Chapter 7

General discussion
Chapter 7

The main aim of 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. This chapter includes an overview of the main findings and a discussion of the findings in the light of the relevant literature. Finally, implications for clinical practice, policy, and research are given.

MAIN FINDINGS

Research question 1 (Chapter 2): Are moderate prematurity and low SES independently associated with developmental delay at pre-school age, or do they have joint effects?

We hypothesized that differences in SES could partially explain the association of moderate prematurity with developmental delay. Findings from multivariate logistic regression analyses showed that this was not the case: moderate prematurity and low SES had separate, multiplicative effects on developmental delay. Prevalence rates for overall developmental delay were 12.5% in MP children with low SES, compared to 2.8% in full-term children with high SES. In particular, the developmental domains fine motor skills, communication, and personal-social skills were affected in MP children. Neither moderate prematurity nor low SES was associated with delay in gross motor skills, and finally, low SES mainly explained the occurrence of problem-solving skills at the age of four years.

Research question 2 (Chapter 3): 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?

We found that the rates of behavioural and emotional problems were higher in MP children than in full-term children. MP children had poorer mean scores on all CBCL syndrome scales, i.e. emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, and aggressive behaviour. They were also more likely to have scores in the clinical range, on total problems, externalizing problems, internalizing problems, and somatic complaints. Lastly, prevalence rates of behavioural and emotional problems differed by gender: overall the prevalence rates were higher among preterm-born boys and full-term boys, while being born moderately preterm affected girls more than boys.
Research question 3 (Chapter 4): Are moderate prematurity and low SES independently associated with behavioural and emotional problems at pre-school age, or do they have joint effects?

We hypothesized that low SES could explain why 8% to 10% of MP children struggle with behavioural and emotional problems. Therefore, our aim was to determine the separate and joint effects of moderate prematurity and low SES. We demonstrated that MP birth and low SES had separate, multiplicative effects on behavioural and emotional problems. This result did not confirm our hypothesis since we expected that low SES would partly explain the effects of moderate prematurity. In line with the gender differences shown in Chapter 3, girls were also more susceptible to the effects of low SES than boys. The difference between MP girls from low and from high SES families was great: 13.0% of the low SES girls had clinical-range problems, compared to an average of 4.9% in all girls participating in the study.

Research question 4 (Chapter 5): What is the prevalence of developmental delay co-occurring with emotional and behavioural problems in four-year-old, moderately preterm-born children compared to the prevalence in full-term controls?

In the total study population, 100 out of 1 441 children (6.9%) had some form of co-occurring developmental delay and emotional and behavioural problems. In the subgroup of MP children with developmental delay, on average 8%, rates of emotional and behavioural problems varied from 25% to 39% depending on the type of developmental delay. We also found that male gender, young maternal age, low SES, and non-Dutch ethnicity were significantly associated with co-occurrence. These factors were all included in the statistical analyses. The final statistical model showed a nearly twofold increase in the risk of co-occurrence in MP children compared to full-term children.

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

Emotion regulation may be a fundamental competence contributing to the pathophysiology of coronary heart disease (CHD), in that it may influence the ability to cope with emotional events. We found that poor emotion regulation at the age of 18 was associated with a higher cumulative incidence of CHD, bridging a time span of nearly 40 years. Overall, the point estimates were fairly robust in multivariable models including childhood socioeconomic position, anxiety,
depression, and parental history of CHD mortality. Full adjustment for lifestyle-associated factors largely attenuated the increased risk, and tests for mediation showed that the association between poor emotion regulation and CHD in the majority of the population was mainly through smoking, education, and cardiorespiratory fitness. Unexpectedly, we found that the association between poor emotion regulation and CHD was more pronounced in participants with a parental history of CHD than in those without, showing that the effect of poor emotion regulation on CHD goes beyond lifestyle-associated factors.

**DISCUSSION OF THE MAIN FINDINGS**

### Neurodevelopmental problems in MP children with low SES: some possible explanations

In Chapters 2 and 4 we found that moderate prematurity and low SES had separate effects on most developmental and behavioural outcomes. In other words, MP children are at risk of neurodevelopmental problems and low family SES further increases this risk. This finding coincides with other recent population-based studies: the effects of moderate prematurity seem to be robust, with low SES acting as an additional risk factor that contributes significantly to poorer neurodevelopmental outcomes.¹,²

Moderate prematurity and low SES may lead to neurodevelopmental problems via the following three pathways: 1) prenatal influences, 2) parental well-being and parental involvement during the pre-school years, and 3) disruptive effects of moderate prematurity and low SES on brain development. Many of the factors involved in these pathways have been linked to moderate prematurity as well as to low SES, suggesting common aetiological grounds.

#### Prenatal influences

Several prenatal factors, such as smoking, poor nutrition, and inadequate use of prenatal care, may lead to poorer neurodevelopmental outcomes in preterm-born and low SES children. These socioeconomically graded factors increase the risk of spontaneous preterm birth and other adverse pregnancy outcomes.³,⁴ We also know that antenatal maternal stress and anxiety contribute for approximately 15% to developmental and behavioural problems in offspring.⁵ Psychological stress during pregnancy is a strong and consistent risk factor for preterm birth, and
low SES has been identified as one of the main determinants of maternal distress during pregnancy.6, 7 The effects of maternal psychological stress on child health seem to persist long after birth: antenatal maternal stress has been associated with emotional and behavioural problems in childhood8 and with depression in adolescence.9

*Parental well-being and involvement during the pre-school years*

Neurodevelopmental problems may arise as a consequence of poor parental psychological well-being during the early pre-school years. Due to increased levels of stress, the quality of parenting and parent-child interactions decreases. Parents who experience psychological stress tend to be less attentive and less sensitive, or conversely, they tend to be overprotective.10-13 Either extreme may increase the risk of emotional and behavioural problems in children.14

Preterm birth and low SES have both been identified as potential sources of stress for families.10, 15, 16 Mothers of preterm children may experience more psychological stress due to concern about their child's health, which results in worrying, anxiety, and feeling depressed. Even mothers of children born late preterm experience more emotional distress than mothers of full-term children.10 Moreover, low SES may increase feelings of distress among parents, for example, concern about how to meet the family's needs.12 To stop young children from crying, parents exposed to high levels of SES-related stressors, such as unemployment and/or low income, also tend to resort to actions that could be qualified as child abuse.13 At the same time, low SES parents often have limited resources for financial and emotional support and more difficulties in accessing healthcare services.15 If parental psychological stress is not recognized and alleviated in time, the effects of psychosocial problems on offspring can be long-lasting, as illustrated by depressive symptoms in the long term.9

*Disruptive effects of moderate prematurity and low SES on brain development*

Moderate prematurity and low SES may have direct effects on brain development. At 32 weeks' gestation, the volume of the brain has reached only 60% of its volume at full-term gestation.17 At three months of age, after a period of rapid brain growth, the infant’s brain has already grown from one third to one half of adult brain volume.18 The lack of three to eight weeks of intrauterine brain growth may have consequences for neurodevelopment. Indeed, some specific alterations in
microstructural and neural connectivity processes have been found in the brains of preterm children. Given their developmental stage at birth, particularly MP and late preterm children particularly lack part of the intrauterine development of the limbic system and cerebellum, in which structural changes take place after 32 weeks of gestation. Therefore, lacking the last stage of intrauterine brain growth may later become manifest as difficulties in controlling complex motor or mental tasks. Corresponding with this biological explanation, impairments of MP children mainly include fine motor skills, handwriting, coordination, and verbal fluency, contrary to the much broader array of developmental problems, including gross motor problems, in very preterm children.

Findings from the field of neuroscience indicate that low SES affects brain development, in particular involving those brain structures that are relevant for language processing. Our study supports this notion, since low SES affected communication skills, including language comprehension, more so than other developmental domains. We found that 12.5% of full-term children with low SES had delay in communication skills compared to 2% of full-term children with high SES (Chapter 2). Importantly, the adverse effects of low SES in childhood do not stand on their own: prenatal factors, parent-child interactions, cognitive stimulation, and stress are all candidate mediators for the effects of low SES on brain development. For example, stress may mediate effects of low SES because it has been related directly to the altered functioning of several brain areas and regulation systems, including the limbic system, the cerebellum, and the hypothalamic-pituitary-adrenal axis.

**Influence of SES on specific developmental domains**

Low family SES had a greater influence on certain cognitive skills than on other developmental domains. First, problem solving skills in MP and full-term children were largely explained by SES, which confirms findings from prior studies. In preterm children born after 30 weeks of gestation, low parental educational level largely explained poorer cognitive outcomes, instead of preterm birth itself. Other researchers have estimated that the intelligence quotient decreases with two points per week of decrease in gestational age, but it is unclear whether this translates directly into delayed cognitive development and eventually lower educational attainment. The latter seems to depend on genetic and socioeconomic determinants rather than on the gestational age of the child, pointing at the prominent role of low family SES in long-term neurocognitive performance, in
particular regarding executive functioning. In summary, low SES is an important risk factor for delay in problem-solving skills, also in MP children.

We found intriguing, mixed effects of low SES and moderate prematurity on communication skills, implying that SES had less influence on these skills in MP children (Chapter 2). Across all SES levels, 8% to 10% of MP children had delay in communication skills, contrary to full-term children, in whom these rates increased markedly with decreasing SES (from 2% to 13%), as expected. One explanation for this finding may be that MP children with low SES had received more special care than full-term children with low SES, which may have diminished the adverse effects of low SES. This explanation is, however, refuted by the fact that MP children were generally not recognized as at risk of developmental delay before the LOLLIPPOP study commenced.

**Behavioural and emotional problems in MP children with developmental delay**

In comparison to full-term children, we found that MP children had higher rates of behavioural and emotional problems at pre-school age, which is consistent with findings from other studies. Most children, however, will not develop these problems at an early age, but some children are at high risk of developing such problems later on. Co-occurrence of developmental and behavioural problems is one of the predictors of persistent problems. Of the MP children with developmental delay, up to a third had some form of co-occurring developmental and behavioural problems, which is considerable. To the best of our knowledge, no prior studies on co-occurrence have been done on MP children, although it has been suggested previously that in these children motor coordination problems, such as clumsy, uncoordinated movements, occurred frequently in combination with inattention, hyperactivity, and impulsivity.

A number of neurophysiologic and psychosocial hypotheses have been proposed to explain why developmental and behavioural problems frequently co-occur. These hypotheses are partly in line with the main pathways that we proposed in order to explain higher rates of neurodevelopmental problems in MP and low SES children, i.e. the degree of parental well-being and involvement in the pre-school years, and the disruptive effects of moderate prematurity and low SES on brain development. Below, we briefly discuss two hypotheses that have been proposed in prior studies, and which may offer explanations for the emergence of co-occurring problems.
First, adverse family factors in the pre-school years may strengthen the effects of developmental delay on behavioural problems. As such, heightened levels of parental stress and negative parent-child interactions influence developmental delay as well as behavioural and emotional problems.\textsuperscript{41, 42} Due to the bi-directional relation between negative parenting and behavioural problems in children,\textsuperscript{43} an enduring downward spiral may ensue, and the risk of developmental delay co-occurring with behavioural and emotional problems may increase.

Second, co-occurrence of developmental and behavioural problems may be a consequence of disruptions in brain networks.\textsuperscript{40, 44} Children with specific brain network disruptions may be more vulnerable to exogenous or endogenous disturbances, resulting in a high risk of experiencing both developmental and behavioural problems. This hypothesis could explain why MP and late preterm-born children are more likely than full-term children to have co-occurring problems. Their lack of three to eight weeks of intrauterine brain development compared to full-term children may increase susceptibility to brain network disruptions.\textsuperscript{21, 22}

**Gender differences in behavioural and emotional outcomes**

Gender is an important determinant in the assessment of behavioural and emotional problems. In general, boys are more likely to have externalizing problems and girls have more internalizing problems, which is similar in preterm children.\textsuperscript{32, 45, 46} Our results confirm these general differences between boys and girls. However, in contrast to our expectations, MP boys did not differ in behavioural outcomes compared to full-term boys. By contrast, MP girls showed significantly more behavioural and emotional problems than their full-term peers, as reported in Chapters 3 to 5. Previous reports on such gender differences between MP and full-term children are scarce. One recent study on precursors of symptoms of attention deficit hyperactivity disorder in 5-year-old MP children reported similar outcomes: preterm girls showed significantly more inattentive behaviour, hyperactivity, and impulsivity than full-term girls and boys, as rated by mothers and teachers.\textsuperscript{38} A significant interaction between gender and gestational age was also found, indicating a stronger association between preterm birth and behaviour problems in girls.\textsuperscript{38}

In prior studies on MP children, a greater susceptibility of girls to moderate prematurity may have gone unnoticed because of insufficient sample sizes to perform stratified analyses. First of all, outcomes in MP girls have often been
compared with outcomes in MP boys, leaving out comparisons with full-term peers of the same gender. By doing so, the effects of gender were assessed instead of the gender-differential effects of moderate prematurity. Moreover, comparisons with other studies were limited because of variations in gestational age and age of assessment of developmental and behavioural outcomes.38, 46, 47 For a better comparison with our findings, larger cohorts of pre-school aged MP children are needed.

We also found that particularly preterm girls with low SES had poorer scores on externalizing and internalizing problems than girls overall. The prevalence rate of elevated total problems was 14% in MP girls with low SES compared to 4% in girls overall (Chapter 4). This may indicate that each additional neonatal or childhood adversity may have a multiplicative effect on girls’ emotions and behaviour. As such, low birth weight in combination with multiple socioeconomic adversities also has a greater effect on adolescent mental health than if only low birth weight were present.48 Nearly 100% of low birth weight girls with three or more adversities had depressive symptoms in adolescence.48 In summary, our findings are in agreement with the evidence that boys are more likely to have behavioural problems, but that girls, in particular, developed emotional and behavioural problems as a consequence of preterm birth and early socioeconomic adversity.

Explanations for gender differences

Previous research may provide some clues for explaining the gender differences we found. In the first place, gender differences in vulnerability to neonatal and social adversities may have their origins in foetal development. Evidence indicates that boys and girls have a different physiological response to increased levels of stress hormones.49, 50 A higher level of cortisol in pregnancy, as measure of maternal stress, has only been associated with more affective problems in 7-year-old girls, accounting for the effects of maternal depression during follow-up.49 Interestingly, the association between high maternal cortisol levels and affective problems was partly mediated by volume changes of the right-sided amygdala, a region of the brain involved in emotional functioning.49

Second, girls go through a more rapid process of cognitive and emotional development in the pre-school years than boys, and this may increase their vulnerability to emotional events and social-environmental adversities that influence normal development,51 such as lack of maternal warmth following
complications at birth. This hypothesis is supported by evidence showing that early experiences of stressful events, such as being bullied or the loss of a family member, have a greater impact on the mental health of girls than of boys throughout childhood, adolescence, and adulthood.\textsuperscript{52, 53}

Furthermore, cognitive perception of life adversities differs by gender. In boys and girls, cognitive errors, for example, overgeneralization and catastrophizing, influence emotion and behaviour in a different way. In boys, cognitive errors mediate the association between life adversity and hyperactivity while in girls they mediate the association between life adversity and peer and emotional problems.\textsuperscript{54}

It is unclear, however, to what extent such mechanisms have an impact at preschool age, considering the early stage of cognitive development.

**Poor emotional functioning and the risk of coronary heart disease**

Throughout life, indicators of poor emotional health have been associated with an increased risk of CHD and its metabolic precursors, including early life adversities,\textsuperscript{55} chronic psychological stress,\textsuperscript{56} mood disorders, and social isolation.\textsuperscript{57, 58} In Chapter 6, we provide evidence that the emotion regulation capacities of young people are not only associated with affective disorders, but also with CHD. This association was largely mediated through heavy smoking, poor cardiovascular fitness, and lower educational attainment in adulthood. Similarly, in prior research, lifestyle-associated factors were found to mediate the association between depression and CHD.\textsuperscript{59} Because of this link with lifestyle, improvement of emotion regulation skills may provide possibilities for the prevention of CHD, even in children. For example, 13-year-old teenagers with poor emotion regulation skills were more likely to consume junk food and to have sedentary lifestyles than peers with fair or good emotion regulation skills.\textsuperscript{60}

In men with a parental history of CHD, we found an association between poor emotion regulation and CHD beyond effects of lifestyle and education. This was an unexpected finding, which generated some thoughts regarding possible explanations. First, the association could partly be explained by the impact of parental mortality due to CHD. Conscript data were linked to data on CHD mortality of the conscripts’ parents, i.e. parental mortality before the age of 60 years. This meant that the conscripts were relatively young when one of their parents died. Therefore, the impact of early parental death may have caused mental and physical dysregulation that could eventually predispose to CHD. However, additional analyses for all-cause mortality, not due to CHD, did not explain the
association between poor emotion regulation and CHD risk. Second, the men with a familial risk of CHD might have had greater cardiovascular reactivity in response to emotionally charged events. Evidence from prior studies showed that individual differences in cardiovascular reactivity in response to psychological stress may have its origins in genetics.\textsuperscript{61-63} This theory may also have links with certain personality traits and mental disorders that predispose to a higher risk of CHD. For example, neuroticism, adjustment disorders, hostility, and anger have been associated with unhealthy responses to daily psychological stressors and higher risk of cardiovascular disease.\textsuperscript{58,64,65}

\textit{Developmental origins of emotional functioning}

The foundations for long-term emotional health are laid in the prenatal period and early postnatal years, which are characterized by rapid cognitive and social-emotional development.\textsuperscript{66} Therefore, the prenatal period and the early postnatal years are the most plastic and sensitive periods of life. This also implies a high vulnerability to early adverse environments.\textsuperscript{67} It is clear that experiences of early life adversity affect social-emotional functioning, but the exact mechanisms and links with long-term health problems are unclear. Emotion regulation capacity may be involved here, since it may function as a buffer for harmful effects of early adverse events and environments.\textsuperscript{15} For example, low SES children are more likely to have difficulties in emotion regulation, which hinders them in adequately responding on adverse events.\textsuperscript{66} This calls for further research.

Early adversities may also increase vulnerability in some individuals and promote resilience in others. One explanation for this finding is that coping with adverse experiences effectively has the function of preparing a child for similar challenges in adulthood.\textsuperscript{68} This may, however, only hold true if the child is capable of managing the challenges confronting him or her later on in life. Individuals who did not develop mental health problems after maltreatment in childhood were characterized by a higher number of protective factors, involving parental care, quality of relationships, and personality characteristics.\textsuperscript{69} In these cases, it is the sum of adversities and protective factors that determines health outcomes after experiencing early life adversity.\textsuperscript{48,69} This fits with the evidence that cumulative experiences throughout life of socioeconomic and other disadvantages predict higher levels of cardiovascular and metabolic biomarkers.\textsuperscript{70,71}
METHODOLOGICAL CONSIDERATIONS

The LOLLIPOP study
LOLLIPOP is one of the largest community-based cohort studies on MP and late preterm-born children. Moreover, unlike many other cohorts, LOLLIPOP comprises a control group of full-term children who were sampled from the same preventive child healthcare (PCH) centres and who were in the same age-range as the preterm children. Children born between 36⁰ to 36⁶ weeks’ gestation were not included since the main focus of the LOLLIPOP study was on outcomes of children born at 32⁰-35⁶ weeks’ gestation. The effect of not including these children is likely to be small because many MP children were born at 34 and 35 weeks’ of gestation, relative to 32 and 33 weeks’ of gestation. Numbers of MP children increased for every week of gestation, reflecting the community-based character of the cohort. The sample size of LOLLIPOP was based on numbers in order to compile growth curves for Dutch preterm children, which asked for a large number of children.

Parents could choose between joining the full study, which included follow-up measurements, or only the ‘growth curves’ part of the study. As a consequence, the number of participants joining the follow-up part was lower. Among the non-participating children low SES was more common (P<0.001), which may have influenced our results. However, we think that the effects of SES would then have been an underestimation of the real effects. Gender and SGA did not differ significantly between participating and non-participating children.

For the purpose of this thesis only data from the first measurement were used, i.e. when the children were nearly four years old. This measurement was planned as part of the scheduled PCH visit of the children, resulting in high responses (up to 95%) on the study questionnaires. Since the PCH doctors and nurses were very much involved in the study, they actively reminded the parents to fill in the questionnaires. Moreover, population coverage was high because in the Netherlands around 95% to 97% of children visit PCH centres regularly from birth up to four years of age.

Measurement of SES
We chose to use a composite measure of SES rather than single SES indicators, in order to fully account for effects that can be attributed to socioeconomic conditions.⁷²,⁷³ We computed the composite score on the basis of five indicators: educational level of the mother, educational level of the father, the family income,
occupational level of the mother, and occupational level of the father. All five indicators were available for the majority of the participants. For some participants, however, data on one of the indicators was missing, in particular family income or the occupational level of the mother. The composite SES was measured using the available indicators. Since data on educational level of both parents was most complete, it is likely that these two indicators weighed somewhat heavier in the overall effect of SES than the other indicators.

Data on SES indicators were collected at different points in time. In a general questionnaire, parents were asked to fill in their highest completed educational level and the net monthly family income shortly before the scheduled PCH visit at four years of age. Data on occupational level, however, were collected retrospectively from the medical birth registers kept by the PCH centres. It is possible that the occupational level of the parents had changed between birth and four years later, for example, due to losing a job or obtaining a higher position. In this way, changes in occupational level could have led to positive or negative deviations regarding the effect on neurodevelopmental problems. For the same reason, the family income when the child was four years old may not fully represent the level of income from birth up to four years of age. It is likely that the composite SES gives a better impression of the SES from birth up to four years than each of the indicators alone.

Assessment of neurodevelopmental outcomes
We used parental questionnaires to assess developmental delay and behavioural and emotional problems. Parental reports have proven to be valid when it comes to signalling psychosocial problems in preventive child healthcare. Nevertheless, additional testing by medical specialists or psychologists would have had added value, in the sense of providing a professional view on developmental and behavioural problems of the children in the LOLLIPOP study.

Using the ASQ as a screening instrument for measuring developmental delay has both advantages and disadvantages. The ASQ is a reliable and valid questionnaire for developmental screening, also in preterm children. Practical advantages are that the ASQ is cheap and, generally, completed quickly. Most parents consider the questionnaire easy to fill in and 97% can do so without the help of others. Nevertheless, in the LOLLIPOP study not all ASQ domain scores were completely filled in by all the parents, which indicates that some parents may have had difficulties in comprehending the questions. For example, the 25 (9.9%) of the low SES mothers who originated from non-European countries may have
had some trouble filling in the ASQ. Nevertheless, the effects on study outcomes were likely to be small, given the relatively small number of this group.

We assessed behavioural and emotional problems at the age of four using the CBCL. This questionnaire has good psychometric properties, is widely used in research and clinical settings, and is easily filled in by parents.\textsuperscript{81} Some psychometric properties, for example, are the high test-retest reliability (\(r=0.85\)) and good predictive validity, with a correlation of 0.64 for the total problems score over a period of six years.\textsuperscript{81} Most scores on the CBCL syndrome scales at pre-school age significantly predict higher CBCL scores at school age, with sometimes even better correlations over a longer time span.\textsuperscript{81} Pre-school scores on the withdrawn syndrome scale, for example, correlate better with outcomes at the age of nine than at younger ages. Therefore, pre-school CBCL scores seem to reflect underlying problems that predict long-term psychosocial functioning.\textsuperscript{81} From other studies we know that behavioural and emotional problems in children tend to persist into adolescence and even into adulthood.\textsuperscript{82-84}

\textit{Clinical meaning of statistical significance and interaction}

In the studies reported on in this thesis, we found statistically significant associations of gestational age and SES with developmental and behavioural outcomes. Statistical significance, however, is not always equal to clinical significance. For measuring clinical significance, effect size is the appropriate measure. By way of example, we measured the effect sizes of associations between moderate prematurity and behavioural and emotional problems, a measure which is relevant for clinicians taking care of children who have elevated CBCL scores. The effect sizes for elevated total, externalizing, and internalizing problems were 0.34, 0.27, and 0.50, respectively, meaning small (0.34 and 0.27) to moderate effects (0.50). This means that the threshold to initiate individual treatment for internalizing problems was reached. When looking at population level, the effects of all outcomes are rather important, given the prevalence of moderate preterm birth, and imply a major global burden of disease.

To determine the effect of SES on the association between moderate prematurity and neurodevelopmental problems, we measured statistical interaction between moderate prematurity and low SES. In logistic models, we found that SES did not interact with moderate prematurity with regard to most neurodevelopmental outcomes. This meant that the effects of SES and gestational age were multiplicative, as is the case for any logistic model without significant interactions. This absence
of statistical interaction in logistic models implies that having both risk factors increases the risk of neurodevelopmental problems considerably, relative to having only one of the risk factors. In other words, a multiplicative risk model applies.

**The Swedish conscript study**

The Swedish conscript study is a register-based study using data of over 45,000 men who were conscripted for military service in 1969 and 1970, and it covers a follow-up period of nearly 40 years. For this reason the study is well-suited to assess effects of mental and physical well-being on health during the course of the conscripts’ lives. Therefore, the possibility of reverse causation is limited, enabling the researcher to disentangle cause and effect. On the other hand, long time spans between exposure and outcomes may either underestimate or overestimate the real effects. Emotion regulation was measured at conscription in 1969 and 1970 and follow-up for CHD occurred until 2009. The effect of emotion regulation might have been diluted over the long follow-up period, but it is unknown to which degree emotion regulation relates to healthy ageing. Furthermore, lifestyle-associated factors, i.e. BMI, cardiorespiratory fitness, smoking, and blood pressure, were likely to change during follow-up. However, changes in these risk factors later on were consequences rather than causes of emotion regulation capacity, which may have led to an underestimation of the real effects.

As mentioned above, the assessment of the conscripts’ mental functioning took place at conscription, which limited us in interpreting what the psychologists had exactly measured in relation to current theory on emotion regulation. The available information on the assessment of emotion regulation fits with core features of emotion regulation, although the described concept may also fit related constructs, such as coping and mood regulation. As yet it is unknown how the constructs of emotion regulation, coping ability, and mood regulation are interrelated. The interrater reliability of the interviewing psychologists was tested a few years after conscription, on the basis of 30 tape-recorded interviews scored by 30 psychologists, and was rated as ‘very high’ ($r=0.86$) for the overall assessment of mental functioning.

Lastly, the generalizability of study outcomes is limited, in the sense that only men participated in the study. As a consequence, our findings cannot be generalized to women. Furthermore, the findings do not necessarily apply to CHD events at older ages because participants were about 60 years of age at the end of follow-up. Besides the fact that participants consisted of Swedish men only, the probability
of selection bias was very limited since only 2% to 3% of the male population was exempted from conscription, in most cases due to severe handicaps or congenital disorders.

**IMPLICATIONS**

The findings of the studies reported on in this thesis provide new insights relevant to preventive healthcare. On the basis of these finding, we offer recommendations for clinical practice and policy in PCH and we put forward several suggestions for further research aimed at two dimensions: 1) disentangling the pathways that lead to neurodevelopmental problems, and 2) the role of emotion regulation in promoting and maintaining mental and physical health in the long term.

**Implications for clinical practice and policy**

The greater part of the findings in this thesis applies to clinical practice in Dutch PCH centres. From our results it follows that indicators of low family SES and signs of co-occurring problems could contribute to the efficient detection of early emerging developmental and psychosocial problems in MP children.

In 2013, the Dutch National Centre for Preventive Youth Healthcare published a guideline on the early identification of developmental and psychosocial problems in preterm and small-for-gestational-age children. This guideline also aimed at early detection of developmental and health problems in MP children, but specific recommendations were lacking. The findings presented in this thesis will help to specify the guidelines for MP children, who comprise by far the largest group of preterm children with whom PCH professionals are confronted. In particular, refinement of the guideline is needed because most, i.e. approximately 80% to 90%, of MP children will have no significant developmental or psychosocial problems. In other words, PCH professionals know which MP children would benefit most from interventions, and we believe that the findings presented here will contribute to understanding this.

First, we found that the combined biological and social risk of MP children with low SES translates into a substantial increased risk of neurodevelopmental problems. This implies that increased awareness is warranted for the relatively large group of MP children with low family SES. Preterm birth occurs more often in low SES families, but low SES was not an explanation for the association between
preterm birth and neurodevelopmental problems. In addition, we found that those children with low family SES were characterized by certain features such as being part of a single-parent family, having a mother younger than 25 years, and having a mother of non-European ethnicity. This fits with the current PCH guidelines that identify these features as risk factors for psychosocial problems.87, 89

Second, co-occurrence of developmental and behavioural problems needs more attention in MP children. PCH professionals should be aware of the high probability of co-occurring behavioural and emotional problems if MP children have delays in one or more developmental domains. In particular, the combination of developmental delay with externalizing problems occurred frequently in MP children. Early identification of co-occurring developmental and behavioural problems is important because it predicts psychosocial problems at school age and beyond.90-92

Implications for further research
The findings presented in this thesis provide more insight into the pathways via which moderate prematurity and low SES lead to neurodevelopmental problems and via which emotion regulation may promote long-term health. Further research is needed to reveal the clinical implications of these findings.

Disentangling the pathways leading to neurodevelopmental problems
We proposed three pathways via which moderate prematurity and low SES may lead to neurodevelopmental problems: 1) prenatal influences, 2) parental well-being and parental involvement in the pre-school years, and 3) the disruptive effects of moderate prematurity and low SES on brain development. As we describe below, each of these pathways leads to ideas for further research.

1) Prenatal influences
Poorer mental and physical health during pregnancy increases the risk of mortality and morbidity in newborns. We proposed that antenatal maternal stress may initiate mechanisms leading to neurodevelopmental problems in preterm and low SES children due to the associations of antenatal maternal stress with all of these factors.5, 7 A better understanding of these mechanisms may offer new possibilities for the prevention of preterm birth and neurodevelopmental problems. One suggestion is to investigate which part of the association between antenatal maternal stress and neurodevelopmental problems is through preterm
birth, while taking into account the effects of low family SES. Another idea would be to investigate to what extent higher levels of antenatal maternal stress lead to behaviour that is detrimental to the mother’s health behaviour during pregnancy, such as smoking, malnutrition, and inadequate use of prenatal care, which in turn could cause neonatal morbidities and neurodevelopmental problems.

2) Parental well-being and parental involvement during the pre-school years
Preterm birth and low SES are sources of stress for families that may lead to the disruption of family interaction patterns. Parent-child and child-family interactions provide potential targets, i.e. risk and protective factors, for preventing neurodevelopmental problems in case a family is exposed to child-stressors, such as preterm birth, or SES-related stressors. Below, we briefly describe what is known on the effectiveness of interventions in preterm and low SES children and we offer suggestions for intervention studies based on the findings presented in this thesis.

Intervention studies on very preterm children have shown positive effects in the short term, but long-term results are indifferent. The effectiveness of interventions in MP children are largely unknown. In one study, no effect was found of a ‘mother-infant transaction program’ regarding cognitive, motor, or behavioural development of MP children. The authors suggested that the intervention might be more effective in those children at higher social or developmental risk. In low SES families, interventions may better meet the needs of the family, for example, because of limited financial and social resources. Furthermore, children with multiple developmental delays may benefit more from interventions, given the lack of developmental resources and poor organizational capacities, i.e. executive functioning, meta-cognition, social cognition, motivation, and emotion regulation. Future intervention studies should investigate whether indeed MP children with low SES and/or with multiple developmental delays benefit more from interventions.

It is largely unknown whether interventions should be mainly directed to the competencies of the child, to well-being and parenting style of the parents, or to family resources. For example, interventions aimed at parenting style seem to be less effective in very preterm children regarding long-term developmental outcomes. Furthermore, nurse visits from birth up to two years of age especially benefited low SES children in terms of language, attention, and internalizing problems that were measured at 6 and 9 years of age.
Lastly, the findings presented in this thesis imply that a gender-specific approach may be called for. Early detection and intervention may be more effective in girls, since they were more disadvantaged by the effects of moderate prematurity and low SES than boys. Because we were the first to assess these gender differences in behavioural and emotional outcomes after moderate prematurity, we call for confirmation of our findings and for further research to fully explain them.

3) Disruptive effects on brain development
Further research on brain development may improve our understanding of the pathophysiology of specific neurodevelopmental outcomes in MP and low SES children. For example, we have no adequate social-environmental explanation for the finding that effects of SES on communication skills were less pronounced in MP children. Insights from the field of neuroscience may provide an explanation for this finding. Questions also remain regarding the pathophysiology of behavioural problems in preterm-born children, such as: 1) Can the type of brain network aberrations explain the co-occurrence of specific developmental and behavioural problems? And 2) Do aberrations in the limbic system correspond with internalizing problems in preterm children, and in which way are gender differences involved?

The role of emotion regulation in maintaining mental and physical health
The findings presented in this thesis give rise to further research involving the role of emotion regulation in maintaining mental and physical health throughout life. To start with, little is known about the effectiveness of emotion regulation interventions in individuals who are at risk of CHD. In recent years, the role of emotion regulation has gained interest in health research, but the possibilities for preventive child healthcare are largely unknown. Applicability of emotion regulation interventions are currently explored for a widening array of neurodevelopmental problems and disorders, such as attention deficit and hyperactivity disorder and co-occurring conditions, and in various risk subgroups, including preterm-born and low SES children.

Our findings also show that the association between emotion regulation and CHD was partly explained via smoking, cardiorespiratory fitness, and education. Because emotion regulation is a competence acquired mainly in early childhood, this implies that early investments in social-emotional competencies may pay off in health-promoting behaviours and lower risks of long-term health problems.
We recommend further research to disentangle the associations between emotion regulation, affective disorders, and CHD. Additionally, it is unknown why the effect of emotion regulation goes beyond lifestyle-associated factors in individuals with a parental history of CHD. This finding may, for example, be explained by genetic factors which predispose an individual to stronger bodily responses to psychological stress. If at the same time the emotion regulation capacities are low as well, there is no safeguard against the harmful effects of stress.

CONCLUSION

In children and adolescents, biological risk factors and socioeconomic circumstances may threaten neurocognitive and social-emotional development, potentially affecting the foundations for life-long mental and physical health. At the start of life, birth complications and socioeconomic disadvantages pose major risks for neonatal health and neurodevelopment. With the studies presented in this thesis, we demonstrated that moderate prematurity and low SES are separate risk factors that have multiplicative effects on neurodevelopmental problems in early childhood. Our findings imply that interventions should be directed at those MP children with the highest risk, since the majority of MP children will develop normally. In clinical practice, therefore, increased awareness is needed to identify those MP children with low SES and those with multiple developmental and behavioural problems. Furthermore, a gender-specific approach is called for since we found that girls were more vulnerable to the effects of moderate prematurity and low SES than boys.

Throughout life, emotion regulation skills acquired during childhood may help to promote the maintenance of mental and physical health. We found that young people's emotion regulation capacities predicted CHD across a lifespan of 40 years, which was partly explained by higher rates of unhealthy lifestyles among those individuals with poor emotion regulation capacities. Moreover, emotion regulation affected the risk of CHD beyond lifestyle-associated factors, specifically in men with a high familial risk of CHD.

In summary, moderate prematurity and low SES increase the risk of pre-school neurodevelopmental problems, potentially affecting the foundations of mental and physical health, and from a life course perspective, social-emotional competencies that are acquired in early childhood may promote long-term health.
References


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