TAMARA VAN BATENBURG-EDDES

Causes and consequences of infant neuromotor development

The Generation R Study

Stellingen behorend bij het proefschrift

Causes and consequences of infant neuromotor development
The Generation R Study

Tamara van Batenburg-Eddes, 27 september 2012

1. Minor infant neuromotor delays can be explained by variations of gestational duration within the normal range *(dit proefschrift).*

2. A larger foetal size predicts a better infant neuromotor development *(dit proefschrift).*

3. Infants of mothers with anxiety symptoms during pregnancy are at risk of a less optimal neuromotor development *(dit proefschrift).*

4. Subtle deviances from normal neuromotor development predict cognitive delay, behavioural and emotional problems *(dit proefschrift).*

5. Residual familial confounding and genetic inheritance partly explain the observed association of maternal depression and anxiety during pregnancy with offspring behavioural problems *(dit proefschrift).*

6. Het is onmogelijk iets te zeggen over iets wat we niet kunnen zien *(Sijbolt Noorda, Volkskrant 14-15 januari 2012).*

7. Wetende dat dagelijkse lichaamsbeweging de leerprestatie verbetert, de sociaal-maatschappelijke integratie van kinderen bevordert en de zelfontplooiing en het zelfvertrouwen een boost geeft, is het aan te raden beleid te voeren op bewegingsonderwijs en motorisch remedial teaching, opdat kinderen goed leren bewegen *(Singh et al. BMC Advies Management, 2012).*

8. Validiteit en betrouwbaarheid van zelfrapportagevragenlijsten worden bepaald door de mensen die ze (niet) invullen.

9. The one important thing I have learned over the years is the difference between taking one's work seriously and taking oneself seriously. The first is imperative and the second disastrous *(Dame Margot Fonteyn).*

10. Naast dat het RIS-klachten veroorzaakt zijn er vele andere redenen te bedenken waarom langdurig en intensief gebruik van (spel)computers en mobiele telefoons bij kinderen verminderd moet worden.

11. From the dark end of the street, to the bright side of the road *(Van Morrison)*

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Acknowledgements

The Generation R Study is conducted by the Erasmus Medical Center Rotterdam in close collaboration with the Erasmus University Rotterdam, School of Law and Faculty of Social Sciences, the Rotterdam-Rijnmond Public Health Service, the Rotterdam Homecare Foundation, and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR).

We gratefully acknowledge the contribution of the participating pregnant women and their partners, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The first phase of the Generation R Study is made possible by financial support from: Erasmus Medical Center Rotterdam; Erasmus University Rotterdam and the Netherlands Organization for Health Research and Development (ZonMW). The studies presented in this thesis were supported by an additional grant from the Sophia Children's Hospital Foundation (project number 443).

Financial support for the publication of this thesis was provided by the Generation R Study, the Department of Child and Adolescent Psychiatry, and the Erasmus University Rotterdam.

ISBN: 978-90-9026924-5

Printing: DMC, Fijnaart, The Netherlands
Cover: Melanie van Dijk

Causes and Consequences of Infant Neuromotor Development

The Generation R Study

Oorzaken en gevolgen van vroeg neuromotorische ontwikkeling

Het Generation R Onderzoek

Proefschrift

ter verkrijging van de graad van doctor aan de

Erasmus Universiteit Rotterdam

op gezag van de

rector magnificus

Prof.dr. H.G. Schmidt

en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op

donderdag 27 september 2012 om 11:30 uur

door

Tamara van Batenburg-Eddes

geboren te Dordrecht

Promotiecommissie

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Copromotor: Dr. L. de Groot

Paranymfen: Jens Henrichs
Enver Meeng

Many things we need can wait

The child cannot

Now is the time

His bones are being formed, his mind is being developed

To him we cannot say tomorrow

His name is today

Gabrielle Mistral

Contents

Chapter 1

Introduction

"*The human brain represents the product of a construction project that has been going on for 6 billion years….Consisting of an estimated 100 billion neurons and many more glial cells organized into thousands of regions, the human brain delivers a wide variety of motoric, behavioural, cognitive and emotional capacities." (Goldstein & Reynolds, 2010).*[1]

Due to the complexity of the brain, and the many genetic and environmental determinants, there are endless ways in which the brain can develop, leading to at least as many possibilities in the expression of these variations in behaviours or cognitive functioning.
Although the study of the brain is as old as science itself, it is just until recently that we have begun to understand more about how the brain works. Historically, scientists who dedicated their work to understanding the central nervous system came from different disciplines: medicine, biology, psychology, physics, chemistry, mathematics. However, the study of the brain has been revolutionized when an interdisciplinary approach was taken, yielding a new synthesized perspective.[2]

Similarly, existing knowledge on infant neurological development has increased during the past decades. It is based on insights generated by paediatrics (developmental neurology), movement science and neuropsychology. Currently, neuromotor development is an accepted means of measuring the maturity and intactness of an infant's central nervous system.[3] Impaired development of the central nervous system in the first year of life is mainly expressed in deviances in neuromotor development.[3,4]

The opposing theories that have been postulated that describe infant neuromotor development include, the Neuromaturation Theory and the Dynamic Systems Theory. More recently, a third, more integrative theory, the Neural Group Selection Theory, has been formulated. According to the Neuromaturation Theory, neuromotor development can be seen as a gradual unfolding of predetermined patterns in the central nervous system. As a result, development is not influenced by environmental factors, but is largely a consequence of the maturation of the central nervous system.[5] Alternatively, under the Dynamic Systems Theory, a central role in neuromotor development is played by interaction with the environment, to

which maturation of the brain is subordinate.[6] The Neural Group Selection Theory combines the 'nature' part of the Neuromaturation Theory with the 'nurture' part of the Dynamic Systems Theory. The theory emphasizes that development is the result of a complicated combination of genetic and environmental factors.[7]

Previous research suggests that deviant brain functioning underlies several psychiatric and neurodevelopmental disorders, such as schizophrenia, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder, and dyslexia. In populations with these disorders, subtle abnormalities in brain structures have been consistently found.[8] As these disorders often emerge during developmental stages, i.e. during childhood or adolescence, it seems plausible that they originate from abnormal brain maturation. Support for this hypothesis comes from the observation that early neuromotor impairment represents a vulnerability marker for different psychiatric and neurodevelopmental disorders.[9-14] However, these disorders can even originate in foetal life. In the Dutch Famine Study, the effects of maternal undernutrition during pregnancy and adult mental performance were investigated.[15] Initially, no evidence was found for an association between prenatal exposure to undernutrition and mental performance later. However, higher prevalence of other neurodevelopmental deviances, i.e. congenital anomalies of the central nervous system, including spina bifida and cerebral palsy, were found.[16] Several decades later, data of the same study revealed that maternal undernutrition during pregnancy increased the risk of schizophrenia,[17] antisocial personality disorder,[18] and affective disorders.[19]

A large body of literature on the origins of neurodevelopmental disorders focused on high-risk populations, for example preterm born children or children born with low birth weight. In these populations, the prevalence of major disabilities is high, but also in preterm or low birth weight infants without major dysfunctions, such as late preterm infants (born with a gestational duration between 34 and 37 weeks), increased risks of neurodevelopmental disorders are found.[20-25] Comparatively few researchers studied the effects of normal variations in gestational duration and birth weight on later neurodevelopment. Furthermore, large population-based studies on early markers of cognitive function and

behavioural problems mainly used age of achieving motor milestones as outcome measure.[9,26] Although motor milestones represent a good tool to monitor the more general gross motor development,[27] it is a rather unspecific and crude measure of neuromotor development. In contrast to full neurological assessments, motor milestone achievements do no justice to the complexity in and quality of movements. It is important to detect markers of impaired cognitive function or behavioural problems as early in life as possible, although this seems to be a difficult endeavour. Full neurological assessments early in life may provide a solution.

Case report

Norah is 11 years old and has school performance problems. She has an average IQ, is very social, and not dyslectic. She has, however, problems with certain competencies, such as spelling or arithmetics. These competencies involve execution of integrated procedures obtained through repetitive learning until they can be produced automatically. With Norah, apparently, something inhibits this 'procedural learning' process. After all kinds of neuropsychological screenings and tests that revealed negative results, Norah was tested on motor development. This motor assessment showed that some of the motor developmental stages were not successfully acquired. For example, Norah still partly displays the asymmetric tonic neck reflex, an infant reflex that should be inhibited at her age. An age-adequate and symmetric motor development had not been achieved, resulting in non-optimal fine motor skills and non-optimal spatial orientation. Norah has to do many tasks consciously, whereas these should be automated. This drains her energy, and quickly she loses her concentration and starts to make a lot of mistakes. She invests a lot of effort in her work but mainly produces poor results, which is discouraging for her. Sometimes she appears to have a bad working attitude and seems unmotivated.

The general aim of this thesis is to enlarge current knowledge on prenatal determinants of later neuromotor development and on the predictive value of early neuromotor development on later behaviour and cognitive functioning. The studies were part of the Generation R Study, which is a prospective population-based cohort study from foetal life onwards conducted in Rotterdam, the Netherlands. This study offers a unique opportunity to examine the effects of prenatal and postnatal factors on later growth and development.

The main aims of this thesis were: 1) to examine whether prenatal adverse factors are associated with less optimal neuromotor development, and 2) to study the effect of early neuromotor development on later behavioural problems and cognitive functioning.

The Generation R Study is a prospective population-based cohort study from foetal life onwards.[28] For the current thesis, data from two study populations within this cohort were used. All mothers who were resident in the study area and had their delivery date between April 2002 and January 2006 were eligible for enrolment in the Generation R Study from early pregnancy until birth. In total, 9778 mothers were enrolled in the cohort (Figure 1). Of these mothers, 8880 (91%) were enrolled during pregnancy. For postnatal consent, 8544 mothers and their children were approached (Sample 1). Of these 8544 mothers, 7620 (96%) were prenatally recruited (Sample 2). Differences in the prenatal and postnatal definition of the samples are due to twin pregnancies, withdrawal or loss to follow-up during pregnancy, time of enrolment, perinatal death of the child, and exclusion of participants in the pilot phase who lived outside the definite study area (Figure 1).

Figure 1. Generation R cohort

	Cohort	
Enrolment:	**Prenatal**	**At birth**
Pregnancies:	**8880**	**898**
Pregnancy outcomes		
Singleton pregnancy	8638	872
Twin pregnancy	93	26
Abortion	29	
IUVD	78	
Loss to follow-up during pregnancy	45	
Live birth:	**8821**	**924**
Pilot participants	1163	
Neonatal deaths	38	
Children eligible for postnatal participation:	**7620**	**924**
Neuromotor assessment (9-15 weeks)	3048	176
Total:		**8544**

Outline

In chapter 2, the effects of prenatal factors on neuromotor development are studied. These factors include gestational age and foetal size, and maternal symptoms of anxiety or depression during pregnancy. In chapter 3, we examine whether infant neuromotor development is associated with child behaviour problems and cognitive function. In chapter 4, we explored the possibility of an intrauterine effect of maternal symptoms of depression and anxiety on child behaviour. Finally, chapter 5 provides a general discussion of the main findings, discusses methodological aspects of the study, and we conclude with some implications for clinical practice and future research.

References

1 Goldstein S and Reynolds CR, eds. *Handbook of neurodevelopmental disorders and genetic disorders in children.* 2nd ed. New York: Guilford Press; 2010.

2 Bear MF, Connors BW and Paradiso MA. *Neuroscience: exploring the brain*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2007.

3 Touwen BC. *Neurological development in infancy*. London: Heinemann; 1976.

4 Prechtl HF. *The Neurological Examination of the Full-term Newborn Infant*. 2nd ed. London: Heinemann; 1977.

5 Gesell A and Amatruda CS. *Developmental Diagnosis. Normal and Abnormal Child Development*. Second edition ed. New York: Harper & Row; 1947.

6 Thelen E. Motor development. A new synthesis. *Am Psychol.* 1995; **50** (2): 79-95.

7 Hadders-Algra M. The neuronal group selection theory: a framework to explain variation in normal motor development. *Dev Med Child Neurol.* 2000; **42** (8): 566-72.

8 Giedd JN. Anatomic brain imaging studies of normal and abnormal brain development in children and adolescents. *Developmental psychopathology.* Vol two: Neurodevelopmental neuroscience. 2nd ed. New York: Whiley; 2006:127-96.

9 Murray GK, Jones PB, Kuh D and Richards M. Infant developmental milestones and subsequent cognitive function. *Ann Neurol.* 2007; **62** (2): 128-36.

10 Murray GK, Jones PB, Moilanen K, Veijola J, Miettunen J, Cannon TD and Isohanni M. Infant motor development and adult cognitive functions in schizophrenia. *Schizophr Res.* 2006; **81** (1): 65-74.

11 Piek JP, Dawson L, Smith LM and Gasson N. The role of early fine and gross motor development on later motor and cognitive ability. *Hum Mov Sci.* 2008; **27** (5): 668-81.

12 Ming X, Brimacombe M and Wagner GC. Prevalence of motor impairment in autism spectrum disorders. *Brain Dev.* 2007; **29** (9): 565-70.

13 Rosso IM, Bearden CE, Hollister JM, Gasperoni TL, Sanchez LE, Hadley T and Cannon TD. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull.* 2000; **26** (2): 367-78.

14 Burns Y, O'Callaghan M, McDonell B and Rogers Y. Movement and motor development in ELBW infants at 1 year is related to cognitive and motor abilities at 4 years. *Early Hum Dev.* 2004; **80** (1): 19-29.

15 Stein Z, Susser M, Saenger G and Marolla F. Nutrition and mental performance. *Science.* 1972; **178** (62): 708-13.

16 Stein Z, Susser M, Saenger G and Marolla F. *Famine and human development: the Dutch hunger winter of 1944-1945*. New York: Oxford University Press; 1975.

17 Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D and Gorman JM. Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psychiatry.* 1996; **53** (1): 25-31.

18 Neugebauer R, Hoek HW and Susser E. Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. *Jama.* 1999; **282** (5): 455-62.

19 Brown AS, van Os J, Driessens C, Hoek HW and Susser ES. Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry.* 2000; **157** (2): 190-5.

20 Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr.* 2005; **26** (6): 427-40.

21 Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB and Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics.* 2009; **124** (2): 717-28.

22 Marlow N, Hennessy EM, Bracewell MA and Wolke D. Motor and executive function at 6 years of age after extremely preterm birth. *Pediatrics.* 2007; **120** (4): 793-804.

23 Arpino C, Compagnone E, Montanaro ML, Cacciatore D, De Luca A, Cerulli A, Di Girolamo S and Curatolo P. Preterm birth and neurodevelopmental outcome: a review. *Childs Nerv Syst.* 2010; **26** (9): 1139-49.

24 Woythaler MA, McCormick MC and Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. *Pediatrics.* 2011; **127** (3): e622-9.

25 McGowan JE, Alderdice FA, Holmes VA and Johnston L. Early childhood development of late-preterm infants: a systematic review. *Pediatrics.* 2011; **127** (6): 1111-24.

26 Taanila A, Murray GK, Jokelainen J, Isohanni M and Rantakallio P. Infant developmental milestones: a 31-year follow-up. *Dev Med Child Neurol.* 2005; **47** (9): 581-6.

27 Wijnhoven TM, de Onis M, Onyango AW, Wang T, Bjoerneboe GE, Bhandari N, Lartey A and al Rashidi B. Assessment of gross motor development in the WHO Multicentre Growth Reference Study. *Food Nutr Bull.* 2004; **25** (1 Suppl): S37-45.

28 Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC and Hofman A. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol.* 2010; **25** (11): 823-41.

Chapter 2

Prenatal determinants of infant neuromotor development

Chapter 2.1

Gestational age and infant neuromotor development

Abstract

Aim: To examine the extent to which infant neuromotor development is determined by gestational duration and birth weight within the normal range.

Methods: The study was embedded within the Generation R Study, a population-based cohort in Rotterdam, the Netherlands. An adapted version of Touwen's Neurodevelopmental Examination in Infancy was used to assess 3,224 infants (1,576 males and 1,648 females) at corrected ages between 9 to 15 weeks. Non-optimal neuromotor development was defined as a score in the highest tertile.

Results: Infant neuromotor development was significantly affected by gestational duration (odds ratio 0.8, 95% confidence interval 0.7; 0.8). Adding a quadratic term of gestational duration to the model revealed a highly significant curvilinear association between gestational duration and neuromotor development; after adjusting for postconceptional age this was still significant. Although babies with a one kilogram lower birth weight had a 30% higher risk of non-optimal neuromotor development, this association disappeared after adjustment for postconceptional age.

Conclusions: Our findings indicate that differences in infant neuromotor development can be explained even by variations in gestational duration within the normal range. If an infant is found to have minor neuromotor delays, account should be taken of this.

Introduction

Neuromotor assessment is an accepted means of measuring the maturity and intactness of an infant's central nervous system. Its relevance is demonstrated by the fact that impaired development of the central nervous system in the first year of life is expressed mainly in neuromotor delay. As numerous follow-up studies have shown,[1-4] neuromotor development in preterm and low birth weight infants can often be slightly or even markedly delayed. However, in infants born in the normal range of gestational duration or birth weight, it is unknown whether there is an association between gestational duration and neuromotor development.

Research on infant neuromotor development has led to the postulation of several theories. According to the neuromaturational theory, development is not influenced by exposure to the intrauterine or extrauterine environment, but is merely a consequence of the maturation of the central nervous system. Following this reasoning, neuromotor development is thus determined particularly by postconceptional age.[5] Alternatively, under the dynamic systems theory, a central role in neuromotor development is played by interaction with the environment, to which maturation of the brain is subordinate.[6] The degree of neuromotor development is thus determined largely by exposure to the extrauterine environment, i.e. postnatal age.

Different associations between birth weight and neuromotor development are also postulated in two seemingly opposing theories. The foetal origins theory posits that an adverse foetal environment leads to developmental adaptations that permanently program the foetus' structure, physiology and metabolism.[7] The adverse foetal environment manifests itself in foetal growth retardation and low birth weight. According to the same theory, foetal growth retardation and subsequent low birth weight are risk factors for health and developmental problems in both childhood and adulthood. In the brain sparing theory, however, it is assumed that the brain is comparatively well protected against an inadequate supply of nutrients. This would mean that birth weight in the normal range is not associated with neuromotor developmental delays.

Our study therefore had three objectives. The first was to examine whether gestational duration within the normal range determines

neuromotor development. The second was to establish how important it is that this time is spent in utero – in other words, whether an infant's risk of neuromotor problems is still affected by gestational duration when postconceptional age is kept constant. The third was to determine whether there is a relationship between birth weight within the normal range and neuromotor development.

Methods

Participants and design

This study was embedded within the Generation R Study, a population-based cohort study from foetal life until young adulthood. The Generation R Study has been described in detail elsewhere.[8,9] Briefly, pregnant women who were resident in the city of Rotterdam at the time of their delivery and whose delivery data lay between April 2002 and January 2006, were asked by their midwives to participate. For the current study, the parents of a total of 7,893 children were approached for postnatal participation; 7,045 children were eligible for a neuromotor assessment.

The aim was to visit all eligible children at the corrected age of three months, as this is when a major transition in neuromotor development takes place.[10] In order to examine all children at this age, our planning of the date of assessment took account of the expected date of delivery. Because the assessments were conducted during a home visit, it was not logistically possible to visit all children at exactly the same age. As a result, neuromotor assessment was performed in 4,721 children at the corrected ages between 9 and 20 weeks (response rate 67%). For the present study, only the measurements between 9 to 15 weeks corrected age were used (*n*=3,224). Because assessments after 15 weeks corrected age were collected using an age-adapted version of the neuromotor instrument, results cannot be compared easily with assessments in the 9-15 week age range.

The study was approved by the Medical Ethics Committee of Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants.

Age and birth weight

Although gestational duration was first determined by foetal ultrasound examinations, we also calculated it on the basis of the last menstrual period.[11] We then calculated postnatal age or chronological age as the difference between the date of assessment and date of birth. Finally, we operationalized postconceptional age as the sum of gestational duration and postnatal age. Date of birth and birth weight were obtained from midwives and hospital registries.

Outcome: Neuromotor assessment

Because it has proved to be difficult to identify abnormal development in infancy, a full neurological age-adequate examination should always be carried out to assess tone, elicited responses, and other observations, such as the infant's spontaneous movements and behaviour. We therefore selected items from Touwen's Neurodevelopmental Examination, adding items to measure active and passive muscle tone according to the modified method of de Groot et al., which is described in detail elsewhere.[12] Briefly, this method maintains the multiple domains of the original Touwen instrument, but puts extra emphasis on the notion that a discrepancy between active and passive tone serves as an early sign of poor posture and deviant motor development. We categorized all measured items in three groups: tone, responses, and other observations. Most tone items were scored as normal, low and high tone. Responses, and other observations, could be present, absent, or excessive. All assessments were performed by trained research assistants who were blinded for the gestational duration of the infants.

We calculated scale values by summing the non-optimal items. This produced a total score and three subscale scores for tone items, responses, and other items. A low value for each scale indicates appropriate neuromotor development; a high value indicates impairment. Due to their low reliability, asymmetry items were not included (see below). As we were studying a non-clinical population, the outcome measures were very skewed. For this reason, and also because we wished to study the effects of small variations, we categorized the sumscores of the total and the subscales into tertiles, subsequently classifying the lowest and middle

tertiles as optimal neuromotor development, and the highest as non-optimal.

To investigate the short-interval test-retest interobserver reliability and the interobserver reliability, we also performed a reliability study. The short-interval test-retest interobserver reliability test (*n*=61) consisted of a first assessment by a research assistant, followed within one week by a second assessment by another research assistant. For the interobserver reliability test (*n*=76), two research assistants together went on a home visit in which they independently conducted two consecutive neuromotor assessments in the same child.

Intra-class correlation coefficients (ICC) were calculated for the total score. Because the ICC for the asymmetry scale was unacceptable, items measuring asymmetry were not included in the total score. The ICC for the short-interval test-retest interobserver reliability was 0.52; for the interobserver reliability it was 0.64. To calculate the latter, we used only the paired measurements of infants in the same behavioural state.

Covariates

Postal questionnaires were used to obtain information on the mother's parity and educational level, on her smoking and alcohol use during pregnancy, and also on the ethnicity of her child. Educational level was divided into five categories, ranging from 'primary education only' to 'higher education with a university degree'.[13] Ethnicity of the child was based on the parents' country or countries of birth.[14] Maternal smoking and alcohol use were categorized as 'no', 'until pregnancy was known', and 'continued after pregnancy was known'. Midwife and hospital registries provided information on gender and obstetric variables (maternal hypertension, pre-eclampsia, gestational diabetes, Apgar score after 1 minute, and mode of delivery).

Statistical analysis

Chi-square and T-tests were used for a crude comparison between selected variables regarding infants with optimal and non-optimal neuromotor development.

Logistic regression was used to assess the effect of gestational duration and birth weight on infant neuromotor development. To test whether the associations between gestational duration and neuromotor development were curvilinear, a quadratic term was added to the models. To further explore the nature of the association between gestational duration and neuromotor development, we categorized gestational duration in weeks and calculated the odds ratios for each category. All models were adjusted for postnatal age, a well-established determinant of neuromotor development. In infants of the same corrected age, the effect on neuromotor development of time spent in the uterus is reflected in models in which gestational duration was adjusted for postconceptional age rather than for postnatal age. Models were also adjusted for the gender and ethnicity of the child, for the educational level and age of the mother, and for her smoking and alcohol use during pregnancy. Obstetric variables and parity were not included in the analyses, as these variables did not change the associations we observed (<5% change).

To check for possible bias, we also performed additional analyses in which gestational duration was based on last menstrual period rather than on foetal ultrasound measurements.

For the non-response analysis, we compared the characteristics of participants examined at a corrected age of 9 to 15 weeks not only with those of infants seen after the corrected age of 15 weeks, but also with those of infants who had not undergone neuromotor assessment. Compared to included mothers (primary school 14%, mean maternal age 30.4 years), we found that mothers of infants who had not been assessed, or had been assessed late, had a lower educational level (primary school 9%, p<.001) and were younger (mean maternal age 29.4 years, p <.001). Compared to infants who had been included, excluded infants were more often of non-Dutch origin (62% versus 58%, p<.001), had a lower mean birth weight (3,355 grams versus 3,422 grams, p<.001), and had been born after a shorter period of gestation (39.7 weeks versus 39.9 weeks, p<.001).

Statistical analyses were performed using the Statistical Package of Social Sciences version 11.5 for Windows.

Results

Table 1 shows the sample characteristics of mothers and infants with optimal and non-optimal neuromotor development as defined by a score in the highest tertile. Infants whose neuromotor development was non-optimal were more likely to be male (52%) and to be non-Dutch (42%), than those whose neuromotor development was optimal (male 47%, p=.006, non-Dutch 35%, p<.001).

Table 2 presents the associations of gestational duration and birth weight with the different measures of neuromotor development. This development was 23% more likely to be non-optimal in an infant who spent one week less in the uterus. After adjustment for postconceptional age, the linear association between gestational duration and neuromotor development was no longer significant. However, in a model with a linear and a quadratic term of gestational duration, both terms were highly significant, indicating that gestational duration has a curvilinear association with neuromotor development, irrespective of correction for postnatal age or postconceptional age.

The strengths of associations for all subscales were similar to that of the overall scale, except for the scale measuring responses, which was associated neither with gestational duration nor with birth weight (Table 2). The risk of non-optimal neuromotor development was 10% higher in infants assessed a week younger in terms of postnatal age (95% confidence interval 0.86, 0.94). This risk was also 24% higher in infants whose postconceptional age was one week shorter (95% confidence interval 0.71, 0.81).

In infants whose birth weight was one kilogram lower, the risk of non-optimal motor development was 30% higher. However, this relationship disappeared after adjustment for postconceptional age.

Figure 1 shows the risk of a non-optimal neuromotor development on a logarithmic scale for each week of gestational duration. Infants born between 40 and 41 weeks of gestational duration are the reference category. This analysis illustrates the curvilinear association between gestational duration and neuromotor development.

After adjustment for postconceptional age, infants born before 40 weeks of gestation did not have a higher risk of non-optimal motor development than controls born between 40 and 41 weeks of gestation. In

contrast, the same risk was significantly higher in infants born after 41 weeks of gestation (Figure 2).

Table 1. Selected characteristics of study population

	Neuromotor development		
	Optimal Low+mid tertile *n*=2,001 %	**Non-optimal High tertile *n*=1,144 %**	**p**
Maternal characteristics			
Educational level[a]			
Primary school	7%	12%	<.001
Secondary school, phase I	11%	15%	
Secondary school, phase II	30%	29%	
Higher education, phase I	23%	21%	
Higher education, phase II	28%	23%	
Age enrolment, years *(SD)* [b]	30.7 *(5.02)*	30.0 *(5.18)*	<.001
Smoking during pregnancy[a]			
No smoking	79%	79%	.57
Smoking until pregnancy was known	8%	7%	
Continued smoking during pregnancy	13%	14%	
Alcohol use during pregnancy[a]			
No alcohol use	46%	53%	.002
Alcohol use until pregnancy was known	14%	11%	
Continued alcohol use during pregnancy	40%	36%	
Child characteristics			
Gender [a]			
Male	47%	52%	.006
Female	53%	48%	
Ethnicity [a]			
Dutch, European	65%	58%	<.001
Surinamese	8%	8%	
Moroccan	5%	9%	
Turkish	6%	9%	
Dutch Antilles	3%	4%	
Cape Verdean	3%	4%	
Other	10%	9%	
Corrected age at assessment, weeks *(SD)* [b]	12.6 *(1.2)*	12.2 *(1.1)*	<.001
Birth weight, gram *(SD)* [b]	3,439 *(529)*	3,407 *(571)*	.11
Gestational duration, weeks *(SD)* [b]	39.9 *(1.6)*	39.9 *(1.8)*	.82

[a] Analyzed by Chi-square test
[b] Analyzed by T-test

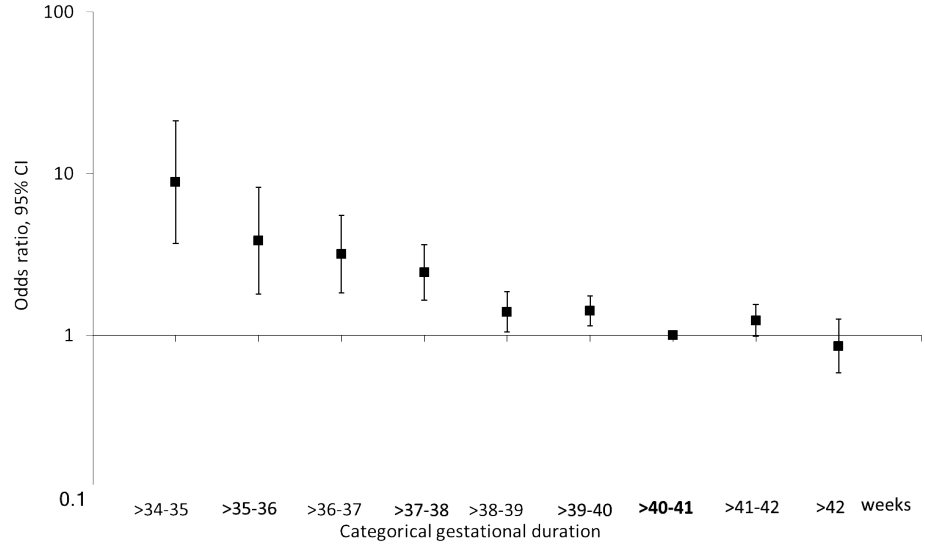
Table 2. The association between gestational duration and neuromotor development (*n*=3,224)

	Risk of non-optimal neuromotor development							
	Total		Tone		Responses		Other	
Child characteristics	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
Linear models								
Gestational duration (per week)	0.77 (0.71, 0.83)	<.001	0.78 (0.72, 0.84)	<.001	1.06 (0.98, 1.14)	.14	0.86 (0.80, 0.93)	<.001
Gestational duration (per week), adjusted for PCA	1.02 (0.98, 1.07)	.35	1.03 (0.98, 1.08)	.21	1.00 (0.96, 1.05)	.94	0.99 (0.94, 1.03)	.59
Quadratic models								
Gestational duration (per week)	0.13 (0.05, 0.32)	<.001	0.12 (0.05, 0.30)	<.001	1.16 (0.49, 2.73)	.74	0.37 (0.16, 0.83)	.02
Quadratic term of gestational duration (per week)	1.02 (1.01, 1.04)	<.001	1.03 (1.01, 1.04)	<.001	1.00 (0.99, 1.01)	.84	1.01 (1.00, 1.02)	.04
Gestational duration (per week)	0.17 (0.07, 0.43)	<.001	0.16 (0.06, 0.40)	<.001	1.09 (0.47, 2.57)	.84	0.43 (0.19, 0.95)	.04
Quadratic term of gestational duration (per week), adjusted for PCA	1.02 (1.01, 1.04)	<.001	1.03 (1.01, 1.04)	<.001	1.00 (0.99, 1.01)	.84	1.01 (1.00, 1.02)	.04
Linear models, birth weight								
Birth weight (per kilo)	0.70 (0.60, 0.82)	<.001	0.72 (0.62, 0.84)	<.001	0.93 (0.79, 1.10)	.40	0.75 (0.64, 0.89)	<.001
Birth weight (per kilo), adjusted for PCA	0.93 (0.81, 1.07)	.30	0.96 (0.83, 1.10)	.55	0.91 (0.79, 1.06)	.21	0.86 (0.75, 1.00)	.05

Note PCA=postconceptional age

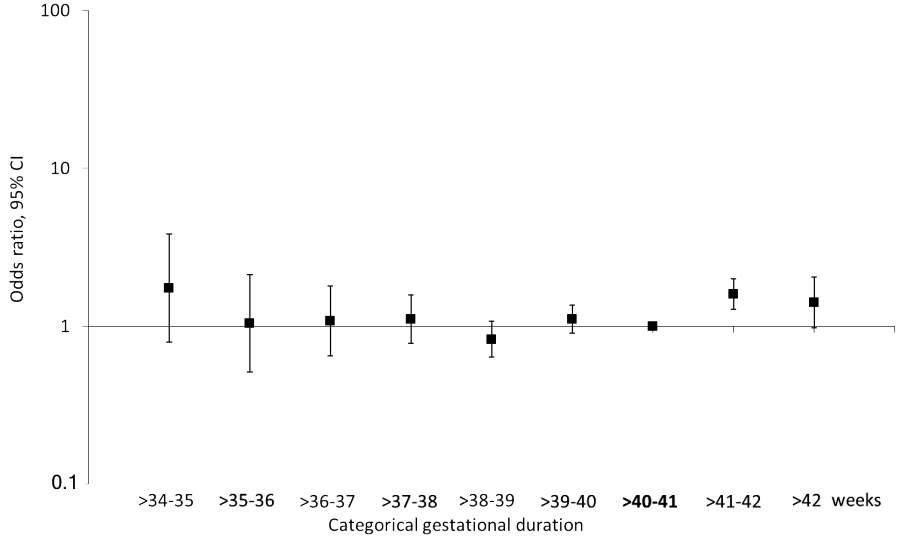
Models are adjusted for postnatal age (unless otherwise specified), gender, educational level and age of the mother, ethnicity of the child, smoking and alcohol use during pregnancy

Figure 1: Associations between gestational duration and neuromotor development



Adjusted for postnatal age, gender, mother's educational level, age, smoking and alcohol use during pregnancy, and ethnicity of the child; log -transformed Y-axis**,** gestational duration reference category of 40 to 41 weeks

Figure 2: Associations between gestational duration and neuromotor development, adjusted for postconceptional age



Adjusted for postconceptional age, gender, mother's educational level, age, smoking and alcohol use during pregnancy, and ethnicity of the child; log-transformed Y-axis**,** gestational duration reference category of 40 to 41 weeks

But even though the higher risk of non-optimal neuromotor development in infants born after 41 weeks disappeared when the analysis was repeated, this time with gestational duration being based on the date of the last menstrual period, the linear and the quadratic terms both remained significant, even after adjustment for postconceptional age (data not shown).

Discussion

This study shows that the risk of non-optimal neuromotor development of infants is increased by a shorter gestational duration even within the normal range. The cause lies more in the younger postconceptional age of these infants than in the shorter time spent in utero. However, the curvilinear association between gestational duration and neuromotor development after correction for postconceptional age suggests that neuromaturation not only lagged in infants who spent 34 weeks or less in utero, but also in those who spent more than 41 weeks in utero. Birth weight, on the other hand, was related to neuromotor development only if the postconceptional age was not accounted for.

Most research on the effect of gestational duration on neuromotor development has been conducted in preterm infants.[1-4] De Groot et al.[15] and Mercuri et al.[16] showed that healthy preterm infants born between 25 and 34 weeks of gestation differ in their quality of movements compared to term infants who were investigated at the expected date of delivery. Furthermore, Wood[17] found that about half of 283 extremely preterm born infants had disabilities in mental development and neuromotor functioning at the corrected age of 30 months. It is therefore acknowledged that infants born preterm follow different developmental trajectories than those born at term, and that they often suffer from neuromotor disabilities, usually caused by damage to the immature brain or by the medical interventions that were necessary.[17-20] Our study found an increased risk of non-optimal neuromotor development not only in infants born preterm, but also in those born at term but before the expected data of delivery. However, we also found that the risk of non-optimal neuromotor development in infants born closer to the expected date of delivery was barely influenced by any change in gestational duration.

When we adjusted for postconceptional age, the linear association between gestational duration and neurodevelopment was no longer significant. This indicates that, in the general population, it is not so much time spent in the uterus that is important, but maturation, i.e. postconceptional age. However, since the categorical analysis showed a higher risk of non-optimal neuromotor development in infants born with a gestational duration of less than 35 weeks, we do expect extremely preterm infants to have an additional delay.

In infants born after 41 weeks of gestation, the association between gestational duration and neuromotor development reversed, indicating that longer gestation increased the risk of non-optimal motor development. Two explanations are relevant here. The first is that a role in this may have been played by postterm delivery, which can have an adverse effect on neuromotor development due to complications stemming from a prolonged stay in the uterus.[21] The second is that foetal ultrasound examination reduces growth variation in early pregnancy, because dating is based on size at age 12 weeks. This may cause the gestational duration of some larger foetuses to be overestimated. And our study did indeed find, that if dating was computed on the basis of the last menstrual period, that gestation longer than 41 weeks did not entail a higher risk.

Most studies have found a higher risk of neuromotor delay in low birth weight infants, Mikkola et al.[3] showing that the development of only a quarter of a cohort of such infants (*n*=351) was considered to be optimal at age 5. Similarly, Davis et al.[20] reported that 10% of extremely low birth weight infants still had a neuromotor delay at 8 years of age, against 2% of normal birth weight infants. However, after adjustment for postconceptional age, we found no associations between birth weight and neuromotor development. One explanation is that, because we studied a population-based cohort, we have only small variations in birth weight, and a very small number of very low birth weight infants (*n* =6, birth weight < 1,250 grams).

Three limitations of the present study should be considered. The first is reduced power for analyses. Due to the design of the study that took account of the expected date of delivery, we had less variation in

postconceptional age. Therefore, part of the variation in neuromotor development was lost.

Second, the results of this study may also have been influenced by sample attrition. There were significant differences between infants whose neuromotor development we assessed, and infants we did not assess. This certainly reduced our power to find associations. And because many high-risk infants did not participate, neither can we rule out the possibility that the associations between the determinants and neuromotor development differed between participants who were included and those who were excluded.

Lastly, the reliability of the instrument may also have reduced our power to detect associations. Despite the fact that the research assistants who performed the neuromotor assessment were well trained, the reliability study indicates that the level of agreement between observers was only moderate.

The strength of this study is that it involved a population-based cohort study with a larger number of low-risk subjects than in earlier research in high-risk populations. And not only were the neuromotor assessments performed by research assistants who were blinded for the gestational duration of the infants, the design of the study also enabled us to control for a large number of confounders.

In conclusion, this study shows that evaluation of neuromotor development in infants should take account of postconceptional age - in other words, of both gestational duration and postnatal age. This is currently common practice only in preterm infants. Simply adjusting for postnatal age might lead to the unjust conclusion that an infant suffers from minor developmental delays, whereas in fact he or she was merely assessed earlier in the maturational process.

References

1 Schmidhauser J, Caflisch J, Rousson V, Bucher HU, Largo RH and Latal B. Impaired motor performance and movement quality in very-low-birthweight children at 6 years of age. *Dev Med Child Neurol.* 2006; **48** (9): 718-22.

2 Aylward GP. Cognitive and neuropsychological outcomes: more than IQ scores. *Ment Retard Dev Disabil Res Rev.* 2002; **8** (4): 234-40.

3 Mikkola K, Ritari N, Tommiska V, Salokorpi T, Lehtonen L, Tammela O, Paakkonen L, Olsen P, Korkman M and Fellman V. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics.* 2005; **116** (6): 1391-400.

4 McCarton CM, Wallace IF, Divon M and Vaughan HG, Jr. Cognitive and neurologic development of the premature, small for gestational age infant through age 6: comparison by birth weight and gestational age. *Pediatrics.* 1996; **98** (6 Pt 1): 1167-78.

5 Gesell A AC. *Developmental Diagnosis. Normal and Abnormal Child Development*. Second edition ed. New York: Harper & Row; 1947.

6 Thelen E. Motor development. A new synthesis. *Am Psychol.* 1995; **50** (2): 79-95.

7 Barker DJ. Fetal origins of coronary heart disease. *Bmj.* 1995; **311** (6998): 171-4.

8 Hofman A, Jaddoe VW, Mackenbach JP, Moll HA, Snijders RF, Steegers EA, Verhulst FC, Witteman JC and Buller HA. Growth, development and health from early fetal life until young adulthood: the Generation R Study. *Paediatr Perinat Epidemiol.* 2004; **18** (1): 61-72.

9 Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, Witteman JC and Hofman A. The Generation R Study: Design and cohort profile. *Eur J Epidemiol.* 2006; **21** (6): 475-84.

10 Hopkins B and Prechtl HF. A qualitative approach to the development of movements during early infancy. In: Prechtl HF, ed. *Continuity of Neurol Function from Prenatal to Postnatal Life* Oxford: Blackwell; 1984:179-97.

11 Verburg BO, Steegers EA, De Ridder M, Snijders RJ, Smith E, Hofman A, Moll HA, Jaddoe VW and Witteman JC. New charts for ultrasound dating of pregnancy and assessment of fetal growth: longitudinal data from a population-based cohort study. *Ultrasound Obstet Gynecol.* 2008; **31** (4): 388-96.

12 de Groot L, Hopkins B and Touwen BC. A method to assess the development of muscle power in preterms after term age. *Neuropediatrics.* 1992; **23** (4): 172-9.

13 Statistics Netherlands. *Standaard onderwijsindeling 2003*. Voorburg/Heerlen; 2004.

14 Statistics Netherlands. *Allochtonen in Nederland 2004*. Voorburg/Heerlen; 2004.

15 de Groot L, Hopkins B and Touwen B. Muscle power, sitting unsupported and trunk rotation in pre-term infants. *Early Hum Dev.* 1995; **43** (1): 37-46.

16 Mercuri E, Guzzetta A, Laroche S, Ricci D, vanhaastert I, Simpson A, Luciano R, Bleakley C, Frisone MF, Haataja L, Tortorolo G, Guzzetta F, de Vries L, Cowan F and Dubowitz L. Neurologic examination of preterm infants at term age: comparison with term infants. *J Pediatr.* 2003; **142** (6): 647-55.

17 Wood NS, Marlow N, Costeloe K, Gibson AT and Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. *N Engl J Med.* 2000; **343** (6): 378-84.

18 Bartlett DJ and Fanning JE. Use of the Alberta Infant Motor Scale to characterize the motor development of infants born preterm at eight months corrected age. *Phys Occup Ther Pediatr.* 2003; **23** (4): 31-45.

19 Marlow N. Neurocognitive outcome after very preterm birth. *Arch Dis Child Fetal Neonatal Ed.* 2004; **89** (3): F224-8.

20 Davis NM, Ford GW, Anderson PJ, Doyle LW and Victorian Infant Collaborative Study G. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. *Dev Med Child Neurol.* 2007; **49** (5): 325-30.

21 Acog Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin. Clinical management guidelines for obstetricians-gynecologists. Number 55, September 2004 (replaces practice pattern number 6, October 1997). Management of Postterm Pregnancy. *Obstet Gynecol.* 2004; **104** (3): 639-46.

Chapter 2.2

Foetal size and infant neuromotor development

Abstract

The objective of the study was to examine whether infant neuromotor development is determined by foetal size and body symmetry in the general population. This study was embedded within the Generation R Study, a population-based cohort in Rotterdam. In 2,965 foetuses, growth parameters were measured in mid- and late pregnancy. After birth, at age 9 to 15 weeks, neuromotor development was assessed with an adapted version of Touwen's Neurodevelopmental Examination. Less optimal neuromotor development was defined as a score in the highest tertile. We found that higher foetal weight was beneficial to infant neurodevelopment. A foetus with a one standard deviation (SD) score higher weight in mid-pregnancy had an 11% lower risk of less optimal neuromotor development (OR 0.89, 95% CI 0.82-0.97). Similarly, a foetus with a 1-SD score larger abdominal-to-head circumference (AC/HC) ratio had a 13% lower risk of less optimal neuromotor development (OR 0.87, 95% CI 0.79-0.96). These associations were also present in late pregnancy. Our findings show that foetal size and body symmetry in pregnancy are associated with infant neuromotor development. These results suggest that differences in infant neuromotor development, a marker of behavioural and cognitive problems, are at least partly caused by processes occurring early in foetal life.

Introduction

Neuromotor development is an accepted means of measuring maturity of the central nervous system. It is a measure of brain development that can be used at an early age. Most importantly, less optimal neuromotor development in infancy is a precursor of impaired motor functioning later in life[1] and can also be considered a marker for behavioural and cognitive problems. [2,3]

Neuromotor impairment in low birth weight infants can be caused by damage to the immature brain during delivery or by medical interventions performed after birth.[4] However, it is more likely that deviances in brain development originate from before birth. A theory that relies on this early origin is the 'foetal programming hypothesis', which states that foetuses adapt to limited supplies of nutrition and oxygen. These adaptations programme the foetus' physiology, metabolism, and growth, increasing the risk of later diseases; not only of cardiovascular diseases[5] but also of mental health problems.[6,7]

Most research on the foetal programming hypothesis has focused on the impact of low birth weight; the effects of normal variations in birth weight on later development are less clear, although several studies have investigated associations of birth weight with various outcomes in the general population.[8-10] Besides, there are only a few population-based studies that assessed foetal size during pregnancy.[11] Commonly, birth weight is used as an indicator of foetal growth. However, birth weight does not provide information on patterns of growth at different stages in gestation. Different growth patterns may lead to differences in body proportions at birth. This symmetrical or asymmetrical growth has been associated with different risk factors for developing diseases.[12,13] While undergoing foetal growth restriction due to environmental influences an individual foetus may still reach a normal birth weight because of his high genetic growth potential.

We measured foetal size in mid-pregnancy, in late pregnancy and at birth, and infant neuromotor development at the age between 9 and 15 weeks. Furthermore, we conducted our study in the general population and investigated the neuromotor effects of variations in foetal size within the

normal range. Smaller foetal size was expected to increase the risk of less optimal infant neuromotor development.

Methods

Design and Participants

This study was embedded within the Generation R Study, a population-based cohort from foetal life until young adulthood in the Netherlands. Briefly, all pregnant women who were resident in the city of Rotterdam at the time of their delivery and whose delivery data lay between April 2002 and January 2006 were invited to participate.[14] In the current study foetal size characteristics were assessed in 5,621 foetuses in mid-pregnancy, and in 5,815 foetuses in late pregnancy. In 5,507 foetuses assessments were carried out both in mid-pregnancy and in late pregnancy. No neuromotor assessment was performed in 1,641 infants, because their mothers did not want a home visit (*n*=1,010, 62%), were difficult to reach and were visited when the infants were too old for a neuromotor assessment (*n*=547, 33%). Another 5% of these mothers could not be reached (*n*=84). A neuromotor assessment was performed in 4,288 infants, but 1,323 infants were assessed outside the 9-15 week age range appropriate for Touwen's Neurodevelopmental Examination. Thus, 2,965 infants were included in one or more analyses. The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and has been approved by Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all participants.

Foetal ultrasound examinations and birth weight

Foetal ultrasound examinations were performed at the research centres in early, mid- and late pregnancy. Ultrasound examinations in early pregnancy were used for establishing gestational age, and could not be used in our analyses. For the present study gestational age-adjusted standard deviation (SD) scores for abdominal circumference, head circumference, abdominal-to-head circumference (AC/HC) ratio, as indicator of asymmetrical foetal growth,[12] and estimated foetal weight were used.[15] In the current study the median (95% range) gestational age for the foetal ultrasound examinations

in mid-pregnancy was 20.4 (18.6-23.5) weeks; in late pregnancy it was 30.2 (28.5-32.9) weeks. Intra- and inter-observer reliability of foetal biometry measurements were assessed in early pregnancy; all intra-observer and inter-observer intra-class correlation coefficients (ICC's) were above 0.982.[16]

Infant birth weight was obtained from medical records completed by midwives and gynaecologists.

Covariates

Postal questionnaires were used to obtain information on the mother's educational level, on her smoking and alcohol use during pregnancy, parity, family functioning, long lasting difficulties and also on ethnicity of the child. Obstetric and perinatal variables (gestational hypertension, gestational diabetes, pre-eclampsia, mode of delivery, gender, date of birth, and Apgar score after 1 minute and after 5 minutes) were obtained from midwife and hospital registries. Gestational age was determined by foetal ultrasound examinations and was used as it is distributed in the study population, including mostly infants born after a normal gestational age (37 weeks or more) and some infants born after a gestational age shorter than 37 weeks (<37 weeks *n*=160; <34 weeks *n*=31). Infant head circumference and height at the age of one month was measured at the Dutch child health centres in the study area using standardized procedures. Maternal age and maternal and paternal anthropometrics were assessed at enrolment in one of the research centres. Antenatal and postnatal maternal anxiety and depression were assessed with the Brief Symptom Inventory.[17] A score in the highest 15% was defined as being anxious or depressed.[18]

Outcome: Neuromotor assessment

We selected age-appropriate items from Touwen's Neurodevelopmental Examination,[19] and categorized all measured items in three groups: tone (24 items), responses (6 items), and other observations (6 items). Tone was assessed in several positions - supine, horizontal, vertical, prone and sitting – and all items, such as adductor angle, were scored as normal, low or high tone. Responses were assessed in supine (e.g. asymmetrical tonic neck reflex), vertical (e.g. Moro response) or prone position (e.g. Bauer

response) and were scored as present, absent or excessive. Other observations, such as following movements, were scored as present, absent or excessive. A full description of the measured items has been published.[20] An age-appropriate response was labeled 'optimal'. If the response indicated a delayed development, the response was labeled 'non-optimal'. Scale values were calculated by summing the non-optimal items. This resulted in a total score and three subscale scores: tone, responses, and other observations. As we studied a non-clinical population, the outcome measures were very skewed; neither square root or log transformation could satisfactorily normalize the data. For this reason, we categorized the sumscores of the total and the subscales into tertiles, subsequently classifying the lowest and middle tertiles as optimal neuromotor development, and the highest as less optimal. For the total scale a subject with a less optimal neuromotor development, i.e. with a score in the highest tertile, was classified as such when they had a non-optimal score on at least four items. Likewise, for the tone subscale a subject had at least three non-optimal scored items in order to be classified in the highest tertile. For the subscales measuring responses and other observations one or more non-optimal scored items resulted in classification in the highest tertile.

Moreover, we performed a reliability study to test the short-interval test-retest interobserver reliability and the interobserver reliability. The short-interval test-retest interobserver reliability test (n=61) consisted of a first assessment by a research assistant, followed within one week by a second assessment by another research assistant. For the interobserver reliability test (n=76), two research assistants together went on a home visit in which they independently conducted two consecutive neuromotor assessments in the same child. The ICC's for the short-interval test-retest reliability and the interobserver reliability were .52 and .64, respectively. The ICC's for the reliability of the neuromotor assessment were in the 'modest' (.41-.60) to 'substantial' (.61-.80) range,[21] and in line with a study by Peters, Maathuis, Kouw, Hamming, and Hadders-Algra[22] who reported a moderate to good reliability of a modified Touwen examination. However, it is difficult to compare these values with a criterion as the ICC is

influenced by features of the data, such as its variability (the ICC will be greater if the observations are more variable).

Over a period of approximately three years (children were born between April 2002 and January 2006) neuromotor assessments were performed by in total 15 trained research assistants. Six of them participated in the reliability study. Furthermore, the trained research assistants were blinded for gestational age of the infants.

Statistical analyses

Chi-square tests and oneway-ANOVA were used for a crude comparison between selected variables regarding infants with optimal and less optimal neuromotor development.

For the present study, we did not use the original data obtained in mid-pregnancy, late pregnancy and at birth, rather we used gestational age-adjusted SD scores of abdominal circumference, head circumference, AC/HC ratio, estimated foetal weight and birth weight.

By calculating the difference between the respective foetal size parameters in late and in mid-pregnancy, i.e. deltascores, we assessed foetal growth from mid- to late pregnancy. Likewise, weight growth from late pregnancy until birth was assessed by calculating the difference between SD scores of birth weight and estimated foetal weight in late pregnancy. We checked whether the 90% CI's of the OR's for weight growth from mid to late pregnancy and from late pregnancy to birth overlapped. This is a crude but conservative test to estimate whether two OR's are different.

We calculated mean foetal size parameters for boys and girls. Pearson correlation coefficients were calculated to determine the associations between foetal size parameters at one point in time, i.e. in mid-pregnancy and in late pregnancy. Also, Pearson correlation coefficients were calculated between the two time points for each foetal size parameter to determine the stability of an individual size measure relative to other children. The associations of foetal size and growth with infant neuromotor development were assessed using logistic regression analysis. All models were adjusted for gestational and postnatal age, and the infant's gender. We also present models adjusted for maternal educational level, smoking

during pregnancy, maternal age, and ethnicity of the child. No other confounders were included in the analyses, as these variables did not change the observed associations (change-in-estimate<5%). The conventional change-in-estimate criterion is a change of 10% or more.[23] Because non-experimental studies, like ours, are very sensitive to residual confounding, we used a more conservative change-in-estimate criterion (5%).

To determine whether the associations between foetal size and infant neuromotor development were independent of birth weight and postnatal size, we added birth weight, head circumference and height at one month of age to the fully adjusted models.

To check whether inclusion of preterm, growth retarded infants, or infants whose mothers had pre-eclampsia, gestational hypertension or gestational diabetes explained our findings, we repeated the analyses without: 1) infants born before 37 weeks of gestation (*n*=113), 2) infants with foetal size or symmetry parameters below the 10th percentile (*n*=292), and 3) infants whose mothers had pre-eclampsia, or gestational hypertension or diabetes (*n*=135).

Results

Excluded infants without a neuromotor assessment or with an assessment conducted too late were on average born earlier (mean gestational age 39.8 weeks) and more often of non-Dutch origin (44%), than included infants with complete data (mean gestational age 40.0 weeks; 40% non-Dutch). Mothers of not included infants were lower educated (primary education 14%), younger (mean age 29.5 years) and more often continued smoking during pregnancy (19%), as compared to mothers of included infants (primary education 10%; mean age 30.3 years; continued smoking 14%; see Table 1).

Table 1. Comparison of Included and Excluded participants

	Included † **(*n* = 2,965)**	**Excluded ‡** **(*n* = 2,964)**
Maternal characteristics		
Educational level		
Primary, %	10	14
Secondary, %	43	46
High, %	48	40
X^2 (df)		40.4 (2) **
Age, years; mean *(SD)*	30.3 *(5.1)*	29.5 *(5.3)* **
Continued smoking during pregnancy, %	14	19 **
Child characteristics		
Male, %	49	51
Ethnicity, non-Dutch, %	40	44 **
Gestational age, weeks; mean *(SD)*	40.0 *(1.6)*	39.8 *(1.8)* **
SD score abdominal circumference in mid-pregnancy; mean *(SD)*	0.05 *(0.95)*	0.02 *(1.02)*
SD score head circumference in mid-pregnancy; mean *(SD)*	0.004 *(0.99)*	-0.03 *(1.03)*
SD score AC/HC ratio in mid-pregnancy; mean *(SD)*	0.06 *(0.79)*	0.06 *(0.80)*
SD score estimated foetal weight in mid-pregnancy; mean *(SD)*	-0.11 *(1.01)*	-0.08 *(0.96)*
SD score birth weight; mean *(SD)*	-0.08 *(1.00)*	-0.13 *(1.04)*

* $p < .05$ ** $p < .01$
Values are percentages for categorical variables, means *(SD)* for continuous normal distributed variables.
Chi-square tests were used for categorical variables, ANOVA was used for continuous variables with a normal distribution.
† Included participants with at least one foetal size parameter in mid-pregnancy or in late pregnancy and neuromotor assessment at corrected age between 9 and 15 weeks.
‡ Comprises 1,641 eligible mothers with children who had a foetal size measurement but no neuromotor assessment and 1,323 eligible mothers and children who had a neuromotor assessment out of the appropriate age range.

Characteristics of the study population are presented in Table 2. Mothers of infants with less optimal neuromotor development were lower educated and younger than mothers of infants with optimal neuromotor development. Infants with less optimal neuromotor development were more often boys and of non-Dutch origin than those of infants with an optimal neuromotor development.

Table 2. Sample characteristics

	Optimal lowest-midst tertile ***n=1,886***	**Non-optimal highest tertile** ***n=1,079***
Maternal characteristics		
Educational level		
Primary, %	8	13
Secondary, %	42	44
High, %	50	43
X^2 (df)		27.5 (2) **
Age, years; mean *(SD)*	30.5 *(5.0)*	29.9 *(5.2)***
Continued smoking during pregnancy, %	13	14
Continued alcohol use during pregnancy, %	40	36 **
Pregnancy complications, %	5	5
Nulliparous, %	56	57
Prenatal maternal anxiety, score > 15th percentile, %	13	18 **
Prenatal maternal depression, score > 15th percentile, %	14	18 *
Postnatal maternal anxiety, score > 15th percentile, %	16	17
Postnatal maternal depression, score > 15th percentile, %	15	18
Height, centimetre; mean *(SD)*	167.7 *(7.4)*	166.6 *(7.3)* **
Height partner, centimetre*;* mean (*SD*)	182.1 *(6.8)*	181.5 *(6.5)* *
Body mass index, kg/m^2*;* mean (*SD*)	24.5 *(4.2)*	24.6 *(4.3)*
Body mass index partner, kg/m^2*;* mean (*SD*)	25.2 *(3.0)*	25.0 *(3.0)*
Child characteristics		
Male, %	47	52 **
Ethnicity		
Dutch, other Western, %	63	57
Surinamese / Antillean, %	12	12
Moroccan / Turkish, %	12	19
Other non-Western, %	14	13
X^2 (df)		28.0 (3) **
Postconceptional age, weeks; mean *(SD)*	52.6 *(1.2)*	52.3 *(1.1)* **
Gestational age, weeks; mean *(SD)*	40.0 *(1.5)*	40.0 *(1.7)*
Birth weight, gram; mean *(SD)*	3,456 *(511)*	3,436 *(545)*
Way of birth		
Spontaneous, %	77	74
Instrumental, %	14	16
Caesarean Sectio, %	9	10
X^2 (df)		2.2 (2)

Table 2. Sample characteristics *(continued)*

	Optimal lowest-midst tertile ***n=1,886***	**Non-optimal highest tertile** ***n=1,079***
Child characteristics		
Apgar 1 minute, score < 25th percentile, %	26	27
Apgar 5 minute, score < 25th percentile, %	26	28
Head circumference at 1 month, cm; mean *(SD)*	37.5 *(1.3)*	37.6 *(1.4)*
Height at 1 month, cm; mean *(SD)*	54.2 *(2.4)*	54.2 *(2.4)*

* $p < .05$ ** $p < .01$
Values are percentages for categorical variables, means *(SD)* for continuous normal distributed variables.
Chi-square tests were used for categorical variables, ANOVA was used for continuous variables with a normal distribution.

Table 3 presents SD scores of foetal size parameters in mid- and late pregnancy for boys and girls. In mid- and late pregnancy boys had on average a significantly larger abdominal circumference and head circumference than girls. Also, in mid- and in late pregnancy, the mean AC/HC ratio was significantly smaller in boys than in girls.

Table 3. Foetal size by gender

	Boys ***n*=1,454**	***Girls*** ***n*=1,511**
Mid-pregnancy SD scores foetal size parameters		
Abdominal circumference	0.12 *(0.97)*	-0.01 *(0.93)* **
Head circumference	0.16 *(0.98)*	-0.15 *(0.97)***
Ratio AC/HC	0.03 (0.78)	0.10 *(0.79)* *
Estimated foetal weight	-0.08 (0.97)	-0.08 *(0.94)*
Late pregnancy SD scores foetal size parameters		
Abdominal circumference	0.11 *(0.95)*	-0.01 *(0.94)* **
Head circumference	0.30 *(0.94)*	-0.10 *(0.92)* **
Ratio AC/HC	-0.09 *(0.77)*	0.03 *(0.75)***
Estimated foetal weight	0.10 *(0.97)*	0.07 *(0.95)*
Delivery SD scores birth weight		
Birth weight	-0.08 *(1.02)*	-0.07 *(0.98)*

* $p < .05$ ** $p < .01$
n = 2,965 infants were included in one or more analyses
Values are means *(SD),* ANOVA for continuous variables.

Abdominal circumference and head circumference were moderately correlated in late pregnancy (*r*=.44). Also, abdominal circumference was moderately correlated with birth weight (*r*=.54). Abdominal circumference had a high correlation with both the AC/HC ratio (*r*=.76), and estimated foetal weight (*r*=.92). In contrast, head circumference had a negative correlation with AC/HC ratio (*r*=-.24), and was moderately correlated with estimated foetal weight and with birth weight (respectively *r*=.45 and *r*=.39). The preceding late pregnancy correlation coefficients were highly similar in mid-pregnancy. Finally, foetal size parameters in mid-pregnancy were significantly correlated with the respective foetal size parameters in late pregnancy (minimum *r*=.30, maximum *r*=.53). Estimated foetal weight in mid-pregnancy and in late pregnancy were moderately correlated with birth weight (respectively *r*=.27 and *r*=.57).

Table 4 shows the associations between foetal size parameters and infant neuromotor development. These associations were of similar strength in mid- and in late pregnancy. For a 1-SD score increase in abdominal circumference the risk of less optimal neuromotor development was 11% lower (OR 0.89, 95% CI 0.82-0.97). For each increase of 1-SD score in AC/HC ratio the risk of less optimal neuromotor development was 13% less (OR 0.87, 95% CI 0.79-0.96). The risk of less optimal neuromotor development was 11% lower for a 1-SD score increase in estimated foetal weight (OR 0.89, 95% CI 0.82-0.97). Adjusting for gender, gestational and postnatal age, or adding the mother's educational level, age and smoking behaviour during pregnancy, and infant's ethnicity resulted in approximately the same effect estimates (Table 4). Exclusion of preterm infants (<37 weeks of gestation), infants with a foetal size parameter below the 10th percentile or infants whose mothers had pre-eclampsia, gestational hypertension or diabetes also did not change the results (data not shown).

Table 4. Associations between foetal size in mid- and late pregnancy and infant neuromotor development

		Risk of non-optimal neuromotor development at 9-15 weeks	
		Model I	**Model II**
		OR (95% CI)	**OR (95% CI)**
	n		
Foetal size parameters, per SD score			
mid-pregnancy			
Abdominal circumference	2,756	0.89 (0.82-0.97)**	0.88 (0.81-0.96)**
Head circumference	2,753	0.99 (0.92-1.08)	0.99 (0.92-1.08)
Ratio AC/HC	2,739	0.87 (0.79-0.96)**	0.86 (0.77-0.95)**
Estimated foetal weight	2,749	0.89 (0.82-0.97)**	0.89 (0.82-0.97)**
late pregnancy			
Abdominal circumference	2,854	0.93 (0.86-1.00)	0.92 (0.85-1.00)*
Head circumference	2,834	0.98 (0.90-1.07)	0.99 (0.91-1.08)
Ratio AC/HC	2,829	0.92 (0.83-1.02)	0.90 (0.81-1.00)*
Estimated foetal weight	2,850	0.92 (0.85-1.00)*	0.92 (0.85-1.00)*
birth			
Birth weight	2,891	0.95 (0.88-1.02)	0.95 (0.88-1.03)

* $p < .05$ ** $p < .01$

n = 2,965 infants were included in one or more analyses

Model I: Logistic regression analyses adjusted for gender child, and gestational and postnatal age

Model II: Logistic regression analyses additionally adjusted for educational level, smoking and age mother, and ethnicity of the child.

As effects were very similar in mid- and in late pregnancy, it followed that infant's neuromotor development was not influenced by foetal growth from mid- to late pregnancy. Also, there was no effect of weight growth from late pregnancy until birth on infant neuromotor development (Table 5). It is unlikely that the OR's for the two weight growth periods are significantly different, since the 90%CI's were very similar (90%CI for weight growth from mid to late pregnancy 0.97-1.13; 90%CI for weight growth from late pregnancy until birth 0.96-1.11).

Table 5. Associations between foetal growth from mid to late pregnancy and infant neuromotor development

		Risk of less optimal neuromotor development at 9-15 weeks OR (95% CI)
	n	
Foetal growth parameters from mid to late pregnancy		
Abdominal circumference, per SD score	2,703	1.05 (0.97-1.14)
Head circumference, per SD score	2,682	1.00 (0.92-1.08)
Ratio AC/HC, per SD score	2,664	1.05 (0.96-1.15)
Estimated foetal weight, per SD score	2,692	1.05 (0.96-1.14)

* $p < .05$ ** $p < .01$
Delta scores, i.e. difference between late and mid-pregnancy.
2,721 of 2,965 had foetal size measurements in mid-pregnancy and in late pregnancy.
Logistic regression analyses adjusted for gender child, and gestational and postnatal age, educational level, smoking and age mother, and ethnicity of the child.

Adding birth weight, head circumference and height at one months to the fully adjusted models did not change the effect estimates for the associations between foetal size in mid-pregnancy and infant neuromotor development. The odds ratio for the association between abdominal circumference and infant neuromotor development was not at all affected by this additional adjustment (OR 0.88, 95% CI 0.81-0.96). With each 1-SD increase in AC/HC ratio the risk of less optimal neuromotor development was 13% lower (OR 0.87, 95% CI 0.78-0.96), which corresponds to a only very marginally reduced effect. Likewise, with a 1-SD increase of estimated foetal weight (OR 0.89, 95% CI 0.82-0.97) the observed risk of less optimal neuromotor development was 11% less, which was exactly the same as without the additional adjustment. Also, the associations between foetal size in late pregnancy and infant neuromotor development were independent of birth weight and postnatal infant anthropometrics (data not shown).

Discussion

The present study shows that a foetus with a lower body weight or with asymmetrical growth is more likely to have less optimal neuromotor development in infancy. Already in mid-pregnancy body size predicted a poorer neuromotor development. These associations were also present in late pregnancy. Foetal size and body symmetry predicted infant neuromotor development independent of birth weight and postnatal growth.

Neuromotor development is a measure of maturation of the central nervous system and an indirect indication of brain dysfunction.[24,25] Brain structures begin to form in the first weeks after conception and the brain is thus from early pregnancy onwards vulnerable to damaging influences.[26] As the brain develops throughout pregnancy, adverse factors impairing foetal growth, such as placental insufficiency, could negatively affect the development of the central nervous system continuously during pregnancy.

Harvey et al.[27] found that small-for-gestational age babies with prolonged growth impairment beginning before 26 weeks of gestation (*n*=10) more often had poor perceptual performance and motor ability at the age of 5 years. This, like our results, suggests that differences in neuromotor development are, at least partly, caused by processes occurring early in foetal life, although the results of this study cannot be compared directly with the results of our study. Also, our results show that differences in infant neuromotor development are explained by foetal size and body symmetry within the normal range.

Most population-based studies on the effects of intrauterine growth restriction are performed in high risk populations. Typically, differences in neuromotor outcomes between a high risk group and a low risk group are investigated.[28,29] We conducted our study in the general population with only few growth retarded infants. Nevertheless, we found that foetal size and body symmetry were associated with the infant's neuromotor development; excluding infants born preterm (<37 weeks), with a foetal size or body symmetry parameter below the 10th percentile or infants whose mothers had pre-eclampsia, gestational hypertension or gestational diabetes did not change our findings. This suggests significant linear trends across continuous distributions.

There are several possible mechanisms that may underlie the associations between foetal size and body symmetry and infant neuromotor development. Firstly, according to the foetal programming hypothesis, malnutrition in mid- or late pregnancy could play a crucial role in foetal growth.[5] The main characteristic of foetal growth is cell division, which occurs at a high pace and depends on nutrition and oxygen. When a lack of nutrition and oxygen occurs, the foetus adapts and slows its rate of cell division, especially in organs that go through a critical period at that time. Consequently, this reduces the number of cells in particular organs[30,31] which may also affect growth or size of the brain and with that influences neuromotor functioning after birth. We did not find that growth from mid-pregnancy until birth affected neuromotor development, but found only that foetal size and body symmetry in mid-pregnancy were related to infant neuromotor development. This may indicate that smaller foetuses in mid-pregnancy continue to be smaller throughout pregnancy and that these foetuses have an increased risk of less optimal neuromotor development in infancy.

Another mechanism that may explain the association of foetal size and body symmetry and infant neuromotor functioning is the regulation of the maternal stress system, in particular the hypothalamic pituitary adrenal axis. Several studies have suggested that antenatal maternal distress impacts on both foetal growth and infant neuromotor development.[32] Since adjusting for antenatal maternal symptoms of anxiety and depression did not change our effect estimates, it is unlikely that this mechanism accounts for a substantial part of our findings.

Thirdly, a shared genetic factor may underlie the association between foetal growth and neuromotor development. The association between maternal length and maternal weight and the offspring's birth weight is in part explained by genetic influences.[33,34] It is also known that maternal height and weight have a genetic influence on neuromotor functioning.[35] Against this background, we considered maternal height and weight as potential confounders. However, they had no influence on the observed associations. The observed link between foetal growth and neuromotor development can thus only be explained by genetic factors unrelated to maternal anthropometrics.

The AC/HC ratio has been shown to be useful in distinguishing symmetrical from asymmetrical growth.[12] Asymmetrical growth suggests that the foetus has a relatively large head circumference as compared to its abdominal circumference. The measure is used as an indicator of foetal blood flow redistribution. Although head circumference, by definition is less affected, it does not mean that brain development is unimpaired. A study by Duncan et al. showed that brain growth slowed well before growth of head circumference in cases of impaired foetal development.[36] Also, Scherjon et al. found poorer cognitive functioning when circulatory adaptation in foetuses occurred.[37] In the present study, we found that head circumference in mid- and in late pregnancy was not associated with infant neuromotor development, whereas smaller abdominal circumference, AC/HC ratio and estimated foetal weight resulted in less optimal neuromotor development in infancy.

A major strength of this study is that both determinants and outcome were measured by trained sonographers and research nurses and were not reported by the mother. Furthermore, this study is embedded in a large population based cohort study, which enabled us to adjust for a large number of confounders. Although selection of these covariates was based on prior studies, only few of them influenced the associations under study. Finally, the multi-ethnic composition of our study population may reduce generalizability of the results to the general Dutch population, but certainly makes the results more generalizable to countries with non-Western populations. Moreover, adjusting for ethnicity did not attenuate the significant associations between foetal size and infant neuromotor development. This suggests that the results may even be relatively independent of ethnicity.

Several methodological limitations need to be discussed. First, selective non-response could have influenced our results, e.g. if participants with impaired grown foetuses were more likely than non-participants to have an infant with less optimal neuromotor development. However, because participants were blinded for the associations under study, and because we are studying the effects of subtle differences in foetal growth, it is unlikely that selective non-response substantially influenced our findings. Second, because foetal ultrasound examinations in early pregnancy were used to

establish gestational age, we were not able to assess the relation between early foetal size and infant neuromotor development. Furthermore, any error in the estimation of gestational age may reduce the variance of infant neuromotor development explained by foetal size. Thirdly, as we studied a non-clinical population neuromotor measures were very skewed and could not be normalized by statistical transformations. Therefore, the scale scores were categorized, resulting in less power for analyses. Finally, although our associations were influenced by only few of the many measured potential confounders, we cannot exclude that residual confounding partly explains our results.

The current study shows that in the general population foetal size and body symmetry in mid-pregnancy and in late pregnancy are associated with infant neuromotor development. Taking account of several influential confounders did not attenuate these significant associations. This study suggests that differences in neuromotor development are, at least partly, caused by processes occurring early in foetal life. Although the effects of foetal size variations on infant neuromotor development were modest and could not be interpreted clinically very easily, they may well have impact on population level. In addition, these effects may shed light on mechanisms underlying optimal child development. Future research is necessary to determine whether the negative effect of impaired foetal growth on infant neuromotor functioning are transient, persistent or progressive.

References

1 Samsom JF, de Groot L, Bezemer PD, Lafeber HN and Fetter WP. Muscle power development during the first year of life predicts neuromotor behaviour at 7 years in preterm born high-risk infants. *Early Hum Dev.* 2002; **68** (2): 103-18.

2 Davis NM, Ford GW, Anderson PJ, Doyle LW and Victorian Infant Collaborative Study Group. Developmental coordination disorder at 8 years of age in a regional cohort of extremely-low-birthweight or very preterm infants. *Dev Med Child Neurol.* 2007; **49** (5): 325-30.

3 Pine DS, Wasserman GA, Fried JE, Parides M and Shaffer D. Neurological soft signs: one-year stability and relationship to psychiatric symptoms in boys. *J Am Acad Child Adolesc Psychiatry.* 1997; **36** (11): 1579-86.

4 Whitaker AH, Feldman JF, Lorenz JM, Shen S, McNicholas F, Nieto M, McCulloch D, Pinto-Martin JA and Paneth N. Motor and cognitive outcomes in nondisabled low-birth-weight adolescents: early determinants. *Arch Pediatr Adolesc Med.* 2006; **160** (10): 1040-6.

5 Barker DJ. Fetal origins of coronary heart disease. *Bmj.* 1995; **311** (6998): 171-4.

6 St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, Zheng X, Gu N, Feng G, Sham P and He L. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. *Jama.* 2005; **294** (5): 557-62.

7 Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D and Gorman JM. Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psychiatry.* 1996; **53** (1): 25-31.

8 Shenkin SD, Starr JM and Deary IJ. Birth weight and cognitive ability in childhood: a systematic review. *Psychol Bull.* 2004; **130** (6): 989-1013.

9 Pearce MS, Deary IJ, Young AH and Parker L. Growth in early life and childhood IQ at age 11 years: the Newcastle Thousand Families Study. *Int J Epidemiol.* 2005; **34** (3): 673-7.

10 Kirkegaard I, Obel C, Hedegaard M and Henriksen TB. Gestational age and birth weight in relation to school performance of 10-year-old children: a follow-up study of children born after 32 completed weeks. *Pediatrics.* 2006; **118** (4): 1600-6.

11 Gale CR, O'Callaghan FJ, Godfrey KM, Law CM and Martyn CN. Critical periods of brain growth and cognitive function in children. *Brain.* 2004; **127** (Pt 2): 321-9.

12 Campbell S and Thoms A. Ultrasound measurement of the fetal head to abdomen circumference ratio in the assessment of growth retardation. *Br J Obstet Gynaecol.* 1977; **84** (3): 165-74.

13 Rasmussen S, Kiserud T and Albrechtsen S. Foetal size and body proportion at 17-19 weeks of gestation and neonatal size, proportion, and outcome. *Early Hum Dev.* 2006; **82** (10): 683-90.

14 Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC and Hofman A. The Generation R Study: design and cohort update until the age of 4 years. *Eur J Epidemiol.* 2008; **23** (12): 801-11.

15 Hadlock FP, Harrist RB, Carpenter RJ, Deter RL and Park SK. Sonographic estimation of fetal weight. The value of femur length in addition to head and abdomen measurements. *Radiology.* 1984; **150** (2): 535-40.
16 Verburg BO, Mulder PG, Hofman A, Jaddoe VW, Witteman JC and Steegers EA. Intra- and interobserver reproducibility study of early fetal growth parameters. *Prenat Diagn.* 2008; **28** (4): 323-31.
17 de Beurs E. *Brief Symptom Inventory, handleiding*. Leiden, the Netherlands; 2004.
18 O'Connor TG, Heron J and Glover V. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry.* 2002; **41** (12): 1470-7.
19 Touwen BC. *Neurological development in infancy*. London: Heinemann; 1976.
20 van Batenburg-Eddes T, de Groot L, Huizink AC, Steegers EAP, Hofman A, Jaddoe VWV, Verhulst FC and Tiemeier H. Maternal symptoms of anxiety during pregnancy affect infant neuromotor development: The Generation R Study. *Dev Neuropsychol.* 2009; **34** (4): 1-18 *in press*.
21 Cohen J. Weighted kappa; nominal scale agreement with provision for scaled disagreement or partial credit. *Psychol Bull.* 1968; **70**: 213-20.
22 Peters LH, Maathuis KG, Kouw E, Hamming M and Hadders-Algra M. Test-retest, inter-assessor and intra-assessor reliability of the modified Touwen examination. *Eur J Paediatr Neurol.* 2008; **12** (4): 328-33.
23 Mickey RM and Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol.* 1989; **129** (1): 125-37.
24 Prechtl HF. *The Neurological Examination of the Full-term Newborn Infant*. 2nd ed. London: Heinemann; 1977.
25 Touwen BC. *Examination of the child with minor neurological dysfynction Clinics in Developmental Medicine*. London: William Heinemann Medical Books; 1979.
26 Rice D and Barone S, Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect.* 2000; **108 Suppl 3**: 511-33.
27 Harvey D, Prince J, Bunton J, Parkinson C and Campbell S. Abilities of children who were small-for-gestational-age babies. *Pediatrics.* 1982; **69** (3): 296-300.
28 Hoff Esbjorn B, Hansen BM, Greisen G and Mortensen EL. Intellectual development in a Danish cohort of prematurely born preschool children: specific or general difficulties? *J Dev Behav Pediatr.* 2006; **27** (6): 477-84.
29 Mikkola K, Ritari N, Tommiska V, Salokorpi T, Lehtonen L, Tammela O, Paakkonen L, Olsen P, Korkman M and Fellman V. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. *Pediatrics.* 2005; **116** (6): 1391-400.
30 Widdowson EM and McCance RA. A review: new thoughts on growth. *Pediatr Res.* 1975; **9** (3): 154-6.
31 McCance RA and Widdowson EM. The determinants of growth and form. *Proc R Soc Lond B Biol Sci.* 1974; **185** (78): 1-17.

32 Huizink AC, de Medina PGR, Mulder EJ, Visser GHA and Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. *J Child Psychol Psychiatry.* 2003; **44** (6): 810-8.

33 Griffiths LJ, Dezateux C and Cole TJ. Differential parental weight and height contributions to offspring birthweight and weight gain in infancy. *Int J Epidemiol.* 2007; **36** (1): 104-7.

34 Knight B, Shields BM, Turner M, Powell RJ, Yajnik CS and Hattersley AT. Evidence of genetic regulation of fetal longitudinal growth. *Early Hum Dev.* 2005; **81** (10): 823-31.

35 Peter I, Vainder M and Livshits G. Genetic analysis of motor milestones attainment in early childhood. *Twin Res.* 1999; **2** (1): 1-9.

36 Duncan KR, Issa B, Moore R, Baker PN, Johnson IR and Gowland PA. A comparison of fetal organ measurements by echo-planar magnetic resonance imaging and ultrasound. *Bjog.* 2005; **112** (1): 43-9.

37 Scherjon S, Briet J, Oosting H and Kok J. The discrepancy between maturation of visual-evoked potentials and cognitive outcome at five years in very preterm infants with and without hemodynamic signs of fetal brain-sparing. *Pediatrics.* 2000; **105** (2): 385-91.

Chapter 2.3

Antenatal maternal anxiety and depression and infant neuromotor development

Abstract

Several studies found that maternal symptoms of anxiety or depression are related to functioning and development of the offspring. Within a population-based study of 2,724 children, we investigated the effect of maternal anxiety or depression on infant neuromotor development. Symptoms of anxiety and depression were measured during pregnancy and after giving birth; infant neuromotor development was assessed by trained research nurses during a home visit at the age of 3 months. The current study showed that mothers who were anxious during pregnancy had an elevated risk of having an infant with non-optimal neuromotor development.

Introduction

There is increasing evidence that antenatal maternal symptoms of anxiety or depression have an adverse effect on the development of the offspring. In part, this evidence comes from experimental studies. Adult rats that were prenatally exposed to several types of fear inducing stressors, exhibited more fearful or escape behaviour towards novel environments, which is interpreted as increased levels of anxiety,[1,2] and emotionality.[3] In pregnant squirrel monkeys repeated psychological disturbances during pregnancy adversely affected the offspring's neuromotor performance.[4] Likewise, when loud noise was randomly administered to pregnant primates this resulted in impaired motor maturity in the animals' offspring.[5,6]

Human studies also provided evidence for an adverse effect of antenatal maternal symptoms of anxiety and depression on the offspring's well-being, such as adverse neonatal outcomes[7-9] or mental health problems.[10,11]

The human studies relating antenatal maternal anxiety or depression to neuromotor development of the child, however, are limited and inconclusive. A study by Field et al. showed that newborns of women who were anxious during pregnancy performed worse on motor behaviour.[12] Lundy et al. found that neonates of depressed mothers performed worse on orientation and reflexes.[13] Conversely, DiPietro, Novak, Costigan, Atella and Reusing found that moderate levels of antenatal maternal anxiety or depression were associated with more advanced neuromotor development in infants,[14] whereas Van den Bergh found no association between antenatal maternal anxiety and the offspring's neuromotor development.[15] These inconsistent findings may be due to methodological differences among these studies, such as timing and type of measurements. For example, the Brazelton Neonatal Behavioral Assessment[16] for neonates and the Bayleys Scales of Infant Development (appropriate for age 1 to 42 months) were both used to determine neuromotor development. The instruments assess different aspects of neuromotor development, because they are used in different age ranges. Therefore, it is difficult to judge whether different findings reflect true differences or use of another instrument.

In contrast to antenatal maternal symptoms of anxiety or depression, which are generally viewed as intrauterine influences, postnatal symptoms

of anxiety or depression are seen as environmental factors that influence parenting or mother-child interaction. Studies of postnatal maternal psychological problems typically examined the effect of maternal depression on infant development. The decreased display of emotions, involvement and warmth may result in less responsive parenting and consequently increases the risk for neurodevelopmental problems.[17,18]

Thus, there is evidence that antenatal and postnatal maternal symptoms of anxiety and depression elevate the risk for a variety of problems in the offspring. Several mechanisms may underlie this association. Firstly, an explanation can be sought in the foetal origins hypothesis which states that an adverse foetal environment leads to permanent changes in the foetus' structure, physiology and metabolism.[19] Anxiety or depression during pregnancy may create an adverse foetal environment by elevating the mother's hypothalamic pituitary adrenal axis (HPA-axis) activity. Consequently, the level of circulating hormones increases. These hormones can be transmitted to the foetus by transplacental transport but may also reach the foetus by release of placental hormones. Higher levels of these hormones may inhibit foetal growth or may alter the formation of the foetal HPA-axis.[20-22] Furthermore, anxiety or depression are associated with poor health behaviours, such as smoking, physical inactivity, obesity or malnutrition which contribute to an adverse foetal environment.[23,24] Secondly, the diminished interaction between mothers with postnatal symptoms of anxiety or depression and their infant may negatively affect the infants' neural development.[25] Depressed mothers show negative cognitions, behaviours and affect towards their child. Due to this lack of positive environmental stimulation, the child has an increased risk of behaviour problems, which in turn may also affect the child's brain functioning.[26] Electroencephalogram-studies have shown that children of depressed mothers exhibit, just like their mothers, greater right frontal brain activity that is associated with 'withdrawal' emotions, like sadness.[27,28]

Thus, maternal symptoms of anxiety or depression can contribute to an adverse antenatal or postnatal environment which can impact on the child's neurodevelopment. One way to assess neurodevelopment is to conduct a neuromotor assessment and determine the maturation and intactness of the central nervous system, i.e. brain development. Furthermore,

neuromotor assessment measures maturation of the brain at a very young age and independently of the mother.[29,30]

When assessing maternal and child behaviour, most cohort studies rely on maternal reports. A major limitation of maternal reports is that anxious or depressed mothers are more likely to report problems in their children. Thus, it is probable that the reported associations are at least partly caused by reporter bias.[31]

The aim of the current study was to explore the association between maternal symptoms of anxiety or depression and infant neuromotor development. Contrary to most cohort studies, infant neuromotor development in the current study was assessed by research nurses independently of the mother, reducing common method bias. Furthermore, due to our large number of participants, we were able to disentangle the antenatal and postnatal effects of anxiety and depression on infant neuromotor development. Most studies point to an adverse effect of antenatal maternal anxiety rather than depression, whereas after birth maternal depression seems to have more impact than anxiety. Therefore, we hypothesized that infants of mothers with symptoms of anxiety during pregnancy and infants of mothers with postnatal symptoms of depression exhibit an increased risk for non-optimal neuromotor development.

Methods

Design and Participants

The current study was embedded in the Generation R Study, a population-based study from foetal life until young adulthood in Rotterdam, the Netherlands.[32] All pregnant women, who were resident in Rotterdam at the time of their delivery and whose delivery data lay between April 2002 and January 2006, were invited to participate. Information on antenatal and postnatal maternal symptoms of anxiety and depression was available for 5,296 mothers. Of these, 3,382 mothers returned both the antenatal and postnatal questionnaire, 1,349 only returned the antenatal questionnaire, and 565 only returned the postnatal questionnaire. In total 1,833 infants of 5,296 mothers who completed a behavioural questionnaire had no neuromotor assessment. Of these mothers 43% (n = 795) did not want a home visit, 52% (n = 949) were difficult to reach and thus visited when the

infants were too old for a neuromotor assessment. Another 5% (*n* = 89) of these mothers could not be reached. Neuromotor assessment was performed in 3,463 infants at the corrected ages between 9 and 20 weeks (*response* 65%). Because neuromotor development in infants with corrected ages between 15 and 20 weeks was measured with another age-appropriate instrument, only the measurements between 9 and 15 weeks corrected age were included in this study. Overall, 2,724 infants were included in one or more analyses.

Determinants

Symptoms of maternal anxiety and depression were assessed with the Brief Symptom Inventory (BSI), at 20 weeks of pregnancy and 2 months after giving birth. The BSI is a validated self-report questionnaire with 53 items on a 5-point scale, ranging from '0 = not at all' to '4 = extremely'.[33-35] The items of the BSI cover nine scales of psychiatric symptoms occurring in the preceding 7 days. For this study we used the anxiety and depression scale, each containing six questions. The questions asking for symptoms of anxiety were 'nervousness or shakiness inside', 'suddenly scared for no reason', 'feeling fearful', 'feeling tense or keyed up', 'spells of terror or panic', or 'feeling so restless you couldn't sit still', tapping both anxious arousal and apprehension.[36] Unfortunately, due to the small number of items measuring anxiety, these two constructs could not be distinguished. The depression scale consisted of six questions addressing among other things 'thoughts of ending life', 'feeling lonely', and 'feelings of worthlessness'. The values (0-4) of the items per scale were summed and divided by the number of endorsed items. If information on more than 25% of the items was lacking, this resulted in a missing scale value. Otherwise, scale scores were corrected for number of missing items. The alpha's for internal consistency in this study for antenatal and postnatal maternal anxiety were .82 and .83, and for antenatal and postnatal depression .87 and .82, respectively.

We dichotomized the reported anxiety and depression scores in order to distinguish the effects of those symptoms occurring only during pregnancy, those occurring only after giving birth and those occurring during both of these times. In line with previous research, we defined 'anxious' or 'depressed' as a score higher than the 85th percentile in our study

population.[37] Moreover, the cut-off in our study to delineate the highest 15% in our sample was 0.5, which lies well within the range used to describe 'high' scores (a score between 0.33 and 0.60) on both the depression and anxiety scale in the Dutch norm population.[33] We applied the Dutch norms, because prevalence and mean levels of psychiatric scores tend to be lower in the Netherlands than in the United States.

The antenatal and postnatal dichotomized anxiety and depression scores were also combined in four mutually exclusive categories: 1) no symptoms, i.e. always scored below the thresholds, 2) only antenatal symptoms, 3) only postnatal symptoms, and 4) both antenatal and postnatal symptoms of anxiety of depression.

In addition to the BSI, we used the Edinburgh Postnatal Depression Scale (EPDS), a widely-used 10-item self-report scale.[38,39] The EPDS is developed by Cox et al. for several reasons.[38] First, the majority of childbearing women with a marked depressive postnatal illness remain undiscovered and untreated. Second, most screening instruments, such as the BSI, focus on somatic symptoms of psychiatric disorder that may be caused by normal physiological changes associated with childbearing. The alpha for internal consistency in this study for the EPDS was .85. The Pearson product-moment correlation *r* between the scale scores of postnatal depressive symptoms measured by the BSI and by the EPDS in the current study was .71 ($p < .001$). Despite this high correlation, we decided not to combine the antenatal BSI measurement with the postnatal EPDS measurement in a categorical analysis. If information on depression from two points in time is combined, the assessment instruments should preferably be the same. Otherwise, any observed effect could be ascribed to both time interval or change of measure.

Outcome: Neuromotor assessment

Early identification of abnormal development in infancy has been proven to be difficult. Ideally, a full neurological age-adequate examination should be carried out, encompassing assessment of tone, elicited responses and other observations, like spontaneous movements and behaviour of the infant.[29,30] From Touwen's Neurodevelopmental Examination age-specific items were selected. Items measuring active and passive muscle tone were added to

these age-specific items according to the modified method of de Groot, Touwen and Hopkins,[40] that has been described in detail elsewhere.[41] In short, this method maintains the multiple domains of the original Touwen instrument, but puts extra emphasis on the notion that a discrepancy between active and passive tone serves as an early sign of poor posture and deviant motor development. All measured items were categorized in three groups: tone, responses, and other observations (see Table 1). Most tone items were scored as normal, low - or high tone; most responses and other observations were scored as present, absent, or excessive. An age-appropriate response was labeled 'optimal'. If the response indicated a delayed development, the response was labeled 'non-optimal'. The response-specific labels are displayed in Table 1. All assessments were performed by trained research assistants, who were blinded for the determinants.

We calculated scale values by summing the number of non-optimal items, which resulted in a total score and three subscale scores for tone items, responses, and other items. As we studied a non-clinical population, the outcome measures were very skewed; neither square root or log transformation could satisfactorily normalize the data. Therefore, we categorized the sum scores into tertiles, and subsequently classified the lowest and middle tertile as optimal and the highest as non-optimal neuromotor development.

Moreover, we performed a reliability study to test the short-interval test-retest interobserver reliability and the interobserver reliability. The short-interval test-retest interobserver reliability test (n=61) consisted of a first assessment by a research assistant, followed within one week by a second assessment by another research assistant. For the interobserver reliability test (n=76), two research assistants went on a home visit together. They each conducted a neuromotor assessment in the child blinded for the colleague's score.[41]

Table 1: Items neuromotor developmental assessment

Subscale	*Position*	*Item description*	*Answering categories*		
			Optimal	***Non-optimal***	***Non-optimal***
Tone	Supine	Resting posture	Semi-flexed legs; slight abduction at the hips	Legs flat on the surface	Legs stretched
		Adductor angle	> 80° - < 140°	> 140°	< 80°
		Popliteal angle	90°-130°	130°-180°	< 90°
		Ankle angle	> 20° - < 90°	< 20°	> 90°
		Head preference	No	Yes	
		Opening & closing hands	Yes	Sometimes closed	Always closed
		Alternating leg movements	Yes	Decreased	Absent
		Grasps with one hand	Yes	Decreased	Absent
		Hyperextension	No	Sometimes	Yes
		Dyskinesia	No	Sometimes	Yes
	Supine-to-sit	Traction response	Arms moderately flexed	Arms fully extended, no resistance	Strong resistance, flexion elbows, legs extended
		Traction response-head control	Active lift of head	Head lag	Exaggerated
	Horizontal	Ventral Tone	Normal tone	Low tone	Back and limbs stretched
	Vertical	Head	Normal tone	Low tone	High tone
		Shoulders	Normal tone	Low tone	High tone
		Trunk	Normal tone	Low tone	High tone
		Legs	Normal tone	Low tone	High tone
	Prone	Pulls arms up	Yes	No	
		Turns head	Yes	No	
		Lifts head	Yes	No	Overstretched
	Sitting	Needs support	Yes	No	
		Head control	Yes	No	
		Shoulder retraction	No	Yes	
		Shape of the back	Round	Straight	Scoliosis
Responses	Supine	Asymmetrical Tonic Neck Reflex	Weak	Yes	Exaggerated
		Babinski	Yes	Exaggerated	Spontaneous
	Prone	Bauer	Yes / weak	Exaggerated	
	Vertical	Stepping movements	No	Yes	Exaggerated
		Moro intensity	Yes / weak	Exaggerated	
		Moro opening hands	Yes	No	
Other	Supine	Strabismus	No	Sometimes	Yes
		Fixation eyes	Yes	Decreased	No
		Following movements eyes	Smooth	Decreased	No
		Hearing	Yes	Moderate	No
		Sweating	No	Yes	
		Startles	No	Sometimes	Yes

The intra-class correlation coefficients (ICC's) for the short-interval test-retest reliability and the interobserver reliability were .52 and .64, respectively. To calculate the latter, we only used the paired measurements of infants in the same behavioural state.[42] The ICC's for the reliability of the neuromotor assessment were in the 'modest' (.41-.60) to 'substantial' (.61-.80) range[43] and in line with a study by Peters, Maathuis, Kouw, Hamming, and Hadders-Algra, who reported a moderate to good reliability of a modified Touwen examination.[44] However, it is difficult to compare these values with a criterion, because the ICC is influenced by features of the data, such as its variability (the ICC will be greater if the observations are more variable).

Covariates

Information on educational level of the mother, maternal smoking and alcohol use during pregnancy, parity, family functioning, long lasting difficulties and ethnicity of the child were all obtained by postal questionnaires. Educational level was categorized in three levels: low (no or primary education), middle (lower and intermediate vocational training), and high education (higher vocational education, and university), which is based on Dutch standard classification criteria.[45] Ethnicity of the child was based on the country or countries of birth of the parents.[46] Maternal smoking and alcohol use were categorized in 'no', 'until pregnancy was known', and 'continued after pregnancy was known'. Family functioning was assessed by the 7th subscale General Functioning (GF) of the Family Assessment Device.[47] GF is a validated overall self-report measure of health or pathology of the family, which consists of 12 items. The item scores were summed and then divided by the number of items yielding a total score from 1 to 4. If the GF score is higher than 2.17 (cut-off), then family functioning is considered to be unhealthy. In the current study, just as in the Ontario Child Health Study,[47] 10 percent of the families scored above this cutting point. Information on stress was obtained by a sum score of an adjusted version of the Dutch long-lasting difficulties list.[48] This is a 12-item checklist which addresses problem situations in the preceding year. Women reported whether they have had difficulties with family members, friends, people from the neighbourhood and difficulties at school or work and

pointed out whether sexual, financial or housing problems had occurred. Obstetric and perinatal variables were also considered as potential confounders (maternal hypertension, pre-eclampsia, gestational diabetes, Apgar score after 1 minute and after 5 minutes, and mode of delivery) and were obtained from midwife and hospital registries. Gestational age was determined by foetal ultrasound examinations. Postnatal age, i.e. chronological age, was calculated as the difference between date of assessment and date of birth. Date of birth, birth weight and gender of the infant were obtained from midwife and hospital registries.

Statistical analyses

We used Chi-square tests, analysis of variance (ANOVA) and Kolmogorov-Smirnov tests for crude comparisons between selected variables of mothers who scored below the threshold of anxiety or depression, mothers with antenatal symptoms of anxiety or depression only, mothers with postnatal symptoms only, or mothers with symptoms at both time points.

Logistic regression was used to assess the relation of antenatal or postnatal anxiety or depression with infant neuromotor development. Firstly, analyses were performed using continuous measurements for antenatal and postnatal anxiety and depression. To compare the odds ratios of the different instruments, BSI and EPDS scale scores were expressed as standard deviation scores. Secondly, we used the categorical BSI measurements to determine the influence of specifically antenatal symptoms, postnatal symptoms, and symptoms at both points in time on infant neuromotor development.

Primarily, analyses with the categorical BSI measurements were conducted in mothers with complete data only. However, there was a substantial group of mothers who scored below the threshold, i.e. who were classified as having no symptoms on one questionnaire, and had missing data on the other questionnaire (n=578 for anxiety, and n=603 for depression). In order to minimize the effects of selection bias, we did not want to discard this information. We classified these mothers without symptoms on one and with missing data on the other questionnaire as having no symptoms. Of course, this results in misclassification; possibly, these mothers had symptoms at the time of the missing questionnaire.

However, accepting some misclassification is a conservative way of dealing with missing data, because it reduces the risk of spurious findings and the change of Type-II errors. To justify the classification, we performed additional non-response analyses and compared mothers without antenatal symptoms but with missing postnatal questionnaires to mothers who had no antenatal symptoms and had completed the postnatal questionnaire. Likewise, we compared mothers without postnatal symptoms but with missing prenatal data to the respective reference group. Comparisons were made in terms of the mother's educational level, her age and the child's ethnicity and for anxiety and depression.

Anxiety and depression often co-occur and also in this study the anxiety and depression scale were highly correlated (antenatal r=.72, postnatal r=.73, both *p-values* <.001). In order to prevent collinearity, analyses were performed on either anxiety or on depression. Anxiety and depression were never included in one model at the same time.

To investigate whether our findings were mainly due to the combined effect of anxiety and depression, we repeated the analyses for anxiety and for depression and excluded mothers who were, according to our definition, respectively depressed (n=428) or anxious (n=549).

To explore whether the foetal origins hypothesis underlies our findings, we tested whether mothers who showed symptoms of anxiety or depression during pregnancy were more likely to have infants with a lower birth weight.

All models were adjusted for gestational and postnatal age, and gender of the infant. Next, we used the change-in-estimate criterion to identify other relevant confounders. The change-in-estimate is calculated as the difference between the unadjusted odds ratio and the adjusted odds ratio divided by the adjusted odds ratio. This results in the percentage change in the estimated odds ratio due to adding a candidate confounder to the model. The conventional change-in-estimate criterion is a change of 10% or more.[49,50] Because non-experimental studies, like ours, are very sensitive to residual confounding, we used a more conservative change-in-estimate criterion (5%). The mother's educational level, her age, ethnicity of the child and long lasting difficulties satisfied this change-in-estimate criterion of 5%. Subsequently, educational level and ethnicity of the child were added to

the models, since these covariates may be antecedents in the causal chain between anxiety or depression and neuromotor development. In this case they cannot only be viewed as confounders. Finally, the mother's age and long lasting difficulties were added to the models, which had no influence on the effect estimates. Therefore, we only present the age-and-gender adjusted models and models in which all relevant covariates were included. The other covariates maternal smoking and alcohol use during pregnancy, parity, family functioning, and obstetric and perinatal variables did not fulfill our change-in-estimate criterion and were therefore not included in the analyses.

Statistical analyses were performed using the Statistical Package of Social Sciences version 15 for Windows.

Response analyses

For the non-response analysis, we compared characteristics of participants with data on the questionnaires and the neuromotor assessment to those with missing data. Mothers not included were more often lower educated (26% low) and younger (mean age 29.6 years), as compared to mothers of whom complete data were available (21% low, χ^2 (1) = 15.57, p<.001 and mean age 30.5 years, F (1, 5294) = 33.19, p<.001).

The results of the additional non-response analyses were essentially identical for anxiety and depression, so we only describe those for anxiety. We only report the non-response analysis among those with no antenatal symptoms. In this analysis we compared those with and without postnatal data. The differences between the groups with and without prenatal data were less marked. Mothers without antenatal symptoms of anxiety but with missing postnatal questionnaires were lower educated (36% low education) and younger (mean age 29.3 years) when compared to mothers that also had no antenatal symptoms but completed the postnatal questionnaire (15% low education, χ^2(1) = 76.28, p<.001; mean age 31.1 years, F (1, 1969) = 42.57, p<.001). Children of these mothers were more often of non-Dutch origin (50%) than those whose mothers who completed both questionnaires (30% non-Dutch, χ^2(1) = 41.37, p<.001). Most importantly, analyses without and with mothers with partial missing data

yielded similar results. Therefore, we only report results including mothers with partial missing data.

Results

Baseline variables of the total population were as follows: 20% of mothers was low educated, mean age was 31 years (SD 4.9 years), 13% continued smoking and 40% used alcohol during pregnancy, 5% had medical complications during pregnancy, and 58% of the mothers delivered their first child. The children were 49% male, 35% of non-Dutch origin, mean birth weight was 3,433 gram (SD 544 gram), gestational age was 39.9 weeks (SD 1.7 weeks). Neuromotor development was assessed at an average age of 12.5 weeks (SD 2.0 weeks) postnatally.

Next, we compared baseline variables of mothers scoring below the threshold of anxiety symptoms at all times to the groups of mothers with antenatal and/or postnatal symptoms of anxiety. Mothers with both antenatal and postnatal symptoms of anxiety more often were lower educated (32%) than mothers with no symptoms of anxiety (18%). Mothers with antenatal symptoms of anxiety (mean age 29.8 years, 18% smokers) and mothers with both antenatal and postnatal symptoms of anxiety (mean age 29.5 years, 20% smokers) were younger and more often continued smoking during pregnancy compared to mothers who scored below the threshold of anxiety (mean age 30.8 years, 12% continued smoking). Infants of mothers with antenatal (47% non-Dutch), postnatal (43% non-Dutch), or antenatal and postnatal (49% non-Dutch) symptoms of anxiety were more often of non-Dutch origin than those whose mothers had no symptoms of anxiety (32% non-Dutch). All other variables did not differ between the groups. Comparison of groups based on presence of depressive symptoms were very similar (data not shown).

Age and gender adjusted linear regression analysis showed that antenatal maternal anxiety was significantly associated with birth weight (Beta –26.23, 95% CI –47.67; -4.79, p=.017). However, adjusting for other confounders and possible anteceding factors attenuated the effect (Beta –22.80, 95% CI –47.72; 2.11, p=.073). We found no significant associations between antenatal maternal depression and birth weight.

As was described earlier, anxiety and depression often coincide. Almost half (47%) of the mothers with antenatal and postnatal symptoms of depression (*n* = 159), had antenatal and postnatal symptoms of anxiety as well. In the same way, of the mothers with postnatal (*n* = 162) or antenatal (*n* = 123) symptoms of depression about a third had antenatal or postnatal symptoms of anxiety (37% and 30%, respectively).

Table 2 shows the associations of antenatal and postnatal symptoms of anxiety and depression with infant neuromotor development. In the continuous analyses adjusted for (gestational and postnatal) age and gender only, we found that antenatal anxiety and postnatal depression increase the risk of non-optimal neuromotor development at age 3 months. An increase of one standard deviation in antenatal anxiety resulted in a 11% higher risk of non-optimal neuromotor development. Also, higher scores on postnatal depression, measured by both the BSI as well as the EPDS, increased the risk of non-optimal neuromotor development by 9% and 12%, respectively (see Table 2). After adjusting for the other covariates none of the associations remained significant. This attenuation was mainly due to the effects of educational level of the mother and ethnicity of the child. In the categorical analyses mothers with no anxiety, i.e. who scored below the threshold, are the reference category (Table 2). Even after including all relevant covariates in the model, the overall *p*-value remained significant (*p*=.017). An effect was mainly found in the group of mothers with only antenatal symptoms of anxiety, whose children showed an increased risk of non-optimal neuromotor development (OR 1.49, 95% CI 1.10; 2.03, *p*=.01) as compared to the reference group. There was no association between the other categories of anxiety and neuromotor development. When we repeated the analysis and excluded mothers with symptoms of depression, the odds ratio for the association between antenatal maternal symptoms of anxiety and infant neuromotor development increased slightly (OR 1.70, 95% CI 1.14; 2.55, *p*=.01). None of the associations between the different categories of antenatal and postnatal maternal symptoms of depression and infant neuromotor development were significant. Repeating this analysis excluding mothers who were anxious did not change the results (data not shown).

Table 2: Association between antenatal and postnatal maternal symptoms of anxiety or depression, and infant motor development at the age of three months

		Risk of non-optimal neuromotor development			
		Model I		Model II	
	N	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Maternal symptoms of anxiety or depression					
Continuous analyses					
Antenatal anxiety BSI, per SD score	2,427	1.11 (1.03; 1.21)	.01	1.06 (0.96; 1.16)	.28
Postnatal anxiety BSI, per SD score	2,448	1.05 (0.96; 1.14)	.3	0.99 (0.91; 1.09)	.96
Antenatal depression BSI, per SD score	2,421	1.04 (0.96; 1.13)	.31	0.97 (0.87; 1.07)	.51
Postnatal depression BSI, per SD score	2,440	1.09 (1.01; 1.18)	.04	1.03 (0.95; 1.13)	.46
Postnatal depression EPDS, per SD score	2,464	1.12 (1.03; 1.22)	.007	1.08 (0.99; 1.19)	.08
Categorical analyses					
No anxiety	2,076	Reference		Reference	
Antenatal anxiety	213	1.58 (1.18; 2.12)	.002	1.49 (1.10; 2.03)	.01
Postnatal anxiety	162	0.80 (0.56; 1.15)	.23	0.75 (0.52; 1.08)	.12
Antenatal and postnatal anxiety	174	1.22 (0.88; 1.70)	.23	1.07 (0.75; 1.53)	.71
		Overall p-value	.005	*Overall p-value*	.017
No depression	2,197	Reference		Reference	
Antenatal depression	123	1.24 (0.85; 1.81)	.26	1.13 (0.75; 1.68)	.56
Postnatal depression	162	1.11 (0.79; 1.57)	.54	0.99 (0.70; 1.41)	.97
Antenatal and postnatal depression	159	1.15 (0.81; 1.61)	.43	0.91 (0.62; 1.33)	.62
		Overall p-value	.57	*Overall p-value*	.87

Note. OR = odds ratio; CI = confidence interval; all models are based on (valid cases and if applicable on) full case analysis.
Model I: Adjusted for gestational and postnatal age, and gender child.
Model II: Model I + educational level mother, age mother, ethnicity child, and long lasting difficulties.
'No anxiety' or 'No depression' refers to the group of mothers who scored below the threshold.

Discussion

The current study showed that infants of mothers with higher scores of antenatal maternal anxiety symptoms have significantly poorer neuromotor development. This effect disappeared after correction for all covariates. However, mothers with high levels of antenatal maternal anxiety only, i.e. who scored above the threshold, exhibited a significantly increased risk of an infant with non-optimal neuromotor development. Moreover, there remained a non-significant trend for an association of higher levels of postnatal maternal depression and non-optimal neuromotor development. If not a chance finding, this may indicate a specific effect of maternal anxiety during pregnancy.

Accumulating evidence suggests that exposure to maternal symptoms of anxiety or depression during critical periods of development is associated with adverse outcomes of the offspring. In their reviews, Goodman and Gotlib[26] and Sohr-Preston and Scaramella[51] described the antenatal and postnatal effects of maternal depressive symptoms on psychopathology, and neurodevelopment of the offspring, whereas Huizink, Mulder and Buitelaar[20] and Van den Bergh, Mulder, Mennes and Glover[22] point out the possible effects of maternal stress and anxiety during pregnancy on psychopathology and neurobehavioural development of the infant. The results described in these reviews are reasonably in line with the adverse effect we found between specifically antenatal maternal anxiety and infant neuromotor development.

There are several explanations for the adverse effect of antenatal maternal anxiety on infant neuromotor development. The first explanation can be sought in the foetal origins hypothesis.[19] According to this hypothesis prenatal factors such as antenatal maternal anxiety can contribute to an adverse foetal environment, which manifests itself in low birth weight. This adverse environment significantly affects the infant's neuromotor development. Although we found a trend for the association between antenatal maternal symptoms of anxiety and the child's birth weight, birth weight was no relevant confounder and therefore cannot explain the association between antenatal maternal symptoms of anxiety and infant neuromotor development. Thus, in our study we could not find a direct mechanism in line with the foetal origins hypothesis.

A second explanation for the association between antenatal maternal anxiety and neuromotor development may be a shared genetic factor underlying both antenatal maternal anxiety and infant neuromotor development. Infants from anxious mothers possibly inherit traits that increase their vulnerability for neurodevelopmental delays. Variations in genes coding sex steroids, for example, have been related to anxiety disorders.[52] Sex steroids also have neurodevelopmental properties.[53,54] In addition, a polymorphism in the brain-derived neurotrophic factor (BDNF) gene has been associated with alterations in brain anatomy and memory, and the genetic variation also plays a role in the predispositions for anxiety and depressive disorders.[55,56] However, experimental animal studies, in which genetic factors are typically controlled for, also reported an association between antenatal maternal anxiety and neuromotor development. This raises doubt whether the observed link between antenatal maternal anxiety and neuromotor development can largely be explained by genetic factors.

Anxiety and depression often coincide and several studies could not differentiate their effects.[12-14] Although the group of mothers with both symptoms of anxiety and depression in the current study was large, we had a sufficient number of mothers with antenatal symptoms of anxiety only. Infants of mothers with antenatal symptoms of anxiety but no symptoms of depression showed a somewhat higher risk of non-optimal neuromotor development as compared to infants of mothers with antenatal symptoms of anxiety and depression, although this difference was not significant. Furthermore, we found no association between antenatal maternal depression and infant neuromotor development, which suggests that antenatal maternal anxiety and depression influence the offspring's development differently.

This specific effect of antenatal anxiety on infant neuromotor development may be related to the measurement instrument we used to assess anxiety. The items measuring anxiety represent both anxiety apprehension and anxiety arousal, of which apprehension corresponds with the more chronic trait anxiety, while arousal more resembles stress. However, four out of six items measured arousal, thus the anxiety we measured better reflects arousal or stress than apprehension. Arousal

rather than trait anxiety or depression is analogous to the stress condition used in animal studies of pregnancy effects.[37] Such studies have repeatedly shown an impact of stressing conditions on the offspring's development.[1-3] On the other hand, any possible differential effect of antenatal anxiety and depression on the development of the offspring has to be interpreted carefully, because anxiety and depression are highly correlated. Moreover, we measured psychological symptoms instead of clinical disorders. This might also have contributed to a specific effect of antenatal anxiety; in our study the maternal symptoms of depression may not be sufficiently severe to influence the foetus' development.

There are few studies investigating a possible effect of postnatal maternal anxiety on infant development, whereas several studies showed an effect of postnatal depression on infant development. Depressed mothers typically show less emotional warmth, and less interaction, verbally or physically, with their infants.[17,18] This may result in less exploratory and more passive behaviour in the infants, which in turn can impact on the maturation of the brain in early infancy.[25] In line with these results, the age and gender adjusted analyses of postnatal maternal symptoms of depression showed a significant effect on neuromotor development. However, adding educational level and ethnicity to the model attenuated this significant effect. Educational level and ethnicity are causally related to anxiety or depression. There are numerous studies relating socioeconomic status to psychiatric disorders.[57-61] Individuals with deprived socioeconomic status have low control and high unpredictability of their income and their environment, making them more vulnerable to anxiety and mood disorders.[59] In our sample, the ethnic minorities are generally less educated, have lower income and thus have lower socioeconomic status.[62] Since, educational level and ethnicity are causally related to anxiety or depression, it can be argued that they are actually anteceding factors in the causal chain between maternal symptoms of anxiety and depression and infant neuromotor development, and cannot be solely seen as confounders. Arguably, we overcorrected to some extent and in the model adjusted for educational level and ethnicity thus underestimated the true association between postnatal maternal depression and neuromotor development. In short, a diminished

interaction between mother and child as a result of maternal postnatal depressive symptoms may contribute to impaired neuromotor development.

However, other pathways via which low socioeconomic status may impact on infant neuromotor development are conceivable. Low socioeconomic status generally is associated with poor health care and poor health behaviours [63]. Mothers with low socioeconomic status have higher chances to create a less stimulating and less healthy environment for their children. This may adversely impact on the child's development either during pregnancy or after birth. For example, mothers with low socioeconomic status are more likely to smoke,[64] have a poor diet,[65] or inadequately use folic acid supplementation during pregnancy.[66] These are all known risk factors of various neurodevelopmental problems.[67,68]

No effect of postnatal maternal depression on neuromotor development was observed in the analysis of categorized antenatal and postnatal maternal depression measured with the Brief Symptom Inventory (BSI). This may be due to the instrument we used. From the literature it is known that the Edinburgh Postnatal Depression Scale (EPDS) actually is the better suited instrument to assess postnatal depressive symptoms.[38,39] The BSI may measure postnatal depressive symptoms less accurately than the EPDS, which may have reduced the power.

Because we investigated the general population, clinical cut-offs for maternal symptoms of anxiety or depression would yield too small groups, resulting in insufficient power for analyses. Despite this, we found, albeit moderate, associations between antenatal maternal anxiety and infant neuromotor development. As for postnatal maternal depression, we can argue that educational level and ethnicity are anteceding factors rather than merely confounders. Hence, we overcorrected to some extent and underestimated the strength of the association between antenatal maternal anxiety and infant neuromotor development. Also, the timing of the measurement may have contributed to the moderate effect size of antenatal maternal anxiety. For example, Huizink et al. found that high levels of pregnancy-specific anxiety in mid-pregnancy impacted on neuromotor development of the offspring.[69] On the other hand, O'Connor, Heron, Golding et al. found an association of anxiety in late pregnancy with

infant behaviour and emotional problems.[10] Thus, studies consistently find an adverse effect of antenatal maternal symptoms of anxiety, but the timing of relevant exposure to antenatal maternal stress varies. This may suggest that several mechanisms operate during different stages of pregnancy.[22] We measured symptoms of anxiety and depression only in mid-pregnancy, and it is conceivable that the effects of maternal anxiety in early or late pregnancy are stronger.

In the current study, analyses were conducted using continuous and categorical determinants. Analyses with continuous determinants were performed to determine whether there was a dose-response effect of antenatal or postnatal maternal anxiety or depression on infant neuromotor development. Additionally, analyses were repeated with categorized determinants. By categorizing the determinants, antenatal and postnatal measurements could be combined in one analysis despite their high interrelations and effects of symptoms above a relevant cut-off could be tested. Consequently, the specific effect of antenatal and postnatal anxiety (or depression) on infant neuromotor development could be distinguished. A disadvantage of categorization, however, is loss of power. This, and the presence of a threshold effect can explain the differences in results.

Strengths of the current study are that the neuromotor assessment was applied at a very young age and scoring was independent of the mother. To our knowledge, this is the first study in which neuromotor development is assessed in a large birth cohort without the use of parent reports, as opposed to most cohort studies who, by necessity, collect their data by means of questionnaires, and thus rely on maternal report of both her own and her child's behaviour. Since anxious mothers perceive their children to have more problems, it is often argued that the observed associations are at least partly due to the use of similar methods of measurement, i.e. associations due to 'shared method variance'.[31]

A drawback of this study is that we suffered from considerable attrition. Possibly, selective non-response partly accounts for our positive findings, e.g. if participants with symptoms of anxiety or depression were more likely to have an infant with non-optimal neuromotor development than non-participants with anxiety. However, because mothers were blinded for the

associations under study, and because we are studying the effects of subtle differences in maternal symptoms of anxiety and depression, it is unlikely that selective non-response substantially influenced our findings.

The results of our additional non-response analyses confirmed the potential selection bias which was reduced by including mothers who reported no symptoms on one questionnaire and did not complete the other questionnaire. We classified these mothers as having 'no symptoms' in the respective missing questionnaire. This is a conservative way of dealing with missing data that may obscure existing differences but is less likely to produce spurious results. Most importantly, analyses without and with mothers with partial missing data yielded similar results. Secondly, we measured antenatal and postnatal symptoms with a 7-months-interval. A study by Derogatis and Melisaratos has shown high test-retest reliability.[35] This makes chronicity of the symptoms plausible when present at both points in time, but it is also possible that the symptoms were absent during the interval. Therefore, it is difficult to make inferences about the duration of the symptoms. Thirdly, as we studied a non-clinical population, the neurodevelopmental measures were very skewed and we had to categorize the score, which resulted in less power for analyses.

In conclusion, we found an adverse effect of antenatal maternal anxiety and a trend for postnatal maternal depression on infant neuromotor development. Although effect sizes were relatively small - which might limit implications for treatment of antenatal maternal anxiety or postnatal maternal depression - results could shed light on mechanisms underlying optimal child development. Our results indicate that in particular the combination of maternal symptoms of anxiety or depression and low socioeconomic status increases the vulnerability for an impaired neuromotor development of the offspring. Studies mostly in high risk populations, such as low birth weight and preterm born infants, have shown that impaired motor functioning is a marker for developmental delay,[70] minor neurological dysfunction,[71] attention problems and aggressive behaviour[72] in childhood. Recently, Aylward suggested that subtle, transient infant neuromotor dysfunction may be an early sign of central nervous system perturbation that may later reemerge as cognitive and behavioural problems.[73] Future research is necessary to investigate

whether the negative effects of maternal symptoms of anxiety or depression are transient, persistent or progressive and whether they lead to long-term cognitive and behavioural problems of the offspring.

References

1 Poltyrev T, Keshet GI, Kay G and Weinstock M. Role of experimental conditions in determining differences in exploratory behavior of prenatally stressed rats. *Dev Psychobiol.* 1996; **29** (5): 453-62.

2 Vallee M, Mayo W, Dellu F, Le Moal M, Simon H and Maccari S. Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. *J Neurosci.* 1997; **17** (7): 2626-36.

3 Wakshlak A and Weinstock M. Neonatal handling reverses behavioral abnormalities induced in rats by prenatal stress. *Physiol Behav.* 1990; **48** (2): 289-92.

4 Schneider ML and Coe C. Repeated social stress during pregnancy impairs neuromotor development of the primate infant. *J Dev Behav Pediatr.* 1993; **14** (2): 81-7.

5 Schneider ML, Roughton EC, Koehler AJ and Lubach GR. Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. *Child Dev.* 1999; **70** (2): 263-74.

6 Schneider ML. The effect of mild stress during pregnancy on birthweight and neuromotor maturation in rhesus monkey infants *(Macaca mulatta)*. *Infant Behavior & Development.* 1992; **15**: 389-403.

7 Hedegaard M, Henriksen TB, Sabroe S and Secher NJ. Psychological distress in pregnancy and preterm delivery. *Bmj.* 1993; **307** (6898): 234-9.

8 Dayan J, Creveuil C, Herlicoviez M, Herbel C, Baranger E, Savoye C and Thouin A. Role of anxiety and depression in the onset of spontaneous preterm labor. *Am J Epidemiol.* 2002; **155** (4): 293-301.

9 Zimmer-Gembeck MJ and Helfand M. Low birthweight in a public prenatal care program: behavioral and psychosocial risk factors and psychosocial intervention. *Soc Sci Med.* 1996; **43** (2): 187-97.

10 O'Connor TG, Heron J, Golding J, Beveridge M and Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br J Psychiatry.* 2002; **180**: 502-8.

11 Van den Bergh BR, Van Calster B, Smits T, Van Huffel S and Lagae L. Antenatal Maternal Anxiety is Related to HPA-Axis Dysregulation and Self-Reported Depressive Symptoms in Adolescence: A Prospective Study on the Fetal Origins of Depressed Mood. *Neuropsychopharmacology.* 2008; **33** (3): 536-45.

12 Field T, Diego M, Hernandez-Reif M, Schanberg S, Kuhn C, Yando R and Bendell D. Pregnancy anxiety and comorbid depression and anger: effects on the fetus and neonate. *Depress Anxiety.* 2003; **17** (3): 140-51.

13 Lundy BL, Jones NA, Field T, Nearing G, Davalos M, Pietro PA, Schanberg S and Kuhn C. Prenatal depression effects on neonates. *Infant Behavior & Development.* 1999; **22** (1): 119-29.

14 DiPietro JA, Novak MF, Costigan KA, Atella LD and Reusing SP. Maternal psychological distress during pregnancy in relation to child development at age two. *Child Dev.* 2006; **77** (3): 573-87.

15 Van den Bergh BR. The influence of maternal emotions during pregnancy on fetal and neonatal behavior. *Journal of Prenatal and Perinatal Psychology and Health.* 1990; **5**: 119-30.
16 Brazelton TB and Nugent JK. *Neonatal Behavioral Assessment Scale.* Vol 137. 3rd ed. London: MacKeith Press; 1995.
17 Murray L, Sinclair D, Cooper P, Ducournau P, Turner P and Stein A. The socioemotional development of 5-year-old children of postnatally depressed mothers. *J Child Psychol Psychiatry.* 1999; **40** (8): 1259-71.
18 Paulson JF, Dauber S and Leiferman JA. Individual and combined effects of postpartum depression in mothers and fathers on parenting behavior. *Pediatrics.* 2006; **118** (2): 659-68.
19 Barker DJ. Fetal origins of coronary heart disease. *Bmj.* 1995; **311** (6998): 171-4.
20 Huizink AC, Mulder EJ and Buitelaar JK. Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility? *Psychol Bull.* 2004; **130** (1): 115-42.
21 Talge NM, Neal C and Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry.* 2007; **48** (3-4): 245-61.
22 Van den Bergh BR, Mulder EJ, Mennes M and Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev.* 2005; **29** (2): 237-58.
23 Hurley KM, Caulfield LE, Sacco LM, Costigan KA and Dipietro JA. Psychosocial influences in dietary patterns during pregnancy. *J Am Diet Assoc.* 2005; **105** (6): 963-6.
24 Strine TW, Mokdad AH, Dube SR, Balluz LS, Gonzalez O, Berry JT, Manderscheid R and Kroenke K. The association of depression and anxiety with obesity and unhealthy behaviors among community-dwelling US adults. *Gen Hosp Psychiatry.* 2008; **30** (2): 127-37.
25 Weiss SJ, Wilson P and Morrison D. Maternal Tactile Stimulation and the Neurodevelopment of Low Birth Weight Infants. *Infancy.* 2004; **5**: 85-107.
26 Goodman SH and Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychol Rev.* 1999; **106** (3): 458-90.
27 Dawson G, Frey K, Panagiotides H, Yamada E, Hessl D and Osterling J. Infants of depressed mothers exhibit atypical frontal electrical brain activity during interactions with mother and with a familiar, nondepressed adult. *Child Dev.* 1999; **70** (5): 1058-66.
28 Jones NA, Field T and Davalos M. Right frontal EEG asymmetry and lack of empathy in preschool children of depressed mothers. *Child Psychiatry Hum Dev.* 2000; **30** (3): 189-204.
29 Prechtl HF. *The Neurological Examination of the Full-term Newborn Infant*. 2nd ed. London: Heinemann; 1977.
30 Touwen BC. *Neurological development in infancy*. London: Heinemann; 1976.
31 Podsakoff PM, MacKenzie SB, Lee JY and Podsakoff NP. Common method biases in behavioral research: a critical review of the literature and recommended remedies. *J Appl Psychol.* 2003; **88** (5): 879-903.

32 Jaddoe VW, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Verhulst FC, Witteman JC and Hofman A. The Generation R Study: Design and cohort profile. *Eur J Epidemiol.* 2006; **21** (6): 475-84.

33 de Beurs E. *Brief Symptom Inventory, handleiding*. Leiden, the Netherlands; 2004.

34 Derogatis LR. *Brief Symptom Inventory (BSI): Administration, scoring and procedures manual*. 3rd ed. Minneapolis, MN; 1993.

35 Derogatis LR and Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983; **13** (3): 595-605.

36 Heller W, Nitschke JB, Etienne MA and Miller GA. Patterns of regional brain activity differentiate types of anxiety. *J Abnorm Psychol.* 1997; **106** (3): 376-85.

37 O'Connor TG, Heron J and Glover V. Antenatal anxiety predicts child behavioral/emotional problems independently of postnatal depression. *J Am Acad Child Adolesc Psychiatry.* 2002; **41** (12): 1470-7.

38 Cox JL, Holden JM and Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987; **150**: 782-6.

39 Murray L and Carothers AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. *Br J Psychiatry.* 1990; **157**: 288-90.

40 de Groot L, Hopkins B and Touwen BC. A method to assess the development of muscle power in preterms after term age. *Neuropediatrics.* 1992; **23** (4): 172-9.

41 van Batenburg-Eddes T, de Groot L, Arends L, de Vries A, Moll HA, Steegers EA, Hofman A, Jaddoe VW, Verhulst FC and Tiemeier H. Does gestational duration within the normal range predict infant neuromotor development? *Early Hum Dev.* 2008; **84** (10): 659-65.

42 Prechtl HF. The behavioural states of the newborn infant (a review). *Brain Res.* 1974; **76** (2): 185-212.

43 Cohen J. Weighted kappa; nominal scale agreement with provision for scaled disagreement or partial credit. *Psychol Bull.* 1968; **70**: 213-20.

44 Peters LH, Maathuis KG, Kouw E, Hamming M and Hadders-Algra M. Test-retest, inter-assessor and intra-assessor reliability of the modified Touwen examination. *Eur J Paediatr Neurol.* 2007.

45 Statistics Netherlands. *Standaard onderwijsindeling 2003*. Voorburg/Heerlen; 2004.

46 Statistics Netherlands. *Allochtonen in Nederland 2004*. Voorburg/Heerlen; 2004.

47 Byles J, Byrne C, Boyle MH and Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process.* 1988; **27** (1): 97-104.

48 Hendriks AAJ, Ormel J and van de Willige G. Long lasting difficulties measured with a self-assessment questionnaire and semistructured interview: a theoretical and empirical comparison [in Dutch]. *Gedrag en gezondheid.* 1990; **18**: 273-83.

49 Mickey RM and Greenland S. The impact of confounder selection criteria on effect estimation. *Am J Epidemiol.* 1989; **129** (1): 125-37.

50 Rothman KJ and Greenland S. *Modern Epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven Publishers; 1998.

51 Sohr-Preston SL and Scaramella LV. Implications of timing of maternal depressive symptoms for early cognitive and language development. *Clin Child Fam Psychol Rev.* 2006; **9** (1): 65-83.

52 Tiemeier H, Schuit SC, den Heijer T, van Meurs JB, van Tuijl HR, Hofman A, Breteler MM, Pols HA and Uitterlinden AG. Estrogen receptor alpha gene polymorphisms and anxiety disorder in an elderly population. *Mol Psychiatry.* 2005; **10** (9): 806-7.

53 Gonzalez M, Cabrera-Socorro A, Perez-Garcia CG, Fraser JD, Lopez FJ, Alonso R and Meyer G. Distribution patterns of estrogen receptor alpha and beta in the human cortex and hippocampus during development and adulthood. *J Comp Neurol.* 2007; **503** (6): 790-802.

54 Belcher SM and Zsarnovszky A. Estrogenic actions in the brain: estrogen, phytoestrogens, and rapid intracellular signaling mechanisms. *J Pharmacol Exp Ther.* 2001; **299** (2): 408-14.

55 Chen ZY, Jing D, Bath KG, Ieraci A, Khan T, Siao CJ, Herrera DG, Toth M, Yang C, McEwen BS, Hempstead BL and Lee FS. Genetic variant BDNF (Val66Met) polymorphism alters anxiety-related behavior. *Science.* 2006; **314** (5796): 140-3.

56 Hashimoto K. BDNF variant linked to anxiety-related behaviors. *Bioessays.* 2007; **29** (2): 116-9.

57 Adler NE, Singh-Manoux A, Schwartz J, Stewart J, Matthews K and Marmot MG. Social status and health: a comparison of British civil servants in Whitehall-II with European- and African-Americans in CARDIA. *Soc Sci Med.* 2008; **66** (5): 1034-45.

58 Mendelson T, Kubzansky LD, Datta GD and Buka SL. Relation of female gender and low socioeconomic status to internalizing symptoms among adolescents: a case of double jeopardy? *Soc Sci Med.* 2008; **66** (6): 1284-96.

59 Muntaner C, Eaton WW, Diala C, Kessler RC and Sorlie PD. Social class, assets, organizational control and the prevalence of common groups of psychiatric disorders. *Soc Sci Med.* 1998; **47** (12): 2043-53.

60 Stansfeld SA, Clark C, Rodgers B, Caldwell T and Power C. Childhood and adulthood socio-economic position and midlife depressive and anxiety disorders. *Br J Psychiatry.* 2008; **192** (2): 152-3.

61 Stansfeld SA, Head J, Fuhrer R, Wardle J and Cattell V. Social inequalities in depressive symptoms and physical functioning in the Whitehall II study: exploring a common cause explanation. *J Epidemiol Community Health.* 2003; **57** (5): 361-7.

62 Jansen PW, Raat H, Mackenbach JP, Jaddoe VW, Hofman A, Verhulst FC and Tiemeier H. Socioeconomic inequalities in infant temperament : The Generation R Study. *Soc Psychiatry Psychiatr Epidemiol.* 2008.

63 Adler NE and Newman K. Socioeconomic disparities in health: pathways and policies. *Health Aff (Millwood).* 2002; **21** (2): 60-76.

64 Pierce JP, Fiore MC, Novotny TE, Hatziandreu EJ and Davis RM. Trends in cigarette smoking in the United States. Educational differences are increasing. *Jama.* 1989; **261** (1): 56-60.

65 Darmon N and Drewnowski A. Does social class predict diet quality? *Am J Clin Nutr.* 2008; **87** (5): 1107-17.

66 Timmermans S, Jaddoe VW, Mackenbach JP, Hofman A, Steegers-Theunissen RP and Steegers EA. Determinants of folic acid use in early pregnancy in a multi-ethnic urban population in The Netherlands: The Generation R study. *Prev Med.* 2008.

67 Eskenazi B and Castorina R. Association of prenatal maternal or postnatal child environmental tobacco smoke exposure and neurodevelopmental and behavioral problems in children. *Environ Health Perspect.* 1999; **107** (12): 991-1000.

68 Williams JH and Ross L. Consequences of prenatal toxin exposure for mental health in children and adolescents: a systematic review. *Eur Child Adolesc Psychiatry.* 2007; **16** (4): 243-53.

69 Huizink AC, de Medina PGR, Mulder EJ, Visser GHA and Buitelaar JK. Stress during pregnancy is associated with developmental outcome in infancy. *J Child Psychol Psychiatry.* 2003; **44** (6): 810-8.

70 Georgieff MK, Bernbaum JC, Hoffman-Williamson M and Daft A. Abnormal truncal muscle tone as a useful early marker for developmental delay in low birth weight infants. *Pediatrics.* 1986; **77** (5): 659-63.

71 Samsom JF, de Groot L, Bezemer PD, Lafeber HN and Fetter WP. Muscle power development during the first year of life predicts neuromotor behaviour at 7 years in preterm born high-risk infants. *Early Hum Dev.* 2002; **68** (2): 103-18.

72 Hadders-Algra M and Groothuis AM. Quality of general movements in infancy is related to neurological dysfunction, ADHD, and aggressive behaviour. *Dev Med Child Neurol.* 1999; **41** (6): 381-91.

73 Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr.* 2005; **26** (6): 427-40.

Chapter 3

Behavioural and cognitive outcomes of infant neuromotor development

Chapter 3.1

Infant neuromotor development and child behaviour problems

Abstract

Background: Research in adult and school-aged children suggests that many psychiatric disorders have a neurodevelopmental basis. In particular, schizophrenia and autism have been associated with neuromotor impairments or delayed achievement of motor milestones. However, it is unclear whether problem behaviour at a young age, which can be classified as internalizing problems and externalizing problems, also has a neurodevelopmental basis. In a large population-based cohort, we investigated whether infant neuromotor development is associated with problem behaviour in toddlers.

Methods: This study was conducted within the Generation R Study, a birth cohort in the Netherlands. Infant neuromotor development was assessed in 2,309 infants by research nurses during a home visit at the age of approximately 3 months. For each neuromotor (sub-)scale, the number of non-optimal items were summed and expressed as standard deviation scores. Behavioural and emotional problems were assessed with the Child Behavior Checklist at age 18 months. Dutch norms were used to define a score in the borderline range.

Results: Higher scores on overall neuromotor development were associated with an increased risk of Internalizing problems (OR per standard deviation (SD) score of neuromotor development = 1.22, 95% CI = 1.05-1.41). In particular, Emotional Reactivity (OR = 1.37, 95% CI = 1.11-1.69) and Somatic Complaints (OR = 1.29, 95% CI = 1.09-1.51) were affected. On the contrary, there was no consistent association between neuromotor development and Externalizing problems, although infants with high tone showed a significantly increased risk of Aggressive Behavior.

Conclusions: Infant neuromotor development predicted Internalizing problems and Aggressive Behavior. This study suggests that common behavioural and emotional problems in toddlers have a neuro-developmental basis.

Keywords: neuromotor development, problem behaviour, cohort study, longitudinal

Introduction

Early problem behaviour is of concern to parents, teachers and mental health care workers. Estimates of toddler problem behaviour in the general population vary between 8% and 18%.[1-3]

Several studies have shown that problem behaviour tends to persist into later ages. Mesman and Koot conducted a study in the general population and found that early preschool behavioural and emotional problems - independent of family risk factors - predicted their DSM-IV counterparts 8 years later.[4] Preschool child physical health and stressful life events partly determined the persistence of behavioural and emotional problems.[4] Furthermore, Caspi, Moffitt, Newman and Silva linked behavioural differences in the first 3 years of life to specific adult psychiatric disorders at the age of 21 years, and concluded that problem behaviour at a young age increases the risk of later psychopathology.[5]

Problem behaviour often coincides with early developmental problems. For example, Plomin, Price, Eley, Dale and Stevenson found in their community-based sample of twins a modest association between problem behaviour and verbal as well as nonverbal cognitive problems.[6] Skovgaard et al. observed in a population-based cohort that early developmental impairments, such as delay in motor functioning and deviant language development, may predict later psychiatric disorders.[7] The results of these studies are in accordance with the idea that there is an association between early neurodevelopmental problems and later problem behaviour, although the underlying mechanisms remain to be elucidated. A possible explanation for this link comes from research on autism and schizophrenia. Patients with these disorders often suffer from motor impairments. This line of research suggests that early motor impairment, reflecting diffuse neural dysfunctioning, represents a vulnerability marker for psychopathology.[8,9]

In the past, mental health and child care registries have been used to study developmental precursors of schizophrenia and autism. Registry studies using routine assessment of motor mile stones have yielded important findings in psychopathology research, but they have several limitations, e.g. a restricted number of confounders that can be addressed and precision of results.[8,10] Studies that assessed motor functioning and psychiatric disorders in large numbers of participants relied on age of motor

milestone achievement as reported by parents.[11] Studies that used full neurological examinations carried out by professionals to assess neuromotor development as a precursor of psychopathology at a later age were often conducted in small or clinical samples.[9] Finally, to the best of our knowledge, only Skovgaard et al. investigated early motor development as an antecedent of toddler problem behaviour, but they studied a relatively small sample (n = 210).[7]

In the current study infant neuromotor development was assessed by research nurses independently of the mother, eliminating common method bias.[12] Furthermore, we conducted full neurological examinations to assess early motor functioning, notwithstanding the large number of participants. Our objective was to test the 'neurodevelopmental hypothesis'. To this aim we investigated within the general population whether infant neuromotor development at the age of three months was associated with common behavioural and emotional problems in toddlers. We hypothesized that infants with non-optimal neuromotor development had an increased risk of behavioural and emotional problems at the age of 18 months.

Methods

Study population

This study was conducted within the Generation R Study, a population-based cohort study from fetal life onwards, which has been described previously.[13] Briefly, pregnant women who were resident in the city of Rotterdam at the time of their delivery between April 2002 and January 2006 were asked by their midwives to participate.

A total of 3224 infants underwent a neuromotor assessment at corrected ages between 9 and 15 weeks during a home visit. Information on child behavioural problems at age 18 months was available in 2309 toddlers (71.6% of 3224). Some mothers participated with two or more children. Since random exclusion of one or two of these siblings did not change our results, they were included in the analyses.

The Medical Ethics Committee of the Erasmus Medical Center Rotterdam has approved the study. Written informed consent was obtained from all participants.

Neuromotor development

Early identification of abnormal development in infancy has been proven to be difficult and therefore a full neurological age-adequate examination should be carried out, encompassing assessment of tone, elicited responses and other observations, like spontaneous movements and behaviour of the infant.[14] From Touwen's Neurodevelopmental Examination age-appropriate items were selected.[14] All measured items were categorized in three groups: tone, responses, and other observations. Most tone items were scored as normal, low - or high tone; most responses and other observations were scored as present, absent, or excessive. An age-appropriate response was labeled 'optimal'; a response that indicated delayed development was labeled 'non-optimal'. Scale values were calculated by summing the non-optimal items. This resulted in a total score and three subscale scores: tone, responses, and other observations.[15] Within the subscale measuring tone, a further distinction was made between low tone and high tone, resulting in two additional scales for tone: 'low tone symptoms' and 'high tone symptoms'. A low value for each scale indicates normal neuromotor development; a high value indicates delay in neuromotor development. For the current study all scale values were used continuously and were standardized by dividing them by the corresponding standard deviation.

We performed a reliability study to test the short-interval test-retest interobserver reliability and the interobserver reliability. The short-interval test-retest interobserver reliability test (n=61) consisted of a first assessment by a research assistant, followed within one week by a second assessment by another research assistant. For the interobserver reliability test (n=76), two research assistants together went on a home visit in which they independently conducted two consecutive neuromotor assessments in the same child. The intra-class correlation coefficients (ICC's) for the short-interval test-retest reliability and the interobserver reliability were .52 and .64, respectively. The ICC's for the reliability of the neuromotor assessment were in the 'modest' (.41-.60) to 'substantial' (.61-.80) range,[16] and in line with a study by Peters, Maathuis, Kouw, Hamming, and Hadders-Algra who reported a moderate to good reliability of a modified Touwen examination.[17]

Child behavioural and emotional problems

The Child Behavior Checklist for toddlers (CBCL/1½-5) was used to obtain standardized parent reports of children's problem behaviours. The CBCL/1½-5 contains 99 problems items, which are scored on seven empirically based syndromes: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, Withdrawn, Sleep Problems, Attention Problems, and Aggressive Behavior. The broadband scale Internalizing is the sum score of items in the first four syndrome scales, whereas Externalizing is the sum score of Attention Problems and Aggressive Behavior. Total Problems is the sum score of all 99 problem items. Each item is scored 0 = 'not true', 1 = 'somewhat true', and 2 = 'very true or often true', based on the preceding two months. Good reliability and validity have been reported for the CBCL.[18] Since our scores were highly skewed and could not be normalized, all scales were dichotomized. We used the borderline cut-off scores (83rd percentile for the broadband scales and 93rd percentile for the syndrome scales) of a Dutch norm group[19] to classify children as having behavioural and emotional problems in the borderline or clinical range, termed 'borderline' in this manuscript.

Covariates

Postal questionnaires were used to obtain information on the mother's marital status, educational level, age, smoking and alcohol use during pregnancy, antenatal and postnatal psychological symptoms, family functioning, long lasting difficulties, ethnicity of the child, and whether regular GP or hospital visits occurred in the last 6 months. The highest completed education (primary school, secondary school, and higher education) determined educational level of the mother. Maternal smoking and alcohol use were categorized into 'yes, during pregnancy' and 'no use during pregnancy'. We used the Brief Symptom Inventory to assess antenatal and postnatal maternal psychological symptoms.[20,21] Family functioning was measured with the subscale 'General Functioning' of the Family Assessment Device, in which a score higher than 2.17, is considered unhealthy.[22] To measure situational and relational difficulties in the preceding year, the Long Lasting Difficulties List was completed.[23] Ethnicity of the child was based on the parents' countries of birth.[24]

Fetal ultrasound examinations were used to establish gestational age. Midwife and hospital registries provided information on birth order, the infant's date of birth, birth weight and gender, and obstetric variables, such as maternal hypertension, pre-eclampsia, gestational diabetes, Apgar score after 5 minutes, and mode of delivery.

Statistical analyses

Differences in baseline characteristics between children with and without problem behaviour and their mothers were compared by chi-square tests, independent samples T-tests and Kolmogorov-Smirnov tests.

Logistic regression analysis was used to determine the association between neuromotor developmental scales and problem behaviour. All models were adjusted for the child's age at time of the questionnaire, child gender, the mother's educational level, maternal age, alcohol use during pregnancy, antenatal and postnatal maternal psychopathology, family functioning and long lasting difficulties. The other potential confounders - marital status, smoking during pregnancy, obstetric variables, birth order, birth weight and gestational age, and GP or hospital visits in the last 6 months - did not change the effect estimates, i.e. change in odds ratio was smaller than 5%, and were therefore excluded from our analyses. As we studied both Internalizing and Externalizing broadband scales, the level of significance was set at 2.5% to adjust for multiple comparisons. In addition, interaction terms of neuromotor development with gender, ethnicity and educational level were tested. Since all alpha's exceeded .15, the interaction terms were not included in the models.

Response analyses

For the non-response analyses, participants with a neuromotor assessment at the age between 9 and 15 weeks and a behavioural questionnaire were compared to participants with a missing behavioural questionnaire. Mothers of infants with missing data were lower educated (lower education 17% vs. 7%, χ^2=219.45, df=2, p<.001), more often scored in the pathological range of family functioning (pathological 14% vs. 8%, χ^2=19.92, df=1, p<.001), and suffered from more antenatal (median 0.27 vs. 0.19, Z=-11.76, p<.001), and postnatal psychological symptoms (median 0.24 vs. 0.13, Z=-

11.67, p<.001). Infants with missing data were more often of non-Dutch origin, than infants with complete data (Dutch 41% vs. 69%, χ^2=191.65, df=3, p<.001).

Results

In Table 1, subject characteristics of children with and without problem behaviour are given. Mothers of children with problem behaviour were significantly lower educated (18% primary education), younger (age mean 29.2 years), and had more psychological symptoms both during pregnancy (median 0.27) as well as after giving birth (median 0.24), than mothers of children without problem behaviour (5.4% primary education, age mean 31.4 years, antenatal and postnatal psychological symptoms median 0.17 and 0.13, respectively; all p-values < .001). Toddlers with problem behaviour were more often of non-Dutch origin (58% non-Dutch), as compared to toddlers without problem behaviour (28% non-Dutch p<.001).

Table 1. Subject characteristics in children with and without behavioral problems at the age of 18 months

	No behavioral problems *n*=2064	**Total Problems score in borderline range** *n*=216
Maternal characteristics		
Educational level, %**		
Primary	5.4	18.0
Secondary	36.7	44.5
Higher	57.9	37.5
Age at intake, years (SD)**	31.4 (4.5)	29.2 (5.9)
Marital status, %		
Married or living together	53.4	52.5
No partner	46.6	47.5
Smoking during pregnancy, yes %*	10.5	18.9
Alcohol use during pregnancy, yes %**	44.1	30.6
Eclampsia/hypertension/diabetes, yes %	5.2	6.0
Family functioning, pathological %**	7.0	18.2
Long lasting difficulties, median (95% range)**	2.0 (0-10.0)	2.7 (0-16.6)
Antenatal psychiatric symptoms, median (95% range)**	0.17 (0-1.01)	0.27 (0-1.58)
Postnatal psychiatric symptoms, median (95% range)**	0.13 (0-1.01)	0.24 (0-1.75)

Table 1. Subject characteristics in children with and without behavioral problems at the age of 18 months (*continued)*

	No behavioral problems *n*=2064	**Total Problems score in borderline range *n*=216**
Child characteristics		
Gender, male %	48.0	52.8
National origin, %**		
Dutch/other Western	71.5	42.0
Turkish/Moroccan	9.1	23.2
Surinamese/Antillean	8.9	15.5
Other non-Western	10.5	19.3
Age, months; mean (SD)*	18.3 (0.8)	18.5 (1.0)
First born child, %	58.5	63.7
Gestational age, weeks; median (95% range)	40.1 (36.0-42.3)	40.1 (33.5-42.5)
Birth weight, gram; mean (SD)*	3456 (548)	3327 (5757)

*p<.01 **p<.001

Values are means ± standard deviations for continuous, normally distributed variables, medians (95% range) for continuous non-normally distributed variables, and percentages for categorical variables. P-values are derived from independent t-tests for continuous normally distributed variables, Kolmogorov-Smirnov tests for continuous non-normally distributed variables, or chi-square tests for categorical variables.

Table 2 shows the relations of infant neuromotor developmental scales with total behavioural problems and its two broadband scales Internalizing and Externalizing. These associations were highly similar for overall neuromotor development and the subscale measuring tone. The odds ratio for Total Problems per SD increase in overall neuromotor development was 1.15 (95% CI 1.01-1.32). Delay in infant neuromotor development was mainly related to Internalizing problems (OR 1.22, 95% CI 1.05-1.41) and not to Externalizing problems (OR 1.03, 95% CI 0.91-1.16). A crude but conservative test to calculate whether two odds ratios are different is to check whether the 90% CI's overlap. This shows that it is unlikely that the odds ratios for the Internalizing and Externalizing scale are significantly different from each other, since the 90% CI's of both scales overlap (90% CI Internalizing problems 1.08-1.38; 90% CI Externalizing problems 0.93-1.14). Infants with symptoms of high muscle tone had a higher risk of a borderline score for Total Problems (OR 1.14, 95% CI 1.01-1.28) as well as for Internalizing Problems (OR 1.19, 95% CI 1.05-1.34).

Table 2: Associations between infant neuromotor development and toddler problem behavior

	Risk of score in borderline range					
	Total Problems		**Internalizing**		**Externalizing**	
	OR (95% CI)	***p* ***	**OR (95% CI)**	***p* ****	**OR (95% CI)**	***p* ****
Neuromotor developmental scales,						
all per SD score						
Overall neuromotor development	**1.15 (1.01-1.32)**	**.043**	**1.22 (1.05-1.41)**	**.008**	1.03 (0.91-1.16)	.629
Tone	**1.15 (1.01-1.32)**	**.042**	**1.22 (1.05-1.41)**	**.008**	1.04 (0.92-1.18)	.501
Low tone symptoms	1.07 (0.92-1.24)	.382	1.11 (0.95-1.30)	.199	1.01 (0.89-1.14)	.935
High tone symptoms	**1.14 (1.01-1.28)**	**.028**	**1.19 (1.05-1.34)**	**.006**	1.05 (0.95-1.18)	.340
Responses	1.13 (0.98-1.30)	.085	1.13 (0.96-1.32)	.140	1.07 (0.95-1.21)	.274

*Note.** p<.05. Bonferonni adjusted: **p<.025. All models adjusted for gender and ethnicity child, age, educational level mother, ante-and postnatal maternal psychiatric symptoms, alcohol use during pregnancy, family functioning, long lasting difficulties.

Table 3 shows the associations between infant neuromotor development and the syndromes constituting the Internalizing and Externalizing broadband scale. Infants with delay in overall neuromotor development, i.e. had a 1 SD score higher on the subscale tone showed a 37% higher risk of being Emotionally Reactive (OR 1.37, 95% CI 1.11-1.69). Similar effect estimates were found for the association between neuromotor developmental scales and Somatic Complaints (overall OR 1.29, 95% CI 1.09-1.51; tone OR 1.27, 95% CI 1.08-1.50). Infants with higher muscle tone had a 23% higher risk of Aggressive Behavior when they were toddlers (OR 1.23, 95% CI 1.07-1.41).

Discussion

We found a relation between infant neuromotor development and behavioural and emotional problems in toddlers. Infants with non-optimal neuromotor development were more likely to have Internalizing problems; in particular, these infants had an increased risk of being Emotionally Reactive and of having Somatic Complaints when they were toddlers. There was little evidence for an effect of delay in neuromotor development on Externalizing problems, although high muscle tone predicted Aggressive Behavior.

Research has shown that motor problems are one of the most frequently reported deficits in children with autism spectrum disorders[9] and in schizophrenia,[25] but less is known about the relation between early motor development and problem behaviour at toddler age. Autism and schizophrenia are relatively rare disorders. These disorders are often preceded or accompanied by behavioural or emotional problems, while the opposite does not apply: only a small percentage of children with problem behaviour are autistic or develop schizophrenia. On the other hand, behavioural or emotional problems are highly predictive of later problem behaviour,[4,25] and often coincide with neurodevelopmental problems.[6]

The effect of early motor functioning on Total Problems was mainly accounted for by the high level of Internalizing problems, although the difference between the effect estimates for Internalizing and Externalizing problems was non-significant. An explanation for this finding may be that 'true' Internalizing problems at toddler age are reported more validly than

Table 3: Associations between infant neuromotor development and toddler problem behavior

	Risk of Internalizing problems							
	Emotionally Reactive		Anxious /Depressed		Somatic Complaints		Withdrawn	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Neuromotor developmental scales, all per SD score								
Overall neuromotor development	**1.37 (1.11-1.70)**	**.003**	1.22 (1.00-1.50)	.054	**1.29 (1.09-1.51)**	**.002**	1.07 (0.92-1.25)	.395
Tone	**1.37 (1.11-1.69)**	**.003**	1.21 (0.98-1.49)	.071	**1.27 (1.08-1.50)**	**.004**	1.08 (0.92-1.26)	.360
Low tone symptoms	1.18 (0.93-1.50)	.171	1.16 (0.94-1.44)	.171	1.20 (1.01-1.43)	.036	1.06 (0.90-1.24)	.578
High tone symptoms	**1.30 (1.11-1.52)**	**.001**	1.13 (0.94-1.36)	.198	1.17 (1.01-1.35)	.033	1.06 (0.92-1.22)	.421
Responses	**1.31 (1.04-1.65)**	**.021**	1.16 (0.93-1.44)	.186	1.18 (0.98-1.42)	.080	1.04 (0.88-1.22)	.651

	Risk of Externalizing problems			
	Attention		Aggressive	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Neuromotor developmental scales, all per SD score				
Overall neuromotor development	1.04 (0.92-1.19)	.523	1.17 (0.97-1.41)	.097
Tone	1.05 (0.93-1.20)	. 427	1.21 (1.01-1.46)	.038
Low tone symptoms	1.02 (0.89-1.17)	.734	1.04 (0.84-1.30)	.699
High tone symptoms	1.05 (0.93-1.19)	.398	**1.23 (1.07-1.41)**	**.004**
Responses	1.04 (0.91-1.19)	.596	1.02 (0.82-1.26)	.875

Note. Bonferonni adjusted: $p<.025$. All models adjusted for gender and ethnicity child, age, educational level mother, ante-and postnatal maternal psychiatric symptoms, alcohol use during pregnancy, family functioning, long lasting difficulties

Externalizing problems. Externalizing problems, like aggression, are highly prevalent in young children.[26] This probably reflects a normal developmental stage that toddlers have at certain age, i.e. they develop a sense of autonomy, and a strong will and determination to become independent of their caregivers. This typically involves conflicts with parents and other caregivers. This would imply that in toddlers scores in the borderline range of externalizing behaviour are less likely to have a neurodevelopmental basis.

Deviant brain development may underlie the association between infant neuromotor functioning and problem behaviour. Research on neurodevelopmental disorders, such as neuromotor development, cognitive functioning and behavioural and emotional problems, indicates that comorbidity of problems is the rule rather than the exception.[27-29] Pine, Wasserman, Fried, Parides and Schaffer found that neurological soft signs, as measured by observation of several motor tasks, was highly correlated with internalizing and externalizing problems.[30] They suggest that several brain parts or circuits may be involved in these associations. However, they conclude that the extent to which neurological soft signs index brain abnormalities remains to be elucidated in children with psychopathology. Also, Kaplan, Wilson, Dewey, and Crawford found considerable overlap between neurodevelopmental disorders, such as developmental coordination disorder, ADHD and reading disability.[28] Co-occurrence of at least two disorders was present in 67% of all participants. They acknowledge the existence of broad subgroups of developmental disorders, but argue that these usually do not occur on their own. Kaplan et al.[28] and Gilger and Kaplan[27] propose that the general underlying etiology of all behaviour are individual differences in brain development, activity and ability, which come to expression in a wide variety of symptoms.

Several factors may impact on early brain development. Severe brain disorders are frequently caused by chromosomal abnormalities. Chromosomal abnormalities are unlikely to explain the results in the current study because they are rare in the general population. Subtle genetic variations, represented by single nucleotide polymorphisms (SNP) or copy number variation (CNV), are common and probably underlie more subtle abnormalities of brain development. At the same time, behavioural

traits are powerfully shaped by the environment.[31] Teratogens may cause brain abnormalities during prenatal development, which in turn lead to neurodevelopmental problems during the course of life. For example, nicotine and alcohol may pass through the placenta and may directly interfere with fetal brain development.[32,33] Some substances may affect the mother physically or psychologically and have an indirect impact on the unborn child. Furthermore, a variety of diseases are known to have harmful effects on prenatal development, such as rubella and influenza.[34,35] Finally, maternal stress, nutrition[36,37] and age seem to play a crucial role in healthy prenatal development. In this study, several environmental factors were measured and controlled for. Gestational age and birth weight, as indicators of malnutrition during pregnancy, and smoking did not substantially affect the associations under study and were therefore not included in analyses. As proxies of maternal stress during pregnancy, we used maternal psychological symptoms, family functioning and long lasting difficulties. These indicators of antenatal maternal stress and also alcohol use partly explained the relation between neuromotor development and problem behaviour. Though the relation between neuromotor development problem behaviour was attenuated, it did not disappear. In essence, we found little evidence for a significant contribution of specific prenatal environmental influences to the association between infant neuromotor development and behavioural and emotional problems in toddlers.

Not only prenatal influences but also perinatal factors, such as birth complications, may impact on early brain development.[38] Finally, postnatal factors may underlie the association between infant neuromotor development and behavioural and emotional problems in toddlers. Several studies addressed infant physical health problems as a risk factor of problem behaviour.[4,39] Postnatal maternal psychopathology has been shown to have detrimental effects on infant development.[40,41] Goodman and Gottlieb[42] postulate that depressed mothers who are characterized by negative cognition, behaviour and affect are inadequate social partners for their child and cannot meet their child's social and emotional needs. These factors limit the child's development and increase the risk of psychopathology in the child itself.[42] In the present study, regular GP or

hospital visits did not influence the association between infant neuromotor development and behavioural and emotional problems in toddlers, whereas postnatal maternal psychological symptoms did influence the observed association, but it remained significant after adjustment.

Some methodological considerations need to be discussed. Despite our large number of participants neuromotor development was assessed by full neurological examinations conducted by research nurses independently of the mother. This is in contrast to other studies in which both determinant and outcome were reported by the mother or parent. Reliance on maternal report of both neurodevelopment and the child's behaviour may bias the observed associations due to the use of similar methods of measurement, i.e. due to 'shared method variance'.[12] Other strengths of the current study are the population-base, the large number of participants and confounders.

A limitation of the present study is that we experienced some attrition. If the associations in participants and non-participants were substantially different, this could introduce some selection bias. Secondly, toddler behavioural and emotional problems were reported by the mother. In theory, mothers who are aware of their infant's delay in neuromotor development could have been more attentive to their child's problem behaviour. However, mothers were essentially blinded to delayed neuromotor development, because we reported no results as these were of uncertain medical consequences. Finally, observational studies are susceptible to residual confounding. Although we were able to consider many confounders, of which only few significantly affected the associations in the study, we cannot rule out that other factors contributed to our findings.

Conclusions

We found in a prospective population-based study that infant's with non-optimal neuromotor development are more prone to behavioural and emotional problems when they are toddlers. We suggest further research with a longer follow-up period to determine whether toddler problem behaviour, due to an early delay in neuromotor development worsens, persists or attenuates in time. Also, structural and functional MRI research may explore whether a delay in neuromotor development in a child with

problem behaviour has indeed a neurological origin. And if so, answer the question whether the structural variations that underlie the association between a delay in neuromotor development and problem behaviour can already be detected in toddlers.

References

1 Skovgaard AM, Houmann T, Christiansen E, Landorph S, Jorgensen T, C. C. C. 2000 Study Team, Olsen EM, Heering K, Kaas-Nielsen S, Samberg V and Lichtenberg A. The prevalence of mental health problems in children 1(1/2) years of age - the Copenhagen Child Cohort 2000. *J Child Psychol Psychiatry.* 2007; **48** (1): 62-70.

2 Koot HM and Verhulst FC. Prevalence of problem behavior in Dutch children aged 2-3. *Acta Psychiatr Scand Suppl.* 1991; **367**: 1-37.

3 Sourander A. Emotional and behavioural problems in a sample of Finnish three-year-olds. *Eur Child Adolesc Psychiatry.* 2001; **10** (2): 98-104.

4 Mesman J and Koot HM. Early preschool predictors of preadolescent internalizing and externalizing DSM-IV diagnoses. *J Am Acad Child Adolesc Psychiatry.* 2001; **40** (9): 1029-36.

5 Caspi A, Moffitt TE, Newman DL and Silva PA. Behavioral observations at age 3 years predict adult psychiatric disorders. Longitudinal evidence from a birth cohort. *Arch Gen Psychiatry.* 1996; **53** (11): 1033-9.

6 Plomin R, Price TS, Eley TC, Dale PS and Stevenson J. Associations between behaviour problems and verbal and nonverbal cognitive abilities and disabilities in early childhood. *J Child Psychol Psychiatry.* 2002; **43** (5): 619-33.

7 Skovgaard AM, Olsen EM, Christiansen E, Houmann T, Landorph SL, Jorgensen T and Group CCCS. Predictors (0-10 months) of psychopathology at age 11/2 years - a general population study in The Copenhagen Child Cohort CCC 2000. *J Child Psychol Psychiatry.* 2008; **49** (5): 553-62.

8 Rosso IM, Bearden CE, Hollister JM, Gasperoni TL, Sanchez LE, Hadley T and Cannon TD. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull.* 2000; **26** (2): 367-78.

9 Ming X, Brimacombe M and Wagner GC. Prevalence of motor impairment in autism spectrum disorders. *Brain Dev.* 2007; **29** (9): 565-70.

10 Susser E and Bresnahan M. Epidemiologic approaches to neurodevelopmental disorders. *Mol Psychiatry.* 2002; **7 Suppl 2**: S2-3.

11 Sigurdsson E, Van Os J and Fombonne E. Are impaired childhood motor skills a risk factor for adolescent anxiety? Results from the 1958 U.K. birth cohort and the National Child Development Study. *Am J Psychiatry.* 2002; **159** (6): 1044-6.

12 Podsakoff PM, MacKenzie SB, Lee JY and Podsakoff NP. Common method biases in behavioral research: a critical review of the literature and recommended remedies. *J Appl Psychol.* 2003; **88** (5): 879-903.

13 Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC and Hofman A. The Generation R Study: design and cohort update until the age of 4 years. *Eur J Epidemiol.* 2008; **23** (12): 801-11.

14 Touwen BC. *Neurological development in infancy*. London: Heinemann; 1976.

15 van Batenburg-Eddes T, de Groot L, Arends L, de Vries A, Moll HA, Steegers EA, Hofman A, Jaddoe VW, Verhulst FC and Tiemeier H. Does gestational duration within the normal range predict infant neuromotor development? *Early Hum Dev.* 2008; **84** (10): 659-65.
16 Cohen J. Weighted kappa; nominal scale agreement with provision for scaled disagreement or partial credit. *Psychol Bull.* 1968; **70**: 213-20.
17 Peters LH, Maathuis KG, Kouw E, Hamming M and Hadders-Algra M. Test-retest, inter-assessor and intra-assessor reliability of the modified Touwen examination. *Eur J Paediatr Neurol.* 2008; **12** (4): 328-33.
18 Achenbach TM and Rescorla LA. *Manual for the ASEBA Preschool Forms & Profiles*. Burlington: VT: University of Vermont, Research Center for Children, Youth, & Families; 2000.
19 Tick NT, van der Ende J, Koot HM and Verhulst FC. 14-year changes in emotional and behavioral problems of very young Dutch children. *J Am Acad Child Adolesc Psychiatry.* 2007; **46** (10): 1333-40.
20 de Beurs E. *Brief Symptom Inventory, handleiding*. Leiden, the Netherlands; 2004.
21 Derogatis LR and Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983; **13** (3): 595-605.
22 Byles J, Byrne C, Boyle MH and Offord DR. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process.* 1988; **27** (1): 97-104.
23 Hendriks AAJ, Ormel J and van de Willige G. Long lasting difficulties measured with a self-assessment questionnaire and semistructured interview: a theoretical and empirical comparison [in Dutch]. *Gedrag en gezondheid.* 1990; **18**: 273-83.
24 Statistics Netherlands. *Allochtonen in Nederland 2004*. Voorburg/Heerlen; 2004.
25 Rutter M, Kim-Cohen J and Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *J Child Psychol Psychiatry.* 2006; **47** (3-4): 276-95.
26 Tremblay RE, Nagin DS, Seguin JR, Zoccolillo M, Zelazo PD, Boivin M, Perusse D and Japel C. Physical aggression during early childhood: trajectories and predictors. *Pediatrics.* 2004; **114** (1): e43-50.
27 Gilger JW and Kaplan BJ. Atypical brain development: a conceptual framework for understanding developmental learning disabilities. *Dev Neuropsychol.* 2001; **20** (2): 465-81.
28 Kaplan BJ, Wilson BN, Dewey D and Crawford SG. DCD may not be a discrete disorder. *Hum Mov Science.* 1998; **17**: 417-90.
29 Gillberg C and Kadesjo B. Why bother about clumsiness? The implications of having developmental coordination disorder (DCD). *Neural Plast.* 2003; **10** (1-2): 59-68.
30 Pine DS, Wasserman GA, Fried JE, Parides M and Shaffer D. Neurological soft signs: one-year stability and relationship to psychiatric symptoms in boys. *J Am Acad Child Adolesc Psychiatry.* 1997; **36** (11): 1579-86.
31 Altshuler D, Daly MJ and Lander ES. Genetic mapping in human disease. *Science.* 2008; **322** (5903): 881-8.

32 Roza SJ, Verburg BO, Jaddoe VW, Hofman A, Mackenbach JP, Steegers EA, Witteman JC, Verhulst FC and Tiemeier H. Effects of maternal smoking in pregnancy on prenatal brain development. The Generation R Study. *Eur J Neurosci.* 2007; **25** (3): 611-7.

33 Spadoni AD, McGee CL, Fryer SL and Riley EP. Neuroimaging and fetal alcohol spectrum disorders. *Neurosci Biobehav Rev.* 2007; **31** (2): 239-45.

34 O'Callaghan E, Sham P, Takei N, Glover G and Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet.* 1991; **337** (8752): 1248-50.

35 Sever JL, Nelson KB and Gilkeson MR. Rubella epidemic, 1964: effect on 6,000 pregnancies. *Am J Dis Child.* 1965; **110** (4): 395-407.

36 Susser E, St Clair D and He L. Latent effects of prenatal malnutrition on adult health: the example of schizophrenia. *Ann N Y Acad Sci.* 2008; **1136**: 185-92.

37 Brown AS, van Os J, Driessens C, Hoek HW and Susser ES. Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry.* 2000; **157** (2): 190-5.

38 Arnaud C, Daubisse-Marliac L, White-Koning M, Pierrat V, Larroque B, Grandjean H, Alberge C, Marret S, Burguet A, Ancel PY, Supernant K and Kaminski M. Prevalence and associated factors of minor neuromotor dysfunctions at age 5 years in prematurely born children: the EPIPAGE Study. *Arch Pediatr Adolesc Med.* 2007; **161** (11): 1053-61.

39 Allen NB, Lewinsohn PM and Seeley JR. Prenatal and perinatal influences on risk for psychopathology in childhood and adolescence. *Dev Psychopathol.* 1998; **10** (3): 513-29.

40 Murray L, Sinclair D, Cooper P, Ducournau P, Turner P and Stein A. The socioemotional development of 5-year-old children of postnatally depressed mothers. *J Child Psychol Psychiatry.* 1999; **40** (8): 1259-71.

41 Stein A, Malmberg LE, Sylva K, Barnes J and Leach P. The influence of maternal depression, caregiving, and socioeconomic status in the post-natal year on children's language development. *Child Care Health Dev.* 2008; **34** (5): 603-12.

42 Goodman SH and Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychol Rev.* 1999; **106** (3): 458-90.

Chapter 3.2

Infant neuromotor development and child cognitive function

Abstract

Objective

Numerous studies in high-risk populations established that variations in infant neuromotor development predict poor cognitive function. It is unclear whether this association is found in the general population, as well. Moreover, previous population-based studies mostly focused on motor milestone achievement

Method

This study was embedded in the Generation R Study, a population-based cohort in Rotterdam, the Netherlands. Neuromotor development was assessed with an adapted version of Touwen's Neurodevelopmental Examination when infants (1205 males, 1278 females) were on average 12 weeks old (SD 1, range 9-15 weeks). To measure verbal cognitive development at age 1.5 years, the MacArthur Short Form Vocabulary Checklist was used. At 2.5 years, mothers completed the Language Development Survey and the Parent Report of Children's Abilities measuring verbal and nonverbal cognitive functioning, respectively.

Results

After adjustment for confounders, less optimal neuromotor development was associated with a delay in receptive language at 1.5 years (OR 1.18, 95% CI 1.05-1.34), in expressive language across ages (OR 1.11, 95% CI 1.02-1.21), and in nonverbal cognitive function at 2.5 years (OR 1.19, 95% CI 1.05-1.35). These associations were due to higher scores on Touwen's subscale measuring low muscle tone.

Interpretation

This study suggests that subtle deviances from normal early neuromotor development can be a marker of later verbal and nonverbal cognitive delays.

Key terms

Neuromotor development, infant, verbal cognitive functioning, nonverbal cognitive functioning

Introduction

As a result of advances in perinatal care survival of high-risk populations, such as preterm born infants and infants born with low birth weight, has increased. Many of these infants suffer from major disabilities, but even in infants without major dysfunctions, high rates of poor neurodevelopmental outcomes are reported.[1] In addition, recent findings suggest that also late preterm infants are at risk of adverse neurodevelopmental outcomes.[2] Preterm birth or late preterm birth may disrupt a critical period in which substantial brain growth, development and networking occurs. Interruption of these vulnerable processes may result in injuries to developing tissues or disruption of critical pathways.[2] Additionally, adverse concomitant sequelae, such as complications during delivery, pre-eclampsia, pregnancy induced hypertension or diabetes, may have a direct adverse impact on neurodevelopmental outcomes.[3]

Adverse neurodevelopmental outcomes usually occur across multiple domains, e.g. in neuromotor development and cognitive functioning.[4] The association between neuromotor development and cognitive function has been studied cross-sectionally. Korkman et al. found that very preterm born children with neuromotor problems had widespread impairments in the neurocognitive domain when they were 5 years old.[5] Also, Seitz et al. found in children born with low birth weight but without major disabilities correlations between motor deficits and cognitive impairments at the age of 6 years.[6] In addition, only few studies have investigated whether neuromotor development also predicts later cognitive function. In a prospective cohort study which was conducted in 60 preterm born infants without cerebral palsy, the quality of general movements in the early postterm period was found to predict intelligence when the children were between 7 and 11 years old.[7] In 132 children born with a birthweight less than 1000 gram, a significant association between motor development at 1 year and cognitive performance at 4 years was observed; this relation was independent of biological and social factors and presence of cerebral palsy.[8]

Although it was long assumed that the relation between neuromotor development and later cognitive function was confined to high-risk populations, several recent studies casted doubt on this assumption. First, based on a literature review, Iverson (2010) argues that neuromotor

development and language development cannot be seen separately.[9] According to Iverson (2010) the achievement of motor skills gives infants the opportunity to practice skills that are necessary for later language acquisition.[9] Moreover, she argues that the achievement of motor skills changes the infants' interaction with its environment in such a way that it facilitates subsequent language development.[9] Second, the association between neuromotor development and subsequent cognitive function was investigated in a small number of population-based cohort studies. A population-based study in the UK (*n*=5362) found that reaching certain motor milestones at an earlier age was associated with better intellectual performance at ages 8, 26, and 53 years.[10] Similarly, a study performed with data from the Northern Finland 1966 Birth Cohort (*n*=12058) found that infants who reached motor milestones at an earlier age achieved higher levels of education in adolescence and in adulthood.[11] These studies assessed motor functioning in large numbers of participants but relied on the age of motor milestone achievement as registered in children's welfare centers[10] or as reported by parents.[11] Children visit welfare centers only a limited number of times. Most likely, children achieve a milestone in between visits or the registered age of achieving the milestone is reported by parents. Because this data is collected retrospectively it usually has reduced precision of results.[12] Furthermore, age of achieving motor milestones can be a good tool for monitoring the more general gross motor development but these measures only represent one specific domain of neuromotor development. Detailed examinations of the neurological system, however, are a measure of integrity or maturity of the brain and give a broad view of a child's neurological repertoire.[13]

In the current study, variations in early neuromotor development were assessed in a large number of young infants in the general population. Trained research nurses performed a detailed assessment of neuromotor development at home when the infants were as young as 9 to 15 weeks of age. Children's verbal and nonverbal cognitive functioning was assessed using parent-report measures at age 1.5 and 2.5 years. We hypothesised that infants with less optimal early neuromotor development were more often likely to have a cognitive delay in early childhood.

Methods

Design and participants

Data were collected within the Generation R Study, a prospective population-based cohort in Rotterdam, the Netherlands. This study followed urban children from fetal life until young adulthood and is described in detail previously.[14] Full participant recruitment started in April 2002 and baseline data collection was completed in January 2006.

When infants were 9-15 weeks old, their neuromotor development was assessed (*n*=3224) by research nurses during a home visit. Language assessment at the age of 1.5 years was completed in 2321 of the children and at the age of 2.5 years in 1973 children. Information on nonverbal cognitive development at the age of 2.5 years was available in 1818 children. After multiple imputations, 2483 toddlers (77% of 3224 toddlers) with at least one cognitive assessment were included in the analyses. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center and written informed consent was obtained from all adult participants.

Neuromotor assessment

We selected age-appropriate items from Touwen's Neurodevelopmental Examination,[13] and categorized items in three groups: tone (24 items), responses (6 items), and other observations (6 items). A description of the items has been published.[15] For each item, an age-appropriate response was labeled 'optimal'. If the response indicated a delayed development, it was labeled 'non-optimal'. By summing the non-optimal items, we obtained a total score and three subscale scores: tone, responses, and other observations. Within the subscale measuring tone, a distinction was made between low and high tone, resulting in two additional scales: 'low muscle tone' and 'high muscle tone'. On each scale, high values indicate a less optimal neuromotor development. Scale values were used continuously and standardized by dividing them by their standard deviation. To assess non-linear effects, we categorized the total sumscore and the subscale scores into tertiles in line with previous studies. Trained research assistants conducted the assessments during a home visit.

To investigate interobserver reliability, two research assistants independently conducted a neuromotor assessment in a sample of 76 children (intra-class correlation coefficient was 0.64).

Verbal and nonverbal cognitive development

Verbal and nonverbal cognitive development was assessed using three parent-report measures at 1.5 years and 2.5 years.

To measure language development, i.e. word production and word comprehension, at the age of 1.5 years, we used the Dutch version of the MacArthur Short Form Vocabulary Checklists, which is appropriate for measuring word production and comprehension of children aged 16 to 30 months.[16] The instrument contains a list of 112 words and is based on the complete Dutch version of the MacArthur Communicative Development Inventory (MCDI).[16] Parents reported on their child's production and comprehension using the same set of monomorphemic root words. The number of positive responses was summed for expressive and receptive vocabulary. The Dutch short form has excellent internal consistency and concurrent validity.[16] In the current sample, internal consistency was 0.97 for word production and 0.98 for comprehension.

Expressive language at 2.5 years was assessed using parent report on a Dutch translation of the Language Development Survey (LDS).[17] The LDS contains a 310-words vocabulary checklist with words arranged alphabetically within 14 semantic categories (e.g. animals, foods, modifiers, vehicles etc.). Parents were asked to identify each word that a child uses spontaneously, yielding a total vocabulary score. Furthermore, parents were asked to indicate whether a child combined words into phrases or not. The LDS total vocabulary score has very good test-retest reliability, strong concurrent validity, and predictive validity.[17-18] In this study, in line with previous research,[17] internal consistency of the LDS was 0.99.

Nonverbal cognitive functioning at 2.5 years of age was assessed using the Parent Report of Children's Abilities (PARCA).[19] The parent-administered part consists of three subtests based on 22 items: matching-to-sample, block building, and imitation. The parent-report part comprises 26 questions assessing quantitative skills, spatial abilities, symbolic play, planning and organizing, adaptive behaviors and memory. We calculated an

overall PARCA score by adding the sum score of the parent-administered part and the parent-report part. In a validation study (*n*=107), overall PARCA scores were significantly correlated with the Mental Development Index of the Bayley Scales of Infant Development-II (*r*=0.55).[19] In the current sample, internal consistency was 0.60 for the parent-administered and 0.66 for the parent-report part of the PARCA.

To identify verbal or nonverbal cognitive delay, for each measurement we converted the raw total scores into age- and gender-specific percentile scores using one month age brackets. In line with a previous definition of language delay based on the MCDI,[20] for all measurements delays were defined as scores below the 10th percentile. Additionally, at 2.5 years, expressive language delay was defined as scores below that 10th percentile or as the inability to combine words into phrases.

Covariates

The following covariates were selected a priori and based on earlier research:[10-11] birth weight, gestational age, educational level of the mother, family income, and marital status. Also, we considered maternal age, smoking and alcohol use during pregnancy, parity, obstetric variables (eclampsia, gestational hypertension or diabetes), family functioning, long lasting difficulties, breastfeeding, maternal postnatal depressive and anxiety symptoms and the child's ethnicity, gender, Apgar score after 1 minute, and age at time of the cognitive assessments as potential confounders.

Postal questionnaires were used to assess the mother's educational level, family income, marital status, age, her smoking and alcohol use during pregnancy, parity, family functioning, long lasting difficulties, breastfeeding, postnatal depressive and anxiety symptoms, and ethnicity of the child. Educational level was categorized into three levels: low, middle (lower and intermediate vocational training), and high education (higher vocational training, and university) based on Dutch standard classification criteria. Family income was categorized as '<1200 euros' (below social security level), '1200-2000 euros', and '>2000 euros' (more than modal income). Family functioning was measured with the subscale 'General Functioning' (GF) of the Family Assessment Device. GF is a validated 12-

item measure of family health. The item scores were summed and divided by 12 yielding a total score from 1 to 4. A GF score higher than 2.17 (cut-off) denotes unhealthy family functioning.[21] To measure situational and relational difficulties, we used the Long Lasting Difficulties List.[22] To assess postnatal maternal symptoms of depression or anxiety, the Brief Symptom Inventory (BSI) was completed, a validated self-report.[23] Child ethnicity was based on the country of birth of the child and that of its parents. Midwife and hospital registries provided information on gender, date of birth, birth weight and obstetric variables. Gestational age was determined by fetal ultrasound examinations.

Statistical analysis

Logistic regression was used to examine the effect of neuromotor development on verbal and nonverbal cognitive function. As expressive language delay was measured repeatedly, we used the Generalized Estimating Equations (GEE) method to estimate the possible effects on language delay across ages more precisely and to reduce the effect of multiple testing.

Based on earlier research, birth weight, gestational age, educational level of the mother, family income, and marital status were included as covariates.[10-11] Due to the ethnic diversity of the current sample, we also included ethnicity of the child as a confounder. Because our outcome measures were all converted into age- and gender-specific percentile scores, age and gender were not adjusted for.

Next, we investigated whether maternal smoking or alcohol use during pregnancy, maternal age, parity, eclampsia, gestational hypertension or diabetes, Apgar score, breastfeeding, postnatal maternal depressive or anxiety symptoms changed the effect estimates meaningfully (>5%). Following this change-in-estimate criterion none of the above variables were retained in the final models.

A total of 8% of the children had missing data on at least one cognitive outcome variable or confounder. Missing data ranged between 0 to 26% per variable and were assumed to be missing at random. We performed multiple imputation of missing data. Because the missing data had a non-monotone pattern, the iterative Markov chain Monte Carlo method was

used (10 iterations). All covariates including potential confounders not selected for analyses were used to impute missing data. Analyses were conducted on the original data and five imputed datasets, but only pooled imputed results are reported, as changes were marginal.

Response analyses

In comparison to those included in the analyses (*n*=2483), mothers of children who were excluded because of loss to follow-up (*n*=741) were more often lower educated (55% versus 33% low educational level, $\chi^2(2)=237.6$, $p<.001$) and were more often single mothers (24% versus 10% no partner, $\chi^2(1)=80.6$, $p<.001$). Children of these excluded mothers were more often of non-Dutch origin (61% versus 33% non-Dutch, $\chi^2(1)=160.8$, $p<.001$), and had a lower mean birth weight (3339 versus 3446 grams, $F(1,3222)=22.0$, $p<.001$).

Results

Table 1 presents the baseline characteristics of the study participants. Eight percent of the participating mothers had a low educational level, 15% had a monthly net income lower than 1200 euros and 10% had no partner. A third of the children (33%) were of non-Dutch ethnic origin.

Table 2 presents adjusted associations of infant neuromotor developmental scales with language delay at 1.5 and 2.5 years. Per 1 SD increase in overall neuromotor development, the odds ratio for receptive language delay at 1.5 years was 1.18 (95% CI 1.05-1.34). A 1 SD increase in low tone symptoms was also associated with an increased risk of receptive language delay at 1.5 years (OR 1.24, 95% CI 1.11-1.40). Higher scores on overall neuromotor development or on the subscale measuring low tone symptoms, indicating a poorer motor development, were associated with an increased risk of repeatedly assessed expressive language delay (overall neuromotor: OR 1.11, 95% CI 1.02-1.21; low tone: OR 1.13, 95% CI 1.04-1.24).

Table 1. Sample characteristics (*n*=2483)

Maternal characteristics	M *(SD)* / %
Educational level *(%)*	
Low	8
Middle	39
High	54
Family income *(%)*	
< 1200 euro	15
1200-2000 euro	17
> 2000 euro	68
Age at intake, years, M *(SD)*	31.1 (4.8)
Marital status *(%)*	
Married or living together	90
No partner	10
Smoking during pregnancy, yes *(%)*	20
Alcohol use during pregnancy, yes *(%)*	56
Eclampsia/hypertension/diabetes, yes *(%)*	5
Family functioning, pathological *(%)*	9
Long lasting difficulties, score, median *(95% range)*	2 (0-11.0)
Postnatal depressive symptoms at 6 months, score, median *(95% range)*	0 (0-1.50)
Postnatal anxiety symptoms at 6 months, score, median *(95% range)*	0.17 (0-1.45)

Child characteristics	M *(SD)* / %
Birth weight, gram, M *(SD)*	3446 (549)
Gestational age, weeks, M *(SD)*	39.9 (1.7)
Ethnicity, non-Dutch *(%)*	33
First born child, yes, *(%)*	58
Gender, boys (%)	49
Apgar score 1 minute after birth, score, median (95% range)	9 (5-10)
Breastfeeding after 2 months, no *(%)*	31
Age at 1.5 years assessment, years	1.5 (0.1)
Age at 2.5 years assessment, years	2.6 (0.1)
Word comprehension at 1.5 years, score, median (95% range)	55 (12-111)
Word production at 1.5 years, score, median (95% range)	13 (0-78)
Word production at 2.5 years, score, median (95% range)	251 (58-308)
Wordcombinations, no *(%)*	8
Nonverbal cognitive functioning at 2.5 years, score, M *(SD)*	46.8 (5.6)

Table 2. Associations between neuromotor development and cognitive delay (*n*=2483)

	Receptive language delay at 1.5 years OR (95% CI) *p*	Expressive language delay at 1.5 years OR (95% CI) *p*	Expressive language delay at 2.5 years OR (95% CI) *p*	Expressive language delay across ages[a] OR (95% CI) *p*
Neuromotor development at 9-15 weeks, per SD score				
Overall neuromotor development	1.18 (1.05-1.34) .008	1.09 (0.95-1.24) .22	1.13 (1.01-1.26) .031	1.11 (1.02-1.21) .02
Low tone	1.24 (1.11-1.40) <.001	1.15 (1.02-1.31) .028	1.13 (1.02-1.25) .026	1.13 (1.04-1.24) .003
High tone	1.05 (0.93-1.19) .44	0.97 (0.84-1.12) .67	1.07 (0.97-1.19) .20	1.03 (0.94-1.13) .49
Responses	0.90 (0.79-1.05) .19	0.90 (0.78-1.05) .17	0.92 (0.76-1.10) .33	0.92 (0.81-1.01) .21
Other items	1.02 (0.89-1.17) .78	1.07 (0.94-1.22) .30	1.06 (0.95-1.17) .31	1.06 (0.97-1.15) .19

Values represent odds ratios from logistic regression models adjusted for birth weight, gestational age, ethnicity of the child, educational level of the mother, family income and marital status

[a] Pooled estimates (1.5 and 2.5 years) of GEE-analyses

Table 3 shows associations between infant neuromotor developmental scales and nonverbal cognitive delay at 2.5 years after adjustment for confounders. Per 1 SD increase in overall neuromotor development, the odds ratio of nonverbal cognitive delay at 2.5 years was 1.19 (95% CI 1.05-1.35). The increased risk of nonverbal cognitive delay in children with less optimal, i.e. higher scores, neuromotor development was accounted for by the subscale measuring low tone symptoms (OR 1.17, 95% CI 1.02-1.34).

Table 3. Associations between neuromotor development and nonverbal cognitive delay (*n*=2483)

	Nonverbal cognitive delay at 2.5 years	
	OR (95% CI)	***p***
Neuromotor development at 9-15 weeks per SD score		
Overall neuromotor development	1.19 (1.05-1.35)	.005
Low tone	1.17 (1.02-1.34)	.029
High tone	1.12 (0.99-1.26)	.076
Responses	1.05 (0.92-1.21)	.47
Other items	1.03 (0.89-1.19)	.71

Values represent odds ratios from logistic regression models adjusted for birth weight, gestational age, ethnicity of the child, educational level of the mother, family income and marital status

In Figure 1a and 1b the prospective associations are presented per tertile of low muscle tone in relation to receptive and expressive language delay at 1.5 years. Children with a score in the highest tertile for low muscle tone had an increased risk of receptive language delay at 1.5 years (OR 1.44, 95% CI 1.05-1.99) and an increased risk of expressive language delay at 1.5 years (OR 1.66, 95% CI 1.18-2.33). Likewise, a score in the highest tertile for low muscle tone was associated with an increased risk of expressive language delay at 2.5 years (OR 1.44, 95% CI 1.08-1.93; figure not shown).

Figure 1a. Association between low muscle tone and receptive language delay at 1.5 years

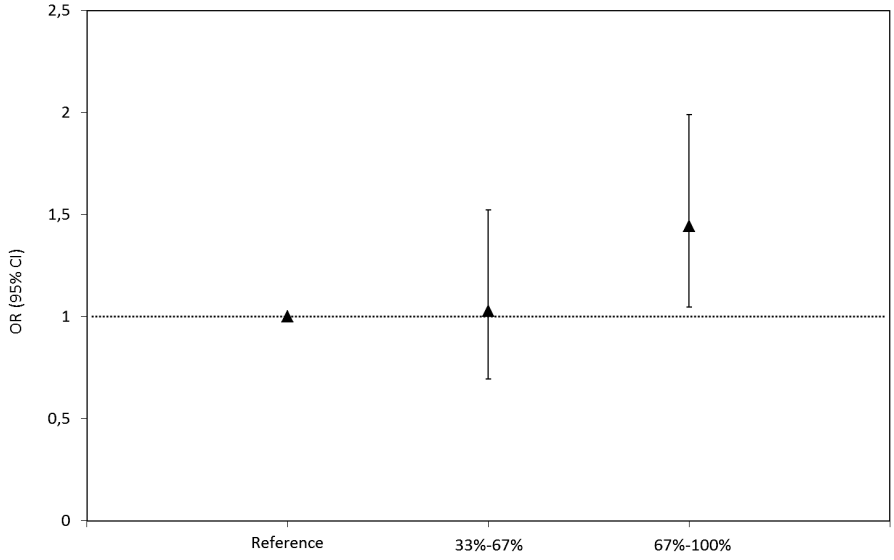
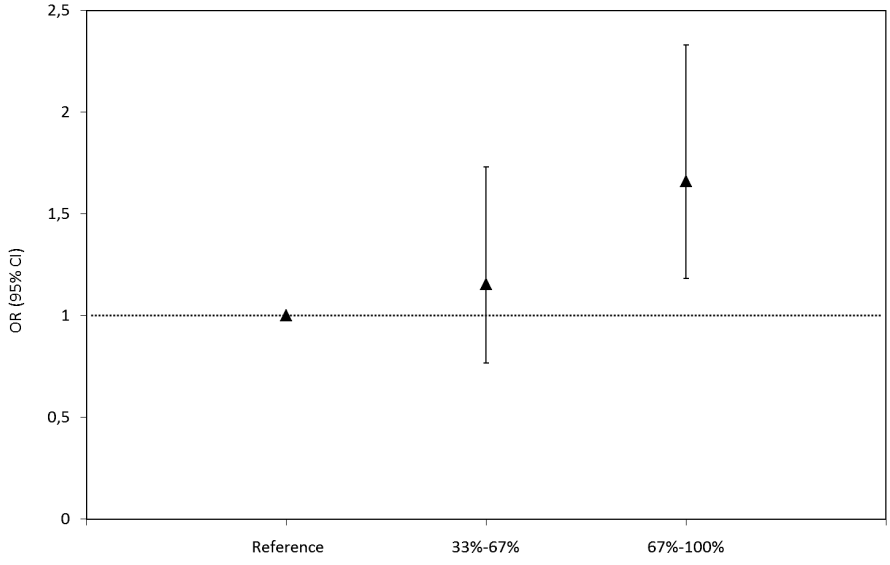


Figure 1b. Association between low muscle tone and expressive language delay at 1.5 years



Results presented in Figure 1 were based on logistic regression analyses that were adjusted for birth weight, gestational age, ethnicity of the child, educational level of the mother, family income and marital status

Discussion

The present study showed that in the general population poorer neuromotor development in infants was associated with verbal cognitive delay at 1.5 and 2.5 years and with nonverbal cognitive delays at 2.5 years. In particular, low muscle tone was consistently predictive of cognitive delay in early childhood.

A few large-scale studies have investigated the association between motor development and subsequent cognitive function in the general population. Data from English and Finnish birth cohorts suggest that children who reach motor milestones earlier achieved a better educational level later in life.[10-11] These results are in line with our findings, despite some fundamental differences in timing and method of assessments. First, our assessments were conducted when children were quite young and some investigators have argued that a delay in neurodevelopment at such an early age has low predictive value for later neuromotor or cognitive functioning. For example, in healthy term born children, low correlations between neuromotor development assessed after birth and cognitive functioning at school age were found.[24] In contrast, Bruggink et al.[7] found an association between the quality of general movements in preterm born infants and cognitive development nine years later. Possibly, some neurological dysfunctions that originated early in life do not manifest until more complex neurological functions are required and thus are not easy to measure early.[25] Indeed, it is unclear whether early neuromotor delays are transient, persistent or progressive.[1] This makes it difficult to determine the optimal and even the earliest age to assess predictors of adverse cognitive outcomes. Second, the few large-scale studies on the association between motor development and subsequent education level assessed motor milestone achievement. This is a valid and reliable way to investigate neurological sequelae of poor infant development,[10-11] but it has limitations. For example, age at standing or walking are assessed most often; milestones that are reached around the age of one year.[13] Preferably, we want to detect even earlier markers of cognitive delay.[1] This may facilitate timely interventions[25] because at a young age the central nervous system is characterized by considerable plasticity. Many studies have evaluated the effects of early intervention programs that aim to improve neuromotor and

cognitive outcomes in high-risk populations. Previous research indicates possible short-term improvement in cognitive outcomes, but uncertainty remains about long-term effects.[26]

Hypotonia, i.e. decreased muscle strength and hypermobility of the joints, is associated with many different disorders, such as diseases of the motor unit, genetic and metabolic disorders, as well as central nervous system dysfunction.[27] If severe brain damage is the cause of hypotonia, like in cerebral palsy, intellectual impairment often co-occurs. Strubhar et al.[28] compared children with no known cause for their hypotonia, termed idiopathic hypotonia, to children with mental retardation. The group with idiopathic hypotonia had higher scores on fine motor, cognitive and receptive language development than the impaired group, but scores were lower than in the general population. We did not assess idiopathic hypotonia but early infant low muscle tone, which was nevertheless consistently associated with poorer verbal and nonverbal cognitive functioning in early childhood.

Infant responses, formerly termed 'primitive reflexes', are reactions to particular stimuli originating in the central nervous system. These responses are exhibited by all normal developing infants, but in children who display typical developmental patterns, they are inhibited later in life. Both the absence of a response at a certain age and the presence of a response after a certain age can be signs of damage to the central nervous system.[13] In our study, more non-optimal responses were not associated with cognitive delays. Infants with brain damage were not part of our study population, which may explain the absence of an association between non-optimal responses and cognitive delay. Furthermore, the timing of the assessment may have contributed to this finding. Half of the assessed responses should have disappeared at age 3 months (asymmetric tonic neck response, walking response and the Bauer response), whereas the other half should start to disappear around the age of 3 months (dorsiflexion of the toe and the Moro response), resulting in less variation in the observed responses. This may have limited the power to find consistent associations in a general population sample.

The relation between neuromotor development and cognitive function may be due to variations in neurological maturation or minor neurological

abnormalities. Support for this idea comes from research on specific language impairment (SLI). Although it has been assumed that SLI is specifically a linguistic disorder, Hill in her review casts doubt on this assumption.[29] The substantial co-morbidity between SLI and poor motor skills indicates that children with SLI suffer from a broader range of neurodevelopmental difficulties.[29] Furthermore, motor difficulties and several aspects of cognitive (dys-) functioning also tend to occur in other neurodevelopmental disorders, such as developmental coordination disorder (DCD), autism or attention deficit hyperactivity disorder suggesting that immaturity of brain development may underlie these disorders.[29] This compromised neurological maturation may originate from adversities during the prenatal, perinatal or postnatal period.[1] However, it is also conceivable that the maturation of the central nervous system is influenced by genetic variations that determine the development of complex neural circuits involved in higher cognitive processes. Results from a study by Bishop, in which data from two twin studies were used, suggest that genes that act as a risk factor for language delays also affect motor skills.[30]

Strengths and limitations

This study has a number of strengths, in particular, its population-based and longitudinal design, and the availability of information about numerous confounders. In contrast to our population-based study, most previous studies on the association between neuromotor development and cognitive function were conducted in high-risk populations.[1-2] Furthermore, neurological examinations were conducted in a large number of participants and assessments were performed by trained research nurses.

Potential limitations of this study must also be discussed. First, a limitation of the present study is that we experienced attrition. Children with missing cognitive outcome measures had lower birth weights, were more often of non-Dutch origin, and had less well educated mothers than children included in our sample. Because these factors are associated with physical and mental health problems, it is often hypothesized that selective non-response introduces selection bias. Selective non-response only poses a threat to validity if the associations between neuromotor development

and cognitive function are different in those who participate compared to those who do not participate, which may seem implausible. A large study on selective drop-out in longitudinal studies showed that the prevalence and incidence of disorders are indeed likely to be underestimated due to selection mechanisms. Yet, the selective non-response did not invalidate the prediction of the outcome.[31] Unfortunately, the findings of this study were based on teacher-reports and studied the effect of selective non-response on the prediction of disruptive behaviors. Therefore, generalizability of these findings to the current study may be limited. In any case, if participants are healthier than non-participants, associations are more likely to be underestimated rather than overestimated. Secondly, we cannot completely rule out that our results regarding nonverbal cognitive development may be less accurate as the internal consistency of the parent-administered and parent-report part of the PARCA were only .60 and .66 in the current study. Thirdly, verbal and nonverbal cognitive function was assessed by parent reports. In theory, parents who are aware of their infant's delay in neuromotor development could have been more attentive to their child's cognitive delay. However, parents were essentially blinded to delayed neuromotor development, because neuromotor assessment results were not reported to the respective parents. Finally, the short period of follow-up may be a drawback because neurodevelopmental delays at a young age have limited predictive value. However, the LDS vocabulary score at 2 to 2.5 years significantly predicts expressive language outcomes up to age 17.[18] In addition, results from a study conducted within the population-based Twins' Early Development Study (TEDS) indicate longitudinal relationships between verbal and nonverbal abilities and behavioural problems at 2, 3 and 4 years and low language scores at 4.5 years.[32]

Conclusions

In this prospective population-based study, we found that infants with less optimal neuromotor development were more likely to have cognitive delays at preschool age. This association was mainly due to low muscle tone. The cognitive delays predicted by less optimal motor development included both verbal and nonverbal cognitive function. While the

associations between less optimal neuromotor development and cognitive delay in early childhood were modest such effects may still be important in public health terms. The results of the current population-based study raise the question whether interventions in early infancy resulting in more optimal neuromotor development may lead to beneficial cognitive outcome later in life. However, before developing and evaluating such interventions, further research with a longer follow-up is necessary to determine whether these delays in cognitive function will persist or attenuate in time.

References

1 Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr* 2005; 26 (6): 427-440.

2 McGowan JE, Alderdice FA, Holmes VA, et al. Early childhood development of late-preterm infants: a systematic review. *Pediatrics* 2011; 127 (6): 1111-1124.

3 Nosarti C, Murray R, Hack M, eds. Neurodevelopmental outcomes of preterm birth: from childhood to adult life. New York: Cambridge University Press; 2010. Cambridge medicine.

4 Woodward LJ, Moor S, Hood KM, et al. Very preterm children show impairments across multiple neurodevelopmental domains by age 4 years. *Arch Dis Child Fetal Neonatal Ed* 2009; 94 (5): F339-344.

5 Korkman M, Mikkola K, Ritari N, et al. Neurocognitive test profiles of extremely low birth weight five-year-old children differ according to neuromotor status. *Dev Neuropsychol* 2008; 33 (5): 637-655.

6 Seitz J, Jenni OG, Molinari L, et al. Correlations between motor performance and cognitive functions in children born < 1250 g at school age. *Neuropediatrics* 2006; 37 (1): 6-12.

7 Bruggink JL, Van Braeckel KN, Bos AF. The early motor repertoire of children born preterm is associated with intelligence at school age. *Pediatrics* 2010; 125 (6): e1356-1363.

8 Burns Y, O'Callaghan M, McDonell B, et al. Movement and motor development in ELBW infants at 1 year is related to cognitive and motor abilities at 4 years. *Early Hum Dev* 2004; 80 (1): 19-29.

9 Iverson JM. Developing language in a developing body: the relationship between motor development and language development. *J Child Lang* 2010; 37 (2): 229-261.

10 Murray GK, Jones PB, Kuh D, et al. Infant developmental milestones and subsequent cognitive function. *Ann Neurol* 2007; 62 (2): 128-136.

11 Taanila A, Murray GK, Jokelainen J, et al. Infant developmental milestones: a 31-year follow-up. *Dev Med Child Neurol* 2005; 47 (9): 581-586.

12 Susser E, Bresnahan M. Epidemiologic approaches to neurodevelopmental disorders. *Mol Psychiatry* 2002; 7 Suppl 2: S2-3.

13 Touwen BC. *Neurological development in infancy*. London: Heinemann; 1976.

14 Jaddoe VW, van Duijn CM, van der Heijden AJ, et al. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol* 2010; 25 (11): 823-841.

15 van Batenburg-Eddes T, de Groot L, Huizink AC, et al. Maternal symptoms of anxiety during pregnancy affect infant neuromotor development: the generation R study. *Dev Neuropsychol* 2009; 34 (4): 476-493.

16 Zink I, Lejaegere M. *N-CDI's Lijsten voor Communicatieve ontwikkeling: korte vormen 2003; Aanpassing en hernormering van de MacArthur Short Form Vocabulary Checklists van Fenson et al.* Leuven/Leusden: Acco; 2002.

17 Rescorla L. The Language Development Survey: a screening tool for delayed language in toddlers. *J Speech Hear Disord* 1989; 54 (4): 587-599.
18 Rescorla L. Age 17 language and reading outcomes in late-talking toddlers: support for a dimensional perspective on language delay. *J Speech Lang Hear Res* 2009; 52 (1): 16-30.
19 Saudino KJ, Dale PS, Oliver B, et al. The validity of parent-based assessment of the cognitive abilities of 2-year-olds. *Br J Dev Psychol* 1998; 16: 349-363.
20 Dale PS. Parent report assessment of language and communication. In: Cole KN, Dale PS and Thal DJ, eds. Assessment of communication and language Baltimore: Paul H. Brookes; 1996.
21 Byles J, Byrne C, Boyle MH, et al. Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Fam Process* 1988; 27 (1): 97-104.
22 Hendriks AAJ, Ormel J, van de Willige G. Long lasting difficulties measured with a self-assessment questionnaire and semistructured interview: a theoretical and empirical comparison [in Dutch]. *Gedrag en gezondheid* 1990; 18: 273-283.
23 de Beurs E. *Brief Symptom Inventory, handleiding*. Leiden, the Netherlands; 2004.
24 Roze E, Meijer L, Van Braeckel KN, et al. Developmental trajectories from birth to school age in healthy term-born children. *Pediatrics* 2010; 126 (5): e1134-1142.
25 Hadders-Algra M. Two distinct forms of minor neurological dysfunction: perspectives emerging from a review of data of the Groningen Perinatal Project. *Dev Med Child Neurol* 2002; 44 (8): 561-571.
26 Orton J, Spittle A, Doyle L, et al. Do early intervention programmes improve cognitive and motor outcomes for preterm infants after discharge? A systematic review. *Dev Med Child Neurol* 2009; 51 (11): 851-859.
27 Brooke MH, Carroll JE, Ringel SP. Congenital hypotonia revisited. *Muscle & Nerve* 1979; 2 (2): 84-100.
28 Strubhar AJ, Meranda K, Morgan A. Outcomes of infants with idiopathic hypotonia. *Pediatr Phys Ther* 2007; 19 (3): 227-235.
29 Hill EL. Non-specific nature of specific language impairment: a review of the literature with regard to concomitant motor impairments. *Int J Lang Commun Disord* 2001; 36 (2): 149-171.
30 Bishop DV. Motor immaturity and specific speech and language impairment: evidence for a common genetic basis. *Am J Med Genet* 2002; 114 (1): 56-63.
31 Wolke D, Waylen A, Samara M, et al. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *Br J Psychiatry* 2009; 195 (3): 249-256.
32 Oliver B, Dale PS, Plomin R. Verbal and nonverbal predictors of early language problems: an analysis of twins in early childhood back to infancy. *J Child Lang* 2004; 31 (3): 609-631.

Chapter 4

Prenatal determinants of behaviour

Chapter 4.1

Antenatal maternal anxiety and depression and child attention problems

Abstract

Background

Maternal depression and anxiety during pregnancy have been associated with offspring attention deficit problems.

Aim

We explored possible intrauterine effects by comparing maternal and paternal symptoms during pregnancy, by investigating cross-cohort consistency, and by investigating whether parental symptoms in early childhood may explain any observed intrauterine effect.

Methods

This study was conducted in two cohorts (Generation R, *n*=2280 and ALSPAC, *n*=3442). Pregnant women and their partners completed questionnaires to assess symptoms of depression and anxiety. Child attention problems were measured in Generation R at age 3 with the Child Behavior Checklist, and in ALSPAC at age 4 with the Strengths and Difficulties Questionnaire.

Results

In both cohorts, antenatal maternal symptoms of depression (Generation R: OR 1.23, 95% CI 1.05-1.43; ALSPAC: OR 1.22, 95% CI 1.12-1.34) and anxiety (Generation R: OR 1.24, 95% CI 1.06-1.46; ALSPAC: OR 1.22, 95% CI 1.12-1.33) were associated with a higher risk of child attention problems. In ALSPAC, paternal depression was also associated with a higher risk of child attention problems (OR 1.11, 95% CI 1.02-1.22). After adjusting for the respective symptoms 3 years after giving birth, antenatal maternal depression and anxiety, and paternal depression were all no longer associated with child attention problems.

Conclusions

The apparent intrauterine effect of maternal depression and anxiety on offspring behavioural problems may be largely explained by residual confounding. The persistence of maternal symptoms after childbirth may indicate genetic inheritance which may be more relevant than intrauterine mechanisms.

Keywords

Parental depression or anxiety, child attention problems, cohort studies, intrauterine effect

Key points:

- Adverse intrauterine factors may have long term consequences for the offspring's development
- Maternal antenatal depression and anxiety are associated with offspring behavioural and emotional problems, but this could represent residual confounding or genetic inheritance
- The intrauterine influence of maternal depression or anxiety on child attention problems was investigated
  - by comparing the effects of maternal and paternal symptoms of depression and anxiety on child attention problems
  - by exploring the extent to which parental depression or anxiety in early childhood might explain any association
  - by studying cross-cohort consistency
- The associations between antenatal maternal depression and anxiety and child attention problems were mostly accounted for by residual confounding and by parental symptoms after childbirth

Introduction

Several studies have suggested that an adverse environment in utero has long-term consequences for development, behaviour and physical health in the offspring.[1,2] A sub-optimal foetal environment may be created by undernutrition,[1] exposure to teratogens, such as nicotine,[3] or maternal disease.[4] Psychological well-being of the mother during pregnancy has been posited to also play a role in healthy development of the offspring.[5] Most of the evidence for the link between antenatal maternal psychological health and offspring development comes from animal studies. These studies suggest that exposure to antenatal maternal stress can adversely affect somatic health outcome, such as birth weight and brain development[6] and psychological outcomes, such as behavioural functioning.[7]

Several reviews suggested that exposure to antenatal maternal depression or anxiety increase the offspring's susceptibility to behavioural or emotional problems.[5,8] Early human studies investigating the influence of maternal stress on behavioural problems were limited because of their retrospective designs and small sample sizes. In the past decade, however, several prospective studies have shown that antenatal maternal depression or anxiety were associated with emotional and behavioural problems in the offspring.[5] In a small study (*n*=143) from Belgium, an association between antenatal maternal anxiety and offspring attention deficit hyperactivity disorder symptoms, externalizing problems, and anxiety at 8- and 9-year-old was found.[9] In previous publications from the Avon Longitudinal Study of Parents and their Children (ALSPAC), one of the cohorts used in the present study, an almost two-fold higher risk of behavioural and emotional problems was found in 4 year olds exposed to maternal anxiety during pregnancy,[10] and in further follow-up these associations were found to persist to age 7 years.[11] Finally, in an Australian birth cohort children of mothers who were anxious during pregnancy were more likely to have persistent attention problems at age 5 and 14.[12]

Any association of maternal depression or anxiety during pregnancy with later offspring outcomes could be caused by intrauterine mechanisms. For example, maternal depression or anxiety may alter the mother's HPA-axis activity and thereby create an adverse foetal environment. Maternal symptoms may thus impact on foetal development and this may in turn

affect offspring behaviour.[5] In addition, maternal depression or anxiety may be associated with behaviours that have an adverse effect on placenta functioning, blood flow, or nutritional supply to the developing foetus and impact on the risk of offspring behavioural problems.[13]

However, it is also possible that these associations are due to residual confounding. Unmeasured or inaccurately measured characteristics, such as lifestyle, maternal physical health or socioeconomic factors, that are related to both maternal depression or anxiety and offspring behaviours can generate spurious associations.[14] Furthermore, mothers who have more depressive and anxiety symptoms during pregnancy are likely to have more of such symptoms after childbirth. Symptoms during their offspring's infancy and childhood can affect parenting skills and mother-child attachment. Such consequences of maternal depression or anxiety could underlie an observed association of antenatal depression or anxiety with offspring behaviours rather than any intrauterine mechanism. Lastly, a genetic predisposition for depression and anxiety that could manifest as behavioural problems in childhood could be inherited by the child from their mother. Distinguishing between these possibilities is important for public health interventions aimed at reducing behavioural problems in children.

One approach that has been suggested to explore whether maternal pregnancy exposures with offspring outcomes are operating via intrauterine or alternative mechanisms is to include comparisons with paternal exposures in the same prenatal period and child outcomes.[15] Where maternal exposures result in direct intrauterine effects, we would expect the maternal associations to be stronger than the paternal associations with child outcomes. Conversely, associations with child outcomes that are similar for maternal and paternal exposures suggest that familial, socioeconomic, environmental or genetic factors, rather than a direct intrauterine mechanism, are likely to be driving the associations.[15]

This study investigates whether there is evidence for an intrauterine influence of maternal depression or anxiety on child attention problems. Firstly, this is done by comparing the effects of maternal and paternal symptoms of depression and anxiety on child attention problems. Secondly, we explore the extent to which parental depression or anxiety when the

child is 3 years old might explain any association. Finally, data were used from two different cohorts, which enabled us to study cross-cohort consistency.

Methods

Design and Participants

This study is based on the Generation R Study and ALSPAC, two prospective population-based studies.

The Generation R Study is conducted in Rotterdam, the Netherlands and follows children from foetal life onwards.[16] In short, all pregnant women who were resident in Rotterdam at the time of their delivery and whose delivery data lay between April 2002 and January 2006 were invited to participate. There were 7893 live-born singletons eligible for follow-up. Information on maternal symptoms of depression and anxiety during pregnancy was available in 5596 mothers, but only 3584 partners completed questions on depression and anxiety. In 2638 children, maternal report about the child's behaviour at age 3 years was available, and in 2280 children, maternal and paternal reports about their own depressive and anxiety symptoms at 3 years were available. The study has been approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, and written informed consent was obtained from all adult participants.

ALSPAC is a geographically-based prospective cohort study investigating the health and development of children.[17] Pregnant women residing in three health districts in the South West of England with an expected date of delivery between 1st April 1991 and 31st December 1992 were eligible to enrol. There were 13,678 live-born singletons. Data on antenatal maternal anxiety and depression were available in 11,812 children and 8715 children had data on both antenatal maternal and paternal anxiety and depression. Of these, 6555 children also had data on their own behavioural problems. Maternal and paternal anxiety and depression 3 years after childbirth was available in 4019 of these children. The final analyses were conducted in 3442 singleton children in whom complete confounder data were available. Ethical approval of the study was obtained from the ALSPAC Law and Ethics Committee (IRB00003312) and three Local Research Ethics Committees.

Parental depression and anxiety

Generation R: Symptoms of parental depression and anxiety were assessed with the Brief Symptom Inventory (BSI) at 20 weeks of pregnancy. The BSI is a validated self-report questionnaire with 53 items on a 5-point scale, ranging from 0='not at all' to 4='extremely'.[18] The items of the BSI cover nine scales of psychiatric symptoms occurring in the preceding 7 days. For this study we used the depression and anxiety scale, each containing six questions. The values (0-4) of the items per scale were summed and divided by the number of endorsed items. In this study, the alpha's for internal consistency for maternal and paternal depression and anxiety were between .69 and .79. This assessment was repeated when the child was 3 years old.

ALSPAC: Parental depression and anxiety were measured at 18 weeks of pregnancy. Parental depressive symptoms were assessed using the Edinburgh Postnatal Depression Scale (EPDS), a widely-used 10-item self-report questionnaire that has been shown to be valid in and outside the postnatal period.[19] Parental symptoms of anxiety were measured using items from the Crown-Crisp index (CCEI), a validated self-rating inventory.[20] Maternal and paternal postnatal anxiety and depression were assessed again at 33 months using the same instruments.

In both studies, each parent completed the depression and anxiety questionnaires themselves (i.e. these were not administered by interview and one parent did not answer for the other parent).

Outcome: Attention problems

Generation R: the Child Behavior Checklist (CBCL/1½-5) was used to obtain standardized maternal reports of children's problem behaviours at 3 years. The CBCL/1½-5 contains 99 problem items, which are scored 0='not true', 1='somewhat true', and 2='very true or often true', based on the preceding two months. The items are scored on seven empirically based syndromes. Good reliability and validity have been reported for the CBCL.[21] For this study, the Attention Problems syndrome scale was used, which consists of items such as: 'Can't concentrate', 'Can't sit still', and 'Wanders away'.

Since our scores were highly skewed and could not be normalized, the Attention Problems syndrome scale was dichotomized. We used the borderline cut-off scores (93rd percentile) of a Dutch norm group[22] to classify children as having Attention Problems in the borderline range.

ALSPAC: When children were 4 years old, the primary caregiver (generally the mothers) reported on children's behavioural or emotional problems using the Strengths and Difficulties Questionnaire (SDQ),[23] an adaptation of a widely used index of psychiatric symptoms in children.[24] The SDQ includes three subscales concerning specific kinds of behavioural or emotional disturbance and has established links with clinical levels of disturbance.[25] In this study, we used the SDQ hyperactivity/inattention subscale, which comprised items such as: 'Constantly fidgeting or squirming', 'Easily distracted, concentration wanders', and 'Thinks things out before acting'. Attention problems were categorized as those falling into the 'borderline' or 'abnormal' categories for this scale.[26]

Covariables

Generation R: Information on educational level of the mother, maternal smoking and alcohol use during pregnancy, family income, and ethnicity of the child were all obtained by postal questionnaires. Educational level was categorized in three levels: low, middle (lower and intermediate vocational training), and high education (higher vocational education, and university) based on Dutch standard classification criteria. Family income, i.e. the net monthly income per month, was reported by the mother and was categorized as '<1200 euros' (below social security level), '1200-2000 euros', and '>2000 euros' (more than modal income). Child ethnicity was based on the country of birth of the child and its parents. The child's gender and birth weight were obtained from midwife and hospital registries.

ALSPAC: Infant gender and birth weight were obtained from obstetric records or birth notifications. In the 32-week questionnaire, mothers were asked to record their highest educational level, which was collapsed into 'none/Certificate of Secondary Education' (national school exams at 16 years), 'vocational', 'O-level' (national school exams at 16 years, higher than certificate of secondary education), 'A-level' (national school exams at 18 years), or 'university degree'. Family income per week was assessed at 4

years after delivery. Information on ethnicity of mothers and their partners were reported from questionnaires sent to mothers at 32 weeks gestation. Information on maternal smoking and alcohol use was collected from antenatal questionnaires sent to mothers at 18 and 32 weeks gestation.

Statistical analyses

In each cohort, we calculated Spearman's Rho correlation coefficients between depressive and anxiety symptoms, between maternal and paternal symptoms and between antenatal and postnatal symptoms over time.

In the non-response analyses, we compared characteristics of mothers and their children with data on attention problems to those with missing data on this outcome with Chi-square tests, analysis of variance (ANOVA), and Mann-Whitney U-test. To assess the representativeness of the final analysis samples in the two cohorts, we calculated the prevalence of attention problems in children of mothers without (participating) partners, i.e. excluded mothers. Further, we examined the key maternal antenatal symptom-offspring outcome associations in the maximal sample possible (i.e. restricting only to those where there were maternal antenatal exposure data, offspring outcome data and data on all covariables).

Logistic regression was used to assess the association between parental symptoms of depression or anxiety and child attention problems. Parental depressive and anxiety symptoms during pregnancy were studied as continuous variables. The depression and anxiety scores were divided by their standard deviations to improve comparability of the odds ratios between parents and across studies, although effect estimates may not be entirely comparable if distributions differ across studies. All analyses were repeated using raw scores (i.e. not SD scores) which gave very consistent results (data not shown).

Confounders were selected a priori. The selection was based on earlier research on the association between antenatal maternal anxiety and childhood behavioural problems.[10] All models were adjusted for age, gender and ethnicity of the child, educational level and age of the mother, family income, maternal smoking and alcohol use during pregnancy.

We conducted a series of analyses to test our hypotheses. First, we studied the relation between maternal symptoms of depression and anxiety with child attention problems within Generation R and within the ALSPAC. Second, we compared the associations of antenatal maternal symptoms with child attention problems to those of antenatal paternal symptoms with the same child outcomes. An F-statistic was used to compare the parental associations. In these analyses we also adjusted for all potential confounders and performed mutual adjustments for the other parent's symptoms. The rationale for this adjustment is depicted in Supplemental Figure 1 and 2. Third, we investigated whether maternal depressive and anxiety symptoms 3 years after childbirth were independently of antenatal symptoms associated with child behavioural and emotional problems at the same time. In addition, in both cohorts we examined whether maternal or paternal symptoms 3 years after the child was born statistically explained the association of antenatal depression or anxiety with offspring behaviour. We explored whether adding depression or anxiety when the child was 3 years old to the confounder adjusted antenatal depression or anxiety model resulted in attenuation to the null of the antenatal association. In this final model we examined whether the results may have been biased by collinearity between the maternal antenatal and postnatal depression or anxiety measurements by examining the variance inflation factor. Finally, we tested consistency of results between the two cohorts. If magnitudes and patterns of association are similar in these two cohorts this provides more robust evidence that they are not a chance finding in one cohort.

We performed several additional analyses. First, though child attention problems were our main outcome, results were contrasted to another outcome, i.e. emotional problems, in order to examine specificity of association. A specific association with either attention or emotional problems would further support a causal inference. In Generation R, emotional problems were measured by the CBCL broadband scale Internalizing Problems and in ALSPAC the SDQ subscale Emotional Problems was used. Second, we repeated the analyses using dichotomized determinants, because the distributions of parental depression and anxiety scores were skewed and we wanted to examine a possible threshold effect. In both cohorts, we defined "anxious" or "depressed" as a score higher than

the 85th percentile in the whole cohort in line with previous studies.[27] Finally, we tested whether any association between antenatal depression or anxiety of a parent and child attention problems was independent of birth weight and gestational age. In both cohorts, birth weight and gestational age did not change the effect estimates. Results of these analyses are not presented.

Statistical analyses were performed using the Statistical Package of Social Sciences version 15 for Windows and SAS version 9.2 (Generation R) and STATA (ALSPAC).

Non-response analyses

Generation R: In comparison to those included in the analyses, mothers of children who were excluded, because of loss to follow-up or missing data had more antenatal depressive symptoms (median (90% range): 0(0-1.17) versus 0(0-0.67), $p<.001$) and anxiety symptoms (median (90% range): 0.17(0-1.17) versus 0(0-0.83), $p<.001$), were more often lower educated (56% versus 32% low education, $\chi^2(2)=255.5$, $p<.001$) and on average younger (29.9 versus 31.7 years, $F(1, 3582)=154.4$; their partners had more depressive symptoms (median (90% range): 0(0-0.67) versus 0(0-0.50), $p<.001$).

ALSPAC: As with the Generation R sample, compared to ALSPAC mothers included in analyses, the excluded mothers had more antenatal depressive symptoms (median (90% range): 7(0-16) versus 5(0-14), $p<.001$) and antenatal anxiety symptoms (median (90% range): 4(0-12) versus 4(0-0.11), $p<.001$), were less educated (24% versus 11% no higher than CSE; $\chi^2(4)=422.6$, $p<.001$), and on average younger at childbirth (27.5 versus 29.2 years $F(1, 13678)=319.2$, $p<.001$); their partners also had more depressive symptoms (median (90% range): 4(0-12) versus 3(0-11), $p<.001$) and more anxiety symptoms in the prenatal period (median (90% range): 2(0-9) versus 2(0-8), $p=.01$).

Results

Sample Characteristics

In the Generation R Study, participating mothers were mostly high educated (68%) and were on average 32 years old at enrolment. In ALSPAC,

47% of mothers were educated to the level of national school exams at 18 or higher, and were on average 29 years at childbirth. In Generation R, 14% were of non-Dutch ethnic origin, however, in ALSPAC 1% of mothers were not of white European origin. In Generation R and ALSPAC, respectively 4% and 22% of the children had a score in the borderline or clinical range of attention problems. Detailed participant characteristics are shown in Supplemental Table 1.

In both cohorts, maternal depressive and anxiety symptoms were correlated with paternal depressive and anxiety symptoms (see Supplemental Table 2).

Attention problems

Associations between parental depressive and anxiety symptoms during pregnancy and attention problems in their children are presented in Table 1.

Maternal depressive symptoms during pregnancy were associated with child attention problems, adjusted for confounders and paternal symptoms. Associations for paternal depressive symptoms and child attention problems were substantially weaker than those observed for maternal depressive symptoms. However, there was no strong evidence that the paternal associations differed statistically from the maternal associations with respect to child attention problems (p for equality between maternal and paternal effect estimates, Generation R: $\chi^2(1)=21.12$, $p=0.15$; ALSPAC: $\chi^2(1)=1.77$, $p=0.18$).

Antenatal maternal anxiety was associated with an increased risk of child attention problems in both cohorts, after adjusting for confounders and paternal symptoms. As observed for parental depressive symptoms, associations for paternal anxiety and child attention were substantially weaker than those observed for maternal anxiety. There was no strong statistical evidence that the association of paternal anxiety symptoms with child attention problems differed from the same association with maternal anxiety symptoms in Generation R but some evidence that in ALSPAC the two associations did differ from each other (p for equality between maternal and paternal effect estimates, Generation R: $\chi^2(1)=0.89$, $p=0.34$; ALSPAC: $\chi^2(1)=5.75$, $p=0.02$).

Table 1. Associations between parental symptoms of depression and anxiety during pregnancy and child attention problems

	Odds of attention problems by parental depression or anxiety in Generation R[a]								
	Unadjusted			Adjusted for confounders			Additionally adjusted for symptoms 3 years after the child was born		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Parental distress, per SD									
Maternal depressive symptoms	1.32	(1.15-1.52)	<.001	1.23	(1.05-1.43)	.009	1.11	(0.92-1.33)	.27
Paternal depressive symptoms	1.13	(0.96-1.33)	.14	1.02	(0.84-1.23)	.85	0.96	(0.78-1.18)	.68
Maternal anxiety symptoms	1.33	(1.15-1.55)	<.001	1.24	(1.06-1.46)	.008	1.12	(0.93-1.35)	.24
Paternal anxiety symptoms	1.16	(0.98-1.39)	.09	1.10	(0.91-1.32)	.35	1.00	(0.81-1.23)	.99
	Odds of attention problems by parental depression or anxiety in ALSPAC[b]								
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Parental distress, per SD									
Maternal depressive symptoms	1.31	(1.21-1.43)	<.001	1.22	(1.12-1.34)	<.001	1.09	(0.98-1.20)	.13
Paternal depressive symptoms	1.20	(1.10-1.30)	<.001	1.11	(1.02-1.22)	.02	1.09	(0.99-1.20)	.10
Maternal anxiety symptoms	1.27	(1.16-1.38)	<.001	1.22	(1.12-1.33)	<.001	1.08	(0.98-1.20)	.14
Paternal anxiety symptoms	1.06	(0.97-1.15)	.21	1.04	(0.95-1.14)	.40	0.98	(0.88-1.09)	.69

Note. OR=odds ratio. CI = confidence interval.
In one or more analyses *n*=2280 in the Generation R Study and *n*=3442 in the ALSPAC.
[a] Generation R attention problems (including the borderline range) were defined using a cut-off at the 93rd percentile based on a Dutch norm group.
Models are unadjusted models; adjusted for gender, age and ethnicity of the child, maternal education, age, alcohol use and smoking during pregnancy, family income, and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for symptoms when the child is 3 years old.
[b] ALSPAC attention problems were based on the SDQ hyperactivity/inattention subscale classification of 'abnormal' or 'borderline' groups.
Models are unadjusted models; adjusted for gender, and age of the child, ethnicity and age of mother and partner, maternal education, smoking and alcohol use during pregnancy, family income when the child is 4 years old, and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for anxiety or depression at 33 months.

The associations between maternal and paternal symptoms of depression and anxiety during pregnancy and child attention problems were additionally adjusted for the respective postnatal symptoms of the parents around the time of child behaviour assessment. Maternal symptoms 3 years after childbirth were independently of antenatal symptoms associated with child attention problems. Maternal depressive and anxiety symptoms 3 years after birth were associated with concurrent child attention problems in Generation R ($OR_{depression}$1.25, 95% CI 1.10-1.41; $OR_{anxiety}$1.24, 95% CI 1.08-1.41) and in ALSPAC ($OR_{depression}$1.15, 95% CI 1.07-1.24; $OR_{anxiety}$1.11, 95% CI 1.03-1.21), adjusted for confounders and antenatal symptoms. Adjusting for symptoms 3 years after childbirth strongly attenuated all parental associations (see Table 1). The attenuation was not due to collinearity of antenatal symptoms and symptoms when the child was 3 years old as variance inflation factors did not exceed 1.22 in Generation R and 1.40 in ALSPAC in any of the regression models.

Emotional problems

In Table 2 associations between parental antenatal depressive and anxiety symptoms and child emotional problems are presented. In both cohorts, antenatal maternal depression and antenatal maternal anxiety were associated with increased risk of child emotional problems after adjustment for confounders and symptoms of the partner.

Maternal depressive and anxiety symptoms 3 years after childbirth were independently of confounders and antenatal symptoms associated with child emotional problems (Generation R $OR_{depression}$1.37, 95% CI 1.22-1.53, $OR_{anxiety}$1.36, 95% CI 1.21-1.52; ALSPAC $OR_{depression}$1.20, 95% CI 1.09-1.33, $OR_{anxiety}$1.19, 95% CI 1.07-1.32).

The associations between antenatal maternal depressive and anxiety symptoms and child emotional problems were attenuated but remained after additional adjustment for maternal symptoms when the child was 3 years old. There was one exception: antenatal maternal depressive symptoms were no longer robustly associated with an increased risk of child emotional problems in Generation R (see Table 2).

Table 2. Associations between parental symptoms of depression and anxiety during pregnancy and child emotional problems

	Odds of emotional problems by parental depression or anxiety in Generation R[a]								
	Unadjusted			Adjusted for confounders			Additionally adjusted for postnatal symptoms		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Parental distress, per SD									
Maternal depressive symptoms	1.31	(1.16-1.48)	<.001	1.23	(1.07-1.41)	.003	1.07	(0.91-1.26)	.44
Paternal depressive symptoms	1.17	(1.03-1.34)	.02	1.05	(0.90-1.21)	.56	1.00	(0.86-1.17)	.99
Maternal anxiety symptoms	1.41	(1.25-1.60)	<.001	1.32	(1.16-1.51)	<.001	1.17	(1.00-1.37)	.05
Paternal anxiety symptoms	1.20	(1.04-1.38)	.01	1.11	(0.95-1.30)	.18	0.99	(0.84-1.18)	.93
	Odds of emotional problems by parental depression or anxiety in ALSPAC[b]								
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Parental distress, per SD									
Maternal depressive symptoms	1.39	(1.24-1.55)	<.001	1.36	(1.21-1.54)	<.001	1.16	(1.01-1.33)	.04
Paternal depressive symptoms	1.13	(1.01-1.27)	.04	1.06	(0.94-1.20)	.32	1.00	(1.19-1.52)	.95
Maternal anxiety symptoms	1.46	(1.31-1.63)	<.001	1.44	(1.28-1.61)	<.001	1.22	(1.06-1.39)	.004
Paternal anxiety symptoms	1.08	(0.96-1.21)	.21	1.03	(0.92-1.17)	.60	0.99	(0.86-1.14)	.89

Note. OR=odds ratio. CI = confidence interval.

In one or more analyses *n*=2280 in the Generation R Study and *n*=3442 in the ALSPAC.

[a] Generation R emotional problems (including the borderline range) were defined using a cut-off at the 83rd percentile based on a Dutch norm group.

[b] ALSPAC emotional problems were based on the SDQ emotional problems subscale classification of 'abnormal' or 'borderline' groups.

See Table 1 for explanation of the models (same covariates throughout).

Additional analyses

Supplemental Table 3-a (attention problems) and 3-b (emotional problems) show how the magnitude of the associations change after adjustment for potential confounders. For both depression and anxiety, adjustment for partner symptoms did not alter the strength of the associations between antenatal maternal depressive or anxiety symptoms and child attention or emotional problems (data not shown). Adding other confounders slightly reduced the magnitude of the associations. Smoking during pregnancy and age of the mother were the strongest confounders. After maternal symptoms at 3 years were also taken into account, antenatal maternal depressive or anxiety symptoms were no longer associated with child attention problems.

When maternal and paternal depression and anxiety symptoms were studied as categorical variables, only in ALSPAC, maternal depression and anxiety and paternal depression were associated with increased risk of child attention problems. Again, all associations were markedly attenuated after adjustment for the respective parental symptoms when the child was 3 years old (Supplemental Table 4).

Representativeness

The study population was limited to mothers with participating partners (*n*=2280 in Generation R and *n*=3442 in ALSPAC). We also calculated the prevalence of attention problems (Generation R: 7%; ALSPAC: 28%) and the associations between maternal exposure and child attention problems in mothers without (participating) partners (Generation R: *n*=2012; ALSPAC *n*= 1392). In these mothers, antenatal maternal symptoms of depression or anxiety were associated with attention problems (adjusted OR for maternal depression: Generation R 1.24, 95% CI 1.03-1.50 and ALSPAC 1.30, 95% CI 1.15-1.46; adjusted OR for maternal anxiety: Generation R 1.22, 95% CI 1.01-1.48, and ALSPAC 1.23, 95% CI 1.09-1.38). The associations attenuated after correction for maternal symptoms 3 years after childbirth. These results were very similar to those in mothers with participating partners.

Discussion

The present study showed that, across the cohorts, antenatal maternal depressive and anxiety symptoms were associated with child attention problems. Although associations of antenatal paternal symptoms of depression and anxiety were weaker than those observed for maternal symptoms, the paternal associations were not statistically different from the associations of maternal symptoms and child attention. Furthermore, observed associations were largely accounted for by maternal anxiety and depression when the child was 3 years old. Taken together these findings do not support a direct intrauterine mechanism for attention problems. Rather the findings suggest that the observed associations can partly be explained by measured confounders (e.g. socioeconomic factors) as well as unmeasured familial or socioeconomic factors (i.e. residual confounders) shared by both parents. Alternatively, it could be explained by genetic confounding; if genetic variants underlie both maternal depression and child attention problems, a similar association pattern should be observable in the fathers that also share 50% of the genetic variants with the child. The persistence of depressive or anxiety symptoms from pregnancy to the postnatal period (and the relationship of these postnatal symptoms to the child's attention behaviours) further accounts for the observed association of maternal depressive and anxiety symptoms in pregnancy with offspring attention problems. In contrast, in both cohorts, the association between antenatal maternal anxiety and child emotional problems was independent of confounders and symptoms when the child was 3 years old, which may suggest that attenuation due to residual confounding may be particular for the intrauterine effect on child attention problems.

Several authors interpreted their findings as indicative of an intrauterine effect of depression during pregnancy on child behaviour. Repeatedly an association between antenatal maternal depression and child behaviour was reported, but most of these studies adjusted only for postnatal psychological state of the mother and not for other important confounders.[28-30] In Generation R and ALSPAC, we found an association between antenatal maternal depressive symptoms and child attention problems, independent of multiple potential confounders. However, there was no strong statistical evidence that the association between antenatal

maternal depressive symptoms and child attention problems differed from that of paternal depressive symptoms with child attention problems. This casts some doubt on the notion that the associations are due to effects of foetal programming caused by antenatal maternal depressive symptoms, and suggests they could be due to shared familial characteristics (genetic, socioeconomic, lifestyle) that relate to depressive symptoms in both parents and to offspring behaviours.

Moreover, the association between maternal depressive symptoms during pregnancy and child attention problems attenuated when depressive symptoms round the time child behaviour was assessed were taken into account. This suggests that an important driver of the association is persistence of the symptoms into the postnatal period and the impact of these postnatal symptoms on the child rather than an intrauterine mechanism.

In Generation R and ALSPAC, antenatal maternal anxiety but not paternal anxiety was associated with child attention problems. Yet, we found no strong statistical evidence that the magnitude of the associations for maternal anxiety were higher than those of the father. Furthermore, correcting for anxiety symptoms 3 years after the child was born attenuated all associations of maternal anxiety. So, the results of this study give little evidence that antenatal maternal anxiety symptoms are specifically related to child attention problems via intrauterine mechanisms. This is in contrast to results of previous studies of the association between antenatal maternal anxiety and child behavioural problems.[9,10] However, none of these studies investigated the effect of exposure to antenatal paternal anxiety symptoms on child behaviour.

We included child emotional problems as an outcome to test the specificity of the confounding in the association with attention problems. Our results suggest that maternal anxiety might be directly related to offspring emotional problems, which could be due to intrauterine programming. In addition, results indicate that residual confounding does not explain all intrauterine effects of maternal depressive or anxiety symptoms on child outcomes, but that shared familial factors are particularly important confounders of the observed association with child attention problems. However, our study was able to show the effect of

residual confounders shared (familial factors) or similarly effective in mothers and fathers (genetic factors). Any confounder specific for mothers, such as pregnancy related work stress could underlie the association between antenatal maternal anxiety and child emotional problems.

Strengths and limitations

This study has several strengths. First, data from two large cohorts made it possible to replicate the results in different populations. Second, we could compare the effects of maternal and paternal depression and anxiety on child attention problems. Third, in both cohorts we had the opportunity to adjust for a large number of confounders.

Several methodological limitations need to be discussed. First, non-random attrition may have influenced our results, for example, if non-participating parents with depression or anxiety were more likely than participating parents to have a child with attention problems. Those lost to follow-up were less well educated, younger and had more depressive and anxiety symptoms than their participating counterparts. Moreover, mothers without (participating) partners more often had children with behavioural problems than the included mothers. However, the associations in mothers without (participating) partners were of similar magnitude as those in the included sample. Second, child behaviour was assessed by the mother, hence reporter bias may have influenced the results of this study. It is possible that depressed or anxious mothers reported more attention problems in their children than mothers without these symptoms.[31] Third, different instruments were used in both cohorts to measure parental depression and anxiety and child attention problems. Good validity has been demonstrated for the BSI,[18] the CCEI,[20] and the EPDS.[19] Using different instruments might have contributed to some inconsistency of findings regarding paternal depression. Overall, the findings largely concur; hence the use of different instruments strengthens conclusions. Furthermore, the CBCL and the SDQ were used to assess child attention problems within Generation R and the ALSPAC, respectively. Goodman and Scott showed that scores from the SDQ and the CBLC were highly correlated and the instruments were equivalent at detecting inattention and hyperactivity.[23] However, the two instruments yielded

different rates of attention problems; the CBCL is a more detailed behavioural and emotional assessment instrument, that was developed for clinical and non-clinical populations, whereas the SDQ is a brief instrument mainly used to assess non-clinical populations.

Conclusions

Antenatal maternal depression or anxiety regardless of its effect on child attention problems poses a threat to maternal well-being and healthy development in the offspring. However, in two large population-based cohorts, we found no strong evidence for a direct intrauterine effect of maternal symptoms of depression and anxiety on child attention problems. Most of the observed effects could be explained by residual confounding as indexed by the relation observed with paternal symptoms, or postnatal effects of chronic or recurring parental symptoms. Thus, intrauterine mechanisms as a consequence of maternal psychopathology may not be a relevant aetiological factor for the development of attention problems in children. As the associations between antenatal maternal anxiety and child emotional problems were not explained by residual confounding, this suggests that outcomes other than child attention problems may indeed be affected by intrauterine exposure to maternal depression or anxiety. Research should perhaps focus on other outcomes, alternative mechanisms such as genetic factors, postnatal environment or other risk factors during foetal life such as antenatal infections.

References

1 Barker DJ. Fetal origins of coronary heart disease. *Bmj.* 1995; **311** (6998): 171-4.

2 Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D and Gorman JM. Schizophrenia after prenatal famine. Further evidence. *Arch Gen Psychiatry.* 1996; **53** (1): 25-31.

3 Roza SJ, Verburg BO, Jaddoe VW, Hofman A, Mackenbach JP, Steegers EA, Witteman JC, Verhulst FC and Tiemeier H. Effects of maternal smoking in pregnancy on prenatal brain development. The Generation R Study. *Eur J Neurosci.* 2007; **25** (3): 611-7.

4 O'Callaghan E, Sham P, Takei N, Glover G and Murray RM. Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic. *Lancet.* 1991; **337** (8752): 1248-50.

5 Talge NM, Neal C and Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry.* 2007; **48** (3-4): 245-61.

6 Lesage J, Del-Favero F, Leonhardt M, Louvart H, Maccari S, Vieau D and Darnaudery M. Prenatal stress induces intrauterine growth restriction and programmes glucose intolerance and feeding behaviour disturbances in the aged rat. *J Endocrinol.* 2004; **181** (2): 291-6.

7 Weinstock M. Alterations induced by gestational stress in brain morphology and behaviour of the offspring. *Prog Neurobiol.* 2001; **65** (5): 427-51.

8 Van den Bergh BR, Mulder EJ, Mennes M and Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev.* 2005; **29** (2): 237-58.

9 Van den Bergh BR and Marcoen A. High antenatal maternal anxiety is related to ADHD symptoms, externalizing problems, and anxiety in 8- and 9-year-olds. *Child Dev.* 2004; **75** (4): 1085-97.

10 O'Connor TG, Heron J, Golding J, Beveridge M and Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br J Psychiatry.* 2002; **180**: 502-8.

11 O'Connor TG, Heron J, Golding J and Glover V. Maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. *J Child Psychol Psychiatry.* 2003; **44** (7): 1025-36.

12 Clavarino AM, Mamun AA, O'Callaghan M, Aird R, Bor W, O'Callaghan F, Williams GM, Marrington S, Najman JM and Alati R. Maternal anxiety and attention problems in children at 5 and 14 years. *J Atten Disord.* 2010; **13** (6): 658-67.

13 Brown AS, van Os J, Driessens C, Hoek HW and Susser ES. Further evidence of relation between prenatal famine and major affective disorder. *Am J Psychiatry.* 2000; **157** (2): 190-5.

14 Rothman KJ, Greenland S and Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

15 Davey Smith G. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol.* 2008; **102** (2): 245-56.

16 Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC and Hofman A. The Generation R Study: design and cohort update 2010. *Eur J Epidemiol.* 2010; **25** (11): 823-41.

17 Golding J, Pembrey M and Jones R. ALSPAC--the Avon Longitudinal Study of Parents and Children. I. Study methodology. *Paediatr Perinat Epidemiol.* 2001; **15** (1): 74-87.

18 Derogatis LR and Melisaratos N. The Brief Symptom Inventory: an introductory report. *Psychol Med.* 1983; **13** (3): 595-605.

19 Cox JL, Holden JM and Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987; **150**: 782-6.

20 Birtchnell J, Evans C and Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol.* 1988; **61 (Pt 3)**: 255-66.

21 Achenbach TM and Rescorla LA. *Manual for the ASEBA Preschool Forms & Profiles*. Burlington: VT: University of Vermont, Research Center for Children, Youth, & Families; 2000.

22 Tick NT, van der Ende J, Koot HM and Verhulst FC. 14-year changes in emotional and behavioral problems of very young Dutch children. *J Am Acad Child Adolesc Psychiatry.* 2007; **46** (10): 1333-40.

23 Goodman R and Scott S. Comparing the Strengths and Difficulties Questionnaire and the Child Behavior Checklist: is small beautiful? *J Abnorm Child Psychol.* 1999; **27** (1): 17-24.

24 Elander J and Rutter M. Use and development of the Rutter parents' and teachers' scales. *Int J Methods Psychiatry.* 1996; **6**: 63-78.

25 Goodman R. The extended version of the Strengths and Difficulties Questionnaire as a guide to child psychiatric caseness and consequent burden. *J Child Psychol Psychiatry.* 1999; **40** (5): 791-9.

26 Goodman R. SDQ: Scoring the SDQ. Retrieved from http://www.sdqinfo.org/py/doc/c0.py

27 van Batenburg-Eddes T, de Groot L, Huizink AC, Steegers EA, Hofman A, Jaddoe VW, Verhulst FC and Tiemeier H. Maternal symptoms of anxiety during pregnancy affect infant neuromotor development: the generation R study. *Dev Neuropsychol.* 2009; **34** (4): 476-93.

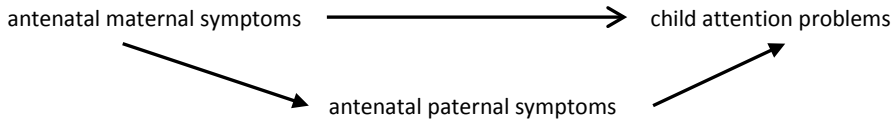
28 Davis EP, Snidman N, Wadhwa PD, Glynn LM, Schetter CD and Sandman CA. Prenatal maternal anxiety and depression predict negative behavioral reactivity in infancy. *Infancy.* 2004; **6** (3): 319-31.

29 Field T, Diego M, Dieter J, Hernandez-Reif M, Schanberg S, Kuhn C, Yando R and Bendell D. Prenatal depression effects on the fetus and the newborn. *Infant Behavior & Development.* 2004; **27** (2): 216-29.

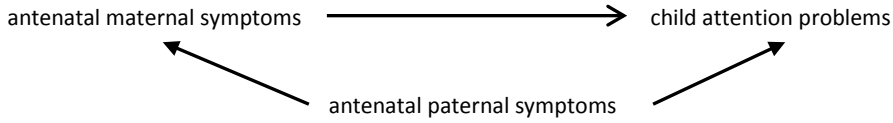
30 Luoma I, Tamminen T, Kaukonen P, Laippala P, Puura K, Salmelin R and Almqvist F. Longitudinal study of maternal depressive symptoms and child well-being. *J Am Acad Child Psy.* 2001; **40** (12): 1367-74.

31 Najman JM, Williams GM, Nikles J, Spence S, Bor W, O'Callaghan M, Le Brocque R and Andersen MJ. Mothers' mental illness and child behavior problems: Cause-effect association or observation bias? *J Am Acad Child Psy.* 2000; **39** (5): 592-602.

Supplemental Figure 1.



Supplemental Figure 2.



Supplemental table 1. Summary of Sample Characteristics

	Generation R Study population *n*=2280 in one or more analyses
Maternal characteristics	
Educational level	
Low	2%
Middle	31%
High	68%
Smoking during pregnancy, yes	10%
Alcohol use during pregnancy, yes	58%
Age at intake, mean (s.d.), years	31.7(3.9)
Family income, per month	
< 1200 euro	3%
1200-2000 euro	11%
> 2000 euro	86%
Prenatal maternal depressive symptoms, median (90% range)	0(0-0.67)
Prenatal paternal depressive symptoms, median (90% range)	0(0-0.50)
Prenatal maternal anxiety symptoms, median (90% range)	0(0-0.83)
Prenatal paternal anxiety symptoms, median (90% range)	0(0-0.67)
Maternal depressive symptoms at 3 years, median (90% range)	0(0-0.50)
Paternal depressive symptoms at 3 years, median (90% range)	0(0-0.50)
Maternal anxiety symptoms at 3 years, median (90% range)	0(0-0.67)
Paternal anxiety symptoms at 3 years, median (90% range)	0(0-0.67)
Child characteristics	
Attention problems, CBCL score in borderline range	4%
Age at CBCL 3 years, mean (s.d.), years	3.1(0.1)
Gender, boys	49%
Ethnicity, non-Dutch	14%
Gestational age, mean (s.d.), weeks	40.0(1.6)
Birth weight, mean (s.d.), grams	3500(548)

Supplemental table 1. Summary of Sample Characteristics (*continued)*

	ALSPAC Study population *n*=3442
Maternal characteristics	
Educational level	
Certificate of Secondary Education/None	11%
Vocational	8%
O-level	35%
A-level	28%
University Degree	19%
Smoking during pregnancy, yes	16%
Alcohol use during pregnancy, yes	46%
Age at childbirth, mean (s.d.) years	29.3(4.4)
Family Income, per week	
<£100	3%
£100-199	11%
£200-299	26%
£300-399	26%
>£400	35%
Prenatal maternal depressive symptoms, median (90% range)	5(0-14)
Prenatal paternal depressive symptoms, median (90% range)	3(0-11)
Prenatal maternal anxiety symptoms, median (90% range)	4(0-11)
Prenatal paternal anxiety symptoms, median (90% range)	2(0-8)
Maternal depressive symptoms at 33 months, median (90% range)	5(0-15)
Paternal depressive symptoms at 33 months, median (90% range)	2.5(0-11)
Maternal anxiety symptoms at 33 months, median (90% range)	4(1-11)
Paternal anxiety symptoms at 33 months, median (90% range)	2(0-8)
Ethnicity, caucasian	99%
Ethnicity partner, caucasian	99%
Child characteristics	
Attention problems, SDQ 'borderline'/'abnormal'	22%
Age at SDQ 4 years, median (90% range), years	4.0(3.9-4.2)
Gender, boys	52%
Gestational age, median (90% range), weeks	40(37-42)
Birth weight, mean(s.d.), grams	3455(522)

Supplemental table 2. For each cohort, correlations between antenatal (maternal and paternal) symptoms of depression and anxiety and (maternal and paternal) symptoms of depression and anxiety 3 years after childbirth

	Antenatal symptoms of:				**Three years after childbirth symptoms of:**			
	maternal		**paternal**		**maternal**		**paternal**	
	depression	**anxiety**	**depression**	**anxiety**	**depression**	**anxiety**	**depression**	**anxiety**
	r_s	r_s	r_s	r_s	r_s	r_s	r_s	r_s
Antenatal symptoms of								
maternal depression	-	0.69	0.24	0.15	0.49	0.43	0.18	0.13
maternal anxiety	0.67	-	0.17	0.13	0.44	0.51	0.18	0.14
paternal depression	0.20	0.15	-	0.60	0.18	0.14	0.45	0.43
paternal anxiety	0.13	0.14	0.57	-	0.13	0.13	0.40	0.56
Three years after childbirth symptoms of								
maternal depression	0.37	0.33	0.13	0.09	-	0.67	0.26	0.19
maternal anxiety	0.26	0.35	0.12	0.12	0.59	-	0.21	0.19
paternal depression	0.14	0.11	0.28	0.22	0.25	0.16	-	0.60
paternal anxiety	0.12	0.13	0.22	0.37	0.20	0.18	0.54	-

From diagonal to lower left corner Spearman's rho correlation coefficients for Generation R (n=2280; all p-values <.001); from diagonal to upper right corner Spearman's rho correlation coefficients for ALSPAC (n=3442; all p-values < .001)

Supplemental table 3-a. Stepwise regression analyses showing the associations between antenatal maternal and paternal symptoms of depression and anxiety with child attention problems

	Odds of attention problems by parental depression or anxiety in Generation R[a]								
	Unadjusted			Mutual adjustment and adjusted for confounders			Additionally adjusted for postnatal symptoms		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Parental distress, per SD									
Maternal depressive symptoms	1.32	(1.15-1.52)	<.001	1.23	(1.05-1.43)	.009	1.11	(0.92-1.35)	.27
Paternal depressive symptoms		-		1.02	(0.84-1.23)	.85	1.03	(0.85-1.24)	.81
Gender		-							
Boys				1.20	(0.76-1.90)	.43	1.19	(0.75-1.88)	.46
Girls					*reference*			*reference*	
Age of the child		-		0.97	(0.80-1.18)	.77	0.96	(0.79-1.17)	.71
Ethnicity of the child		-							
Dutch					*reference*	.75	0.99	*reference*	.98
Non-Dutch				1.11	(0.59-2.09)			(0.51-1.91)	
Educational level of the mother		-							
Low				0.90	(0.19-4.21)	.89	0.85	(0.18-4.10)	.84
Middle				1.18	(0.69-2.02)	.55	1.16	(0.68-2.00)	.58
High					*reference*			*reference*	
Family income		-							
< 1200 euro				1.08	(0.33-3.53)	.90	1.00	(0.29-3.48)	1.00
1200-2000 euro				1.41	(0.73-2.73)	.31	1.32	(0.67-2.60)	.42
> 2000 euro					*reference*			*reference*	
Alcohol use during pregnancy		-							
No					*reference*			*reference*	
Yes				0.91	(0.55-1.51)	.72	0.90	(0.54-1.50)	.69
Smoking during pregnancy		-							
No					*reference*			*reference*	
Yes				1.82	(0.98-3.38)	.06	1.81	(0.97 -3.36)	.06
Age of the mother		-		0.93	(0.88-0.99)	.02	0.93	(0.88-0.99)	.02
Maternal depressive symptoms at 3 years		-			-		1.25	(1.07-1.45)	.005
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Paternal depressive symptoms	1.13	(0.96-1.33)	.14	1.02	(0.84-1.23)	.85	0.96	(0.78-1.18)	.68
Maternal depressive symptoms		-		1.23	(1.05-1.43)	.009	1.21	(1.03-1.42)	.02
	Associations of confounders with the outcome are not shown here; effect estimates were highly similar as in the (previous) models in which maternal depressive symptoms was the determinant								
Paternal depressive symptoms at 3 years		-			-		1.22	(1.05-1.42)	.01

Supplemental table 3-a. Stepwise regression analyses showing the associations between antenatal maternal and paternal symptoms of depression and anxiety with child attention problems *(continued)*

	Odds of attention problems by parental depression or anxiety in Generation R[a]								
	Unadjusted			Mutual adjustment and adjusted for confounders			Additionally adjusted for postnatal symptoms		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Parental distress, per SD									
Maternal anxiety symptoms	1.33	(1.15-1.55)	<.001	1.24	(1.06-1.46)	.008	1.12	(0.93-1.35)	.24
Paternal anxiety symptoms		-		1.10	(0.91-1.32)	.34	1.06	(0.88-1.29)	.53
Gender		-							
Boys				1.27	(0.81-2.01)	.30	1.24	(0.78-1.96)	.37
Girls					*reference*			*reference*	
Age of the child		-		0.96	(0.78-1.17)	.67	0.94	(0.77-1.15)	.57
Ethnicity of the child		-							
Dutch					*reference*			*reference*	
Non-Dutch				1.17	(0.62-2.18)	.63	1.13	(0.60-2.13)	.72
Educational level of the mother		-							
Low				0.93	(0.20-4.40)	.93	0.84	(0.18-3.97)	.82
Middle				1.17	(0.68-1.99)	.58	1.15	(0.67-1.96)	.62
High					*reference*			*reference*	
Family income		-							
< 1200 euro				0.74	(0.20-2.79)	.66	0.67	(0.17-2.64)	.56
1200-2000 euro				1.37	(0.71-2.65)	.35	1.35	(0.669-2.63)	.38
> 2000 euro					*reference*			*reference*	
Alcohol use during pregnancy		-							
No					*reference*			*reference*	
Yes				0.89	(0.54-1.48)	.67	0.89	(0.54-1.49)	.67
Smoking during pregnancy		-							
No					*reference*			*reference*	
Yes				1.87	(1.01-3.45)	.05	1.93	(1.04-3.58)	.04
Age of the mother		-		0.93	(0.88-0.99)	.02	0.93	(0.87-0.99)	.02
Maternal anxiety symptoms at 3 years		-			-		1.27	(1.09-1.49)	.002
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Paternal anxiety symptoms	1.17	(0.98-1.39)	.09	1.10	(0.91-1.32)	.35	1.00	(0.81-1.23)	.99
Maternal anxiety symptoms		-		1.24	(1.06-1.46)	.008	1.22	(1.03-1.44)	.02
	Associations of confounders with the outcome are not shown here; effect estimates were highly similar as in the (previous) models in which maternal anxiety symptoms was the determinant								
Paternal anxiety symptoms at 3 years		-			-		1.27	(1.07-1.51)	.007

Note. OR=odds ratio. CI = confidence interval.
In one or more analyses *n*=2280 in the Generation R Study.
[a] Generation R attention problems (including the borderline range) were defined using a cut-off at the 93rd percentile based on a Dutch norm group.
Models are unadjusted models; adjusted for gender, age and ethnicity of the child, maternal education, age, alcohol use and smoking during pregnancy, family income, and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for symptoms when the child is 3 years old.

Supplemental table 3-b. Stepwise regression analyses showing the associations between antenatal maternal and paternal symptoms of depression and anxiety with child emotional problems

	Odds of emotional problems by parental depression or anxiety in Generation R[a]								
	Unadjusted			Mutual adjustment and adjusted for confounders			Additionally adjusted for postnatal symptoms		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Parental distress, per SD									
Maternal depressive symptoms	1.31	(1.16-1.48)	<.001	1.23	(1.07-1.41)	.003	1.07	(0.91-1.26)	.44
Paternal depressive symptoms		-		1.05	(0.90-1.21)	.56	1.04	(0.89-1.21)	.62
Gender									
Boys		-		0.92	(0.62-1.35)	.66	0.89	(0.60-1.32)	.55
Girls					*reference*			*reference*	
Age of the child		-		1.10	(0.98-1.25)	.11	1.10	(0.97-1.24)	.15
Ethnicity of the child									
Dutch		-			*reference*			*reference*	
Non-Dutch				1.85	(1.12-3.03)	.02	1.68	(1.00-2.80)	.05
Educational level of the mother									
Low		-		1.69	(0.66-4.30)	.28	1.58	(0.60-4.14)	.35
Middle				0.58	(0.35-0.96)	.03	0.55	(0.33-0.91)	.02
High					*reference*			*reference*	
Family income									
< 1200 euro		-		2.01	(0.85-4.78)	.11	2.00	(0.82-4.92)	.13
1200-2000 euro				1.51	(0.85-2.70)	.16	1.39	(0.76-2.52)	.28
> 2000 euro					*reference*			*reference*	
Alcohol use during pregnancy									
No		-			*reference*			*reference*	
Yes				0.88	(0.57-1.35)	.54	0.86	(0.56-1.32)	.48
Smoking during pregnancy									
No		-			*reference*			*reference*	
Yes				1.13	(0.61-2.11)	.69	1.08	(0.57-2.04)	.82
Age of the mother		-		0.93	(0.88-0.98)	.01	0.93	(0.88-0.99)	.01
Maternal depressive symptoms at 3 years		-			-		1.39	(1.21-1.59)	<.001
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Paternal depressive symptoms	1.17	(1.03-1.34)	.02	1.05	(0.90-1.21)	.56	1.00	(0.86-1.17)	.99
Maternal depressive symptoms		-		1.23	(1.07-1.41)	.003	1.21	(1.05-1.39)	.009
	Associations of confounders with the outcome are not shown here; effect estimates were highly similar as in the (previous) models in which maternal depressive symptoms was the determinant								
Paternal depressive symptoms at 3 years		-			-		1.19	(1.04-1.36)	.01

Supplemental table 3-b. Stepwise regression analyses showing the associations between antenatal maternal and paternal symptoms of depression and anxiety with child emotional problems *(continued)*

	Odds of emotional problems by parental depression or anxiety in Generation R[a]								
	Unadjusted			**Mutual adjustment and adjusted for confounders**			**Additionally adjusted for postnatal symptoms**		
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Parental distress, per SD									
Maternal anxiety symptoms	1.41	(1.25-1.60)	<.001	1.32	(1.16-1.51)	<.001	1.17	(1.00-1.37)	.046
Paternal anxiety symptoms		-		1.11	(0.95-1.30)	.18	1.07	(0.92-1.26)	.39
Gender									
Boys		-		0.91	(0.62-1.34)	.65	0.88	(0.60-1.30)	.52
Girls					*reference*			*reference*	
Age of the child		-		1.09	(0.97-1.23)	.16	1.08	(0.96-1.22)	.23
Ethnicity of the child									
Dutch		-			*reference*			*reference*	
Non-Dutch				1.94	(1.19-3.16)	.008	1.95	(1.19-3.20)	.008
Educational level of the mother									
Low		-		1.84	(0.72-4.71)	.20	1.57	(0.61-4.03)	.35
Middle				0.63	(0.38-1.03)	.07	0.60	(0.37-0.99)	.047
High					*reference*			*reference*	
Family income									
< 1200 euro		-		1.81	(0.77-4.27)	.17	1.78	(0.74-4.31)	.20
1200-2000 euro				1.38	(0.78-2.46)	.27	1.35	(0.75-2.44)	.31
> 2000 euro					*reference*			*reference*	
Alcohol use during pregnancy		-							
No					*reference*			*reference*	
Yes				0.87	(0.57-1.34)	.54	0.87	(0.57-1.34)	.53
Smoking during pregnancy									
No		-			*reference*			*reference*	
Yes				1.07	(0.57-1.98)	.84	1.09	(0.58-2.04)	.79
Age of the mother		-		0.94	(0.89-0.99)	.03	0.94	(0.89-0.99)	.02
Maternal anxiety symptoms at 3 years		-			-		1.35	(1.19-1.54)	<.001
	OR	**95% CI**	***p***	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Paternal anxiety symptoms	1.20	(1.04-1.38)	.014	1.11	(0.95-1.30)	.18	0.99	(0.84-1.18)	.93
Maternal anxiety symptoms		-		1.32	(1.16-1.51)	<.001	1.29	(1.12-1.48)	<.001
	Associations of confounders with the outcome are not shown here; effect estimates were highly similar as in the (previous) models in which maternal anxiety symptoms was the determinant								
Paternal anxiety symptoms at 3 years		-			-		1.36	(1.17-1.58)	<.001

Note. OR=odds ratio. CI = confidence interval.
In one or more analyses *n*=2280 in the Generation R Study.
[a] Generation R emotional problems (including the borderline range) were defined using a cut-off at the 83rd percentile based on a Dutch norm group.
Models are unadjusted models; adjusted for gender, age and ethnicity of the child, maternal education, age, alcohol use and smoking during pregnancy, family income, and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for symptoms when the child is 3 years old.

Supplemental table 4. Associations between high levels of parental symptoms of depression and anxiety during pregnancy (categorical) and child attention problems

	Odds of attention problems by parental depression or anxiety in Generation R[a]								
	Unadjusted			Adjusted for confounders			Additionally adjusted for postnatal symptoms		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Parental distress (>85th %)									
Maternal depression	2.29	(1.26-4.15)	.007	1.79	(0.95-3.37)	.07	1.31	(0.66-2.61)	.44
Paternal depression	1.97	(1.21-3.20)	.006	1.62	(0.96-2.73)	.07	1.43	(0.83-2.46)	.20
Maternal anxiety	1.88	(1.00-3.54)	.05	1.51	(0.78-2.92)	.22	1.01	(0.48-2.12)	.98
Paternal anxiety	1.60	(0.98-2.59)	.06	1.34	(0.80-2.22)	.26	1.13	(0.67-1.92)	.65
	Odds of attention problems by parental depression or anxiety in ALSPAC[b]								
	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Parental distress (>85th %)									
Maternal depression	1.69	(1.32-2.18)	<.001	1.46	(1.12-1.90)	.005	1.10	(0.83-1.45)	.5
Paternal depression	1.56	(1.23-1.99)	<.001	1.39	(1.08-1.78)	.01	1.29	(0.98-1.68)	.07
Maternal anxiety	1.59	(1.21-2.07)	.001	1.41	(1.07-1.86)	.01	1.04	(0.78-1.40)	.8
Paternal anxiety	1.15	(0.87-1.53)	.3	1.06	(0.79-1.41)	.7	0.91	(0.67-1.24)	.6

Note. OR=odds ratio. CI = confidence interval.

In one or more analyses *n*=2280 in the Generation R Study and *n*=3442 in the ALSPAC.

[a] Generation R parental distress was defined as a score higher than the 85th percentile in the whole cohort; attention problems (including the borderline range) were defined using a cut-off at the 93rd percentile based on a Dutch norm group.

Models are unadjusted models; adjusted for gender, age and ethnicity of the child, maternal education, age, alcohol use and smoking during pregnancy, family income, and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for symptoms when the child is 3 years old.

[b] ALSPAC attention problems were based on the SDQ hyperactivity/inattention subscale classification of 'abnormal' or 'borderline' groups.

Models are unadjusted models; adjusted for gender, and age of the child, ethnicity and age of mother and partner, maternal education, smoking and alcohol use during pregnancy, family income when the child is 4 years old, and adjusted for depression or anxiety of the partner during pregnancy (i.e. mutual adjustment); last models are additionally adjusted for anxiety or depression at 33 months.

Chapter 5

General discussion

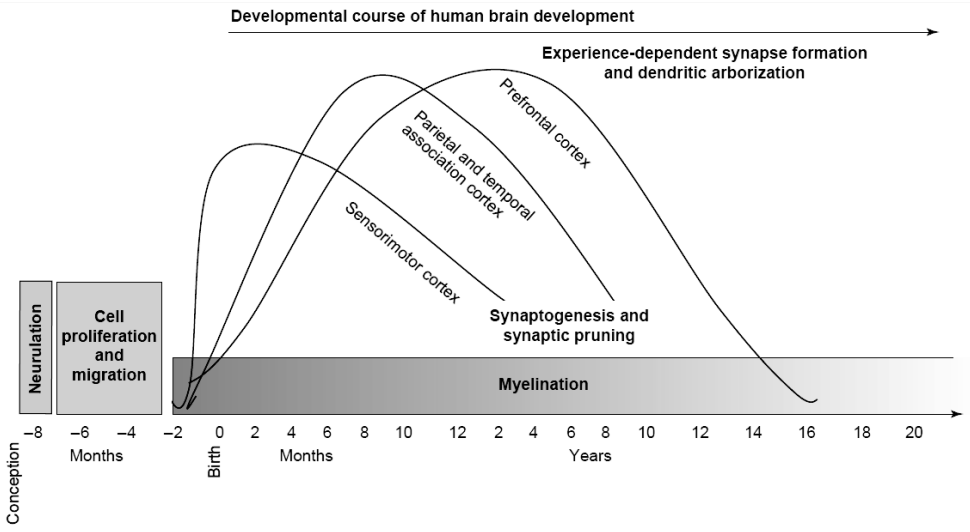
The studies in this thesis had two main aims: to examine whether prenatal adverse factors are associated with less optimal neuromotor development, and to study the effect of early neuromotor development on later behavioural problems and cognitive functioning, i.e. to examine causes and consequences of less optimal neuromotor development in early infancy.

All studies in this thesis were embedded in the Generation R Study, a multi-ethnic population-based cohort study among 9778 pregnant women and their children in Rotterdam, the Netherlands. In the current chapter, I will first sketch some background of neurodevelopment. Next, I will discuss the main findings of the studies in this thesis in a broader context, address methodological considerations, and I will conclude with implications for clinical practice and suggestions for future research.

Background of early neurodevelopment

The formation of the central nervous system (CNS) is a complex process which starts as soon as the second week of uterine life.[1-2]

Figure 1. Human Brain Development[3-4]



The prenatal development of the CNS proceeds through a series of mechanisms: neural induction, neurulation, proliferation, migration, axonal outgrowth, synaptogenesis, differentiation, and apoptosis. These

mechanisms enable the CNS to evolve from one cell into an intricate system that can process information and execute actions.[5] Unlike, for example skin, liver, kidneys and intestines, which functions remain similar after birth, the CNS's development continues well into adolescence and adulthood,[1] as is shown in Figure 1.[3-4]

The integrity of the central nervous system can be evaluated in several ways. One way is with neuroimaging techniques, such as magnetic resonance imaging (MRI). MRI is particularly useful in brain research because magnetic resonance properties differ in major brain parts such as neurons, myelin and cerebrospinal fluids, which enables detailed anatomical maps of brain structures.[6] However, in the studies reported in this thesis, MRI was not feasible, because this technique is very burdensome for small infants and too expensive to conduct in very large numbers of young participants.

Another way to evaluate the intactness of the central nervous system is to observe and assess the quality of a certain type of spontaneous movements, termed General Movements (GMs). Normal GMs typically involve the whole body and are characterized by complexity and variability in duration of the movements, in intensity, force and speed of movements, as well as in sequences of extension and flexion movements of limbs.[7] In impaired brain function, this complexity and variability in GMs is reduced or even lost.[8] Direct observation of the infant's movements is possible, but video recordings are highly recommended because these considerably improve the quality of assessments.[7] Prediction of an individual's neurological development is preferably based on two or three recordings during the preterm period, one recording at term or early post-term age or both, and at least one recording between 9 and 15 weeks post-term.[8] Assessments of GMs are very reliable and have high predictive value, if the prescribed procedure is strictly followed.[7-8] As assessment of GMs necessitates at least four measurements, which should preferably be video recorded, data collection and data processing are very time-consuming and thus expensive.

Neuromotor assessment is another accepted means of measuring the maturity and intactness of an infant's central nervous system.[9] Any impairment of the central nervous system in the first year of life is

expressed mainly in deviances in neuromotor development.[9-10] There are many instruments to assess neuromotor development, and each instrument has its specific characteristics. For example, in the Brazelton Neonatal Behavioral Assessment the emphasis is on behaviour and coping with the environment. The instrument determines capacities for taking in, utilizing and responding to stimuli, which enable socially interactive behaviours and create opportunities to learn from the environment.[11-12] In contrast, the traditional French school mainly assessed tone and primitive reflexes.[13-14] There are also instruments in which these components are combined, like in the Prechtl Neurological Examination of the full-term newborn infant,[10] the Dubowitz Neurological Examination of the full-term Newborn[15] and in Touwen's Neurological Examination of the young infant.[9] These instruments consist of several (shared) subscales measuring tone, primitive reflexes, abnormal movements, and behaviour.

The intactness of the central nervous system can be evaluated at several ages. Some instruments are well suited for assessments in newborns. However, many mothers participating in our study gave birth to their first child, a visit from a Generation R research nurse within a week after giving birth would have been quit a burden. Another age at which neuromotor development can be assessed well is around the age of 3 months. At this age, major transitions in neuromotor development take place,[16-17] like an increase in head balance,[9] a shift from a body-oriented to space-oriented postural control,[18] and the infant starts vocalizing making him/her an interactive social partner.[19] At the age of 3 months some infant responses, which were formerly termed 'primitive reflexes' should be inhibited (walking response and the asymmetric tonic neck response), whereas other responses such as the Moro and dorsiflexion of the toe just start to be inhibited. Given these major developmental transitions, this age is especially suitable to measure subtle variations in normal neuromotor development.

Within the Generation R Study around the age of 3 months other measurements had to be carried out (participants needed to be informed about the 0-4 year postnatal period and informed consent needed to be obtained for this period; a home observation was planned etc.). Therefore,

a neuromotor assessment at the age of 3 months performed during a home visit also fitted well in the overall design of Generation R.

For these theoretical and practical reasons, the assessment of neuromotor development was planned around the age of 3 months to measure the integrity of the brain in a large number of participants. Touwen's Neurological examination of the young infant is a very appropriate instrument to use at this age and in the general population.[9]

Main findings

Prenatal determinants of infant neuromotor development

Numerous studies have shown that exposure to an adverse foetal environment is related to deviances in (infant) neuromotor development. In this thesis, we focus on gestational duration, foetal growth, and antenatal maternal symptoms of anxiety and depression as determinants of infant neuromotor development.

Being born preterm or with low birth weight increases the risk of subsequent neuromotor delays.[20-21] Neuromotor delays in preterm or low birth weight infants may be partly caused by damage to the immature brain or even by medical interventions performed after birth,[22] but deviances in brain development may also originate from before birth. The effects of normal variations in gestational age and birth weight on infant neuromotor development are less clear, although several studies have investigated associations of gestational age and birth weight with long-term outcomes in the general population.[23-25] Besides, only few population-based studies have assessed foetal size during pregnancy.[26] Commonly, birth weight is used as an indicator of foetal development, which is a rather unspecific and crude summary measure, since it provides no information on patterns of growth at different stages in gestation. While experiencing foetal growth restriction, a foetus may still reach a normal birth weight because of his high genetic growth potential.[27] We investigated in the general population whether gestational age, foetal size and body symmetry were associated with infant neuromotor development. Maternal exposures occurring early in foetal life can, at least partly, explain differences in infant neuromotor development. Some investigators hypothesized that one of these processes

may be initiated by exposure to antenatal maternal anxiety or depression.[28-30]

Prenatal exposure to maternal anxiety or depression may have an adverse effect on development of the offspring. Part of this evidence comes from animal studies. Adult rats prenatally exposed to fear inducing stressors displayed more fearful and escape behaviour in novel environments, which is interpreted as increased levels of anxiety[31-32] and emotionality.[33] In non-human primates, experimentally induced prenatal stress was associated with impaired neuromotor maturity or performance in the offspring.[34-36] Studies in humans also provided evidence for adverse effects of antenatal maternal symptoms of anxiety and depression on offspring's development, such as neonatal outcomes[37-39] or mental health problems.[40-41] Some detailed studies in small samples found a relation between antenatal maternal anxiety and depression and early neuromotor development.[42-43] We studied in the general population the effects of antenatal maternal symptoms of anxiety and depression on infant neuromotor development.

We found that shorter gestational duration-even within the normal range-was associated with an increased risk of less optimal neuromotor development (chapter 2.1). The relation was due to younger postconceptional age, i.e. maturation, rather than to shorter time spent in utero. The risk of less optimal neuromotor development increased in infants born with before 35 weeks of gestation. A higher foetal weight was beneficial to infant neuromotor development. Foetal weight was associated with infant neuromotor development in mid-pregnancy as well as in late pregnancy (chapter 2.2). Higher scores on antenatal maternal anxiety were associated with poorer neuromotor development, though this association was attenuated when confounding factors were taken into account. In contrast, the association of high levels (i.e. a score above the threshold) of specifically antenatal and not postnatal maternal anxiety with infant neuromotor development was independent of confounding factors (chapter 2.3). This may indicate a specific effect of maternal anxiety during pregnancy.

The following mechanisms may explain why gestational age, foetal size and antenatal maternal symptoms of anxiety are associated with infant neuromotor development.

Preterm delivery itself or medical interventions and complications after birth may cause damage to the (immature) brain.[44] Although numerous studies focused on high-risk preterms or low birth weight infants, some recent reviews suggest that late preterm infants are also susceptible to adverse neurodevelopmental outcomes.[22,45-46] Substantial brain growth, development and networking occurs in the last 6 weeks of gestation, which makes these processes vulnerable to injuries. Being born during this critical period may result in injuries to developing tissues or disruption of critical pathways.[45-46] In addition to gestational age, adverse concomitant sequelae, such as complications during delivery, pre-eclampsia, pregnancy induced hypertension or diabetes, may have a direct adverse impact on infant neuromotor development.[47]

Impaired infant neuromotor development may also originate from before birth. Gestational age and foetal size are merely proxies of general well-being of the foetus. A shorter gestational duration or a low birth weight usually indicates that a new born has been exposed to an adverse foetal environment which, in addition to preterm delivery itself, may have an adverse impact on foetal and early postnatal brain development.

The so-called 'foetal programming hypothesis' may partly explain how an adverse foetal environment contributes to the association of gestational age and birth weight with infant neuromotor development. According to the 'foetal programming hypothesis', malnutrition plays a crucial role in foetal growth.[48] During foetal growth cell division occurs at a high pace and depends on nutrition and oxygen. A lack of nutrition or oxygen, for example, due to placental insufficiency, may initiate a complex adaptation process in which the foetus reduces its rate of cell division. This increases the risk of reduced foetal growth and deviant foetal neurodevelopment but also of deviant postnatal neuropsychological development.[49-50]

Several other factors may have direct intrauterine adverse effects on foetal brain development.[47,51] First, teratogens may cause brain abnormalities during prenatal development. Teratogens encompass drugs, diseases or environmental hazards. For example, a well-established risk

factor of preterm birth or low birth weight is maternal smoking during pregnancy. Cigarettes contain many toxic components that not only may have a direct impact on foetal brain development,[52] but also may induce vasoconstriction and reduce oxygen availability, which in turn may shorten gestational age and reduce birth weight.[53] Viral infections, such as the TORCH viruses (i.e. toxoplasmosis, rubella, cytomegalovirus, and herpes simplex virus) are known causes of cerebral palsy.[54] However, at most 5-10% of children with cerebral palsy can be attributed to these viruses because of high maternal immunity due to preconceptional exposure or vaccination.[54-55] Also, prenatal exposure to bacterial infections or rubella result in an increased risk of schizophrenia or autism spectrum disorder.[56-58] In addition, studies have suggested that infections during pregnancy and the inflammatory responses of the mother and foetus increase the risk of preterm delivery, white matter damage and cerebral palsy.[54]

Second, epiphenomena of maternal lifestyle or social disadvantage before or during pregnancy may have a direct intrauterine impact. In our studies, the associations between gestational age and foetal size and infant neuromotor development attenuated but remained after adjusting for many lifestyle factors and indicators of social disadvantage, such as maternal educational level, maternal age, or ethnicity. Still, we can never determine whether these factors were sufficiently measured. Moreover, there are other lifestyle and social disadvantage factors, such as neighbourhood, housing conditions, and nutritional status, which were not measured. Hence, we cannot rule out that residual confounding may partly explain our findings.

Fourth, common genetic factors may underlie the respective associations between gestational age, foetal size and antenatal maternal anxiety symptoms and infant neuromotor developmental outcome.[59-60]

Finally, some studies suggest that antenatal maternal stress may disrupt the regulation of the maternal stress system, in particular increases the hypothalamus-pituitary-adrenal (HPA) axis activity. This elevated HPA-axis activity may increase the level of circulating hormones. Higher levels of these hormones may inhibit foetal growth or alter the formation of the foetal HPA-axis, which in turn may have long-term effects on the offspring's neurodevelopment.[28-30] In line with this hypothesis, another study within

Generation R found that psychological symptoms during pregnancy led to reduced growth of, in particular, foetal head and abdominal circumference.[61] We found that specifically maternal anxiety symptoms during pregnancy were related to an increased risk of infant neuromotor development, which may suggest a direct intrauterine effect (chapter 2.3).

Behavioural and cognitive outcomes of infant neuromotor development

Chapter 3 describes the effects of infant neuromotor development on later behavioural or emotional problems and on later verbal and nonverbal cognitive functioning.

The comorbidity of neuromotor difficulties and psychiatric or neurodevelopmental disorders, such as attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), schizophrenia, and learning, reading or language related disorders has been described repeatedly. Motor problems are reported in a third to about half of children with ADHD.[62-65] Various motor problems are reported in children with ASD;[66] in 19% of these children toe-walking was reported and 89% of them had a delay in overall motor skills.[67] Persons who develop schizophrenia or schizophreniform disorder, compared to those who do not, are characterized with anteceding poorer motor functioning[68-70] or a compromised motor milestone achievement in early childhood.[71] Hill, in her review on specific language impairment (SLI), reported that 40-90% of children with SLI scored at or below the 15th percentile on the Movement ABC and thus have very significant movement difficulties. Furthermore, Hill reported high rates of gross and fine motor deficits and impaired praxis ability in children with SLI.[72]

Evident comorbidity does not necessarily indicate that motor deficits antecede these disorders, although some research on autism and schizophrenia does suggest this. In addition, little is known about the exact or earliest age at which these motor deficits emerge. Age of achieving motor milestones in the first year of life are the earliest measures found to be associated with subsequent ASD or schizophrenia, which suggests that early motor impairment, reflecting diffuse neural dysfunctioning, may represent a vulnerability marker of psychiatric or neurodevelopmental disorders. Moreover, whether infant neuromotor development in the

general population predicts more common behavioural or emotional problems and verbal and nonverbal cognitive functioning is not known.

In chapter 3.1, we report that poorer overall neuromotor development was associated with an increased risk of Internalizing problems, whereas infant neuromotor development was not associated with Externalizing problems. The exception was that infants with high tone had a higher risk of Aggressive Behavior (chapter 3.1). Infant neuromotor development at the age of 3 months was associated with an increased risk of receptive language delay at 1.5 years, with expressive language delay across the ages 1.5 years and 2.5 years, and with nonverbal cognitive delay at 2.5 years (chapter 3.2).

These results suggest that even minor deviances in infant neuromotor development may be a marker of subsequent emotional problems and cognitive delays.

Variations in neurological maturation or minor neurological abnormalities probably underlie the associations between infant neuromotor development and problem behavior and cognitive delays. These abnormalities in early brain development may originate from adversities during the prenatal, perinatal or postnatal period. Most of these mechanisms, such as foetal programming, exposure to teratogens, social disadvantage, and antenatal maternal stress were already discussed in the context of determinants of infant neuromotor development (see previous paragraph).

A substantial part of neuromotor development, behavioural problems, and cognitive functioning is determined by genetic factors.[73-74] It is possible that common genetic factors underlie the associations between infant neuromotor development and behavioural problems and cognitive functioning at preschool age.

Finally, postnatal environmental factors, such as maternal psychopathology, may underlie the associations between infant neuromotor development and behavioural problems and cognitive delays later. For example, depressed mothers and fathers typically show less emotional warmth, and less interaction, verbally and physically, with their infants.[75-77] This may not only result in less exploratory and more passive behaviour in their offspring, which in turn can negatively impact on the maturation of

the brain in early infancy,[78] but these maladaptive parent-child interactions also negatively influence other aspects of child development.[79-80]

Prenatal determinants of behaviour

We found that specifically antenatal and not postnatal maternal anxiety was related to a higher risk of less optimal infant neuromotor development, suggesting a direct intrauterine effect (chapter 2.3). Consequently, we extended our search of evidence for intrauterine effects of antenatal maternal depression and anxiety on child outcomes by investigating the association between antenatal maternal depression and anxiety and child attention problems. Additionally, we were interested whether neuro-development as measured by neuromotor assessment could mediate an association of antenatal exposure to maternal depression or anxiety with child behaviour.

To this aim, another approach was undertaken, which encompasses a comparison between the effect of maternal and paternal exposures in the same prenatal period on child outcomes.[81] Several prospective studies have shown that antenatal maternal depression and anxiety are associated with emotional and behavioural problems in the offspring.[29] However, the associations may be due to residual confounding to which prospective studies in particular are vulnerable. Unmeasured or inaccurately measured characteristics, such as lifestyle, maternal physical health or socioeconomic factors, that are related to both maternal depression or anxiety and offspring behaviours can generate spurious associations.[82] Furthermore, mothers who have more depressive and anxiety symptoms during pregnancy are also likely to have more symptoms after childbirth. Postnatal symptoms can affect parenting skills and mother-child attachment. Such consequences of depression or anxiety could underlie an observed association of antenatal depression or anxiety with offspring behaviours rather than any intrauterine mechanism.

By comparing the effect of maternal and paternal exposures on child outcome, we aimed to reduce the possibility of a biased association, i.e. an association due to residual confounding. Where maternal exposures result in direct intrauterine effects, we would expect the maternal associations to be stronger than the paternal associations with child outcomes. Conversely,

associations with child outcomes that are similar for maternal and paternal exposures suggest that shared familial, socioeconomic, environmental or genetic factors, rather than a direct intrauterine mechanism, are likely to be driving the associations.[81] In addition, to strengthen conclusions, we explored the extent to which parental depression or anxiety when the child is 3 years old explained any association, and we used data from two different cohorts, which enabled us to study cross-cohort consistency.

We found no strong evidence for a direct intrauterine effect of maternal symptoms of depression or anxiety on child attention problems. The observed effects were explained by residual confounding as indexed by the relation observed with paternal symptoms, or by the respective postnatal symptoms which could be an indicator of genetic confounding (chapter 4.1). Given the absence of a consistent main effect of antenatal maternal depressive and anxiety symptoms on child behaviour, mediation was not studied further.

These findings are in contrast to those of the study on antenatal maternal anxiety and infant neuromotor development. Several factors may have contributed to these contradictory findings. First, neuromotor development was assessed around the age of 3 months, whereas attention problems were assessed when the child was 4 years old. It is possible that any true intrauterine effect of maternal anxiety or depression levelled out. Second, somewhat different samples were used in these two studies. To enable the comparison between the maternal and paternal effects, mothers without (participating) partners were excluded in the study on attention problems. Therefore, in this study mothers had lower levels of depression and anxiety symptoms compared to mothers without (participating) partners. However, the associations between antenatal maternal depressive and anxiety symptoms and child attention problems in mothers without (participating) partners were very similar to those in the included sample. Therefore, it is unlikely that this fully explains the difference in findings. Third, in the study in which child attention problems were the outcome, results were contrasted to another outcome, i.e. emotional problems, in order to examine specificity of association. In both cohorts, the association between antenatal maternal anxiety symptoms and child emotional problems remained after confounders and symptoms when

the child was 3 years old were taken into account. This may suggest that attenuation due to residual confounding may be particular for the intrauterine effect on child attention problems, and thus may also not apply to neuromotor development. Future research should investigate how the effect of antenatal paternal anxiety symptoms on infant neuromotor development compares to the effect of maternal anxiety symptoms on infant neuromotor development to reduce the possibility that the maternal association is biased.

Methodological considerations

The strengths and limitations of the different studies in this thesis have been depicted in the respective chapters. Here, I will address more general methodological considerations regarding the design of the present observational studies, and methodological aspects that are related to the instrument used to measure neuromotor development.

Study design

The studies described in this thesis are part of the Generation R Study, which is a population-based prospective cohort study from foetal life onwards. In cohort studies individuals are classified as exposed and unexposed, are followed for a specified period of time, and incidence of the outcome in both groups are compared.[83] The prospective design of the study facilitates establishment of temporal relationships between exposures and outcomes, and identification of potential factors influencing normal and abnormal growth, health, and development. In addition, prospective designs are in contrast to a retrospective design less vulnerable to recall bias.[83] The eligible sample in a population-based cohort study usually is a sample from the general population within a geographic area.

Within Generation R, all mothers with a delivery date between April 2002 and January 2006 who lived in Rotterdam at the time of their delivery were asked to participate. This type of sampling is in fair contrast to studies focusing on high-risk or exposure specific populations, e.g. preterm or low birth weight infants. Following of participants from the general population allows for testing a wide variety of hypotheses, but a considerable proportion of the population needs to be exposed in order to obtain

sufficient power to assess relations with outcomes. We studied the effects of maternal anxiety and depressive symptoms on infant neuromotor development and on attention problems in toddlers. Also, we studied the consequences of less optimal infant neuromotor development in terms of behavioural and cognitive functioning. These latter associations and associations of gestational age and foetal growth with infant neuromotor development most often have been studied in high-risk populations.[84-86] The benefit of studying these high-risk populations is that study participants are selected based on homogeneity of a certain characteristic which reduces the risk of confounding by this characteristic. However, results of these studies in high-risk populations cannot easily be generalized to other populations, because the associations may originate from population specific mechanisms. In contrast, the studies in this thesis aimed to provide support for hypotheses applicable to the general population.

We studied determinants and outcomes of infant neuromotor development in a non-clinical population. However, generalizability of these associations depends on biological, sociodemographic and statistical representativeness of the respective study samples.

In addition, correct scientific inferences can only be made if a study is valid. Types of biases that affect validity are selection bias, information bias and confounding.[87] Each of these biases may have influenced our results.

Selection bias

Selection bias occurs when the relation between the determinant and the outcome is different in those who participate and those who were eligible but do not participate. Of all eligible children at birth, 61% participated in the Generation R Study.[88] Non-response due to non-participation was not random. A smaller proportion of mothers from ethnic minorities and with a lower socioeconomic status and of mothers and children with medical complications participated than was expected from the population figures in Rotterdam.[89] Although it seems likely that selective non-response led to a more affluent and healthy participating population and caused bias, this is not necessarily the case. In the Generation R Study, baseline response rates increased from approximately 51% in 2002 to 68% in 2005. The percentage of women that reported to have smoked during pregnancy decreased from

43% in 2002 to 38% in 2005. In pregnant women of Dutch nationality, mean psychological distress scores based on the Brief Symptom Inventory decreased from 0.21 in 2002 to 0.18 in 2005.[90] Different groups of pregnant women may have had different reasons for (non-) participation, such as health-consciousness or health-related worries.

Selection may also be introduced by selective loss to follow-up. The attrition analyses of the studies in this thesis showed that younger mothers with a lower educational level and with children born after a shorter gestation and with a lower birth weight were more likely to be lost to follow-up. This selective loss to follow-up only poses a threat to validity if the associations between determinants and outcomes differ among those who participate and those who were lost to follow-up. Children with missing data on motor outcome were on average born after a shorter gestation and lower birth weight compared to their participating counterparts. Gestational age and foetal size were risk factors for less optimal motor development. The study on the intrauterine influence of maternal depressive and anxiety symptoms on child attention also showed that maternal depressive and anxiety symptoms and attention problems in their children were more prevalent in the excluded sample of mothers without (participating) partners. Although it is often hypothesized that associations in those lost follow-up are stronger than in those who participate, in this study the associations in the excluded sample were very similar to those in the included sample. In addition, a large study on selective drop-out in longitudinal studies also confirmed that selective drop-out resulted in a lower prevalence, whereas the magnitude of the associations were only marginally reduced.[91] This study was part of a study on disruptive behaviour disorders. In the geographically defined study area of the Avon Longitudinal Study of Parents And Children (ALSPAC), teachers were asked to report on disruptive behaviour when children were approximately 8 years old. The findings of this study support the general idea that psychosocial factors are associated with attrition in longitudinal studies, i.e. that longitudinal studies are likely to underestimate the prevalence and incidence of disorders. Yet, the selective drop-out of participants did not invalidate the prediction of teacher-reported disruptive behaviour disorders by determinants that have previously been shown to

predict these problems. Unfortunately, the findings of this study were based on teacher reports and may not be applicable to studies based on parent reports. Also, a Dutch study yielded similar findings, i.e. non-response caused bias in prevalence estimates, but the examined associations were not affected by non-response.[92] In any case, if associations in those lost to follow-up are stronger in those who participate, this would result in underestimations of the true effects in the general population rather than in an overestimation. Therefore, it remains difficult to speculate about associations between exposure and outcomes in non-participants and about the effect of selective loss to follow-up.

Information bias

Information on the determinants and outcomes in the studies described in this thesis were obtained by assessments performed by trained research nurses, ultrasound examinations, midwives and hospital registries, and parental questionnaires. Random misclassification results in bias towards the null, whereas non-random or differential misclassification, i.e. when misclassification in the determinant is related to the outcome or vice versa, results in less predictable bias.[87]

Neuromotor development which was either a determinant or an outcome in most of our studies was assessed by trained research nurses who were blinded to the exposure status (chapter 2.1, 2.2, and 2.3). Because data were collected prospectively, research nurses who assessed neuromotor development were obviously also blinded to the outcome status (chapter 3.1 and 3.2). This makes differential misclassification in the neuromotor assessments improbable. However, it is possible that epiphenomena of the determinants or outcomes of neuromotor development, such as adversities in the environment, poor households or housing conditions, nutritional status, may have distorted the neuromotor assessment and introduced some misclassification in these measurements. Although research nurses were trained to perform the neuromotor assessments, it cannot be ruled out that this had some effect on our findings.

In chapter 4.1, both information on the exposures (maternal depressive and anxiety symptoms) and information on child behaviour were obtained

using maternal reports, hence reporter bias may have influenced the results of this study. It is possible that depressed or anxious mothers reported more attention problems in their children than mothers without these symptoms.[93] This could have strengthened the association between maternal symptoms and the outcome. In chapter 4.1, maternal effects were contrasted to paternal effects. If the association between maternal symptoms and child attention problems was overestimated one would expect this association to be stronger than the association between paternal symptoms and child attention problems which is not influenced by this type of reporter bias. Yet, we found no evidence for a difference between the maternal and paternal effects. Therefore, this mechanism cannot easily explain why the effects of the mothers were not stronger than those of the father. In addition, some researchers doubt whether depressive or anxious mothers really have distorted perceptions of their children's problems.[94] Ideally, different observers should assess child behaviour. Because children's behaviour may vary across situations and because adult's judgement of a child's behaviour may vary, each informant, e.g. parents, teachers, clinicians, contribute to the validity of the information.[95-96] Therefore, assessment of child behaviour necessitates a multiple informant approach. To draw definite conclusions on the effects of intrauterine environmental factors, future studies will need to integrate child behavioural observations of a diversity of informants.

Confounding

Important strengths of the Generation R Study are its multidisciplinary setting and prospective design. This enabled planned data collection on a wide variety of variables related to growth, development and health of the child and its parents. Therefore, many potential confounders were available for the analyses. Confounding may be considered a confusion of effects, i.e. when there seems to be an effect of the exposure of interest but the effect of extraneous factors are mistaken for or mixed with the actual effect of exposure.[87] An extraneous factor is considered a confounder when it is related to the exposure without being caused by the exposure, and when it is a cause of the outcome independent of the exposure. In addition, a confounder should not be in the causal pathway between the exposure en

the outcome.[87,97-98] In all studies described in this thesis many confounders were included for theoretical or statistical reasons. Indicators of socioeconomic status were the most important confounders, which is best shown in the studies examining the intrauterine effect of antenatal maternal depressive and anxiety symptoms on the offspring. In chapter 2.3, the associations between higher levels of antenatal maternal anxiety and depressive symptoms and infant neuromotor development attenuated when maternal educational level and ethnicity of the child were adjusted for. Likewise, in chapter 4.1, the magnitude of the associations between antenatal maternal depressive and anxiety symptoms and later child attention problems were substantively reduced when socioeconomic factors were taken into account.

As was mentioned earlier, the design of the Generation R Study enabled us to consider and control for many confounders. However, epidemiological studies are always vulnerable for residual confounding, i.e. unmeasured or inaccurately measured characteristics, such as lifestyle, maternal physical health or socioeconomic or genetic factors, that are related to both exposure and outcome can generate spurious associations.[82] The studies on the intrauterine influences of maternal depressive and anxiety symptoms on infant neuromotor development and child attention problems showed that the associations were attenuated or markedly reduced in magnitude by adjusting for socioeconomic factors. In chapter 4.1, we found no statistical evidence that the associations between maternal antenatal exposures and child outcomes differed from those of the paternal exposures. This suggests that shared familial, socioeconomic, and environmental factors or genetic factors, rather than a direct intrauterine mechanism, are likely to be driving the associations.[81] Therefore, it is possible that the influence of antenatal maternal anxiety on infant neuromotor development could also be prone to residual confounding. Future studies on the intrauterine influences of maternal psychological factors should compare these with the respective paternal factors in order to reduce the possibility of a biased association.

Causality

Although causality seems a very logical concept, the definition and concept of causality is subject of a perpetual debate among scientists and philosophers. Accordingly, determining whether an association is causal is difficult.[99] One definition reads: 'a cause of a disease is an event, condition, or characteristic that precedes the disease event without which the disease event would not have occurred or would not have occurred until some later time'.[99] In all studies described in this thesis, the exposure preceded the outcome, but this does not prove that the associations found in these studies are causal. Temporality is one 'criterion' that has been suggested to aid causal inference. Arguably, it is the only criterion that is an essential element for a causal explanation of an observed association.[99] Temporality is also one of the nine 'criteria' which Hill rather called 'viewpoints' or 'perspectives'. The others were strength, consistency, specificity, biological gradient, plausibility, coherence, experimental evidence and analogy.[100] Although Hill proposed these viewpoints, he also indicated that no 'hard-and-fast rules of evidence' exist by which to judge whether an association is causal.[100] Because so many reservations and exceptions are attached to these 'criteria',[99-100] they will not be discussed further.

Several other models have been suggested to define causality. For example, sufficient and component causes, and causal inference based on a probabilistic approach.[101] A sufficient cause refers to a complete causal mechanism in which a set of conditions need to be present in order to produce the outcome.[101] Within epidemiological research the most practical definition most likely is the probabilistic one in which a cause increases the probability of an effect to occur.[102] Notwithstanding which definition of causality is used, it is crucial that researchers understand the consequences of applying a particular definition. In addition, one should always bear in mind that the limits that researchers set to their causal models carry practical consequences.[102]

Since explanatory knowledge about epidemiologic hypotheses is often limited, these hypotheses themselves are sometimes merely vague statements of association between exposure and outcomes.[99] To deal with this vagueness, researchers usually focus on the negation of the null hypothesis that the exposure is not associated with the outcome. Any

observed association, rebuts the null hypothesis. It is important to formulate assumptions about underlying mechanisms. It may be tempting to speculate that variations in infant neuromotor development are causally related to behavioural or emotional problems or cognitive delay. However, it is very likely that early neuromotor development is an indicator of brain maturation, rather than a risk factor for psychiatric or neurodevelopmental problems in itself.

Clinical implications

The main outcomes of the studies in this thesis were infant and toddler behavioural and cognitive functioning. Mental health problems in youth are highly prevalent. The World Health Organisation estimates that up to 20% of children and adolescents suffer from a disabling mental illness.[103] Four to 6% of these children and adolescents are in need of clinical interventions.[104] The prevalence of cognitive problems ranges from 4% for general mental delay to 17.5% for language delay.[105-106] In addition, children with behavioural or cognitive problems also tend to have mental health problems later in life, and are predisposed to school exclusion, offending, anti-social behaviour, marital breakdown, drug misuse and alcoholism.[107-109] Furthermore, behavioural and cognitive problems are a large burden for children, their parents, teachers and society. Early identification can prevent or reduce mental health problems later in life and consequently leads to major health gain.[110]

In the first year of life, it is rather difficult to assess whether an infant has behavioural or cognitive problems. Yet, the studies described in this thesis do suggest that less optimal infant neuromotor development is a precursor of behavioural or cognitive problems later. It is important to notice that, to define ‘a less optimal neuromotor development’, we did not use clinical cut-offs. Therefore, ‘a less optimal neuromotor development’ does not mean that an infant is likely to have brain or neurological damage or a disorder of some kind, but merely indicates that the infant developed somewhat slower than most children in our sample did. A screening instrument for developmental disorders (‘Van Wiechen Onderzoek’) is regularly administered to all children aged 0 to 4 years as part of the preventive child healthcare programme in the Netherlands. A study on the

predictive value of the Van Wiechen Onderzoek yielded that the instrument predicted mental retardation, yet, only from the age of 2 years.[111] This makes the Van Wiechen Onderzoek not suitable as a screening instrument in infants. Further research is necessary to determine the youngest age at which neuromotor development can be assessed to predict behavioural and emotional problems or cognitive delays. Early identification of precursors of behavioural and cognitive problems is important, because this may facilitate timely interventions.[112] In addition, timely and early interventions may result in major health gain and reduce the burden for children, their parents and society. Many studies have evaluated the effects of early intervention programs that aim to improve neuromotor and cognitive outcomes in high-risk populations. Results indicate possible short-term improvement in cognitive outcomes, but uncertainty remains about long-term effects.[113]

When screening for developmental disorders occurs one should take account of the gestational duration, which is normal practice in preterm born infants only. Our study on the association between gestational duration and infant neuromotor development showed that mothers who gave birth to their child before the expected date of delivery but within the normal range of gestational duration, were more likely to have an infant with less optimal neuromotor development at the age of 3 months, but these differences in infant neuromotor development were explained by differences in maturation, i.e. postconceptional age. Therefore, simply taking account of postnatal age might lead to the unjust conclusion that an infant suffers from minor developmental delays, whereas in fact he or she was merely assessed earlier in the maturational process.

We found that smaller foetal size increased the risk of less optimal infant neuromotor development. Screening for intrauterine growth restriction is already part of the routine counselling programme for pregnant women. So, midwives and gynaecologists are already well aware of the possible negative consequences of intrauterine growth restriction, though they may be less aware of the long-term consequences of milder deviances of foetal growth on child neurodevelopment. In addition, the attitudes and knowledge of parents to be with regard to risk factors for reduced foetal growth and its longer term child outcomes can be improved by increasing

public awareness and offering pre-pregnancy visits for couples and persons planning pregnancy as part of standard maternity care.

Results of the studies described in this thesis on the intrauterine effects of antenatal maternal depressive and anxiety symptoms on child outcomes were inconsistent. Women who suffer from mental health problems before or during pregnancy need to receive care for these problems for their own well-being but also because of the possible negative impact on child outcomes. Awareness for maternal mental health problems during pregnancy can easily be integrated as a part of the routine counselling visits to midwives and gynaecologists. Women with elevated scores should be referred to mental health care institutions that can provide counselling or interventions. These interventions should probably continue into the postnatal period since women with antenatal mental health problems are also more likely to have this type of problems after childbirth. Maternal mental health problems in the period after giving birth often have negative effects on the developing child.

Future research

The studies described in this thesis are (graphically) depicted in Figure 2. From the findings of these studies, the following future research is proposed. Some suggestions for future studies are depicted in Figure 3.

First, the association between antenatal maternal anxiety symptoms and child emotional problems was not explained by confounders and maternal symptoms 3 years after childbirth. It is possible that antenatal maternal anxiety has a direct intrauterine effect on child emotional problems. Then, it would be interesting to examine whether this association is mediated by infant neuromotor development (future study 1, Figure 3).

Second, behavioural and cognitive outcomes were assessed at ages 1.5 to 3 years. Whether the negative effects of infant neuromotor development on behavioural, emotional and cognitive problems are transient, persistent or progressive is still unclear. The second study depicted in Figure 3 proposes studying the behavioural and cognitive outcomes of infant neuromotor development at school age.

Third, advanced imaging techniques could be used to determine if specific alterations in brain structures or regions underlie the behavioural

Figure 2. Studies described in this thesis

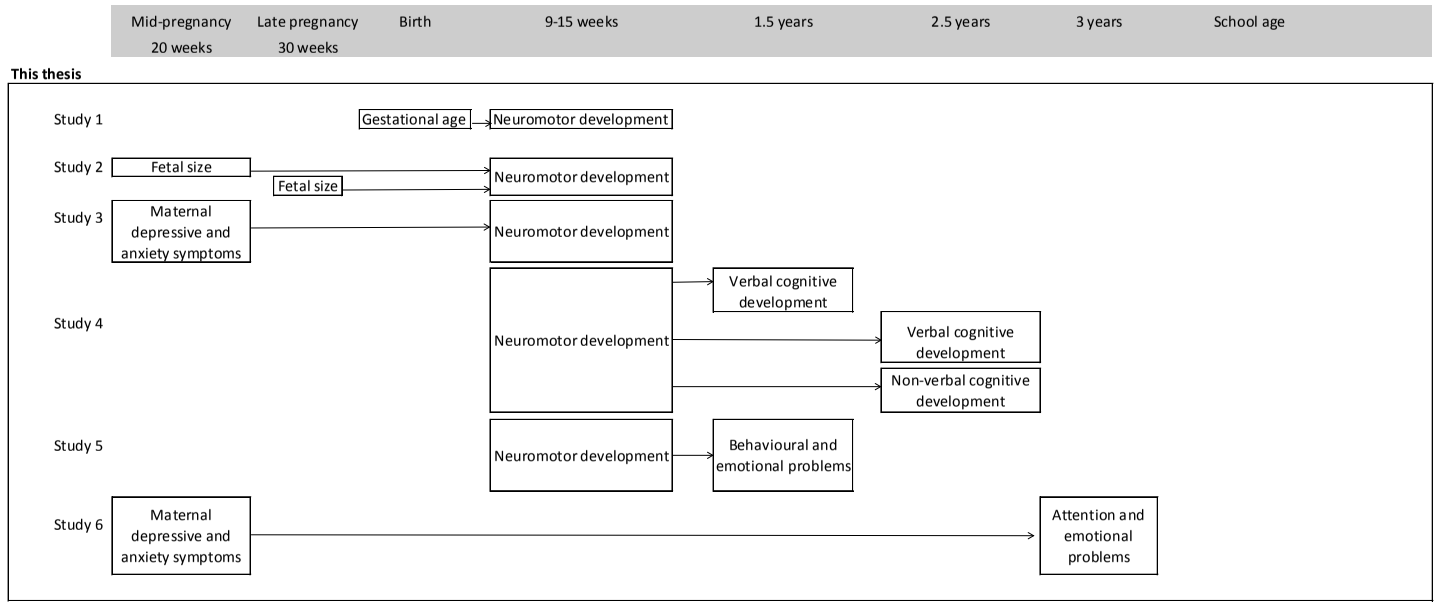
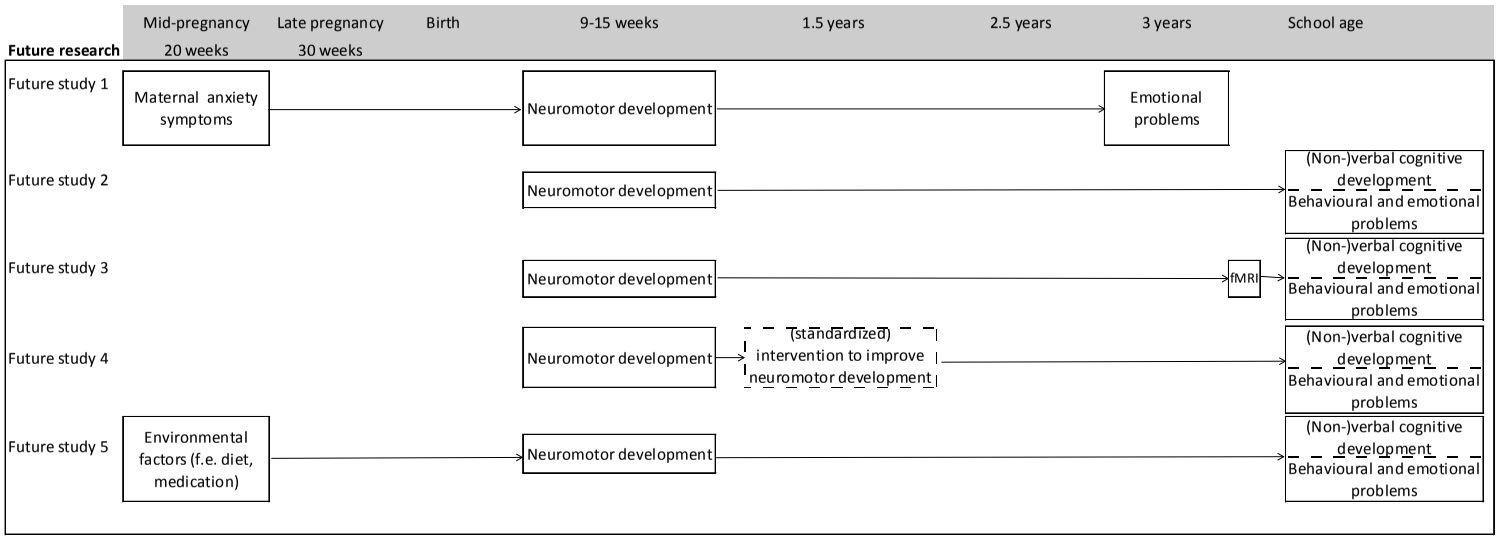


Figure 3. Suggested studies for future research



or emotional problems or cognitive delays due to less optimal infant neuromotor development (future study 3, Figure 3).

Fourth, if future studies find that the adverse behavioural and cognitive consequences of infant neuromotor development persist or even progress, standardized interventions that aim to improve infant neuromotor development should be developed and their effectiveness in terms of decreasing or preventing behavioural or emotional problems or cognitive delays should be studied (future study 4, Figure 3).

Fifth, other antenatal environmental factors, such as maternal diet or medication use during pregnancy, may have a negative impact on foetal and child (neuro)developmental outcomes. Prospective population-based studies are needed to study the associations between maternal nutrition (for example, intake of essential vitamins, minerals and fatty acids) and foetal and postnatal growth and brain development and with subsequent behaviour and cognitive functioning (future study 5, Figure 3).

Sixth, in the studies described in this thesis, parent reports were used to measure behaviour and cognitive functioning. It would be highly valuable if other informants (teachers or the children themselves when they are older) than the parents provided information on child behaviour and cognitive functioning. Also, information on behaviour and cognitive functioning of the children collected via other methods than questionnaires can provide additional and important information. For example, neuropsychological tests can provide (independent from parents) information on executive functioning, intelligence or behaviour.

Finally, most of the suggested future studies can be conducted within the Generation R study (except study 5). In addition, it would strengthen conclusions if we conducted these studies in different cohorts as we did with the study on the association between antenatal maternal symptoms of depression and anxiety and child behaviour (chapter 4.1).

Conclusions

The studies described in this thesis extended our knowledge on causes and consequences of infant neuromotor development. Most associations studied in this thesis have been previously investigated in high-risk populations and have now been studied in the general population as well.

Summarizing, our results demonstrate that variations in gestational duration within the normal range were explained by postconceptional age. In addition, our findings suggest that larger foetal size was beneficial to infant neuromotor development. Although our results are indicative of a direct intrauterine effect of maternal anxiety symptoms on infant neuromotor development, little evidence for such a direct intrauterine effect was found for child attention problems. The observed associations between antenatal maternal depressive and anxiety symptoms and child attention problems were explained by residual confounding as indexed by the relations observed with maternal symptoms, or postnatal effects of chronic or recurring maternal symptoms. Furthermore, our results suggest that subtle deviances from normal infant neuromotor development may be markers of subsequent behavioural or emotional problems and nonverbal or verbal cognitive delays. Further research with a longer follow-up is necessary to determine whether these behavioural or emotional problems and cognitive delays due to less optimal infant neuromotor development will persist or attenuate in time.

References

1 White T and Nelson CA. Neurobiological development during childhood and adolescence. In: Findling RL and Schulz SC, eds. *Schizophrenia in adolescents and children: Assessment, neurobiology, and treatment*. Baltimore, MD: Johns Hopkins University Press.

2 Moscoso G. Early embryonic development of the brain. In: Levene MI and Chervenak FA, eds. *Fetal and Neonatal Neurology and Neurosurgery*. 4th ed. Philadelphia: Churchill Livingstone Elsevier; 2009:13-21.

3 Casey BJ, Tottenham N, Liston C and Durston S. Imaging the developing brain: what have we learned about cognitive development? *Trends Cogn Sci.* 2005; **9** (3): 104-10.

4 Thompson RA and Nelson CA. Developmental science and the media. Early brain development. *Am Psychol.* 2001; **56** (1): 5-15.

5 Monk CS, Webb SJ and Nelson CA. Prenatal neurobiological development: molecular mechanisms and anatomical change. *Dev Neuropsychol.* 2001; **19** (2): 211-36.

6 Giedd JN. Anatomic brain imaging studies of normal and abnormal brain development in children and adolescents. *Developmental psychopathology.* Vol two: Neurodevelopmental neuroscience. 2nd ed. New York: Whiley; 2006:127-96.

7 Einspieler C, Prechtl HF, Ferrari F, Cioni G and Bos AF. The qualitative assessment of general movements in preterm, term and young infants--review of the methodology. *Early Hum Dev.* 1997; **50** (1): 47-60.

8 Einspieler C and Prechtl HF. Prechtl's assessment of general movements: a diagnostic tool for the functional assessment of the young nervous system. *Ment Retard Dev Disabil Res Rev.* 2005; **11** (1): 61-7.

9 Touwen BC. *Neurological development in infancy*. London: Heinemann; 1976.

10 Prechtl HF. *The Neurological Examination of the Full-term Newborn Infant*. 2nd ed. London: Heinemann; 1977.

11 Brazelton TB and Nugent JK. *Neonatal Behavioral Assessment Scale.* Vol 137. 3rd ed. London: MacKeith Press; 1995.

12 Als H, Tronick E, Lester BM and Brazelton TB. The Brazelton Neonatal Behavioral Assessment Scale (BNBAS). *J Abnorm Child Psychol.* 1977; **5** (3): 215-31.

13 André-Thomas A, Chesni Y and Saint-Anne Dargassies S. *The neurological examination of the infant.* Vol 1. London: Heinemann; 1960.

14 Saint-Anne Dargassies S. *Neurological development in the full-term and premature neonate*. Amsterdam: Elsevier; 1977.

15 Dubowitz L, Dubowitz V and Mercuri E. *The neurological assessment of the preterm and full-term newborn infant*. 2nd ed. London (U.K.): McKeith Press; 1999.

16 Hopkins B and Prechtl HF. A qualitative approach to the development of movements during early infancy. In: Prechtl HF, ed. *Continuity of Neurol Function from Prenatal to Postnatal Life* Oxford: Blackwell; 1984:179-97.

17 Zeanah CH, Boris NW and Larrieu JA. Infant development and developmental risk: a review of the past 10 years. *J Am Acad Child Adolesc Psychiatry.* 1997; **36** (2): 165-78.

18 Prechtl HF. Development of postural control in infancy. In: von Euler C, Forssberg H and Lagercrantz H, eds. *Neurobiology of early infant behaviour.* Vol 55. London: Macmillan; 1989:55-68.
19 Van Wulfften-Palthe T and Hopkins B. Development in the infant's social competence during early face-to-face interaction: a longitudinal study. In: Prechtl HF, ed. *Continuity of Neurol Function from Prenatal to Postnatal Life*. Oxford: Blackwell; 1984:198-219.
20 Aylward GP. Neurodevelopmental outcomes of infants born prematurely. *J Dev Behav Pediatr.* 2005; **26** (6): 427-40.
21 Marlow N, Hennessy EM, Bracewell MA and Wolke D. Motor and executive function at 6 years of age after extremely preterm birth. *Pediatrics.* 2007; **120** (4): 793-804.
22 Whitaker AH, Feldman JF, Lorenz JM, Shen S, McNicholas F, Nieto M, McCulloch D, Pinto-Martin JA and Paneth N. Motor and cognitive outcomes in nondisabled low-birth-weight adolescents: early determinants. *Arch Pediatr Adolesc Med.* 2006; **160** (10): 1040-6.
23 Kirkegaard I, Obel C, Hedegaard M and Henriksen TB. Gestational age and birth weight in relation to school performance of 10-year-old children: a follow-up study of children born after 32 completed weeks. *Pediatrics.* 2006; **118** (4): 1600-6.
24 Pearce MS, Deary IJ, Young AH and Parker L. Growth in early life and childhood IQ at age 11 years: the Newcastle Thousand Families Study. *Int J Epidemiol.* 2005; **34** (3): 673-7.
25 Shenkin SD, Starr JM and Deary IJ. Birth weight and cognitive ability in childhood: a systematic review. *Psychol Bull.* 2004; **130** (6): 989-1013.
26 Gale CR, O'Callaghan FJ, Godfrey KM, Law CM and Martyn CN. Critical periods of brain growth and cognitive function in children. *Brain.* 2004; **127** (Pt 2): 321-9.
27 Bloomfield FH, Oliver MH and Harding JE. The late effects of fetal growth patterns. *Arch Dis Child Fetal Neonatal Ed.* 2006; **91** (4): F299-304.
28 Huizink AC, Mulder EJ and Buitelaar JK. Prenatal stress and risk for psychopathology: specific effects or induction of general susceptibility? *Psychol Bull.* 2004; **130** (1): 115-42.
29 Talge NM, Neal C and Glover V. Antenatal maternal stress and long-term effects on child neurodevelopment: how and why? *J Child Psychol Psychiatry.* 2007; **48** (3-4): 245-61.
30 Van den Bergh BR, Mulder EJ, Mennes M and Glover V. Antenatal maternal anxiety and stress and the neurobehavioural development of the fetus and child: links and possible mechanisms. A review. *Neurosci Biobehav Rev.* 2005; **29** (2): 237-58.
31 Poltyrev T, Keshet GI, Kay G and Weinstock M. Role of experimental conditions in determining differences in exploratory behavior of prenatally stressed rats. *Dev Psychobiol.* 1996; **29** (5): 453-62.
32 Vallee M, Mayo W, Dellu F, Le Moal M, Simon H and Maccari S. Prenatal stress induces high anxiety and postnatal handling induces low anxiety in adult offspring: correlation with stress-induced corticosterone secretion. *J Neurosci.* 1997; **17** (7): 2626-36.
33 Wakshlak A and Weinstock M. Neonatal handling reverses behavioral abnormalities induced in rats by prenatal stress. *Physiol Behav.* 1990; **48** (2): 289-92.
34 Schneider ML. The effect of mild stress during pregnancy on birthweight and neuromotor maturation in rhesus monkey infants *(Macaca mulatta)*. *Infant Behavior & Development.* 1992; **15**: 389-403.

35 Schneider ML and Coe C. Repeated social stress during pregnancy impairs neuromotor development of the primate infant. *J Dev Behav Pediatr.* 1993; **14** (2): 81-7.
36 Schneider ML, Roughton EC, Koehler AJ and Lubach GR. Growth and development following prenatal stress exposure in primates: an examination of ontogenetic vulnerability. *Child Dev.* 1999; **70** (2): 263-74.
37 Dayan J, Creveuil C, Herlicoviez M, Herbel C, Baranger E, Savoye C and Thouin A. Role of anxiety and depression in the onset of spontaneous preterm labor. *Am J Epidemiol.* 2002; **155** (4): 293-301.
38 Hedegaard M, Henriksen TB, Secher NJ, Hatch MC and Sabroe S. Do stressful life events affect duration of gestation and risk of preterm delivery? *Epidemiology.* 1996; **7** (4): 339-45.
39 Zimmer-Gembeck MJ and Helfand M. Low birthweight in a public prenatal care program: behavioral and psychosocial risk factors and psychosocial intervention. *Soc Sci Med.* 1996; **43** (2): 187-97.
40 O'Connor TG, Heron J, Golding J, Beveridge M and Glover V. Maternal antenatal anxiety and children's behavioural/emotional problems at 4 years. Report from the Avon Longitudinal Study of Parents and Children. *Br J Psychiatry.* 2002; **180**: 502-8.
41 Van den Bergh BR, Van Calster B, Smits T, Van Huffel S and Lagae L. Antenatal Maternal Anxiety is Related to HPA-Axis Dysregulation and Self-Reported Depressive Symptoms in Adolescence: A Prospective Study on the Fetal Origins of Depressed Mood. *Neuropsychopharmacology.* 2008; **33** (3): 536-45.
42 Field T, Diego M, Hernandez-Reif M, Schanberg S, Kuhn C, Yando R and Bendell D. Pregnancy anxiety and comorbid depression and anger: effects on the fetus and neonate. *Depress Anxiety.* 2003; **17** (3): 140-51.
43 Lundy BL, Jones NA, Field T, Nearing G, Davalos M, Pietro PA, Schanberg S and Kuhn C. Prenatal depression effects on neonates. *Infant Behavior & Development.* 1999; **22** (1): 119-29.
44 Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB and Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics.* 2009; **124** (2): 717-28.
45 Adams-Chapman I. Neurodevelopmental outcome of the late preterm infant. *Clin Perinatol.* 2006; **33** (4): 947-64; abstract xi.
46 McGowan JE, Alderdice FA, Holmes VA and Johnston L. Early childhood development of late-preterm infants: a systematic review. *Pediatrics.* 2011; **127** (6): 1111-24.
47 Nosarti C, Murray R and Hack M, eds. *Neurodevelopmental outcomes of preterm birth: from childhood to adult life*. New York: Cambridge University Press; 2010. Cambridge medicine.
48 Barker DJ. Fetal origins of coronary heart disease. *Bmj.* 1995; **311** (6998): 171-4.
49 Roza SJ, Steegers EA, Verburg BO, Jaddoe VW, Moll HA, Hofman A, Verhulst FC and Tiemeier H. What is spared by fetal brain-sparing? Fetal circulatory redistribution and behavioral problems in the general population. *Am J Epidemiol.* 2008; **168** (10): 1145-52.

50 Scherjon S, Briet J, Oosting H and Kok J. The discrepancy between maturation of visual-evoked potentials and cognitive outcome at five years in very preterm infants with and without hemodynamic signs of fetal brain-sparing. *Pediatrics.* 2000; **105** (2): 385-91.
51 Norwitz ER and Schorge JO. *Obstetrics and gynecology at a glance*. 3rd ed. London: Malden, M.A.: Blackwell Science; 2001.
52 Abel EL. Smoking during pregnancy: a review of effects on growth and development of offspring. *Hum Biol.* 1980; **52** (4): 593-625.
53 Lieberman E, Gremy I, Lang JM and Cohen AP. Low birthweight at term and the timing of fetal exposure to maternal smoking. *Am J Public Health.* 1994; **84** (7): 1127-31.
54 Schendel DE, Schuchat A and Thorsen P. Public health issues related to infection in pregnancy and cerebral palsy. *Ment Retard Dev Disabil Res Rev.* 2002; **8** (1): 39-45.
55 Kriebs JM. Breaking the cycle of infection: TORCH and other infections in women's health. *J Midwifery Womens Health.* 2008; **53** (3): 173-4.
56 Sever JL, Nelson KB and Gilkeson MR. Rubella epidemic, 1964: effect on 6,000 pregnancies. *Am J Dis Child.* 1965; **110** (4): 395-407.
57 Susser E and Bresnahan M. Epidemiologic approaches to neurodevelopmental disorders. *Mol Psychiatry.* 2002; **7 Suppl 2**: S2-3.
58 Sorensen HJ, Mortensen EL, Reinisch JM and Mednick SA. Association between prenatal exposure to bacterial infection and risk of schizophrenia. *Schizophr Bull.* 2009; **35** (3): 631-7.
59 Fox PW, Hershberger SL and Bouchard TJ, Jr. Genetic and environmental contributions to the acquisition of a motor skill. *Nature.* 1996; **384** (6607): 356-8.
60 Johnston LB, Clark AJ and Savage MO. Genetic factors contributing to birth weight. *Arch Dis Child Fetal Neonatal Ed.* 2002; **86** (1): F2-3.
61 Henrichs J, Schenk JJ, Roza SJ, van den Berg MP, Schmidt HG, Steegers EA, Hofman A, Jaddoe VW, Verhulst FC and Tiemeier H. Maternal psychological distress and fetal growth trajectories: the Generation R Study. *Psychol Med.* 2010; **40** (4): 633-43.
62 Fliers E, Rommelse N, Vermeulen SH, Altink M, Buschgens CJ, Faraone SV, Sergeant JA, Franke B and Buitelaar JK. Motor coordination problems in children and adolescents with ADHD rated by parents and teachers: effects of age and gender. *J Neural Transm.* 2008; **115** (2): 211-20.
63 Kadesjo B and Gillberg C. Attention deficits and clumsiness in Swedish 7-year-old children. *Dev Med Child Neurol.* 1998; **40** (12): 796-804.
64 Watemberg N, Waiserberg N, Zuk L and Lerman-Sagie T. Developmental coordination disorder in children with attention-deficit-hyperactivity disorder and physical therapy intervention. *Dev Med Child Neurol.* 2007; **49** (12): 920-5.
65 Kadesjo B and Gillberg C. Developmental coordination disorder in Swedish 7-year-old children. *J Am Acad Child Adolesc Psychiatry.* 1999; **38** (7): 820-8.
66 Matson ML, Matson JL and Beighley JS. Comorbidity of physical and motor problems in children with autism. *Res Dev Disabil.* 2011; **32** (6): 2304-8.
67 Ming X, Brimacombe M and Wagner GC. Prevalence of motor impairment in autism spectrum disorders. *Brain Dev.* 2007; **29** (9): 565-70.

68 Cannon M, Moffitt TE, Caspi A, Murray RM, Harrington H and Poulton R. Neuropsychological performance at the age of 13 years and adult schizophreniform disorder: prospective birth cohort study. *Br J Psychiatry.* 2006; **189**: 463-4.

69 Dickson H, Laurens KR, Cullen AE and Hodgins S. Meta-analyses of cognitive and motor function in youth aged 16 years and younger who subsequently develop schizophrenia. *Psychol Med.* 2011: 1-13.

70 Rosso IM, Bearden CE, Hollister JM, Gasperoni TL, Sanchez LE, Hadley T and Cannon TD. Childhood neuromotor dysfunction in schizophrenia patients and their unaffected siblings: a prospective cohort study. *Schizophr Bull.* 2000; **26** (2): 367-78.

71 Cannon M, Caspi A, Moffitt TE, Harrington H, Taylor A, Murray RM and Poulton R. Evidence for early-childhood, pan-developmental impairment specific to schizophreniform disorder: results from a longitudinal birth cohort. *Arch Gen Psychiatry.* 2002; **59** (5): 449-56.

72 Hill EL. Non-specific nature of specific language impairment: a review of the literature with regard to concomitant motor impairments. *Int J Lang Commun Disord.* 2001; **36** (2): 149-71.

73 Gillberg C. Deficits in attention, motor control, and perception: a brief review. *Arch Dis Child.* 2003; **88** (10): 904-10.

74 Bishop DV. Motor immaturity and specific speech and language impairment: evidence for a common genetic basis. *Am J Med Genet.* 2002; **114** (1): 56-63.

75 Murray L, Sinclair D, Cooper P, Ducournau P, Turner P and Stein A. The socioemotional development of 5-year-old children of postnatally depressed mothers. *J Child Psychol Psychiatry.* 1999; **40** (8): 1259-71.

76 Paulson JF, Dauber S and Leiferman JA. Individual and combined effects of postpartum depression in mothers and fathers on parenting behavior. *Pediatrics.* 2006; **118** (2): 659-68.

77 Goodman SH and Gotlib IH. Risk for psychopathology in the children of depressed mothers: a developmental model for understanding mechanisms of transmission. *Psychol Rev.* 1999; **106** (3): 458-90.

78 Weiss SJ, Wilson P and Morrison D. Maternal Tactile Stimulation and the Neurodevelopment of Low Birth Weight Infants. *Infancy.* 2004; **5**: 85-107.

79 Feldman R, Greenbaum CW, Yirmiya N and Mayes LC. Relations between cyclicity and regulation in mother-infant interaction at 3 and 9 months and cognition at 2 years. *Journal of Applied Developmental Psychology.* 1996; **17** (3): 347-65.

80 Mantymaa M, Puura K, Luoma I, Salmelin RK and Tamminen T. Mother's early perception of her infant's difficult temperament, parenting stress and early mother-infant interaction. *Nordic Journal of Psychiatry.* 2006; **60** (5): 379-86.

81 Davey Smith G. Assessing intrauterine influences on offspring health outcomes: can epidemiological studies yield robust findings? *Basic Clin Pharmacol Toxicol.* 2008; **102** (2): 245-56.

82 Rothman KJ, Greenland S and Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008.

83 Rothman KJ, Greenland S and Lash TL. Types of epidemiological studies. In: Rothman KJ, Greenland S and Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:87-99.

84 Larroque B, Breart G, Kaminski M, Dehan M, Andre M, Burguet A, Grandjean H, Ledesert B, Leveque C, Maillard F, Matis J, Roze JC, Truffert P and Epipage stusy g. Survival of very preterm infants: Epipage, a population based cohort study. *Arch Dis Child Fetal Neonatal Ed.* 2004; **89** (2): F139-44.

85 TNO. *POPS-19 Vervolgonderzoek levenslange zorg voor te vroeg geboren kinderen*. Leiden: TNO Preventie en Gezondheid; 2001.

86 University Medical Center Groningen. Pinkeltje onderzoek - Lollipop http://www.pinkeltje-onderzoek.nl/#.

87 Rothman KJ, Greenland S and Lash TL. Validity in Epidemiological Studies. In: Rothman KJ, Greenland S and Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:128-47.

88 Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC and Hofman A. The Generation R Study: design and cohort update until the age of 4 years. *Eur J Epidemiol.* 2008; **23** (12): 801-11.

89 Center for Research and Statistics. *Demografische gegevens*. Rotterdam: (COS) http://www.cos.rotterdam.nl; 2005.

90 Roza SJ. *Prenatal and early postnatal brain development*. Rotterdam: Department of Child and Adolescent psychiatry, Erasmus MC-Sophia Children's Hospital Rotterdam; 2008.

91 Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T and Lamberts K. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *Br J Psychiatry.* 2009; **195** (3): 249-56.

92 Van Loon AJ, Tijhuis M, Picavet HS, Surtees PG and Ormel J. Survey non-response in the Netherlands: effects on prevalence estimates and associations. *Ann Epidemiol.* 2003; **13** (2): 105-10.

93 Najman JM, Williams GM, Nikles J, Spence S, Bor W, O'Callaghan M, Le Brocque R and Andersen MJ. Mothers' mental illness and child behavior problems: Cause-effect association or observation bias? *J Am Acad Child Psy.* 2000; **39** (5): 592-602.

94 Richters JE. Depressed Mothers as Informants About Their Children - a Critical-Review of the Evidence for Distortion. *Psychol Bull.* 1992; **112** (3): 485-99.

95 Achenbach TM and Edelbrock CS. Psychopathology of childhood. *Annu Rev Psychol.* 1984; **35**: 227-56.

96 Kraemer HC, Measelle JR, Ablow JC, Essex MJ, Boyce WT and Kupfer DJ. A new approach to integrating data from multiple informants in psychiatric assessment and research: mixing and matching contexts and perspectives. *Am J Psychiatry.* 2003; **160** (9): 1566-77.

97 Hernan MA, Hernandez-Diaz S, Werler MM and Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. *Am J Epidemiol.* 2002; **155** (2): 176-84.

98 Schisterman EF, Cole SR and Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology.* 2009; **20** (4): 488-95.

99 Rothman KJ and Greenland S. Causation and causal inference in epidemiology. *Am J Public Health.* 2005; **95 Suppl 1**: S144-50.

100 Hill AB. The Environment and Disease: Association or Causation? *Proc R Soc Med.* 1965; **58**: 295-300.

101 Rothman KJ, Greenland S, Poole C and Lash TL. Causation and Causal Inference. In: Rothman KJ, Greenland S and Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Lippincott Williams & Wilkins; 2008:5-31.

102 Parascandola M and Weed DL. Causation in epidemiology. *J Epidemiol Community Health.* 2001; **55** (12): 905-12.

103 World Health Organization. *World Health Report*. Geneva; 2001.

104 Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR and Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry.* 2005; **62** (6): 593-602.

105 Horwitz SM, Irwin JR, Briggs-Gowan MJ, Bosson Heenan JM, Mendoza J and Carter AS. Language delay in a community cohort of young children. *J Am Acad Child Adolesc Psychiatry.* 2003; **42** (8): 932-40.

106 Simpson GA, Colpe L and Greenspan S. Measuring functional developmental delay in infants and young children: prevalence rates from the NHIS-D. *Paediatr Perinat Epidemiol.* 2003; **17** (1): 68-80.

107 Molina BS and Pelham WE, Jr. Childhood predictors of adolescent substance use in a longitudinal study of children with ADHD. *J Abnorm Psychol.* 2003; **112** (3): 497-507.

108 Wells J, Barlow J and Stewart-Brown S. A systematic review of universal approaches to mental health promotion in schools. *Health Education.* 2003; **103** (4): 197-220.

109 Bradshaw CP, Schaeffer CM, Petras H and Ialongo N. Predicting Negative Life Outcomes from Early Aggressive-Disruptive Behavior Trajectories: Gender Differences in Maladaptation Across Life Domains. *Journal of Youth and Adolescence.* 2010; **39** (8): 953-66.

110 Licence K. Promoting and protecting the health of children and young people. *Child Care Health Dev.* 2004; **30** (6): 623-35.

111 Boere-Boonekamp MM, Dusseldorp E and Verkerk PH. *Onderbouwing van de validiteit van het ontwikkelinsonderzoek bij kinderen van 0 tot en met 4 jaar: het Van Wiechenonderzoek*. Leiden: TNO Kwaliteit van leven; 2009.

112 Hadders-Algra M. Two distinct forms of minor neurological dysfunction: perspectives emerging from a review of data of the Groningen Perinatal Project. *Dev Med Child Neurol.* 2002; **44** (8): 561-71.

113 Orton J, Spittle A, Doyle L, Anderson P and Boyd R. Do early intervention programmes improve cognitive and motor outcomes for preterm infants after discharge? A systematic review. *Dev Med Child Neurol.* 2009; **51** (11): 851-9.

Chapter 6

Summary/samenvatting

Summary

Several behavioural and cognitive disorders in childhood and adulthood have been hypothesized to be neurodevelopmental in origin. Numerous studies have provided evidence for subtle brain abnormalities in children and adults with attention deficit hyperactivity disorder, autism spectrum disorders, dyslexia and schizophrenia, compared to healthy children and adults. These deviations may emerge during brain maturation in childhood or adolescence or even in fetal life. Variations in fetal environment evoked by internal or external factors can have critical and long-lasting effects because of increased sensitivity of the developing brain.

The studies in this thesis aimed to extend existing knowledge on the prenatal and early neurodevelopmental basis of behavioural and cognitive problems. The studies were conducted as part of the Generation R Study, a prospective population-based cohort study from fetal life onwards in Rotterdam, the Netherlands.

In **chapter 2,** we studied the effects of prenatal adverse factors on infant neuromotor development. These prenatal factors included gestational duration, foetal size, and maternal symptoms of anxiety and depression. In *chapter 2.1,* the association between gestational duration and infant neuromotor development was studied. Children who were born before 40 weeks of gestation were more prone to less optimal neuromotor development at 3 months of age than children who were born between 40 and 41 weeks of gestation. This was explained by biological maturation rather than by shorter time spent in utero.

In *chapter 2.2*, we studied the effects of foetal size and body symmetry on infant neuromotor development. We found that higher estimated foetal weight was beneficial to infant neuromotor development. Furthermore, asymmetrical growth increased the risk of less optimal neuromotor development. These effects were found in mid-pregnancy and in late pregnancy. The results suggest that differences in neuromotor development are, at least partly, caused by processes occurring early in foetal life.

In *chapter 2.3*, we examined whether maternal symptoms of anxiety and depression that are temporary or chronic during the prenatal and postnatal period predict infant neuromotor development. We observed a specific

adverse effect of antenatal maternal anxiety and a trend for postnatal maternal depression on infant neuromotor development. As effect sizes were relatively small, implications for treatment of antenatal maternal anxiety and postnatal maternal depression are limited. However, the results could shed light on mechanisms underlying optimal child development.

Chapter 3 comprises two studies in which the relation between less optimal infant neuromotor development and later behavioural and cognitive problems were examined. In *chapter 3.1,* we studied whether infant neuromotor development was associated with behavioural and emotional problems at 1.5 years. Infants with less optimal neuromotor development were more prone to internalizing problems; in particular, these infants had an increased risk of being emotionally reactive and of having somatic complaints when they were toddlers. There was little evidence for an effect of less optimal neuromotor development on externalizing problems, although high muscle tone was associated with aggressive behaviour. These results suggest that behavioural and emotional problems in toddlers may have a neurodevelopmental basis.

The association between infant neuromotor development and verbal and nonverbal cognitive functioning at 1.5 and 2.5 years was studied in *chapter 3.2.* Poorer infant neuromotor development predicted receptive language delay at 1.5 years, expressive language delay across ages, and a delay in nonverbal cognitive function at 2.5 years. Low muscle tone mainly accounted for these findings. The results of this study suggest that subtle deviances from normal early neuromotor development can be a marker of later cognitive delays.

In **Chapter 4** (4.1), the intrauterine influence of maternal depression and anxiety on child attention problems was investigated by comparing maternal and paternal symptoms during pregnancy and by investigating cross-cohort consistency. In both cohorts, antenatal maternal symptoms of depression and anxiety were associated with an increased risk of child attention problems. In one cohort, also paternal depression increased the risk of child attention problems. The associations between paternal symptoms and child attention problems were substantially weaker than those observed for maternal symptoms. However, there was no strong evidence that the paternal associations differed statistically from the

maternal associations with respect to child attention problems. All observed associations attenuated after correction for postnatal symptoms. Thus, the apparent effect of intrauterine exposure to maternal depression and anxiety on offspring behavioural problems may be largely explained by residual confounding and postnatal maternal symptoms.

Chapter 5 provides a general discussion of the main findings and addresses methodological issues regarding the studies presented in this thesis. Furthermore, implications of our findings for clinical practice and possibilities for future research are suggested.

Samenvatting

Verschillende gedrags- en cognitieve stoornissen worden verondersteld een ontwikkelingsneurologische basis te hebben. Talrijke studies hebben subtiele hersenafwijkingen gevonden bij kinderen en volwassenen met een aandachtstekort- of hyperactiviteitsstoornis, een stoornis in het autisme spectrum, dyslexie of schizofrenie in vergelijking met gezonde kinderen en volwassenen. Deze afwijkingen kunnen ontstaan tijdens het proces van hersenrijping in de kindertijd of adolescentie of zelfs gedurende het foetale leven. Interne en externe factoren die de foetale omgeving kunnen beïnvloeden kunnen kritieke en langdurige gevolgen hebben vanwege de toegenomen gevoeligheid van het zich ontwikkelende brein.

De studies die in dit proefschrift beschreven zijn hadden tot doel de bestaande kennis over de prenatale en de vroeg ontwikkelings-neurologische basis van gedrags- en cognitieve problemen uit te breiden. Deze studies zijn uitgevoerd als onderdeel van het Generation R Onderzoek, een prospectief cohortonderzoek waarin Rotterdamse kinderen uit de algemene bevolking worden gevolgd vanaf het moment dat zij bij hun moeder in de buik zaten.

In **hoofdstuk 2** hebben we de effecten bestudeerd van negatieve prenatale factoren op de neuromotorische ontwikkeling in baby's. Deze prenatale factoren omvatten zwangerschapsduur, foetale grootte en symptomen van angst en depressie bij de moeder. In *hoofdstuk 2.1* werd het verband tussen zwangerschapsduur en neuromotorische ontwikkeling in de baby onderzocht. Baby's die werden geboren na een zwangerschap korter dan 40 weken hadden een verhoogd risico op een minder optimale neuromotorische ontwikkeling op de leeftijd van 3 maanden dan kinderen die tussen de 40 en 41 weken zwangerschapsduur werden geboren. Dit werd vooral verklaard door biologische rijping en niet zozeer door het feit dat het kind een kortere tijd in de baarmoeder had doorgebracht.

In *hoofdstuk 2.2* is het effect van foetale grootte en symmetrische groei op de vroeg neuromotorische ontwikkeling onderzocht. We vonden dat een hoger geschat foetaal gewicht een gunstige invloed had op de vroeg neuromotorische ontwikkeling. Verder bleek een asymmetrische groei het risico te vergroten op een minder optimale neuromotorische ontwikkeling in baby's. Deze verbanden werden zowel in het tweede als in het laatste

kwartaal van de zwangerschap gevonden. De resultaten duiden er op dat verschillen in de vroege neuromotorische ontwikkeling mogelijk deels veroorzaakt worden door processen die vroeg in het foetale leven plaatsvinden.

In *hoofdstuk 2.3* is onderzocht of tijdelijke of chronische symptomen van angst en depressie bij de moeder tijdens de zwangerschap of vlak erna van invloed zijn op de neuromotorische ontwikkeling in baby's. Symptomen van angst bij de moeder tijdens de zwangerschap hielden verband met de vroeg neuromotorische ontwikkeling; voor postnatale symptomen van depressie bij de moeder werd er enkel een trend gevonden. Omdat de gevonden verbanden niet sterk waren, hebben de resultaten van dit onderzoek beperkte toepassingsmogelijkheden met betrekking tot behandeling van angst en depressieve symptomen bij de moeder gedurende de zwanger-schap. De resultaten geven mogelijk wel inzicht in de mechanismen die ten grondslag liggen aan een optimale ontwikkeling van het kind.

Hoofdstuk 3 bestaat uit twee studies waarin is onderzocht of er een verband is tussen een minder optimale neuromotorische ontwikkeling in baby's en latere gedrags- en cognitieve problemen. In *hoofdstuk 3.1* is onderzocht of de vroeg neuromotorische ontwikkeling een relatie had met gedrags- en emotionele problemen op de leeftijd van 1.5 jaar. Baby's met een minder optimale neuromotorische ontwikkeling hadden een verhoogd risico op internaliserende problemen. Deze baby's hadden in het bijzonder een verhoogd risico om als peuter emotioneel reactief te zijn of somatische klachten te hebben. Er waren weinig aanwijzingen voor een verband tussen de vroeg neuromotorische ontwikkeling en externaliserende problemen, hoewel een hogere spierspanning wel samenhing met agressief gedrag op de peuterleeftijd. De resultaten wekken de suggestie dat gedrags- en emotionele problemen bij peuters een ontwikkelingsneurologische basis hebben.

Het verband tussen neuromotorische ontwikkeling in baby's en (non-) verbaal cognitief functioneren op 1.5 en 2.5 jaar is onderzocht in *hoofdstuk 3.2.* Een minder goede neuromotorische ontwikkeling op de leeftijd van 3 maanden voorspelde een achterstand in receptief taalgebruik op 1.5 jaar, in expressief taalgebruik op zowel 1.5- als 2.5-jarige leeftijd en een achterstand in nonverbaal cognitief functioneren op 2.5 jaar. Deze

bevindingen werden in het bijzonder gevonden voor de subschaal die een lage spierspanning mat. De resultaten van deze studie wijzen er mogelijk op dat subtiele afwijkingen van een normale neuromotorische ontwikkeling in baby's voorlopers zijn voor een latere achterstand in cognitief functioneren.

In **hoofdstuk 4** (4.1) is de intra-uteriene invloed van depressie en angst bij de moeder op aandachtsproblemen in het kind onderzocht door symptomen bij de moeder en de vader met elkaar te vergelijken en door te onderzoeken of resultaten consistent waren in twee verschillende cohorten. In beide cohorten hadden prenatale symptomen van depressie en angst bij de moeder een verband met een verhoogd risico op aandachtsproblemen in het kind. In één cohort hadden depressieve symptomen in de vader ook een verband met een verhoogd risico op aandachtsproblemen in het kind. De verbanden tussen symptomen in de vader met aandachtsproblemen in het kind waren veel zwakker dan die geobserveerd werden voor symptomen in de moeder. We vonden echter geen sterk bewijs dat de verbanden voor de vader statistisch verschilden van die voor de moeder met betrekking aandachtsproblemen in het kind. Alle geobserveerde verbanden verdwenen na correctie voor postnatale symptomen. Het ogenschijnlijke effect van intra-uteriene blootstelling aan depressie en angst in de moeder op gedragsproblemen in het kind werd in deze studie voornamelijk verklaard door residuele confounding en postnatale symptomen in de moeder.

In **hoofdstuk 5** worden de voornaamste bevindingen en methodologische aspecten van de studies die beschreven worden in dit proefschrift meer in algemene zin bediscussieerd en besproken. Tenslotte worden de mogelijke implicaties van onze bevindingen voor de kliniek beschreven en mogelijkheden voor toekomstig onderzoek voorgesteld.

PhD Portfolio

Name PhD student: Tamara van Batenburg-Eddes
Erasmus MC department: Child and Adolescent Psychiatry
Research school: NIHES **PhD period:** January 2005 - September 2012
Promotors: H. Tiemeier and F.C. Verhulst **Supervisors:** H. Tiemeier and L. de Groot

1. PhD Training	**Year**	**Workload (ECTS)**
Research skills		
Principles of Research in Medicine	2005	0.7
Methods of Public Health Research	2005	0.7
Health Economics	2005	0.7
Topics in Evidence-based Medicine	2005	0.7
Cohort Studies	2005	0.7
Introduction to Public Health in the Changing Global Context	2005	0.7
Study Design	2005	4.3
Methodological Topics in Epidemiological Research	2006	1.4
Modern Statistical Methods	2005	4.3
Public Health Research: Analysis of Population Health	2006	1.4
Public Health Research: Analysis of Determinants	2006	1.4
Public Health Research: Intervention Development and Evaluation	2006	1.4
In-depth courses		
Psychiatric Epidemiology	2006	1.1
Repeated measurements in Clinical Studies	2007	1.4
Analysis of Time-varying Exposures	2007	0.7
Maternal and Child Health	2007	0.9
Ethnicity, Health and Health Care	2007	1.1
(Inter)national conferences – participation and presentations		
IFPE 2007, 11th Congress of the International Federation of Psychiatric Epidemiology, Götenborg, Sweden. Poster presentation: *Maternal symptoms of anxiety during pregnancy affect infant neuromotor development. The Generation R Study.*	2007	1.4
Projectleidersbijeenkomst GeestKracht en LAK GGZ/Vz (2007), Nieuwegein, the Netherlands Poster presentation: *Maternal symptoms of anxiety during pregnancy affect infant neuromotor development. The Generation R Study.*	2007	0.5
IACAPAP, 18th World Congress of the International Association for Child and Adolescent Psychiatry and Allied Professions. Istanbul, Turkey. Oral presentation: *Infant neuromotor development predicts problem behavior in toddlers. The Generation R Study*	2008	1.4
Jeugd in Onderzoek, zesde editie 2010, Nieuwegein, the Netherlands. Poster presentation: *Crossculturele validatie van de Jeugdmonitor Rijnmond op het gebied van politiecontacten.*	2010	0.5
Nederlands Congres voor Volksgezondheid 2010, Rotterdam, the Netherlands. Oral presentation: *Crossculturele validatie van de Jeugdmonitor Rijnmond op het gebied van politiecontacten.*	2010	0.5
WEON 2011, Ijmuiden, the Netherlands. Posterpresentation: *Crosscultural validity of the Rotterdam Youth Monitor: Factorial invariance of the parent-report Strengths and Difficulties Questionnaire.*	2011	0.9
Een Wereld te Winnen: kwaliteit in de zorg voor alle jeugd, 2011, Rotterdam, the Netherlands. Oralpresentation: *Crossculturele validiteit van zelfrapportage vragenlijsten.*	2011	0.5

2. Teaching activities	Year	Workload (ECTS)
Supervised Master thesis Marijke Vlasblom-Bosschieter, student Nursing Science, General Health Science, Utrecht University. Thesis title: Motorisch onderzoek bij zuigelingen	2006	2.0
Supervising practical courses Child and Adolescent Psychiatry for medical students	2008	0.6
Supervised Master thesis Isil Sincer, student Developmental and Educational Psychology, Institute of Psychology, Erasmus University Rotterdam. Thesis title: Neuromotor development and cognitive function	2008	2.0
As a statistics lecturer gave a introductory course in research methods and designs and statistics, and supervised students' own research projects, Roosevelt Academy, Middelburg	2008	7.1
Supervised Master thesis Marvin van der Krogt, student Youth Criminology, Erasmus School of Law, Erasmus University Rotterdam. Thesis title: Een kwantitatief onderzoek naar overeenkomsten tussen liefdespartners in delinquent gedrag	2009	1.0

List of publications

This thesis

van Batenburg-Eddes T, de Groot L, Arends L, de Vries A, Moll HA, Steegers EAP, Hofman A, Jaddoe VWV, Verhulst FC and Tiemeier H. Does gestational duration within the normal range predict infant neuromotor development? *Early Hum Dev.* 2008; **84** (10): 659-65.

van Batenburg-Eddes T, de Groot L, Steegers EAP, Hofman A, Jaddoe VWV, Verhulst FC and Tiemeier H. Fetal programming of infant neuromotor development: the generation R study. *Pediatr Res.* 2010; **67** (2): 132-7.

van Batenburg-Eddes T, de Groot L, Huizink AC, Steegers EAP, Hofman A, Jaddoe VWV, Verhulst FC and Tiemeier H. Maternal symptoms of anxiety during pregnancy affect infant neuromotor development: the generation R study. *Dev Neuropsychol.* 2009; **34** (4): 476-93.

van Batenburg-Eddes T, de Groot L, Hofman A, Jaddoe VWV, Verhulst FC, Tiemeier H Infant neuromotor development predicts problem behaviour in toddlers. The Generation R Study. *To be submitted*

van Batenburg-Eddes T, Henrichs J, Schenk J, Sincer I, de Groot L, Hofman A, Jaddoe VWV, Verhulst FC, Tiemeier H Early infant neuromotor development predicts verbal and non-verbal cognitive functioning of children in the general population. The Generation R Study. S*ubmitted*

van Batenburg-Eddes T, Brion MJ, Henrichs J, Jaddoe VWV, Hofman A, Verhulst FC, Lawlor DA, Davey Smith G and Tiemeier H. Parental depressive and anxiety symptoms during pregnancy and attention problems in children. A cross-cohort consistency study. *Journal of Child Psychology and Psychiatry: provisionally accepted.*

Other publications

van Batenburg-Eddes T, Butte D, van de Looij-Jansen P, Schiethart W, de Waart F, Raat H and Jansen W. Measuring juvenile delinquency: How do self-reports compare with official police statistics? *European Journal of Criminology.* 2011; **9** (1): 23-37.

Roza SJ, van Batenburg-Eddes T, Steegers EAP, Jaddoe VWV, Hofman A, Verhulst FC, Tiemeier H. Maternal folate deficiency in early pregnancy is related to a higher risk of behavioral problems in children. The Generation R Study. *British Journal of Nutrition*. 2010; **103**: 445-452.

van Batenburg-Eddes T, Blanken P, Burger I and Hendriks VM. Alcohol- en druggebruikers bij Parnassia verslavingszorg onder de loep: Den Haag 1999-2001. *Epidemiologisch Bulletin.* 2004; **39** (3): 2-8.

van Batenburg-Eddes T, Blanken P and Hendriks VM. *Cliënt Monitoring Systeem 1999-2001*. Den Haag: Parnassia Addiction Research Centre; 2003.

van Batenburg-Eddes T, Blanken P and Hendriks VM. *Verslavingsproblematiek en zorgtrajecten van Haagse cliënten binnen Parnassia Verslavingszorg, Cliënt Monitoring Systeem 1999-2001*. Den Haag: Parnassia Addiction Research Centre; 2004.

van Batenburg-Eddes T, van den Berg Jeths A, van der Veen AA, Verheij RA and de Neeling AJ. *Slikken in Nederland, Regionale variaties in geneesmiddelengebruik*. Bilthoven: RIVM; 2002.

Dankwoord

Vele mensen hebben direct of indirect een bijdrage geleverd aan de totstandkoming van dit proefschrift. Helaas kan ik niet iedereen persoonlijk hiervoor bedanken, maar sommigen wil ik hier wel noemen.

Deelnemers: Allereerst wil ik alle deelnemers van Generation R bedanken voor alle tijd en energie die zij geïnvesteerd hebben in het onderzoek. Zonder jullie deelname had dit proefschrift nooit geschreven kunnen worden.

Promotoren: Ik ben begonnen met één en geëindigd met twee promotoren. Prof. dr. H. Tiemeier, beste Henning, naast dat je een bevlogen (bijna fanatieke) en buitengewoon goede onderzoeker bent, heb je ook nog eens veel humor. Ik heb de laatste jaren veel plezier gehad in de vele gesprekken over werk en andere dingen. Dank je voor het reageren op de eindeloze mails, het becommentariëren van alles wat er in dit proefschrift geschreven staat, en het delen van je kennis. Prof. dr. F.C. Verhulst, beste Frank, bedankt voor al je positieve reacties op mijn manuscripten en de prettige samenwerking.

Copromotor: Dr. L. de Groot, lieve Laila, ik ben je zeer dankbaar voor alle inzichten die je me hebt gegeven met betrekking tot de motoriek. Ook wil ik je bedanken voor alle mails, kaartjes en telefoontjes niet alleen naar aanleiding van mijn manuscripten maar ook voor de kinderen, verjaardagen, andere aangelegenheden, en ter ondersteuning van die laatste loodjes. Ze gaven me vaak dat extra duwtje dat ik nodig had om toch nog even aan de slag te gaan en dit proefschrift op papier te krijgen!

Commissieleden: Prof. dr. M.A. Frens, bedankt dat u de secretaris van mijn leescommissie wilde zijn. Prof. dr. M. Hadders-Algra en dr. C.E. Catsman-Berrevoets wil ik bedanken voor het lezen en beoordelen van dit proefschrift en hun bereidheid zitting te nemen in de commissie. Prof. dr. J.I.P. de Vries, prof. dr. H. Raat, en prof. dr. F. Verheij wil ik bedanken voor het plaatsnemen in mijn commissie.

(Project)leiders van Generation R: Prof. dr. A. Hofman, dr. Rosalinde Snijders en dr. Vincent Jaddoe wil ik van harte bedanken voor de succesvolle totstandbrenging en –houding van Generation R.

Co-auteurs: Prof. dr. E.A.P. Steegers, prof. dr. H.A. Moll, prof. dr. L. Arends, prof. dr. A.C. Huizink, dr. J.J. Schenk, Isil Sinçer en de overige co-auteurs die elders in dit dankwoord genoemd worden, wil ik bedanken voor de nuttige suggesties die hebben bijgedragen aan de verbetering van de artikelen. Prof. dr. G. Davey Smith, prof. dr. D.A. Lawlor and dr. MJ Brion, thank you for the pleasant collaboration which has been (and still is) an educative experience for me.

Medewerkers motoriek metingen: Marijke, Lies, Tonie, Janneke, Jeanette, Nicoline, Joke, bedankt dat jullie mij op sleeptouw hebben genomen en me wegwijs hebben gemaakt in alles wat er bij de huisbezoeken kwam kijken. Elise, Elizia, Rukiye, Souad, Iris, Leontien, Radia, dank jullie voor het afleggen van de vele huisbezoeken. Alies, bedankt voor alle keren dat je 's avonds nog naar Rotterdam bent gekomen voor de bijscholingsavonden. Jullie enthousiasme en inzet hebben een belangrijke bijdrage geleverd aan de kwaliteit van de motoriek gegevens.

Collega's Erasmus: Jens, Hanan, Pauline, Sabine, Joost, Claudia, Carmelo, Bero, Anne, Maartje, Elise, Laureen, Miranda, Rachel, Lindsay, Noor, Patricia, Alwin, Rose, Jeanine, Ernst-Jan, Ashna, Rianne, Lenie, Annemarie, Ankie, Dennis, Eszter, Nicole, Rianne, Jolien, Rolieke, Fleur, Sarah, Lamise, Jitske, en alle anderen, dank voor jullie inzet voor Generation R, en voor de gezellige koffiemomenten, borrels, feestjes, en uitjes. Jens, Pauline, en Sabine, Götenborg en Istanbul waren superleuk! Patricia, Alwin, Rose, dank voor alle hulp, administratief of anders van aard. Claudia, dank voor al je bezoekjes, gezelligheid en vriendschap. Laureen, wat heb je me fantastisch geholpen die laatste periode; je hebt me heel wat stress bespaard! Mijn kamergenootje, lieve Hanan, door een bizarre samenloop van omstandigheden werd onze vriendschap heel hecht. Wat een intense tijd was dat! Gelukkig kunnen we de positieve ervaringen des levens ook met elkaar delen. Dank je voor alles, toen en nu; ik hoop dat we nog lang vriendinnen blijven.

Collega's GGD: Petra, Dick, Annelies, Cathelijne, Judith, Ralda, Wilma, Sarah, Anja, Nathalie, Marieke, Bram, Jelle, Carolien, Ingrid, Ineke, Lindy, Nandani, Floor, Aline, Alice, Netty, Anke, Tinneke, Frouwkje, wil ik bedanken voor de ontzettend leuke tijd die ik bij de GGD heb gehad. De prettige sfeer, het begrip en medeleven met betrekking tot mijn proefschrift en mijn leven hebben mij zeker gestimuleerd om dit proefschrift af te maken. Petra, dank

je voor alle gezellige treinritjes naar Dordrecht en alle fijne gesprekken over promotie- en ander lief en leed. Dick, ondanks dat we toch redelijk vaak van mening verschilden, kwamen we er altijd wel uit; ik heb daar veel van geleerd.

Paranymfen: mijn matties, Enver en Jens, dank jullie voor alle steun op uiteenlopende fronten, alle plezier en de bereidheid naast mij te staan tijdens mijn promotie.

Vrienden: Leon & Caris, Diederik & Claudia, Reffik, Marisca, Dimitri & Fenna, Robin & Marije en alle anderen; bedankt voor de jarenlange vriendschap; bedankt voor jullie support en interesse; bedankt voor de broodnodige afleiding in de vorm feestjes, etentjes en partijen. Melanie, dank je voor je vriendschap én het ontwerpen van de kaft van mijn proefschrift; ik vind hem heel mooi geworden. Mijn lieve buurtjes, Dea, Maureen: 'Een goede buur is beter dan een verre vriend'; onverwachts worden je buren je vrienden. Alle eetclub-avonden met gesprekken over de (on-)gemakken van het leven, de talloze keren dat jullie de kinderen (of mij) hebben opgevangen: dank jullie voor alles! Hoe moet dat als we ooit verhuizen?

Mijn (aangetrouwde) familie: Anthonie, lieve papa, dank je voor je onvoorwaardelijke steun, je kracht en je doorzettingsvermogen; dank je voor de leuke gesprekken over de inhoud van dit proefschrift waar je vanuit je eigen vak ook veel interesse in hebt. Corry, lieve mama, er gaan maar weinig dagen voorbij zonder dat ik aan je denk. Het afronden van dit boekje en mijn promotie zijn van die levensgebeurtenissen die ik graag met je had willen delen. Jascha, mijn grote broer, ik houd van je. Beste Wim, lieve oom, dank u voor de begeleiding in mijn leven. Marion & Jack, Titia & Arie, en Tiny, dank voor jullie betrokkenheid en enthousiasme voor dit eindeloze project. Nico & Marianne, ik heb me altijd welkom gevoeld bij jullie; dank voor jullie jarenlange steun en jullie lieve zoon. Linda & Ido, Madelief en Jippe, dank voor alle gezelligheid tijdens verjaardagen en vakanties.

Mijn gezin: lieve Jurjen, we hebben flink wat hindernissen moeten overwinnen; zonder jouw positieve kijk op mensen en het leven was ik waarschijnlijk nooit meer op 'the bright sight of the road' gekomen: 'Van the Man' voor jou. Lieve Mees en Roos, bedankt voor het plezier en geluk dat jullie mij brengen.

About the author

Tamara van Batenburg-Eddes was born in Dordrecht, the Netherlands, on June 24th, 1973. In 1991 she graduated secondary school at the Titus Brandsma College in Dordrecht. She was admitted to the Amsterdam School of Arts, Theatre School, National Balletacademy the same year to become a performing dancer. In 1993 she started her study Psychology at Leiden University. She followed her internship at TNO Preventie & Gezondheid. From 1998 until graduation, she worked as a tutor in the field of her specialization, i.e. Methodology and Statistics. After her study she travelled for a year through Asia and New Zealand with her husband Jurjen van Batenburg. In 2001 she started her career as a scientific researcher. She worked for one year on a project on regional variations in medicine use at the National Institute for Public Health and the Environment in Bilthoven. Next, she worked at the Parnassia Addiction Research Centre in the Hague. Here, she worked on a system that was designed to monitor clients who were treated for their addiction problems and to gain insight in these clients' characteristics and their health care use (2002-2005). In 2005 she started at the Erasmus Medical Center with the research project 'Causes and Consequences of Infant Neuromotor Development' described in this thesis. During this research project she obtained a Master of Science degree in Epidemiology from the Netherlands Institute for Health Sciences in 2007. In January 2008 she worked for one trimester as a free-lance statistics lecturer at the Roosevelt Academy in Middelburg. In September 2008, she started as a scientific researcher at the Rotterdam-Rijnmond Public Health Service. Here, she investigated crosscultural validity of self-reported police contacts in adolescents and of parent reported behavioural and emotional problems in 5-6 year old children within the Academic Collaborative Centre for Diversity in Youth Policy (DWARS). In April 2012, she started as a post-doctoral researcher at the Department of Educational Neuroscience at the VU Amsterdam.

Tamara van Batenburg-Eddes and Jurjen van Batenburg have two children: a boy Mees (born on the 15th of April 2009) and a girl Roos (born on the 10th of September 2010).