Chapter 1

General introduction
In foetal life and in early childhood, rapid developmental processes in the central nervous system enable a child to adapt to the demands of the environment. However, if children are exposed to early adversities, such as preterm birth and low socioeconomic status (SES), the normal neurodevelopmental processes may come under threat. Early adversities may cause permanent changes in brain and body functions, potentially affecting the foundations of mental and physical health. The main aim of this thesis was to determine the associations between moderate to late prematurity, SES, and pre-school neurodevelopmental problems, and to consider the underlying neurodevelopmental processes from a life course perspective.

BACKGROUND

Moderate prematurity
Worldwide, approximately 10% of live births are preterm, that is birth before 37 weeks of gestation. Of the 12.9 million children concerned, up to 85% are born between 32 and 37 weeks of gestation. Children born within this gestational age-range are referred to as moderately preterm (MP) and late preterm. In the Netherlands, approximately 10,000 births per year are within this age range. Due to the large number of children involved, MP and late preterm-born children contribute substantially to the societal burden associated with preterm birth. By contrast, the individual burden is higher in very preterm children (born before 32 weeks' gestation), as the risks of mortality and morbidity are much higher. Therefore, up to fifteen years ago researchers were particularly interested in outcomes following very preterm birth, but we now know that MP children too face significantly more neonatal and developmental problems than full-term children do. Examples of neonatal morbidities occurring in MP and late preterm-born children are temperature instability and hyperbilirubinemia, which often lead to a longer stay in hospital. Furthermore, in the longer term, MP and late preterm-born children have an increased risk of developmental and neurobehavioral problems, such as developmental delay, and social and functional difficulties at school age. In the following paragraphs, we describe what is currently known about developmental outcomes, as well as behavioural and emotional outcomes in MP children.
Developmental outcomes

The risk of developmental delay in four-year-old, MP children is twice that of full-term children and half that of very preterm-born children. Developmental delay refers to a condition in which a child has not achieved one or more skills, or 'milestones', at the age at which most other children have reached these particular milestones. Prevalence rates of developmental delay increase exponentially with decreasing gestational age, as depicted in Figure 1. In MP children the prevalence varies from 6% to 11% for gestational weeks 32 to 36, compared to 4% on average in full-term children. More specifically, we found that MP children show more delay in fine motor, communication, problem-solving, and personal-social functioning at preschool age. Later on, developmental impairments may continue to cause problems at primary school, as they may lead to poor handwriting and difficulties in motor coordination and verbal fluency. Furthermore, MP children frequently lag behind their peers in executive functioning, attention, and visuospatial reasoning.

![Figure 1](image)

**Figure 1** Exponential association between gestational age and developmental delay (i.e. abnormal total-problems score on the Ages and Stages Questionnaire, ASQ). The white bars depict the expected percentages of developmental delay according to an exponential model. The black bars depict the real percentages. Adapted from Kerstjens et al.
Behavioural and emotional outcomes

Recent insights showed that developmental and behavioural and emotional disabilities have bumped physical disabilities from the throne as the leading cause of daily limitations in children. From early childhood onwards, prevalence rates of behavioural and emotional problems gradually increase, rising from 5% up to as high as 40% in adolescence, with a high risk of persisting into adulthood. Behavioural and emotional problems have an impact on the developmental and social competencies of children, both at school and in the community at large.

Evidence concerning behavioural and emotional outcomes among MP children is limited compared to the wealth of articles reporting on these outcomes in very preterm-born and/or children with low birth weight. In a Dutch study, 13% of five-year-old, very preterm-born and/or children with low birth weight had clinical-range behavioural and emotional problems, as measured by the Child Behavior Checklist (CBCL). As is the case in full-term girls and boys, preterm girls also tend to have more emotional problems, such as withdrawn behaviour, while preterm boys tend to have more externalizing problems, especially attention problems.

Studies on behavioural and emotional problems in MP and late preterm-born children have shown conflicting results, although most studies did find that behavioural and emotional problems occurred more often in MP children, particularly regarding attention and internalizing problems. Conversely, one study showed no differences in externalizing, internalizing, aggressive, and anxious/depressed problems in comparison to full-term children. The studies mentioned here, however, included relatively small samples of MP and late preterm-born children, or they lacked a control group of full-term children. Moreover, evidence on early emerging behavioural and emotional problems in preschool-aged children is very limited. In summary, there is a need for larger cohort studies on MP children in order to assess the full range of behavioural and emotional problems at pre-school age. These studies should include full-term control groups.

Co-occurrence of developmental and behavioural problems

The presence of co-occurring developmental and behavioural problems in early childhood increases the risk of psychiatric disorders at older ages considerably. Children with developmental delay are much more likely to have co-occurring behavioural and emotional problems than children without developmental delay. A combination frequently seen is motor problems, such as coordination...
problems, co-occurring with attention-deficit/hyperactivity disorder. The origin of co-occurring problems is still unclear. In some cases, the behavioural problems may be caused by the underlying developmental delay.\textsuperscript{38} Children with language problems, for example, may show disruptive behaviour because of their inability to express themselves sufficiently. Another hypothesis is that developmental and behavioural problems have common grounds, such as particular brain network aberrations that may arise in early neurodevelopment.\textsuperscript{39}

Little is known on the subject of co-occurrence of developmental and behavioural problems in preterm-born children. A few studies have shown higher rates of co-occurring problems in very preterm-born children.\textsuperscript{40, 41} Up to half of the preterm-born children appeared to have more than one developmental or behavioural disability at the age of five years, compared to 8% in full-term children.\textsuperscript{40, 41} As yet, in MP children, however, the prevalence of co-occurring developmental and behavioural problems is unknown. Furthermore, to the best of our knowledge, MP children have not been compared with full-term children regarding co-occurrence. If a trend towards increasing co-occurrence rates with decreasing gestational age were to be found, this could provide clues for the underlying mechanisms of co-occurring problems. In the case of MP children, the lack of three to eight weeks of intrauterine brain growth might increase the likelihood of the type of brain network aberrations suggested in the literature.

**Influence of socioeconomic status on neurodevelopmental problems**

Low family SES is strongly associated with developmental and behavioural and emotional problems.\textsuperscript{24, 42} One important pathway explaining this association is the higher prevalence of stress-inducing situations in socioeconomically disadvantaged families.\textsuperscript{43, 44} Experiences of early life adversities show a clear dose-response relationship with cardiovascular and mental health problems throughout life.\textsuperscript{43, 45, 46} Low SES and associated circumstances may even cause permanent changes in brain functions and body regulation systems, affecting the foundations of mental and physical health.\textsuperscript{47, 48}

*Is low SES an explanation for worse neurodevelopmental outcomes in MP children?*

The effects of moderate prematurity on developmental, behavioural, and social-emotional problems may be different in children from low SES families.\textsuperscript{49} First of all, preterm delivery is more likely to occur in mothers with low SES.\textsuperscript{50-52} In
socioeconomically deprived areas up to 12% of deliveries are preterm, compared to 3% to 7% in prosperous areas. One of the explanations for this difference is that many risk factors for preterm delivery are socioeconomically graded, such as obesity, hypertension, smoking, psychological stress, and inadequate use of prenatal care.

As mentioned previously, children from low SES families are more likely to be exposed to early adversities than children from high SES families. Early adversities have been linked with altered functioning of several brain areas and body regulation systems and with lower psychological well-being of parents, which affects parent-child interactions. Anyhow, low family SES increases the likelihood of developmental and behavioural problems in offspring, and this may, at least partly, explain why MP children are at greater risk of neurodevelopmental problems than full-term children.

How to measure SES?
SES is defined as “an individual’s or group’s position within a hierarchical social structure”. Several indicators have been used to measure SES, and they all refer to societal stratification in a slightly different way. Education, occupation, and income are the SES indicators that are most frequently used in health research. The level of education reflects cognitive capacity, opportunities for education, parents’ education and its influence on their children, and the resources available to the family. Occupation is related to social standing, the ability to build up networks, the degree of work-related stress, autonomy, and job-related, exposure to toxic substances. Higher occupational class does not necessarily stand for better health conditions. Effects of work-related stress may, for example, be greater in higher than in lower occupations. Income reflects material resources which could mean easier access to social and medical services, more self-esteem and social standing, and it allows consumption of health-promoting commodities. Because of the interrelationships between different SES indicators, composite SES measures of these indicators provide investigators with the opportunity to fully account for the effects that can be attributed to socioeconomic conditions.

A life course perspective on neurodevelopment
Potentially, disruptions of neurodevelopment in the prenatal period and early postnatal years have lifelong effects on health. Evidence is accumulating that early adverse events and environments, such as maternal stress during pregnancy
and socioeconomic disadvantage early in life, lead to neurodevelopmental disorders in childhood and psychiatric and cardiovascular disorders in adulthood.\textsuperscript{43, 45, 46, 66-68} Nevertheless, much still needs to be unravelled regarding underlying disease mechanisms.\textsuperscript{69, 70} Below, we begin by providing a brief summary of the literature on the developmental origins of health and disease followed by a description of what is known on the subject of healthy emotional functioning in childhood in relation to coronary heart disease (CHD).

**Developmental Origins of Health and Disease (DOHaD)**

The DOHaD concept has its roots in the Barker Hypothesis. In the 1980s and early 1990s, Barker and his colleagues discovered the link between low birth weight, which reflects impaired foetal growth, and CHD. Later, this was referred to as the Barker Hypothesis.\textsuperscript{68, 71} According to Barker, the link could be regarded as a ‘manifestation of developmental plasticity’, which he described as ‘a critical period when a system is plastic and sensitive to the environment, followed by loss of plasticity and fixed functional capacity.’\textsuperscript{68} In other words, the rapid neurodevelopmental processes that take place in foetal life and early childhood,\textsuperscript{1} may function to provide a human being with opportunities to adapt to the demands posed by the environment.

In recent decades, many indicators of early environmental adversity have been incorporated in the DOHaD concept, including malnutrition and exposure to infection and stress,\textsuperscript{72-74} and knowledge on this topic is still expanding. As such, various early stressful experiences have been associated directly with altered functioning of several areas of the brain and regulation systems of the body, for example, those involving the hypothalamic-pituitary-adrenal axis circuitry.\textsuperscript{55, 56, 69, 75} Combined with clinical and epidemiological research, these findings provide further clues for underlying mechanisms explaining the links between early adverse environments, neurodevelopmental problems, affective disorders, and coronary heart disease.\textsuperscript{69, 76}

**Affective disorders, childhood emotional functioning, and the risk of CHD**

During the past sixty years, in their endeavour to understand the aetiology of CHD, investigators have become increasingly interested in psychosocial factors.\textsuperscript{46} Psychosocial risk factors for CHD can be broadly subdivided into affective disorders (anxiety/depression), personality features, and chronic psychological stress, either work-related or private. The strongest evidence was found for the association between
Affective disorders and CHD. The underlying mechanisms for causal associations between psychosocial factors and CHD are gradually becoming clearer. Mainly two pathways were suggested: 1) an indirect mechanism via the effect of psychosocial factors on lifestyle-associated risk factors for CHD, such as body mass index and smoking, and 2) a direct mechanism via the adverse effects of psychological stress on body regulation systems that affect cardiovascular reactivity.\textsuperscript{77,78}

Affective disorders and CHD may have common origins in foetal development and early childhood given the high co-occurrence of depression and CHD.\textsuperscript{69} Nevertheless, as mentioned earlier, many disease mechanisms are yet to be unravelled. This also applies to the pathways between early neurodevelopmental disruptions, depression, and CHD many years later. Recently, associations between several indicators of poor childhood emotional functioning and CHD precursors were investigated.\textsuperscript{79,80} Emotional functioning has its roots in early childhood,\textsuperscript{81,82} and may be a plausible explanation for developmental origins of affective disorders and CHD.\textsuperscript{80,83} More specifically, deficits in emotion regulation, one dimension of emotional functioning, may play a role in the onset of depressive disorders,\textsuperscript{83} but it has not yet been associated with CHD. Refinement of this hypothesis may offer opportunities for clinical and prevention purposes that are potentially beneficial to many individuals, including preterm-born and low SES children.\textsuperscript{84,85}

**OUTLINE OF THE THESIS**

The overall aim of the studies presented in this thesis was to determine the associations between moderate prematurity, SES, and pre-school neurodevelopmental problems, and to consider the underlying neurodevelopmental processes from a life course perspective. The specific research questions were:

1. Are moderate prematurity and low SES independently associated with developmental delay at pre-school age, or do they have joint effects? (Chapter 2)
2. What is the prevalence of behavioural and emotional problems in four-year-old, moderately preterm-born children, compared to the prevalence in full-term children? (Chapter 3)
3. Are moderate prematurity and low SES independently associated with behavioural and emotional problems at pre-school age, or do they have joint effects? (Chapter 4)
4. What is the prevalence of developmental delay co-occurring with behavioural and emotional problems in four-year-old, moderately preterm-born children compared to the prevalence in full-term controls? (Chapter 5)

5. Does poor emotion regulation in 18-year-olds predict the risk of coronary heart disease? (Chapter 6)

In order to answer the first four research questions ( Chapters 2 to 5), we used data from the Longitudinal Preterm Outcome Project (LOLLIPOP), a Dutch prospective cohort study. It was designed to investigate growth, development, and general health of preterm-born children, with a special focus on those children who were born moderately preterm. The participants were recruited from thirteen preventive child healthcare (PCH) centres during 2006 and 2007. In the Netherlands, the development of children is closely monitored by PCH centres from birth up to four years of age. This service, which is free, is offered actively and systematically to all Dutch families and reaches 95% to 97% of the Dutch child population. More details on the sampling procedures are displayed in the flow chart in Appendix 1.

In Chapter 2, we determine the influence of SES on developmental delay in MP children and full-term children. This is followed in Chapters 3 and 4, by our comparison of MP and full-term children regarding behavioural and emotional problems at preschool age, overall and by gender. Chapter 4 focuses on the effect of SES on behavioural and emotional problems in MP children. Next, in Chapter 5, we report on our investigation of the co-occurrence of developmental and behavioural problems in MP and full-term children at the age of four years. The Ages and Stages Questionnaire (ASQ) and CBCL were used to assess developmental and behavioural outcomes. The ASQ is a parent-completed screening instrument that has been validated for many countries, including the Netherlands. It measures development in five developmental domains: fine motor, gross motor, communication, problem solving, and personal-social. The CBCL is also a parental questionnaire that is widely used in various clinical settings and in research. Scores on CBCL items can be added up to provide a score for internalizing and externalizing problems. To serve as an example, the Dutch versions of the ASQ and CBCL that were used in the LOLLIPOP study are included in Appendices 2 and 3, respectively.

In Chapter 6, we describe the role of young individuals’ emotional functioning for lifelong health. We investigated the association between one dimension of
emotional functioning, i.e. emotion regulation, and the long-term risk of heart disease. For this study, we used data from a nationwide survey of Swedish males who were conscripted for compulsory military service in 1969 and 1970. The procedures and variables of this study were described elsewhere.\textsuperscript{89, 90}

Finally, in Chapter 7, which comprises the General discussion, we provide an overview of the main findings and discuss these in the light of the relevant literature. This chapter ends with several implications for clinical practice, policy, and research. Chapter 8 contains the English and Dutch summaries of the research presented in this thesis.
References


55. Huang LT. Early-life stress impacts the developing hippocampus and primes seizure occurrence: cellular, molecular, and epigenetic mechanisms. *Front Mol Neurosci* 2014; Feb 10;7:8.
Chapter 1


