exactly how they relate to neurophysiology.296

As described in Paper IV, we found a strong association between stress in late pregnancy and mixed-handedness at the age of 3½ years. This is probably the first study to report this association in a proper epidemiological design. The association between brain pathology and mixed-handedness may be stronger in childhood, maybe because some of the children are mixed-handed due to a delay in brain maturation.257;297 Still the validity of the hand preference questionnaire used in the study of paper IV is unknown, and a retesting of our findings using more well tested measures motivated the further data collection of handedness described in section 4.

The Annett handedness questionnaire is probably the well-documented questionnaire for use in adult populations, but not all the tasks are normally performed by children and therefore impossible to answer based on recall. As a consequence, the children (and their parents) were asked to perform the tasks they were not used to before answering the questionnaire.

To identify a test of hand performance to be used in larger populations is difficult. Hand performance measures for the use in epidemiology are all ‘paper and pencil methods’ and have been criticised for not being able to evaluate the degree of handedness well.298 The argument is that they test the relative use of the two hands for well-known skills, and as a consequence the ‘other’ hand will perform relatively less well than in unfamiliar tasks. Prolonged practice has been shown to increase performance of both hands, but not to affect the relative hand performance.299 Whether this applies for the fine motor skills of using a pencil is not known.

In any case from about 5-6 years of age the distribution of the relative performance of these tasks are bimodal and not continuous, as shown this study (fig 4.1) as well as in a number of other studies.255;297;300 Unfortunately tests as pegmoving and finger tapping, that are thought to be more sensitive to the continuous nature of handedness are not easily applicable in large epidemiological settings. This presumed distribution of relative performance based on the ‘check a box’ method used in this study may alternatively be revealed by combining hand performance with relative performance.256

Even this level of data collection on handedness is not likely to work when a collection of hand preference questions are used as part of a larger questionnaire. One of the future aspects of this thesis will therefore be to develop the most valid combination and weighting of hand preference questions to identify mixed-handedness in a community sample. The relevance of the use of mixed-handedness or relative hand performance as endpoints in
epidemiological studies seems obvious, but this methodological work seems necessary to enhance comparability and neuropsychological relevance.

6.5 The measurement of child behaviour

Until recently epidemiological studies of child and adolescent psychiatry focused mainly on diagnosis and descriptive epidemiology, which may be the reason why it has been difficult to rule out the role of genetic and early environmental factors in the development of these behaviours. So far the genetic mapping of distinct diagnostic entities such as autism and ADHD has been disappointing, but recent findings suggest that the susceptible genes may be more unspecific and as expected from family studies, cut across the disorders. The phenotypes of these disorders may be overlapping, and many childhood disorders including attention problems and hyperactivity is thought to be a continuous phenomenon more than discrete entities.

As it is also well recognised that clinical psychiatric diagnosis may be influenced by a number of factors that may bias the association to exposures of interest, it was decided to focus on phenotypes instead of diagnosis in the planning of the data collection of this thesis. It appeared that this was also the decision when the designs of a very detailed follow-up study of children of the same years were planned.

The use of psychometric instruments such as CBCL and SDQ may introduce other kinds of bias. In Paper V we used a high score on the ADHD problem scale based on questions from CBCL as the endpoint. CBCL is a questionnaire to be completed by parents, and the questions concerning attention and hyperactivity problems are sensitive to cultural factors. For this reason a score based on Danish children was chosen to be used in the child health questionnaire when the children of the cohort were 9-11 years old. The primary reason for using the original CBCL questions was that there was some experience of its use in Denmark and its wide distribution (translated to more that 60 languages), which would make it easy to specifically retest our findings. The distribution of the scores of the original sample and in our cohort as shown in figure 5.3 were quite close, as would be expected even though some would say that Odense and Aarhus are different cultural settings.

In contrast, the comparison between the SDQ scores shown in figure 5.4 suggests that SDQ scores are generally lower in Denmark than in the UK. This finding is not unique since the same shift is observed in Finland, Sweden, and Norway (personal communication Einar Heirvang, Hans Smedje, and Andre Sourander) and it can be speculated that Scandinavian parents’ attitude to child behaviour is less problem oriented than UK parents. The CBCL and the SDQ are the most widely used instruments in general populations and the findings from this study support the findings by Heubeck that psychometric instruments of child behaviour are dependent on the cultural settings. Unless the cultural differences are related to the exposure of interest these differences are not expected to introduce information bias. Still, it may motivate the use of common as well as distribution based cut-off levels when comparing the results based on different cultural settings.

The content validity of the ADHD problem scale and the SDQ is (according to child and adolescent psychiatrists) satisfactory. Anyhow, the impression from the development and pilot testing of the child health questionnaire that some of the questions could be understood
differently was supported by the responses to the supplementary questions as described in section 5.2. The combination of these answers did not necessarily indicate that the questions were misunderstood, but revealed that there are different levels of interpreting the description. A high ADHD problem score is defined by the report of 5 of the 12 symptoms, and these variations in interpretations may only have moved a minority of children above this cut off level. Anyhow, these problems were kept in mind when the Danish translation of SDQ was planned, and some effort was made to combine expertise of language psychology and child psychiatry during this process.

Another important aspect of collecting information on phenotypical behaviour in children is the acceptability of the instruments used. The majority of the questionnaires screening for deviant child behaviour consist of large numbers of negatively formulated questions. The probably most widely used CBCL consists of 118 such questions\textsuperscript{214} and most other available instruments are like this\textsuperscript{252,313}, and some even seem difficult to interpret without professional assistance\textsuperscript{251}. Maybe the explanation is that most of these instruments have not originally been developed for the use in community samples. The general impression from the contact with a considerable number of parents in relation to the data collection described here, is that questionnaires screening for deviant child behaviour should be short, not entirely negative loaded and formulated simply to give valid information. The SDQ was probably the first child psychiatric screening instrument to fulfil these demands, and has also been shown to be more acceptable than the CBCL\textsuperscript{278}. The idea of a more equal use of positively and negatively worded questions for the use in community samples is finally being accepted and is illustrated by the fifth version of another widely used instrument revised during the last 20 years. The wording of the SNAP-IV\textsuperscript{314} has been reversed to become entirely positively formulated (SWAN). This shift may be of value scientifically\textsuperscript{314}, and prove to extract more valid information from community samples, where only a minority are parents of children with psychiatric problems.

The most serious risk of information bias in follow up studies using maternal reports to evaluate behavioural phenotypes in the child is probably related to maternal psychological well being. Maternal depressive symptoms influence the mother’s evaluation of the child\textsuperscript{216} and this may particularly be a problem in studies using depression and anxiety during pregnancy as an exposure\textsuperscript{23,213}. The importance of this problem will depend on the correlation between the exposure used during pregnancy and maternal psychological well being when the child is evaluated. The correlation is dependent of the temporal distance\textsuperscript{23,29} and evaluations of the child in early life would be expected to be more sensitive to this kind of bias. The impact of this bias is illustrated by the considerable differences in the association found between depressive symptoms during pregnancy and childhood behaviour problems based on mothers and teachers report respectively\textsuperscript{213}. This effect may partly be caused by a higher vulnerability to the stress caused by having a child with behaviour problems\textsuperscript{271}. To reduce the risk of this kind of bias ‘objective’ life events was used as the primary exposure in the studies of this thesis. As described in section 4.4, data on child behaviour was also collected from teachers. Future analyses of our data of the associations between subjective and objective measures of stress and teachers and parents SDQ scores will provide more evidence of these matters.
The use of SDQ scores as endpoints will also allow us to test the hypothesis taking co-existing phenotypes into account and include a more precise measure of parental attention problems. This may be especially important since a proportion of the children with high scores on the attention scales in fact have a conduct disorder, which is thought mainly to be due to postnatal environmental factors. Still, the SDQ data collection will not allow us to distinguish between children, who developed conduct problems (or emotional problems) secondarily i.e. as a ‘reaction’ to their attention disorder, and those where the attention problems are secondary or part of the conduct disorder. This may be possible after collecting further information on these children. A diagnostic procedure was planned in collaboration with the Department of Child and Adolescent Psychiatry in Aarhus. The planning started in early 2001 and the data collection is expected to be completed during the spring of 2003. The parents of the children with a high attention score on the SDQ are interviewed by phone using a part of the Development and Well Being Assessment (DAWBA), which was also invented by Robert Goodman\textsuperscript{266}. These interviews are diagnostic for ADHD and will focus on co-existing conduct problems.

6.6 A biological or evolutionary role of stress in fetal brain development?

Hippocrates is said to have saved the life of a princess who had borne a black child by explaining that the picture of a Moor (at this time this referred to a black man) located near the bed of the princess had so impressed itself on her mind that the baby’s skin had turned black\textsuperscript{315}. Even though we have learned a lot about the epigenetic of antenatal stress since this episode there are still many unanswered questions.

Most researchers within the field are convinced about the adverse effects of stress\textsuperscript{140,316} and with a few exceptions animal as well as human studies has focused on the potential negative effects of stress.

It should be kept in mind though, that in contrast to neurotoxic exposures related to life styles such as smoking and alcohol the fetal exposure to stress hormones is expected also to have beneficial influences on survival of the individual. It is well documented that stress hormones in situations can accelerate the maturation of the organsystems\textsuperscript{316} and induce labour\textsuperscript{317,318}. Whether this ‘ripen and flight’ mechanism of the fetus is an overall advantage, disadvantage or can be both in the long run is still an open question.

The allostasis model of fetal brain development may be the model which best describes the biological role of stress. Within the fetal brain development version of this model exposure to excess stress would trigger ‘an emergency history stage’ of the fetus, that apart from the above mentioned immediate effects, may result in an atypical brain development. If the biological capacity of this system is not exceeded this may prepare the fetus for the living in a stressful extra uterine world.

Although it may be an extreme extension of the findings of the current thesis it is tempting to propose that stress in this way may have played a role in evolution. The central finding of the current thesis was an effect of stress in the later part of pregnancy on endpoints possibly related to the process of lateralisation of the fetal brain. In an evolutionary perspective this would make sense in situations, where the society is threatened by a stressful situation and prenatal stress stimulates the development of individuals which display a deviant
brain development. Dependent of timing and genetic potential the influence of stress may cause psychopathology in some individuals and have a positive influence on brain development in others. An epigenetic role of stress of this kind might be a relatively fast working strategy to enhance the chance of survival of a community in threatening situations.

Cerebral lateralisation is thought to have played a central role in the evolution of language\textsuperscript{319}, and it does not seem unlikely that a ‘natural’ epigenetic factor, such as stress may have triggered this evolutionary development. This proposal is off course speculative and beyond the scope of the current thesis but may still be closer to a biological role of stress than the one mentioned above (the Hippocrates story).

The unique example of Leonardo da Vinci mentioned in the introduction to the current thesis does not have the statistical power to document the possibility of a general advantage of an atypical brain lateralisation. Still, the possible beneficial effects of stress for fetal brain development needs to be included in the designs of future research in order to get a more differentiated understanding of the biology.

6.7 Conclusions
The general conclusion of the findings in the current thesis is that stress may influence fetal brain development as measured by a higher prevalence of high ADHD score and mixed-handedness. This effect was dependent on the gender of the child and timing of exposure. Our findings suggest that stress in the second trimester was more important than stress in the first trimester and the strongest association was found in boys. There was no association between stress and brain growth as measured by head circumference at birth. Perceived stress by life events was only associated with salivary cortisol in late but not in early pregnancy. These associations were weak and little could be concluded on the use of salivary cortisol as a biomarker of stress in pregnancy.

6.8 Perspectives
A considerable proportion of pregnant women are stressed during pregnancy. It is therefore important to further investigate the association found in this thesis. The findings need to be replicated in designs that better allow us to distinguish between genetic prenatal and postnatal factors. This can be done in the Aarhus Birth Cohort using the data described in section 4, but ideally the hypothesis should also be tested in other populations and designs.

A number of other cohorts may have the potential to do so, but the data on stress during pregnancy are unique in the Aarhus Birth Cohort. As far as I am concerned only one other birth cohort, namely the ALSPAC study in Bristol, UK comes close, when it comes to the measurement of this exposure\textsuperscript{29;160}, but the ALSPAC is unique in the consecutive registration of maternal emotions before and after birth. The parallel testing of hypothesis in these cohorts is a large potential, that can be extended further than it already has been.

It may also be obvious to study other relevant endpoints. Severe stress in adults affects memory function and causes atrophy of the hippocampus, which is central to this brain function. In animals prenatal exposure to stress causes the same kind of effects. The study of
the association between stress during pregnancy and memory function and specific learning problems would clearly be of interest.

In general, the data collection connected to this thesis has a large potential to test this and a number of other hypotheses concerning the role of the early environment for the various aspects of mental and physical child health.

A number of cohorts have collected more detailed information on prenatal exposures including biological material\textsuperscript{196,320} and child health\textsuperscript{196}, but only the old American 1959-1966 National Collaborative Perinatal Project has the same potential to investigate the role of pre- and perinatal exposures in a sibling design\textsuperscript{321}. The ABCohort covers all births at the birth department of Aarhus University Hospital from 1990 and on, and data on psychological distress using the 12-item version of the ‘General Health Questionnaire’\textsuperscript{322} has been a constant part of the data collection during the years. The comparison of siblings with variations in prenatal exposures is an effective design, to control for genetic confounding\textsuperscript{321}. A follow-up programme for the siblings of more than 3000 of the participants in the current study (with complete information of stress in late pregnancy) is being planned.

Another strategy that may be valuable is to combine the registers in the Scandinavian countries. Many psychiatric diseases are relatively uncommon as is severe stress in pregnancy, and even though follow-up designs with systematic data collection over decades is favoured from a methodological point of view, this approach is very expensive and time-consuming. A relatively straightforward approach is to extend the nearly 25 year old strategy by Huttunen to combine the registers of countries, where linkage between registers of psychiatric diseases and causes of death and diagnosis of disease is possible. This combination of registers has already been used successfully within the national registers in Denmark to evaluate the role of stress for certain perinatal endpoints\textsuperscript{89,90}. The Nordic network ‘Longitudinal studies of the role of the fetal environment in developing ADHD’ under the Nordic Council of Ministers established within this PhD period would be an obvious platform for the organisation of a register based study of this kind.
7. Summary in English

Background
A considerable number of animal experiments suggest that stress during pregnancy may influence growth and structure of the fetal brain as well as offspring behaviour. In humans, stress during pregnancy has been linked to a smaller head circumference at birth, schizophrenia, homosexuality, depressive symptoms, and deviant child behaviour in the offspring. A number of methodological problems limit the conclusions that can be drawn based on these studies. A review of the literature suggests that some of the findings need to be tested in stronger epidemiological designs and that a focus on specific measures related to fetal brain development is necessary in order to reduce the inherent methodological problems of this research area.

Aims
The aim of the thesis was to study the association between stress during pregnancy and indicators of fetal brain development.

Methods
The experience of life events reported twice during pregnancy was the primary indicator of stress. In order to evaluate if this measure of stress was associated with a hormonal stress response, we studied a cohort of 505 women, who had collected morning and evening samples of salivary cortisol twice during pregnancy. In a follow up design the association between stress during pregnancy and head circumference at birth (N=4225), handedness at the age of 3½ years (N=824) and attention problems at the age of 9-11 years (N=4031) was evaluated. Based on the human literature, it was decided to focus on handedness and attention problems as the primary endpoints. In addition to the measures of these endpoints used in the studies mentioned above it was attempted to develop the methods to epidemiological studies. A new instrument to evaluate child psychopathology was translated into Danish and completed by the teachers and parents of the participants. Data was also collected to evaluate the association between hand preference and hand performance.

Results
The primary results presented in the thesis are as follows:

- Stress was associated with a higher level of salivary cortisol in the third but not second trimester.
- There was no association between stress during pregnancy and head circumference at birth.
- There was a dose response like association between stress in second trimester of pregnancy and mixed handedness in the offspring independent of gender.
- There was a dose response like association between stress in second trimester and attention and hyperactive problems in boys. The association was weaker in girls.
- The evaluation of attention problems is culturally dependent and specific standardisation and validation is needed for each cultural setting.
• Evaluation of handedness in childhood by questionnaires needs further development.

Conclusions and perspective
The thesis added to the knowledge about the possible mechanisms within this research area. The data collection serves as a potential for future methodological and analytic epidemiological studies also in adjacent research areas. In future research, high priority should be given to prospective studies with long follow up time. One line of research should focus on the association between good quality measures of pregnancy stress and specific child behaviours, taking lifestyle factors and continuous levels of parental psychopathology into account. Another line should focus on the combination of national registers to evaluate the association between pregnancy stressors such as divorce, death of spouse, and unemployment with psychiatric diagnosis in the offspring into adulthood.
8. Summary in Danish

Baggrund
En stor mængde dyreekperimentel litteratur tyder på at stress i graviditeten kan have
indflydelse på udviklingen af fostrets hjerne. Dette kommer til udtryk i reduceret vækst
strukturelle ændringer og i afkommets adfærd. I humane undersøgelser er der fundet
sammenhæng mellem stress i graviditeten og et mindre hovedomfang ved fødslen, skizofreni,
homosexualitet, depressive symptomer og adfærdsproblemer i barndomen. Undersøgelserne
er præget af store metodemæssige problemer og en del af disse fund bør undersøges i bedre
epidemiologiske designs med fokus på mål specifikt relaterede til den føtale hjerneudvikling.

Formål
Formålet med afhandlingen var at undersøge sammenhængen mellem stress i graviditeten og
indikatorer for den føtale hjerneudvikling.

Metode
Selvrapporteret information om livsbegivenheder indsamlet to gange under graviditeten blev
anvendt som den primære indikator for stress. For at vurdere om dette mål var relateret til et
hormonelt stress repons i graviditeten analyserede vi spyt prøver opsamlet morgen og aften
for indhold af cortisol (N=505). I et follow up design undersøgte vi sammenhængen mellem
stress i graviditeten og barnets hovedomfang ved fødslen (N=4225), håndethed i 3½ års
alderen (N=824), opmærksomhedsproblemer i 9-11 års alderen (N=4031). Baseret på den
eksisterende litteratur blev en yderligere dataindsamling gennemført for at forbedre
metoderne til at vurdere håndethed og opmærksomhedsproblemer i den tidlige skolealder. Et
nyt instrument til at vurdere børnepsykopathologi på populationsniveau blev oversat til dansk
og udfyld af de deltagende børns forældre og lærere. Der blev endvidere indsamlet data til
vurdering af relationen mellem barnets brug af højre og venstre hånd, som vil tjene til
udvikling af håndethed som effektmål i epidemiologiske studier.

Resultater
Resultaterne af denne afhandling er følgende:

• Stress var associeret med højere spycortisol niveauer sidst, men ikke tidligt i
  graviditeten
• Der var ingen association mellem stress I graviditeten og barnets hovedomfang ved
  fødslen.
• Der var en dosis respons lignende sammenhæng mellem stress i andet trimester af
  graviditeten og en mindre konsekvent brug af den foretrukne hånd hos barnet i 3½ års
  alderen. Dette fund var uafhængigt af barnets køn.
• Der var en dosis respons lignende sammenhæng mellem stress i andet trimester af
  graviditeten og opmærksomheds/hyperaktivitet hos barnet i 9-11 års alderen.
  Sammenhængen var mindre blandt piger.
• Psykometriske instrumenter til vurdering af barnets opmærksomhedsproblemer er
  kultur afhængige og en specifik validering bør overvejes ved anvendelse i de
  skandinaviske lande.

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• Metoder til vurdering af børns håndethed på baggrund af spørgeskemaer bør videreudvikles.

**Konklusioner og perspektiver**

Afhandlingen bidrog med viden om mulige årsagsmekanismer. Data indsamlingen udgør et potentiale for fremtidige epidemiologiske analytiske studier af sammenhængen mellem det tidlige miljø og barnets udvikling og sundhed. Fremtidige studier bør være prospektive med opfølgning over lang tid. En strategi er at indsamle detaljerede oplysninger om stress i graviditeten og specifikke områder af barnets adfærd, med mulighed for at kontrollere for livstilsfaktorer og forældrenes psykopatologi. En anden strategi vil være at kombinere nationale registre for at studere sammenhængen mellem stressorer i graviditeten så som skilsmisse, dødsfald (ægtefælde, børn) og arbejdsløshed og psykiatriske diagnoser blandt børnene født af disse mødre.
9. Acknowledgements

‘Science, after all, is as much a social enterprise as an intellectual adventure’\(^\text{323}\). Even though this statement addresses the acceptance of new knowledge, it also describes well the impression one has after having worked on a follow-up study. I am grateful to a great number of people who contributed to this project.

First I would like to thank all the children, their parents and teachers for taking the time to fill out our questionnaires. The parents, who even after high questionnaire exposure during pregnancy and in the first years of their child’s life, also participated in the latest follow-up programme deserve a special acknowledgement.

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List of appendices

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Appendix 2.
Questionnaires (Q1-Q4)

Appendix 3.I: Paper I

Appendix 3.II: Paper II
Carsten Obel, Søren Dalsgaard, Hanne-Pernille Stax, Niels Bilenberg. Spørgeskema om barnets styrker og vanskeligheder (SDQ-Dan). Danish and english version

Appendix 3.III: Paper III

Appendix 3.IV: Paper IV

Appendix 3.V: Paper V
Carsten Obel, Tine Brink Henriksen, Morten Hedegaard, Niels Bilenberg, Niels Jørgen Secher, Jørn Olsen. Stress during Pregnancy and Attention/hyperactivity Problems in the Offspring?
Appendix 1.

Table 1.1 and table 3.1
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<thead>
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<th>Reference</th>
<th>Design</th>
<th>Participants</th>
<th>Exposure</th>
<th>Gender/ timing</th>
<th>Conf. Contr.</th>
<th>Endpoint</th>
<th>Most important results (95% CI)</th>
<th>Comments</th>
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<td>Peak 3-5 and 9-10 months of gest.</td>
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<td>Schizophrenia/register N=7(2.1%)</td>
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<td>Myhrman 1996/Jones 1998</td>
<td>Follow up</td>
<td>11 017</td>
<td>1: Unwanted ness of pregnancy 2: Depressive mood</td>
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<td>Schizophrenia/register N=76(0.7%)</td>
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<td>Ecol. Historic follow up</td>
<td>133 394 exposed 539 789 unexposed</td>
<td>May 1940 invasion of the Netherlands 1st :♀+ ♂: 2nd: only ♂</td>
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<td>-----------------------------------------------</td>
<td>---------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Watson 1999</td>
<td>Historic follow up</td>
<td>611 exposed</td>
<td>The 1976 Earthquake in Tang Shan, China</td>
<td>2nd, only ♂</td>
<td>-</td>
<td>Upper 10% on the Hamilton depression scale</td>
<td>OR=2.6(1.7-4.1)</td>
<td>Severe depression in 10% of population. Highest prevalence among men</td>
</tr>
<tr>
<td></td>
<td></td>
<td>604 unexposed</td>
<td></td>
<td></td>
<td></td>
<td>N=120(10%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward 1991</td>
<td>Case study</td>
<td>59 cases, 59</td>
<td>Marital discord</td>
<td>-</td>
<td>-</td>
<td>Emotionally disturbed</td>
<td>OR=13.0 (3.2-84.6)</td>
<td>No control for maternal psychiatric diagnosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>controls</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Conner 2002</td>
<td>Follow up</td>
<td>7448</td>
<td>18 and 32nd gestational weeks: Anxiety (Crown Crisp index), Depression</td>
<td>-</td>
<td>++</td>
<td>Age 47 months: SDQ</td>
<td>Emotional scale Boys 1.6(1.2-2.1)</td>
<td>Possibly over controlled: birth weight and postpartum depression and anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Edinburgh postpartum depression Scale)</td>
<td></td>
<td></td>
<td></td>
<td>Girls 1.4(1.0-1.9)</td>
<td></td>
</tr>
<tr>
<td>Dörner 1980</td>
<td>Ecological</td>
<td>865 homosexual men</td>
<td>Born during second world war</td>
<td>only ♂</td>
<td>-</td>
<td>Homosexuality</td>
<td>High proportion born in 1941-47</td>
<td>The selection procedure</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dörner 1983</td>
<td>Case control</td>
<td>60 homosexual, 40 bisexual, 100 heterosexual men</td>
<td>Stressful life events</td>
<td>only ♂</td>
<td>-</td>
<td>Homosexuality</td>
<td>Homosexuals 35% severe Bisexuals 33% moderate Heterosexuals 6% moderate</td>
<td>No description of recruitment</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Participants</td>
<td>Events/Experiences</td>
<td>Sex</td>
<td>Homosexuality</td>
<td>Conclusion</td>
<td></td>
<td></td>
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<tr>
<td>------------------------------</td>
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<td>-----</td>
<td>---------------</td>
<td>----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt 1991155 (West Germany)</td>
<td>Ecological</td>
<td>2941 men</td>
<td>Born during 2. world war</td>
<td>only ♂</td>
<td>Homosexuality</td>
<td>No association between year of birth and homosexuality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bailey 1991163 (USA)</td>
<td>Case control</td>
<td>143 males, 72 females</td>
<td>Stressful life events</td>
<td>♂:+ ass. ♂: no ass.</td>
<td>Kinsey Fantasy rating</td>
<td>2nd trimester: correlation: P&lt;0.05 (females)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellis 1988165 (USA)</td>
<td>Case control</td>
<td>283</td>
<td>Stressful experiences</td>
<td>-</td>
<td>Homosexuality, bisexuality</td>
<td>1st and 2nd month of gestation: One way ANOVA: P=0.03 and P=0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ellis 2001164 (USA)</td>
<td>Case control</td>
<td>7605</td>
<td>Stressful life events, perceived stress, lack of control</td>
<td>♂:no ass. ♂: + ass.</td>
<td>Homosexuality (Males N=39), bisexuality(Males=14)</td>
<td>9-12 month prior to and second trimester: significant correlation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hines 2002160 (UK)</td>
<td>Follow up</td>
<td>8510</td>
<td>Number of stressful life events</td>
<td>♂:+ ass. ♂: no ass.</td>
<td>PSAI: gender role aged 4 years</td>
<td>No risk estimates or graphical description</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Childhood diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ward 1990204 (USA)</td>
<td>Case control</td>
<td>59 cases, 59 controls</td>
<td>Marital discord</td>
<td>-</td>
<td>Infantile autism</td>
<td>OR=13.0 (3.2-84.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clements 1992206 (USA)</td>
<td>Case control</td>
<td>24 cases, 24 sibling controls</td>
<td>Life event</td>
<td>-</td>
<td>ADHD</td>
<td>OR=4.2 (95% CI 1.2-15.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McIntosh162 (USA)</td>
<td>Case Control</td>
<td>74 cases, 135 controls</td>
<td>Prenatal stress</td>
<td>-</td>
<td>ADHD</td>
<td>20% higher stress score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Note: PSAI = Parental Stress Assessment Inventory*
<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Participants</th>
<th>Exposure</th>
<th>Gender or timing</th>
<th>Endpoint</th>
<th>Most important results (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stott 1973 (Scotland)</td>
<td>Follow up</td>
<td>153</td>
<td>Personal tension</td>
<td>-</td>
<td>Attention problems</td>
<td>No exact original data</td>
<td>The first follow up study</td>
</tr>
<tr>
<td>Huizink 2001 (Netherlands)</td>
<td>Follow up</td>
<td>170</td>
<td>Anxiety, perceived stress, daily hassles</td>
<td>-</td>
<td>Difficult behaviour, attention regulation</td>
<td>Stress associated to temperament score</td>
<td>Participation rate = 27%</td>
</tr>
<tr>
<td>Martin 1999 (Finland)</td>
<td>Follow up</td>
<td>1397</td>
<td>Anxiety, depression and an emotional liability index</td>
<td>-</td>
<td>Temperament at 6 month and 5 years (parents)</td>
<td>No exact original data, correlation analysis incomparable</td>
<td>Various number of participants in analysis, unknown significance of endpoints</td>
</tr>
<tr>
<td>Luoma 2001 (Finland)</td>
<td>Follow up</td>
<td>147</td>
<td>Edinburgh postpartum depression Scale</td>
<td>-</td>
<td>Age 8-9; CBCL, TRF</td>
<td>External (CBCL/TRF) OR= 7.3 (1.8-27.8)/1.7 (0.4-6.1) Internal (CBCL/TRF) OR= 2.0 (0.6-6.3)/1.3 (0.3-4.6)</td>
<td>Considerable larger association to CBCL than to TRF (information bias)</td>
</tr>
<tr>
<td>O’Connor 2002 (UK)</td>
<td>Follow up</td>
<td>7448</td>
<td>18 and 32nd gestational weeks: Anxiety(Crown Crisp index), Depression</td>
<td>♂&lt;♀.</td>
<td>Age 47 months: SDQ:</td>
<td>32nd week: Attention scale Boys 1.9 (1.3-2.7) Girls 1.4 (1.0-2.1) Conduct scale</td>
<td>Possibly over controlled: birth weight and postpartum depression and anxiety</td>
</tr>
<tr>
<td>Study</td>
<td>Follow up</td>
<td>Sample Size</td>
<td>Risk Factors</td>
<td>Outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>-----------</td>
<td>-------------</td>
<td>--------------</td>
<td>----------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O’Connor 2002 (UK)</td>
<td>7448</td>
<td>As mentioned above</td>
<td>++</td>
<td>Age 47 months: SDQ Totalt behaviour score 32nd week, anxiety: OR: 1.7(1.1-2.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Other endpoints in childhood**

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow up</th>
<th>Sample Size</th>
<th>Risk Factors</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lou 1998 (Denmark)</td>
<td>70 exposed/ 50 controls</td>
<td>Life events in the previous year</td>
<td>(+)</td>
<td>Head circumference at birth 0.7 cm smaller heads (P&lt;0.01)</td>
</tr>
<tr>
<td>Ellis 1998 (USA)</td>
<td>Case control 270</td>
<td>Stressful experiences</td>
<td>-</td>
<td>Lefthandedness, mixed-handedness</td>
</tr>
<tr>
<td>Papousek 1998 (Germany)</td>
<td>Case control 37 cases, 47 controls</td>
<td>Marital conflicts</td>
<td>-</td>
<td>Persistent crying</td>
</tr>
</tbody>
</table>

Table 1.1 Epidemiological reports of an association between stress during pregnancy and endpoints possibly related to fetal brain development
Table 3.1 The 23 objective life events: Proportion feeling very stressed and Newton Scores

<table>
<thead>
<tr>
<th>Life Event</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>Newton score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  Serious physical illness or injury requiring hospital treatment</td>
<td>222</td>
<td>41</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>2  Sudden or serious impairment of vision or hearing</td>
<td>108</td>
<td>12</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>3  Immediate family member seriously ill</td>
<td>831</td>
<td>198</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>4  Immediate family member attempts suicide</td>
<td>58</td>
<td>21</td>
<td>36</td>
<td>31</td>
</tr>
<tr>
<td>5  Immediate family member dies</td>
<td>497</td>
<td>156</td>
<td>31</td>
<td>40</td>
</tr>
<tr>
<td>6  Husband/boyfriend dies</td>
<td>1</td>
<td>1</td>
<td>100</td>
<td>47</td>
</tr>
<tr>
<td>7  Death of close friend</td>
<td>128</td>
<td>35</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>8  Prolonged ill health in close relative requiring treatment by doctor</td>
<td>875</td>
<td>136</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>9  Your husband uses harsh words to you, is cruel or sarcastic</td>
<td>394</td>
<td>68</td>
<td>17</td>
<td>23</td>
</tr>
<tr>
<td>10 Your husband is physically cruel to you</td>
<td>30</td>
<td>7</td>
<td>23</td>
<td>33</td>
</tr>
<tr>
<td>11 Marital separation or divorce</td>
<td>79</td>
<td>37</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>12 Extramarital sexual affair</td>
<td>27</td>
<td>4</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>13 Your husband/boyfriend unfaithful</td>
<td>32</td>
<td>19</td>
<td>59</td>
<td>37</td>
</tr>
<tr>
<td>14 Been homeless</td>
<td>49</td>
<td>16</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>15 Been involved in a fight</td>
<td>22</td>
<td>9</td>
<td>41</td>
<td>12</td>
</tr>
<tr>
<td>16 Been arrested</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>17 Your husband/boyfriend arrested</td>
<td>26</td>
<td>8</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>18 Had to make a court appearance</td>
<td>48</td>
<td>8</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>19 Convicted of an offence</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>29</td>
</tr>
<tr>
<td>20 Your husband/boyfriend send to jail</td>
<td>21</td>
<td>10</td>
<td>48</td>
<td>38</td>
</tr>
<tr>
<td>21 Your husband becomes unemployed</td>
<td>381</td>
<td>55</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>22 Income decreased substantially (by 25%)</td>
<td>410</td>
<td>85</td>
<td>21</td>
<td>11</td>
</tr>
<tr>
<td>23 Getting into dept beyond your means of repayment</td>
<td>470</td>
<td>93</td>
<td>20</td>
<td>28</td>
</tr>
</tbody>
</table>
Appendix 2.

Questionnaires Q1-Q4
Appendix Q1: The Child Health Questionnaire

Børn født i Århus 1990-92

Spørgeskema til deres forældre
Om spørgeskemaet og hvordan det udfyldes

Kære forældre

Hvad handler spørgeskemaet om?
Skemaet er inddelt i afsnit med spørgsmål
• om barnets familie
• om barnets første 6 leveår
• om hvilken hånd barnet bruger
• om barnets fritid, venner og skole
• om barnets velbefindende, styrker og svagheder
• om barnets mor og far

Hvis du mener, at der mangler væsentlige oplysninger til beskrivelse af dit barn, er der flere steder i spørgeskemaet mulighed for at skrive kommentarer og tilføjelser.

Hvilke typer svar ønsker vi på spørgsmålene i skemaet?

Afkrydsnings-svar, hvor vi vil bede dig svare på spørgsmålet ved at sætte et kryds

Eksempel

Er barnet født i Århus? .......................... JA □ 1  
NEJ □ 2

Tal-svar, hvor vi vil bede dig svare på spørgsmålet ved at skrive et tal

Eksempel

Hvor gammelt er barnet? .......................... _____ år

eller

I hvilken periode boede barnet sidst i Århus? 19 ____ til ____ (årstal)

Tekst-svar, hvor vi vil bede dig svare på spørgsmålet ved at skrive en tekst

Eksempel

I hvilke byer har barnet boet?______________________________

eller

Hvor bor barnet nu?

Har du problemer med at udfyde skemaet?
Du er altid velkommen til at ringe til os på telefon 89496380, hvis du har problemer med at udfyde skemaet.

På Forskningsenhedens vegne
Carsten Obel
Begynd venligst besvarelsen af spørgeskemaet her

Som fødeafdeling har vi fundet det naturligt at sende spørgeskemaet til barnets mor. Det vigtigste er imidlertid, at det er en person, som kender barnet godt, der besvarer spørgsmålene. Det er også vigtigt, at barnet ikke er med til at udfylde skemaet.

1. Dato for udfyldelse af skemaet (dag/måned-år) ..................... ____ / ____ -2001

2. Hvem udfylder spørgeskemaet? .............................  
   Biologisk mor □, 
   Biologisk far □  
   Anden person, som kender barnet: ________________________________ □,

Når resultaterne af undersøgelsen foreligger, kan vi tilbyde at sende dig et brev eller E-mail.

3. Ønsker du at modtage oplysninger om undersøgelsens resultater, når de foreligger? .................................  
   JA □  NEJ □  

   Har du E-mail, vil vi foretrække at bruge den  
   Min E-mail adresse er: _____________________@__________________

Om barnets familie

Den første del af skemaet drejer sig om barnets hjem og familie. Hvis barnet bor flere steder, besvares spørgsmål om barnets hjem/familie ud fra hvor barnet bor mest.

4. Bor barnets biologiske mor og biologiske far sammen? ............  
   JA □  NEJ □  

   Hvis NEJ:
   Hvor mange **dage om måneden** bor barnet:
   - hos biologisk mor? ...................... Antal dage ____
   - hos biologisk far? ...................... Antal dage ____
   - hos andre?: ____________________________ Antal dage ____
5. Hvor mange **andre** børn er der i barnets hjem? ........ Antal helsøskende?______
    Antal halvsøskende?______
    Antal andre børn?______

6. **I barnets første 12 levemånedner:**
   Var der kæledyr med pels i barnets hjem? ....................... NEJ □
   JA, hund □
   JA, kat □
   JA, andet dyr ___________________________________________ □

7. **Efter barnets første 12 levemånedner:**
   Har der været kæledyr med pels i barnets hjem? ................ NEJ □
   JA, hund i perioden: 19 _____ til ____ (årstal)
   JA, kat i perioden: 19 _____ til ____ (årstal)
   JA, andet dyr med pels i perioden: 19 _____ til ____ (årstal)

8. Hvor stor er familiens nuværende bolig (boligareal)? .......... ______Kvm

9. **Pr. måned:** Hvad er familiens samlede indtægt før skat (eventuelle sociale ydelser regnes med) ............. Cirka______________Kr

**Om barnets første seks leveår**

*De næste spørgsmål drejer sig om barnets første seks leveår, det vil sige indtil barnet fyldte 7 år. Hvis du har kommentarer eller tilføjelser, er der plads til dem i slutningen af dette afsnit på side 7 og sidst i skemaet.*

10. Er barnet blevet ammet? ............................................. JA □ NEJ □

**Hvis JA:**
   Hvor længe fik barnet ikke andet end brystmælk? ..... _____ måneder
   Hvor gammelt var barnet, da amningen helt ophørte?
   ____ år og _____ måneder

11. Er barnet vaccineret for: mæslinger, fåresyge og røde hunde (MFR-vaccination)? .......... JA □ NEJ □
12. Har barnet haft skoldkopper? ............................. JA □
                NEJ □
                ved ikke □

13. **I barnets 3 første leveår:**
Blev barnet passet uden for hjemmet i dagtimerne? .......... JA □  NEJ □

**Hvis JA:**
Hvor blev barnet passet? (eventuelt flere krydser) ....... Vuggestue □ 1,
Integrieret institution □ 2,
2-års børnehave □ 3,
Dagpleje □ 4,
Andet sted: ____________________________________ □ 5,
Hvor gammelt var barnet, da han/hun begyndte i pasning uden for hjemmet? ....... _____ år og ____ måneder
Som 2-årig: Hvor mange **timer om dagen,** blev barnet cirka passet uden for hjemmet? .......... _____ timer

14. **Da barnet var 3-6 år:**
Blev barnet i dagtimerne passet uden for hjemmet? .......... JA □  NEJ □

**Hvis JA:**
Hvor blev barnet passet? (eventuelt flere krydser) . . . Alm. børnehave □ 1,
Integrieret institution □ 2,
Skov-børnehave □ 3,
Andet sted: ________________________________ □ 4,
Som 4 årig: Hvor mange **timer om dagen,** blev barnet cirka passet uden for hjemmet? .......... _____ timer

15. I hvilken alder lærte barnet at gå? ................. _____ år og _____ måneder

16. Hvordan har barnets **taleudvikling** været? .... Meget senere end jævnaldrende □ 1,
Meget senere end jævnaldrende □ 2,
Lidt senere end jævnaldrende □ 3,
Nogenlunde som jævnaldrende □ 4,
Tidligere end jævnaldrende □ 5,
Ved ikke □ 6,

**Hvis JA:**
Hvor blev barnet passet? (eventuelt flere krydser) ....... Vuggestue □ 1,
Integrieret institution □ 2,
2-års børnehave □ 3,
Dagpleje □ 4,
Andet sted: ____________________________________ □ 5,
17. Har barnet fået professionel hjælp eller støtte til sin taleudvikling (feks. af en talepædagog)? ........................................ JA □
   NEJ □
   ved ikke □
   **Hvis JA:**
   Beskriv venligst denne hjælp:

18. Har barnet (ud over ved fødslen) været indlagt på sygehus? ............. NEJ □
   JA, på grund af infektion □
   JA, på grund af andet □
   **Hvis JA:**
   Hvad var årsagen til indlæggelse? (hvis flere indlæggelser, er der plads til at skrive mere i slutningen af afsnittet)

19. Har barnet haft mellemørebetændelse? ............................. NEJ □
   JA, 1-3 gange □
   JA. mere end 3 gange □
   ved ikke □
   **Hvis JA:**
   Er barnet blevet behandlet med dræn i ørerne? ............... JA □
   NEJ □
   ved ikke □

20. Har barnet i en periode på mere end 3 måneder fået medicin mindst 1 gang om ugen? ...................... JA □
    NEJ □
    **Hvis JA:**
    Hvilken medicin?
21. Havde barnet i de første 6 leveår nogensinde pibende eller hvæsende vejrtrækning (feks. astmatisk bronkitis)? 

Hvis JA: 
Fik barnet medicin for vejrtrækningen? 

Angiv eventuelt hvilken medicin:

22. Har barnet haft anfald af feberkramper?

Hvis JA: 
Hvor mange anfald af feberkramper har barnet haft i alt? 
Hvor mange minutter varede det første anfald af feberkramper? 
I hvilken alder havde barnet det første anfald af feberkramper? 
Blev barnet tilset af en læge i forbindelse med det første anfald af feberkramper? (sæt eventuelt flere krydser)

23. Har en eller flere af barnets søskende haft feberkramper? (sæt eventuelt flere krydser)
24. Har du i løbet af de første 6 leveår været bekymret for, om barnet udviklede sig normalt? ................. JA □ NEJ □

Hvis JA: beskriv venligst

Her er der plads til eventuelle kommentarer eller tilføjelser:

**Om hvilken hånd barnet bruger mest**

_Nogle mennesker foretrækker at bruge højre hånd til de fleste aktiviteter, mens andre bruger den venstre. Nogle kan bruge begge hænder til mange ting, men bruger ved bestemte aktiviteter kun den ene hånd. Med de næste spørgsmål vil vi bede dig vurdere hvad der passer bedst på barnet og på begge forældre._

25. Hvilken hånd mener du **barnet** bruger mest? ................. Kun højre □ 1  
Mest højre □ 2  
Begge hænder lige meget □ 3  
Mest venstre □ 4  
Kun venstre □ 5

26. Hvilken hånd bruger **barnets biologiske mor** mest? ................. Kun højre □ 1  
Mest højre □ 2  
Begge hænder lige meget □ 3  
Mest venstre □ 4  
Kun venstre □ 5

27. Hvilken hånd bruger **barnets biologiske far** mest? ................. Kun højre □ 1  
Mest højre □ 2  
Begge hænder lige meget □ 3  
Mest venstre □ 4  
Kun venstre □ 5
28. **Hvilken hånd bruger barnet mest, når han/hun:**

<table>
<thead>
<tr>
<th>Sæt kun ét kryds for hver aktivitet</th>
<th>kun venstre</th>
<th>mest venstre</th>
<th>begge hænder</th>
<th>mest højre</th>
<th>kun højre</th>
<th>ved ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. skriver?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>3. holder en ske?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>2. tegner?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>4. kaster en bold?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>5. klipper med saks?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>6. stryger en tændstik?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>7. skærer med en kniv?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>8. børster tænder?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>9. smører brød?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>10. spiser med gaffel (uden kniv)?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>11. visker med viskelæder?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>12. giver kort?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
<tr>
<td>13. lukker en sodavand op?</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
<td>□ 6</td>
</tr>
</tbody>
</table>

**Om barnets fritid, venner og skole**

*De næste spørgsmål drejer sig om barnets interesser, fritidsaktiviteter, venner og eventuelle problemer i skolen. Har du kommentarer eller tilføjelser, er der plads til dem i slutningen af dette afsnit på side 10 og sidst i skemaet.*

29. **Har barnet én særlig interesse, som han/hun går meget op i?** ................. **JA □**

**NEJ □**

ved ikke □

Hvis JA, hvilken
30. Har barnet mange forskellige interesser? ........................................... JA □
          NEJ □
          Ved ikke □

31. Hvor mange timer om ugen er barnet i skole-fritids ordning eller lignende ................... _____ timer pr. uge

32. Hvor mange timer om ugen ser barnet fjernsyn eller video? ................................. _____ timer pr. uge

33. Hvor mange timer om ugen (ud over skolearbejdet) læser barnet bøger eller tegneserier? ............................. _____ timer pr. uge

34. Hvor mange timer om ugen (udover skolearbejdet) sidder barnet ved en computer eller play-station? ....... _____ timer pr. uge

35. Hvor mange timer om ugen (ud over i skolen) er barnet fysisk aktivt udendørs? .................... _____ timer pr. uge

36. Hvor mange ud af ugens 7 dage går barnet til sport uden for skoletiden? (f.eks. fotbold, gymnastik, svømning) ____ dage

37. I forhold til sine jævnaldrende, er barnet så ......... meget mere fysisk aktivt? □ 1
          noget mere fysisk aktivt? □ 2
          nogenlunde lige så fysisk aktivt? □ 3
          noget mindre fysisk aktivt? □ 4
          meget mindre fysisk aktivt? □ 5
          Ved ikke □ 6

38. Har barnet en ‘bedste ven’? ................................................................. JA □
          NEJ □
          Ved ikke □

39. Hvor mange gode venner mener du, dit barn har?

          Antal pigevenner (hvis ingen skriv 0) ........ _____

          Antal drengevenner (hvis ingen skriv 0) ... ____
40. **Hvor mange ud af ugens 7 dage** er barnet sammen med venner
(udover i skolen og i forbindelse med sport)? ............................ _____ dage

_I dette skema er der spørgsmål om barnets eventuelle problemer i skolen._

<table>
<thead>
<tr>
<th>I hvilken grad har barnet følgende problemer i skolen?</th>
<th>NEJ</th>
<th>JA, lidt</th>
<th>JA, noget</th>
<th>JA, meget</th>
<th>Ved ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>41. Har barnet svært ved <strong>at lære at læse</strong>?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>42. Har barnet svært ved <strong>at lære at stave</strong>?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>43. Har barnet svært ved <strong>at lære at regne</strong>?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>44. Har barnet svært ved <strong>at koncentrere sig i skolen</strong>?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>45. Deltager barnet i <strong>mobning af andre</strong> i skolen?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>46. Bliver barnet <strong>selv mobbet</strong> i skolen?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>

47. **Har barnet modtaget special/særlig undervisning** i skolen? .......................... NEJ, aldrig ☐ 1
    JA, tidligere ☐ 2
    JA, nu ☐ 3

_Hvis JA, beskriv venligst_

_Her er der plads til eventuelle kommentarer eller tilføjelser:_
Om barnets velbefindende, styrker og svagheder


I hvilken grad passer følgende beskrivelser på dit barn inden for de sidste 6 måneder?

<table>
<thead>
<tr>
<th>I hvilken grad passer følgende beskrivelser på dit barn inden for de sidste 6 måneder?</th>
<th>Passer ikke</th>
<th>Passer til en vis grad eller nogle gange</th>
<th>Passer godt eller ofte</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mit barn:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48. - har et godt humør</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>49. - vil helst lege for sig selv</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>50. - er god til at forstå en mundtlig besked</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>51. - udtaler ofte ord forkert</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>52. - er god til at samarbejde med andre børn</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>53. - er god til at forklare, hvad han/hun har lavet i løbet af dagen</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>54. - har en god hukommelse</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>55. - lever i sin egen verden</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>56. - foretrækker at være sammen med yngre børn</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>57. - er meget selvstændig</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>58. - har svært ved at opfatte, hvad man siger (spørger tit ‘hvad sagde du?’)</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>59. - har nemt ved at huske navne på dage, måneder, årstider</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>60. - er ikke vellidt af andre børn</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>61. - er god til at være med til gruppelege</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>62. - kan ikke koncentrere sig, kan ikke være opmærksom i længere tid</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>63. - har det bedst sammen med voksne</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
<tr>
<td>64. - kan udtrykke med ord, hvad der er vigtigt for ham/hende</td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
</tr>
</tbody>
</table>
I hvilken grad passer følgende beskrivelser på dit barn inden for de sidste 6 måneder?

<table>
<thead>
<tr>
<th><strong>Mit barn:</strong></th>
<th>Passer ikke</th>
<th>Passer til en vis grad eller nogen gange</th>
<th>Passer godt eller ofte</th>
</tr>
</thead>
<tbody>
<tr>
<td>65. - tror på sig selv, har megen selvtillid</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>66. - er hvileløs og urolig</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>67. - er god til at beskæftige/underholde sig selv</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>68. - er god til at forstå andres følelser, sætte sig i andres sted</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>69. - virker 'gammelklog'</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>70. - er god til at huske ting, som er sket for længe siden</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>71. - misforstår tit ord</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>72. - bliver utryg, når der sker ændringer i hverdagen</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>73. - er glad for fysisk aktivitet</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>74. - kan ikke sidde stille, er rastløs eller hyperaktiv</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>75. - er plaget af at skulle gentage bestemte handlinger (feks. vaske hænder)</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>76. - har mareridt om natten</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>77. - er nysgerrig efter forklaring på ting, han/hun ikke forstår</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>78. - kan give en sammenhængende forklaring</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>79. - opfører sig som yngre, end han/hun er</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>80. - har en sikker tidsfornemmelse (feks. hvor lang tid 5 minutter er)</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>81. - kommer dårligt ud af det med andre børn</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>82. - virker trist eller bekymret</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>83. - har let ved at knappe knapper og binde snørebånd</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>84. - er forvirret eller synes at være i en tåge</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>85. - er spontan og initiativrig</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>86. - kræver megen opmærksomhed</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>87. - er god til at tegne, så det ligner (feks. en bil eller et hus)</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>88. - ødelægger sine ting</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>Nr.</td>
<td>Beskrivelse</td>
<td>Passer ikke</td>
<td>Passer til en vis grad eller nogle gange</td>
</tr>
<tr>
<td>-----</td>
<td>-----------------------------------------------------------------------------</td>
<td>-------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>89</td>
<td>- er god til at lytte, når man fortæller</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>90</td>
<td>- snøfter, grynter eller fløjter meget</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>91</td>
<td>- kan udtale lange ord rigtigt</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>92</td>
<td>- er impulsivt eller handler uden at tænke</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>93</td>
<td>- er god til at lægge puslespil</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>94</td>
<td>- er klodset eller dårlig til at koordinere sine bevægelser</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>95</td>
<td>- kan følge med i underteksterne på fjernsynet</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>96</td>
<td>- er usædvanlig højrøstet</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>97</td>
<td>- er god til at vente til det bliver hans/hendes tur (i spil, under måltider)</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>98</td>
<td>- arbejder dårligt med skolearbejdet</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>99</td>
<td>- dagdrømmer eller fortæber sig i egne tanker</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>100</td>
<td>- er god til at kaste og gribe en bold</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>101</td>
<td>- har nervøse bevægelser eller trækninger</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>102</td>
<td>- er god til at kende forskel på højre og venstre</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>103</td>
<td>- er genert eller sky</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>104</td>
<td>- er veloplagt og energisk</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>105</td>
<td>- er ubetænksom og uforsigtig</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>106</td>
<td>- stammer</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>107</td>
<td>Andre børn kan forstå, hvad barnet siger</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>108</td>
<td>Voksne, som ikke kender barnet, forstår hvad barnet siger</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
<tr>
<td>109</td>
<td>Jeg opfatter mit barn som normalt fungerende</td>
<td>☐ 1</td>
<td>☐ 2</td>
</tr>
</tbody>
</table>

*Her er der plads til eventuelle kommentarer eller tilføjelser:*
Om barnets nuværende sundhed og sygdom

De næste spørgsmål drejer sig om barnets nuværende sundhed og sygdom. Har du kommentarer eller tilføjelser, er der plads til dem i slutningen af dette afsnit på side 17 og sidst i spørgeskemaet.

110. Har barnet nogensinde haft et kløende hududslet, som varede mere end et døgn? ......................... □ JA □ NEJ

Hvis JA:
Hvor gammelt var barnet, da dette hududslet begyndte?

___ år og ____ måneder

Har dette hududslet nogensinde siddet på følgende steder på barnets krop?

a. I hårbund ........................................ JA □ NEJ □
b. Om øjne ........................................ JA □ NEJ □
c. På kinder ........................................ JA □ NEJ □
d. Om munden ..................................... JA □ NEJ □
e. På kroppen (bryst, mave, ryg) .................. JA □ NEJ □
f. I albuebøjninger eller knæhaser ............... JA □ NEJ □
g. Ved hånd eller ankelled ......................... JA □ NEJ □

111. Har barnet **nu** et kløende hududslet, som har varet mere end et døgn? JA □ NEJ □

Hvis JA:
Sidder dette hududslet følgende steder på barnets krop?

a. I hårbund ........................................ JA □ NEJ □
b. Om øjne ........................................ JA □ NEJ □
c. På kinder ........................................ JA □ NEJ □
d. Om mund ....................................... JA □ NEJ □
e. På kroppen (bryst, mave, ryg) ................. JA □ NEJ □
f. I albuebøjninger eller knæhaser ............... JA □ NEJ □
g. Ved hånd eller ankelled ......................... JA □ NEJ □

112. Er der nogensinde en læge, der har sagt, at barnet har børneeksem eller astmaeksem? ................ JA □ NEJ □

113. Har barnet tendens til tør hud? ......................... JA □ NEJ □
114. Inden for de sidste 12 måneder:
Har barnets vejrtrækning lydt pibende eller hvæsende? .......... JA □ NEJ □

**Hvis JA**

Inden for de sidste 12 måneder: I hvor mange perioder har barnets vejrtrækning lydt pibende eller hvæsende? .............
1 periode □,
2-3 perioder □,
4-12 perioder □,
Mere end 12 perioder □.

Inden for de sidste 12 måneder: Hvis barnets søvn været forstyrret på grund af pibende eller hvæsende vejrtrækning? . . . Aldrig □,
Mindre end 1 nat pr. uge □,
1 eller flere nætter pr. uge □.

Inden for de sidste 12 måneder: Har den pibende eller hvæsende vejrtrækning været så slem, at barnet kun har kunnet sige et eller to ord mellem hver vejrtrækning? ............. JA □ NEJ □

Inden for de sidste 12 måneder: Har barnets vejrtrækning under eller efter leg, sport eller anden fysisk anstrengelse lydt pibende eller hvæsende? .................. JA □ NEJ □

115. Inden for de sidste 12 måneder: Har barnet haft tør hoste om natten bortset fra hoste ved forkølelse eller anden luftvejsinfektion? ..... JA □ NEJ □

116. Er der nogensinde en læge, der har sagt, *at barnet har astma?* . . . JA □ NEJ □

117. Er der nogensinde en læge, der har sagt, *at barnet har hofeber?* . . JA □ NEJ □

118. Er der nogensinde en læge, der har sagt, _at barnet har epilepsi?_ . . JA □ NEJ □

**Hvis JA:**

Får barnet medicin mod epilepsi? JA □ NEJ □

119. Har barnet et handicap? ........................... JA □ NEJ □

**Hvis JA:**

beskriv venligst
120. Har barnet en kronisk sygdom .................................. JA □ NEJ □

**Hvis JA:**
beskriv venligst

121. Får barnet medicin 1 gang om ugen eller oftere? JA □ NEJ □

**Hvis JA:**
Hvilken medicin?

122. Har barnet nu eller tidligere skellet? .......................... JA □ NEJ □

123. Bruger barnet briller? ............................................ JA □ NEJ □

124. Har barnet nedsat hørelse? ...................................... JA □ NEJ □

125. Inden for de sidste 12 måneder: Har barnet klaget over **hovedpine**
1 gang om måneden eller mere? ................................. JA □ NEJ □

126. Inden for de sidste 12 måneder: Har barnet klaget over **vokseværk**
1 gang om måneden eller mere? ................................. JA □ NEJ □

127. Inden for de sidste 12 måneder:
Har barnet klaget over **mavesmerter**? .......................... JA □ NEJ □

**Hvis JA:**
Har barnet i **en periode på 3 måneder** klaget over mavesmerter
mere end 3 gange? ................................................. JA □ NEJ □

Har mavesmerterne været så stærke, at barnet holdt op med de
aktiviteter, han/hun var i gang med? ...................... JA □ NEJ □

128. Lider barnet af forstoppelse? ................................. NEJ, aldrig □ □
JA, af og til □ □
JA, ofte □ □

129. Bider barnet negle? ................................................ JA □ NEJ □

130. Inden for de sidste 12 måneder: Har barnet **tisset i sengen om natten**
1 gang om måneden eller mere? ................................. JA □ NEJ □
131. Inden for de sidste 12 måneder: Har barnet **tisset i bukserne i dagtimerne**
1 gang om måneden eller mere? ...............................  JA ☐  NEJ ☐

132. Inden for de sidste 12 måneder: Har barnet været **urenligt med afføring**
1 gang om måneden eller mere? ...............................  JA ☐  NEJ ☐

133. Hvad er barnets seneste højde og vægt?

Måledato: ____ / ____ -____  højde:______ cm  vægt:____ kg

134. Hvor blev barnet målt? ...............................  Hjemme ☐  
Hos skolesundhedsplejersken ☐  
Hos lægen ☐  
Andetsteds ☐

135. Synes du barnet vejer: ...............................  Tilpas ☐  
For meget ☐  
For lidt ☐

136. Får barnet morgenmad? ...............................  NEJ, sjældent/aldrig ☐  
JA, ind imellem ☐  
JA, ofte/altid ☐

137. Får barnet frokost, når det er i skole? ...............................  NEJ, sjældent/aldrig ☐  
JA, ind imellem ☐  
JA, ofte/altid ☐

138. Synes du det er svært, at få barnet til at spise sundt? ...............................  NEJ, sjældent/aldrig ☐  
JA, ind imellem ☐  
JA, ofte/altid ☐

**Her er der plads til eventuelle kommentarer eller tilføjelser:**
Om barnets mor

**De følgende spørgsmål drejer sig om barnets biologiske mor. Har du kommentarer eller tilføjelser, er der plads til dem efter dette afsnit på side 19 og sidst i spørgeskemaet.**

139. Havde barnets mor som barn: Et eller flere tilfælde med feberkramper? ................. NEJ □ JA □ ved ikke □

140. Havde barnets mor som barn astma? ................. NEJ □ JA □ ved ikke □

141. Havde barnets mor som barn: Børneeksem (også kaldet astmaeksem)? ................. NEJ □ JA □ ved ikke □

142. Har barnets mor som voksen haft astma? ............. JA □ NEJ □

143. Har barnets mor som voksen haft høfeber? ............ JA □ NEJ □

144. På hvilket klassetrin har barnets mor afsluttet sin skoleuddannelse?

   - 7.-9. klasse □
   - 10. klasse/realeksamen, teknisk forberedelseseksamen, EFG □
   - Udvidet teknisk forberedelseseksamen □
   - Studentereksamen/HF/HH eller tilsvarende □

145. Har barnets mor afsluttet en uddannelse efter sin skole-uddannelse?

   - NEJ, er under uddannelse □
   - NEJ, har ikke uddannelse □
   - JA, en kort uddannelse (1-2 år) □
   - JA, en mellemlang uddannelse (3-4 år) □
   - JA, en lang uddannelse (mere end 4 år) □

146. Hvilken hovedindtægt har barnets mor?

   - Fuldtids lønmodtager/selvstændig □
   - Deltids lønmodtager/selvstændig □
   - Dagpenge/overførselsindkomst □
   - Uddannelsesstøtte/godtgørelse □

   Andet (beskriv venligst): __________________________________________________________ □

147. Hvilken stilling har barnets mor nu (skriv stilling ved sidste ansættelse, hvis ikke i arbejde). Skriv helst nøjagtig stilling, f.eks. skolelærer (ikke blot lærer), hospitalslaborant (ikke blot laborant) :
148. Hvor mange timer om ugen arbejder barnets mor **uden for hjemmet**? ........................................... ____ timer

149. Har barnets mor røget i perioden efter barnets fødsel? ............... JA □ NEJ □

Hvis JA:
I hvilke perioder har barnets mor røget? ...... 19 ___ til ____ (årstal)
19 ___ til ____ (årstal)
19 ___ til ____ (årstal)

Hvor mange cigaretter ryger barnets mor **nu** om dagen? ........... ____

**De sidste spørgsmål om barnets mor drejer sig om eventuelle problemer i skolen.**

<table>
<thead>
<tr>
<th>Havde barnets mor i folkeskolen:</th>
<th>NEJ</th>
<th>JA, lidt</th>
<th>JA, noget</th>
<th>JA, meget</th>
<th>Ved ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>150. - svært ved <strong>at lære at læse?</strong></td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>151. - svært ved <strong>at lære at stave?</strong></td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>152. - svært ved <strong>at lære at regne?</strong></td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
<tr>
<td>153. - svært ved <strong>at koncentrere sig?</strong></td>
<td>□ 1</td>
<td>□ 2</td>
<td>□ 3</td>
<td>□ 4</td>
<td>□ 5</td>
</tr>
</tbody>
</table>

Her er der plads til eventuelle kommentarer eller tilføjelser:
Om barnets far


154.   Havde barnets far som barn:
Et eller flere tilfælde med feberkramper?  ......................... NEJ □
                       JA □
                       ved ikke □

155.   Havde barnets far som barn astma?  ........................... NEJ □
                       JA □
                       ved ikke □

156.   Havde barnets far som barn:
Børneeksem (også kaldet astma eksem)?  ........................... NEJ □
                       JA □
                       ved ikke □

157.   Har barnets far som voksen haft astma?  ..................... JA □  NEJ □

158.   Har barnets far som voksen haft høfeber?  .................... JA □  NEJ □

159.   På hvilket klassesvare har barnets far afsluttet sin skoleuddannelse?
       7.-9. klasse □
        10. klasse/realeksamen, teknisk forberedelseseksamen, EFG □
        Udvidet teknisk forberedelseseksamen □
        Studentereksamen/HF/HH eller tilsvarende □

160.   Har barnets far afsluttet en uddannelse efter sin skole-uddannelse?
       NEJ, er under uddannelse □
       NEJ, har ikke uddannelse □
       JA, en kort uddannelse (1-2 år) □
       JA, en mellemlang uddannelse (3-4 år) □
       JA, en lang uddannelse (mere end 4 år) □

161.   Hvilken hovedindtægt har barnets far?
       Fuldtids lønmodtager/selvstændig □
       Deltids lønmodtager/selvstændig □
       Dagpenge/overførselsindkomst □
       Uddannelsesstøtte/godtgørelse □

Andet (beskriv venligst):  ........................................................................ □
162. Hvilken stilling har barnets far nu (skriv stilling ved sidste ansættelse, hvis ikke i arbejde). Skriv helst nøjagtig stilling, f.eks. skolelærer (ikke blot lærer), hospitalslaborant (ikke blot laborant):

_____________________________________________________________

163. Hvor mange timer om ugen arbejder barnets far 
**uden for hjemmet**? ........................................... _____ timer

164. Har barnets far røget i perioden efter barnets fødsel? ............. JA □   NEJ □

**Hvis JA:**
I hvilke perioder har barnets far røget? ...... 19 _____ til _____ (årstal)

19 _____ til _____ (årstal)

19 _____ til _____ (årstal)

Hvor mange cigaretter ryger barnets far **nu** om dagen? ............ ______

*De sidste spørgsmål om barnets far drejer sig om eventuelle problemer i skolen.*

<table>
<thead>
<tr>
<th>Havde barnets far i folkeskolen:</th>
<th>NEJ</th>
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<th>JA, noget</th>
<th>JA, meget</th>
<th>Ved ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>165. - svært ved <strong>at lære at læse</strong>?</td>
<td>□₁</td>
<td>□₂</td>
<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
<tr>
<td>166. - svært ved <strong>at lære at stave</strong>?</td>
<td>□₁</td>
<td>□₂</td>
<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
<tr>
<td>167. - svært ved <strong>at lære at regne</strong>?</td>
<td>□₁</td>
<td>□₂</td>
<td>□₃</td>
<td>□₄</td>
<td>□₅</td>
</tr>
</tbody>
</table>
| 168. - svært ved **at koncentrere sig**? | □₁  | □₂      | □₃       | □₄       | □₅     

*Her er der plads til eventuelle kommentarer eller tilføjelser:*
Vi får muligvis brug for yderligere oplysninger om barnets sundhed og udvikling. Der kan også være tilfælde, hvor vi er i tvivl om en besvarelse af spørgeskemaet. Derfor vil vi gerne bede om tilladelse til eventuelt at kontakte dig/Jer igen.

169. Må vi fra projektgruppen kontakte dig/Jer igen pr. telefon eller brev ................................. JA □  NEJ □

Hvis JA
Angiv eventuelt det telefonnummer, hvor du/I bedst træffes på hverdagsaftner:  . . __________________

Mange tak
fordi du ville have ulejlighed med at udfylde spørgeskemaet.
Din indsats har stor betydning for undersøgelsens kvalitet.

Hvis du ikke allerede har gjort det, vil vi bede dig

udfylde skemaets bagside
Spørgskemaets bagside - Bedes venligst udfyldt af alle.

Læs venligst vedlagte brev, før du udfylder denne side og eventuelt resten af spørgeskemaet

DELTAGERE i undersøgelsen: læs venligst nedenstående

For at øge den videnskabelige kvalitet af denne undersøgelse, vil vi gerne bede dig om dit/Jeres samtykke til at anvende medicinske oplysninger og skoleoplysninger om barnet. Ud over at anvende de oplysninger, som findes i forvejen, vil vi gerne bede barnets klasselærer udfylde et spørgeskema om barnets opmærksomheds- og koncentrations evne, samt om hvordan barnet klarer sig i de forskellige fag. Ligesom oplysningerne fra spørgeskemaet behandles disse oplysninger fortroligt og under tavshedspligt.

Hvis du/I kan acceptere, at vi anvender disse oplysninger, vil vi bede om en underskrift på nedenstående samtykke erklæring. Samtykket kan til hver en tid trækkes tilbage.

Hvis du/I ikke ønsker at give dette samtykke, vil vi alligevel gerne have det udfyldte spørgeskema.

SAMTYKKE ERKLÆRING

JA, jeg giver hermed tilladelse til, at Fødeafdelingen på Skejby Sygehus må anvende medicinske- og skoleoplysninger om mit barn til denne undersøgelse

Dato__________ Underskrift__________________________________________

Navnet på barnets skole______________________________________________

NEJ, jeg ønsker ikke at give denne tilladelse ..................................... ☐

IKKE- DELTAGERE i undersøgelsen: sæt venligst kryds i nedenstående rubrik

Jeg/vi ønsker IKKE at deltage i undersøgelsen ................................. ☐

**Hvilken hånd bruger du for det meste til at:**

1. Skrive med?  
Venstre ☐ Begge ☐ Højre ☐
2. Kaste en bold? (hvis du kaster til måls efter noget)  
Venstre ☐ Begge ☐ Højre ☐
3. Holde om en ketsjer? (tennis, badminton e.l.)  
Venstre ☐ Begge ☐ Højre ☐
4. Holde en tændstik når du skal stryge den?  
Venstre ☐ Begge ☐ Højre ☐
5. Klippe med en saks?  
Venstre ☐ Begge ☐ Højre ☐
6. Holde en tråd når den skal igennem et nåleøje?  
Venstre ☐ Begge ☐ Højre ☐
7. Holde øverst på kosten når du fejer?  
Venstre ☐ Begge ☐ Højre ☐
8. Holde øverst på skovlen når du graver?  
Venstre ☐ Begge ☐ Højre ☐
9. Give kort?  
Venstre ☐ Begge ☐ Højre ☐
10. Holde om hammeren når du slår et søm i?  
Venstre ☐ Begge ☐ Højre ☐
11. Holde om tandbørsten når du børster tænder?  
Venstre ☐ Begge ☐ Højre ☐
12. Skru låget af et glas?  
Venstre ☐ Begge ☐ Højre ☐

**Hvilken fod bruger du for det meste til at:**

Sparke til en bold?  
Venstre ☐ Begge ☐ Højre ☐
Sætte af med når du springer?  
Venstre ☐ Begge ☐ Højre ☐

**Hvis du kigger gennem røret på en køkken- eller toiletrulle.**  
Hvilket øje kigger du med?  
Venstre ☐ Højre ☐

**Prøv at kigge gennem et nøglehul (både udefra og indefra):**

Hvilket øje kigger du med når nøglehullet sidder til venstre?  
Venstre ☐ Højre ☐
Hvilket øje kigger du med når nøglehullet sidder til højre?  
Venstre ☐ Højre ☐

**Spiller du på et eller flere instrumenter?**  
JA ☐ NEJ ☐

**Hvis JA:**  
Hvilke(t) instrument?
Hvor mange bokse kan du krydse af på et minut?
Denne øvelse går ud på at sætte kryds i så mange bokse du kan nå på et minut. Lad din mor eller far tage tid med ‘minutglasset’ og sige start, når minutglasset vendes og stop, når det er løbet ud. Start i den grå boks i øverste venstre hjørne og gå mod højre. Når du er færdig med den første række, så gå videre med rækken lige under på samme måde. Øverst på siden har vi vist hvordan (demonstration).
Start med den hånd du normalt bruger til at skrive med. Vi vil bede dig lave to forsøg med hver hånd.

Venstre hånd (demonstration):


Venstre hånd (første forsøg): Sæt så mange krydser du kan nå på 1 minut (et timeglas)


Venstre hånd (andet forsøg): Sæt så mange krydser du kan nå på 1 minut (et timeglas)
Det tager fire minutter at lave de fire forsøg

Højre hånd (demonstration)

Højre hånd (første forsøg): Sæt så mange krydser du kan nå på 1 minut (et timeglas)

Højre hånd (andet forsøg): Sæt så mange krydser du kan nå på 1 minut (et timeglas)
**Tegning rundt om dine fingre:**

Til sidst vil vi bede din mor eller far tegne rundt om dine fingre.

Det er vigtigt, at du:

- holder håndfladen mod papiret så lillefingrene følger de prikkede linier
- samler fingrene helt

Det er også vigtigt, at din mor eller far

- **tegner helt tæt** rundt om fingrene
- tegner med tuschen/kuglepennen/blyanten holdt **lodret**

![Diagram af venstre hånd](image1)

![Diagram af højre hånd](image2)
Forældrene til
Hans Hansen
Hanegalet 2
8462 Harlev J

Projekt nummer: 00001

Deltagere i undersøgelsen
Børn født i Århus 1990-1992

Spørgeskema
om opmærksomhed
og aktivitet
Først vil vi bede dig vurdere om beskrivelserne i skemaet ikke passer, passer delvist eller passer godt på barnet. Det vil være os en stor hjælp, hvis du besvarer alle spørgsmålene også selvom du er i tvivl eller synes at beskrivelserne ikke helt giver mening i forhold til barnets alder. Vi vil bede dig svare ud fra barnets opførsel i det sidste halve år.

<table>
<thead>
<tr>
<th>Denne Beskrivelse</th>
<th>Passer ikke</th>
<th>Passer delvist</th>
<th>Passer godt</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Er hensynsfuld og betænksom over for andre</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Er rastløs, ‘overaktiv’, har svært ved at holde sig i ro i længere tid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Klager ofte over hovedpine, ondt i maven eller kvalme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Er god til at dele med andre børn (slik, legetøj, blyanter)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Har ofte raserianfald eller bliver let hidsig</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Er lidt af en enspænder, leger mest alene</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Gør for det meste, hvad der bliver sagt</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Bekymrer sig om mange ting, virker ofte bekymret</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Prøver at hjælpe, hvis nogen slår sig, er kede af det eller skidt tilpas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10. Sidder konstant uroligt på stolen, har svært ved at holde arme og ben i ro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Har mindst én god ven</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Kommer ofte i slagsmål eller mobber andre børn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Er ofte ked af det, trist eller har let til gråd</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Er generelt vellidt af andre børn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Er nem at distrahere, mister let koncentrationen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Er utryg og klæbende i nye situationer, bliver nemt usikker på sig selv</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Er god mod mindre børn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Lyver eller snyder ofte</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Bliver mobbet eller drillet af andre børn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Tilbyder ofte af sig selv at hjælpe andre (forældre, lærere, børn)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Tænker sig om, før han/hun handler</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Stjæler fra hjemmet, i skolen eller andre steder</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23. Kommer bedre ud af det med voksne end med andre børn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Er bange for mange ting, er nem at skræmme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Gør tingene færdige, er god til at koncentrere sig</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
26. Samlet, mener du barnet har vanskeligheder på et eller flere af følgende områder?
- det følelsesmæssige område
- koncentration
- adfærd
- samspil med andre mennesker

<table>
<thead>
<tr>
<th>NEJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>JA, mindre vanskeligheder</td>
</tr>
<tr>
<td>JA, tydelige vanskelighed</td>
</tr>
<tr>
<td>JA, alvorlige vanskelighed</td>
</tr>
</tbody>
</table>

**Hvis JA:** vær venlig at besvare resten af spørgsmålene på denne side (a-g):

<table>
<thead>
<tr>
<th>a. Hvor længe har disse vanskeligheder stået på?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mindre end 1 måned</td>
</tr>
<tr>
<td>1-5 måneder</td>
</tr>
<tr>
<td>6-12 måneder</td>
</tr>
<tr>
<td>Mere end et år</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. Er barnet ulykkelig eller ked af disse vanskeligheder?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slet ikke</td>
</tr>
<tr>
<td>Kun lidt</td>
</tr>
<tr>
<td>Ret meget</td>
</tr>
<tr>
<td>Virkelig meget</td>
</tr>
</tbody>
</table>

Påvirker disse vanskeligheder barnets dagligdag:

<table>
<thead>
<tr>
<th>c. Derhjemme?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slet ikke</td>
</tr>
<tr>
<td>Kun lidt</td>
</tr>
<tr>
<td>Ret meget</td>
</tr>
<tr>
<td>Virkelig meget</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>d. I barnets forhold til jævnaldrende?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slet ikke</td>
</tr>
<tr>
<td>Kun lidt</td>
</tr>
<tr>
<td>Ret meget</td>
</tr>
<tr>
<td>Virkelig meget</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>e. Med hensyn til indlæring i skolen?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slet ikke</td>
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</tr>
<tr>
<td>Ret meget</td>
</tr>
<tr>
<td>Virkelig meget</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>f. I forbindelse med fritidsaktiviteter?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slet ikke</td>
</tr>
<tr>
<td>Kun lidt</td>
</tr>
<tr>
<td>Ret meget</td>
</tr>
<tr>
<td>Virkelig meget</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>g. Er disse vanskeligheder en belastning for dig eller familien som helhed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slet ikke</td>
</tr>
<tr>
<td>Kun lidt</td>
</tr>
<tr>
<td>Ret meget</td>
</tr>
<tr>
<td>Virkelig meget</td>
</tr>
</tbody>
</table>
De sidste spørgsmål drejer sig om begge forældres opmærksomhed og aktivitet i skoletiden. Vi er klar over, at det kan være svært at huske så langt tilbage, men vi vil bede dig/jer prøve alligevel.

27. Hvordan passede følgende beskrivelser på barnets mor, da hun gik i folkeskolen?

<table>
<thead>
<tr>
<th>Beskrivelse</th>
<th>Passede ikke</th>
<th>Passede delvist</th>
<th>Passede godt</th>
<th>Ved ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Var rastløs, ‘overaktiv’, havde svært ved at holde sig i ro i længere tid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Sad konstant uroligt på stolken, havde svært ved at holde arme og ben i ro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Var nem at distrahere, mistede let koncentrationen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Tænkte sig om før hun handlede</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Gjorde tingene færdige, var god til at koncentrere sig</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

28. Hvordan passede følgende beskrivelser på barnets far, da han gik i folkeskolen?

<table>
<thead>
<tr>
<th>Beskrivelse</th>
<th>Passede ikke</th>
<th>Passede delvist</th>
<th>Passede godt</th>
<th>Ved ikke</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Var rastløs, ‘overaktiv’, havde svært ved at holde sig i ro i længere tid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Sad konstant uroligt på stolken, havde svært ved at holde arme og ben i ro</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Var nem at distrahere, mistede let koncentrationen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Tænkte sig om før han handlede</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>e. Gjorde tingene færdige, var god til at koncentrere sig</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dato for udfyldelse af spørgeskemaet: _________ / _________ 2002

Hvem har udfyldt spørgeskemaet?

Biologisk mor
Biologisk far

Anden person, som kender barnet: ____________________________

Mange tak for hjælp! Har du bemærkninger eller tilføjelser, kan du skrive dem her eller eventuelt vedlægge et ekstra stykke papir.
Børn født i Århus
1990-92

Spørgeskema til deres klasselærer
Dette spørgeskema er besvaret af

Fornavn:_______________________________________________________________

Efternavn:______________________________________________________________

Dato for udfyldelse af skemaet (dag/måned-år) ............................. ____ / ____-2002

Spørgsmål om dette spørgeskema bedes rettet til læge Carsten Obel, Forskningsenheden på fødeafdelingen Skejby Sygehus, 8200 Århus N

telefon 89496380, Email obel@aarhus-born.dk
1. Hvad er din relation til eleven?          Jeg er elevens klasselærer □ 1  

Anden relation________________________________________________________ □ 2

2. Hvor længe har du kendt eleven?          _________________________    år og ______ måneder

3. Hvor godt kender du ham/hende?          _________________________    Meget godt □ 1  

Nogenlunde godt □ 2  

Ikke særlig godt □ 3

4. I hvilke fag har du haft eleven i det forløbne skoleår?  (evt. flere krydser)  _________________________  Dansk □ 1  

Matematik □ 2  

Natur og teknik □ 3  

Engelsk □ 4  

Historie □ 5  

Idræt/svømning □ 6

Andre fag ________________________________ □ 7

5. Har der været iværksat specielle tiltag for eleven? (specialundervisning, støttelærer, centerklasse eller lignende) ________________________________  NEJ, aldrig □ 1  

JA, tidligere □ 2  

JA, aktuelt □ 3  

Ved ikke □ 4

Hvis JA, hvilke tiltag og på hvilket klassetrin?

6. Har eleven mentale eller fysiske handicap?          JA □  NEJ □

Hvis JA, beskriv venligst

•
Sammenlignet med typiske elever på samme alderstrin, hvordan klarer eleven sig i følgende fag?

<table>
<thead>
<tr>
<th></th>
<th>Meget under gennemsnitt</th>
<th>Noget under gennemsnitt</th>
<th>Som gennemsnitt</th>
<th>Noget over gennemsnitt</th>
<th>Meget over gennemsnitt</th>
</tr>
</thead>
<tbody>
<tr>
<td>7. Læsning?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>8. Stavning?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>9. Matematik?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>10. Natur og teknik?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>11. Engelsk?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>12. Historie?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>13. Idræt?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>

Sammenlignet med typiske elever på samme alderstrin, hvordan vurderer du eleven, når det gælder:

<table>
<thead>
<tr>
<th></th>
<th>Meget under gennemsnitt</th>
<th>Noget under gennemsnitt</th>
<th>Som gennemsnitt</th>
<th>Noget over gennemsnitt</th>
<th>Meget over gennemsnitt</th>
</tr>
</thead>
<tbody>
<tr>
<td>14. Arbejdsindsats?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>15. Opførsel?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>16. Indlæringsevne?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>17. Koncentrationsevne?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>18. Humør?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>19. Sproglig formulering?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>20. Grovmotorik?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>21. Finmotorik?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>22. Social funktion?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
<tr>
<td>23. Aktivitetsniveau?</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
<td>☐ 4</td>
<td>☐ 5</td>
</tr>
</tbody>
</table>

24. Når eleven er i gang med noget i klassen, som han/hun kan lide at lave (skrive, regne, tegne eller anden skoleaktivitet):  
Hvor længe er han/hun typisk beskæftiget med denne aktivitet:

- Mindre end 2 minutter ☐ 1  
- 2-4 minutter ☐ 2  
- 5-9 minutter ☐ 3  
- 10-19 minutter ☐ 4  
- 20 minutter eller mere ☐ 5  


25. **Spørgsmål om elevens styrker og vanskeligheder**

Vi vil bede dig vurdere, om beskrivelserne i skemaet ikke passer, passer delvist eller passer godt på eleven. Det vil være os en stor hjælp, hvis du besvarer alle spørgsmålene også selvom du er i tvivl eller synes at beskrivelserne ikke helt giver mening i forhold til elevens alder. Vi vil bede dig svare ud fra elevens opførsel i det forløbne skoleår.

<table>
<thead>
<tr>
<th></th>
<th>Passer ikke</th>
<th>Passer delvist</th>
<th>Passer godt</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Er hensynsfuld og betænksom over for andre</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>b. Er rastløs, ‘overaktiv’, har svært ved at holde sig i ro i længere tid</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>c. Klager ofte over hovedpine, ondt i maven eller kvalme</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>d. Er god til at dele med andre børn (slik, legetøj, blyanter)</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>e. Har ofte raserianfald eller bliver let hidsig</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>f. Er lidt af en enspænder, leger mest alene</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>g. Gør for det meste, hvad der bliver sagt</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>h. Bekymrer sig om mange ting, virker ofte bekymret</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>i. Prøver at hjælpe, hvis nogen slår sig, er kede af det eller skidt tilpas</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>j. Siddes konstant uroligt på stolen, har svært ved at holde arme og ben i ro</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>k. Har mindst én god ven</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>l. Kommer ofte i slagsmål eller mobber andre børn</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>m. Er ofte ked af det, trist eller har let til gråd</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>n. Er generelt vellidt af andre børn</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>o. Er nem at distrahere, mister let koncentrationen</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>p. Er utryg og klæbende i nye situationer, bliver nemt usikker på sig selv</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>q. Er god mod mindre børn</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>r. Lyver eller snyder ofte</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>s. Bliver mobbet eller drillet af andre børn</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>t. Tilbyder ofte af sig selv at hjælpe andre (forældre, lærere, børn)</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>u. Tænker sig om, før han/hun handler</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>v. Stjæler fra hjemmet, i skolen eller andre steder</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>x. Kommer bedre ud af det med voksne end med andre børn</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>y. Er bange for mange ting, er nem at skræmme</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
<tr>
<td>z. Gør tingene færdige, er god til at koncentrere sig</td>
<td>☐ 1</td>
<td>☐ 2</td>
<td>☐ 3</td>
</tr>
</tbody>
</table>
26. Samlet, mener du, at eleven har vanskeligheder på et eller flere af følgende områder?
- det følelsesmæssige område
- koncentration
- adfærd
- samspil med andre mennesker

NEJ □ 1
JA, mindre vanskeligheder □ 2
JA, tydelige vanskeligheder □ 3
JA, alvorlige vanskeligheder □ 4

Hvis JA, vær venlig at besvare følgende spørgsmål:

a. Hvor længe har disse vanskeligheder stået på?
   Mindre end 1 måned □ 1
   1-5 måneder □ 2
   6-12 måneder □ 3
   Mere end et år □ 4

b. Er eleven ulykkelig eller ked af disse vanskeligheder?
   Slet ikke □ 1
   Kun lidt □ 2
   Ret meget □ 3
   Virkelig meget □ 4

Påvirker disse vanskeligheder elevens dagligdag:

c. I elevens forhold til jævnaldrende?
   Slet ikke □ 1
   Kun lidt □ 2
   Ret meget □ 3
   Virkelig meget □ 4

d. Med hensyn til indlæring i skolen?
   Slet ikke □ 1
   Kun lidt □ 2
   Ret meget □ 3
   Virkelig meget □ 4

e. Er disse vanskeligheder en belastning for dig eller klassen som helhed?
   Slet ikke □ 1
   Kun lidt □ 2
   Ret meget □ 3
   Virkelig meget □ 4
27. Har eleven særlige stærke sider, som du ønsker at uddybe, eller som dette spørgeskema ikke dækker?  

JA □  NEJ □ 

Hvis JA: 
beskriv venligst

28. Har eleven særlige vanskeligheder, som du ønsker at uddybe, eller som dette spørgeskema ikke dækker?  

JA □  NEJ □ 

Hvis JA: 
beskriv venligst

29. Må vi eventuelt kontakte dig for yderligere oplysninger om eleven?  
(selv om du svarer ja, forpligter du dig ikke til at svare på en eventuel henvendelse).  

JA □  NEJ □ 

Mange tak

fordi du ville have ulejlighed med at udfylde spørgeskemaet.

På bagsiden af skemaet er der mulighed for at skrive eventuelle bemærkninger
Label med
Skolens navn
Evt lærers navn
Barnets navn
RAPPORTER FRA PERINATAL EPIDEMIOLOGISK FORSKNINGSENHED,
GYNÆKOLOGISK/OBSTRETISK AFDELING, AARHUS UNIVERSITETSHOSPITAL, SKEJBY

Diplom- og forskningsårsopgaver

Henriksen TB. Status over en cohort-undersøgelse i Århus: Et follow-up studie om arbejds-miljømæssige belastningsfaktorers indflydelse på graviditet, fødsel og barn. Aarhus 1990.


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**Ph.D. afhandlinger**


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**Doktorafhandlinger**

RAPPORTER FRA INSTITUT FOR EPIDEMIOLOGI OG SOCIALMEDICIN, AARHUS UNIVERSITET


(continued)
RAPPORter fra INSTITUT FOR EPIDEMIOLOGI OG SOCIALMEDICIN, AARHUS UNIVERSITET


