

Psychological risk factors for pain in young children

The Generation R Study

Noor Wolff

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**Psychological Risk Factors for
Pain in Young Children**
The Generation R Study

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Pijn bij Jonge Kinderen**
Het Generation R Onderzoek

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Promotoren

Prof.dr. J. Passchier
Prof.dr. F.C. Verhulst

Overige leden

Prof.dr. J.J. Van Busschbach
Prof.dr. D. Tibboel
Prof.dr. M.L. Peters

Copromotoren

Dr. A.S.E. Darlington
Dr. H. Tiemeier

Paranimfen

Annemerle Beerthuisen
Eveline Kramer

Voor Rick, Bas en Job

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MANUSCRIPTS BASED ON THIS THESIS

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Chapter 5

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Chapter 6

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Chapter 1

General introduction



WHAT IS PAIN?

Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. Pain is always subjective. Each individual learns the application of the word through experiences related to injury in early life” (IASP, 1979). The biopsychosocial approach to pain states that biological changes, psychological status, and the sociocultural context all need to be considered in order to gain a complete understanding of a person’s perception and response to pain and illness (Gatchel, Peng, Peters, Fuchs, & Turk, 2007).

In children, many of the pains they experience, concern the so-called ‘everyday pains’. These are the pains associated with playing, learning how to stand and walk, and teething, for instance. Almost all children in the Western world also have immunization pain on a regular basis. Fewer children experience acute pain in medical settings, for example during blood sampling or other medical procedures. And many children have chronic pain, defined as continuous or recurrent pain that persists past the normal time of healing – most commonly 3 months duration in the pediatric setting (Merskey & Bogduk, 1994; Perquin et al., 2000).

PREVALENCE OF PAIN IN CHILDREN

Pediatric chronic pain is quite common (Perquin et al., 2000; Roth-Isigkeit, Thyen, Stoven, Schwarzenberger, & Schmucker, 2005). Prevalence figures vary by age group and gender. Chronic pain is most common in adolescent girls, 44% of girls aged 12-15 have recurrent or continuous pain that lasts at least 3 months, whereas 26% of boys in that age group have chronic pain (Perquin et al., 2000). In primary school children, chronic pain occurs in 16% (4 to 7-year-old boys) to 28% (8 to 11-year-old girls) of children (Perquin et al., 2000). Even in infants and toddlers up to age 3, parents often report pain lasting longer than 3 months. Perquin et al. (2000) found a chronic pain prevalence estimate of 11.8% overall, 13.6% in boys and 9.9% in girls. Another study, using another definition and restricting to a certain pain location, found a much lower prevalence estimate in toddlers. Of 2.5-year-old children, 3.8% had 5 or more episodes of stomachaches in the past 12 months (Ramchandani, Hotopf, Sandhu, & Stein, 2005).

During immunizations and other medical procedures, almost all children experience acute pain. In young children, in whom pain cannot be measured by self-report, the term ‘distress’ is used for behavioral expressions of negative emotions. Distress measures are used widely as proxy for the child’s acute pain. For acute pain or distress, it is not a question of presence or absence of pain (i.e. prevalence), but rather a matter of the severity or duration. For example, mean levels of immunization pain severity in 8 to 11-year-old children were 31 ($SD = 39$) on a self-report visual analog scale of 0 to 100 (Cohen, Blount, Cohen, & Johnson, 2004). In 3 to

7-year-old children, observed immunization distress occurred during 49% of procedure duration ($SD = 31\%$), the children's self-reported pain severity was 3.4 ($SD = 1.6$) on a facial rating scale of 1 to 5, and the parent-reported pain severity was 53 ($SD = 27$) on a visual analog scale of 0 to 100 (Blount, Bunke, Cohen, & Forbes, 2001). During immunizations in infants aged 0 to 2 years, infant distress was observed to occur on average during 35% of procedure duration ($SD = 23\%$; Cohen, Bernard, McClellan, & MacLaren, 2005) and parents reported a mean pain severity of 65 ($SD = 24$) on a visual analog scale of 0 to 100 (Bernard & Cohen, 2006).

CONSEQUENCES OF PAIN

There are several consequences of pediatric pain. Chronic pain in children has an adverse impact on daily functioning, quality of life, and health care use (Berger, Gieteling, & Benninga, 2007; Hunfeld et al., 2001; Merlijn et al., 2003; Roth-Isigkeit et al., 2005), and it frequently persists into adolescence and adulthood (Brattberg, 2004; Ramchandani et al., 2005; Solomon, Lipton, & Newman, 1992).

High levels of acute pain during medical procedures may have adverse neurophysiological effects, such as a stronger pain response to subsequent acute pain (Taddio, Katz, Ilersich, & Koren, 1997). Moreover, high levels of acute pain and distress have negative psychological effects, such as increased pain perception (McGrath, 1994) and increased fear and distress in future procedures (Blount, Piira, Cohen, & Cheng, 2006; Rocha, Prkachin, Beaumont, Hardy, & Zumbo, 2003).

As these are significant consequences of both acute and chronic pain, it is important to gain understanding of what determinants might affect differences in children's procedural distress (as proxy of acute pain) and chronic pain.

DETERMINANTS OF PEDIATRIC PAIN

According to the biopsychosocial model, all three aspects (biological, psychological, and social) are important to consider in pain research or patient care. However, research evidence can only be integrated if knowledge on the separate aspects is accumulating. As this is not yet the case in research of infants' and toddlers' pain, this thesis focuses on studying psychological factors only. A recent review noted that considering both pediatric chronic pain and responses to acute pain allows an understanding of pain relations across situations and thus aids in developing and studying a general pain model (Evans et al., 2008). Such a general pain model assumes that a large part of the risk factors for acute pain and chronic pain are the same.

Psychological research thus far has led to the development of a few theoretical causal models of pediatric pain or somatic complaints (Eminson, 2007; Evans et al., 2008; Palermo &

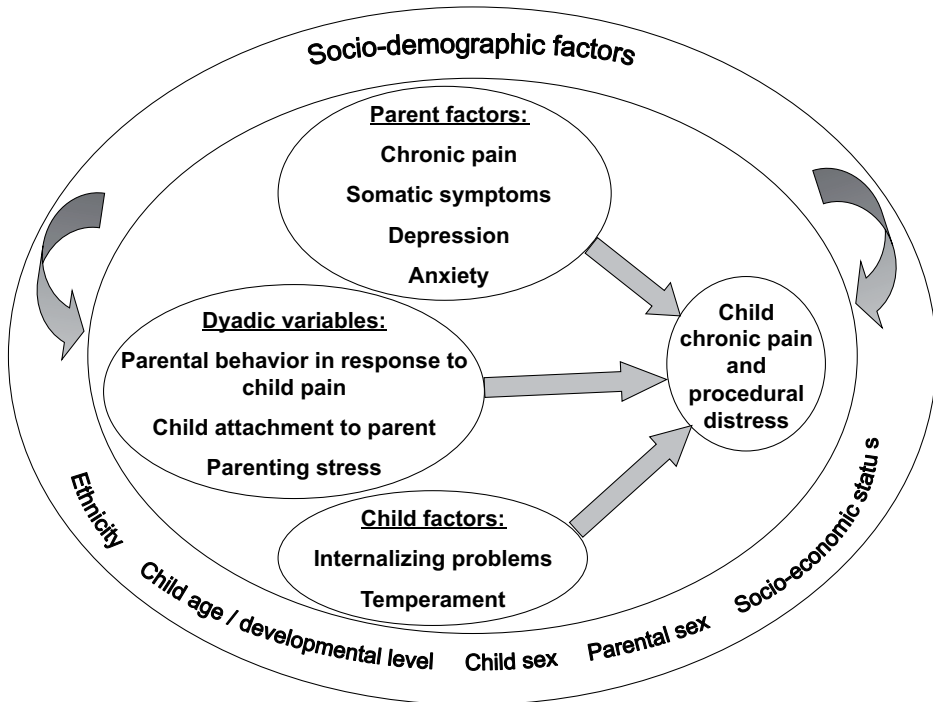


Figure 1.1. Theoretical model of risk factors for child chronic pain and procedural pain/distress

Chambers, 2005). Some of these models include both procedural pain and chronic pain. We based our theoretical model on these three models; it is presented in figure 1.1. The model incorporates both parent and child factors as etiological determinants of pain. In line with Evans et al. (2008), we theorize that high levels of acute pain / distress and the occurrence of chronic pain have similar risk factors. Important factors considered in this model are parents' physical health, especially parents' chronic pain and somatic symptoms, parents' mental health, such as anxiety and depression, parents' behavior in direct response to their child's pain, parenting stress, children's attachment to their parent, children's temperament, and children's internalizing problems. Most of the empirical evidence on which the models by Eminson, Evans et al., and Palermo and Chambers were built, comes from studies of adolescents or school-aged children with chronic pain. Parental chronic pain, anxiety, depression, and children's psychological vulnerability are known to be associated with children's chronic pain and somatic symptoms (for an overview, see Eminson et al., 2007 and Evans et al., 2008). Further, parental behavior in response to procedural pain is known to be related to infants' and children's pain reactivity (e.g. Blount, Devine, Cheng, Simons, & Hayutin, 2008; Cohen et al., 2005; Frank, Blount, Smith, Manimala, & Martin, 1995; Schechter et al., 2007; Walker et al., 2006).

WHAT IS UNKNOWN ABOUT DETERMINANTS OF PAIN?

Most of the studies so far that yielded evidence on psychological determinants of pediatric chronic pain were conducted in clinical samples and many studies used cross-sectional designs. This means that parental or children's psychological symptoms may have been a consequence rather than a determinant of pain. Also, clinical studies may have used very selective samples, resulting in lower generalizability to the population as a whole. Further, almost no studies were performed in children younger than school-age. This means that we do not yet know which early risk factors play a role in the development of young children's chronic pain or which characteristics are a consequence or co-occurring symptom rather than a determinant. The answers to the questions of 'which children develop chronic pain?' and 'which problem/symptom/trait comes first?' are so far not clear.

Concerning the determinants of acute pain, much research has been carried out on parental behavior in response to school-aged children's pain and distress during immunization procedures or ill children's medical procedures, such as bone marrow aspirations or lumbar punctures. Some studies investigated infants' immunization distress. However, it is unclear whether parental behavior affects infants similarly in other medical settings, such as a venipuncture procedure. Also, more distal factors, such as parental psychological traits, child temperament, and child attachment have rarely been studied in relation to infant procedural distress and results thus far are inconsistent.

AIM

The main aim of this thesis was to extend existing knowledge on psychological determinants of pain early in life, using the theoretical model shown in figure 1.1. We thus considered a variety of adverse parent and child factors as potential determinants of young children's pain. We focused on procedural pain (i.e. distress) as well as chronic pain and somatic complaints. This thesis consists of two parts, analogous to the acute and chronic outcomes we studied. Part 1 deals with determinants of distress during a potentially painful medical procedure. Part 2 focuses on risk factors for chronic pain and other (sub)clinical somatic complaints.

RESEARCH QUESTIONS

The main research questions of this thesis were:

1. to examine whether adverse parental and child factors early in life are associated with infants' distress levels during a venipuncture, as proxy for acute pain.

2. to investigate if early parental and child risk factors affect the development of chronic pain and somatic complaints in toddlers.

Based on the theoretical model, we hypothesized that adverse parental and child risk factors impact negatively on (1) the procedural distress level and (2) the occurrence of chronic pain and (sub)clinical levels of somatic complaints in young children.

STUDY DESIGN

For all studies presented in this thesis, data were used from the Generation R Study. The Generation R Study is a prospective population-based study investigating growth, development and health from fetal life onwards in Rotterdam, the Netherlands. In total, 9,778 pregnant women were included. Full consent for the postnatal phase of the Generation R Study, which included obtaining information from child health centers and assessments via postal questionnaires, was obtained from 7,295 children and their parents. Due to missing data on outcomes, the study samples used for analyses differed between the various studies presented in this thesis. Approximately 3,800 to 5,200 families participated in the studies on somatic complaints and chronic pain. The studies on venipuncture distress were conducted in the Generation R Focus Study, a small subgroup within the Generation R Study, which is carried out to obtain more detailed measurements of children's development. There were 275 children and their parents that participated in the studies on venipuncture distress.

OUTLINE OF THESIS

In part 1, parental and child determinants of venipuncture distress in infants are studied. These factors include parental behaviors during the venipuncture procedure, and parental psychological and physical health, such as depression, anxiety, somatic symptoms, and chronic pain (chapter 2), and child factors, such as temperament and attachment (chapter 3). Part 2 concerns the chronic pain and somatic symptoms. We investigated parental depression, anxiety, somatic symptoms, chronic pain, parenting stress, and child temperament as determinants of young children's somatic complaints (chapter 4). We also examined determinants of the development of chronic pain in toddlers. Again, parental depression, anxiety, somatic symptoms, and chronic pain were investigated as risk factors (chapter 5), as well as the relation of children's behavioral and emotional problems with chronic pain (chapter 6). Finally, chapter 7 provides a general discussion of the main findings, addresses methodological aspects of the study, and concludes with implications for clinical practice and future research.

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Part 1

Child venipuncture distress



Chapter 2

Parental behaviors, chronic pain, and psychological problems as risk factors for venipuncture distress



ABSTRACT

Objective: To examine the association of parent behavior with infant distress during a potentially painful medical procedure. A second aim was to investigate the association of parent chronic pain and psychological problems with parent behavior and infant distress during the procedure. **Design:** Population-based cohort study with both cross-sectional and prospective measurements. **Main Outcome Measures:** Video recordings of 275 parents and their 14-month-old infant undergoing venipuncture were coded with an observational instrument to yield measures of infant distress behaviors and parent behaviors, such as reassuring, showing empathy, praising, and distracting. Parent chronic pain and psychological problems were assessed by questionnaires. **Results:** Infants cried 58% of procedure duration. Parent reassuring occurred 34% of procedure duration, parent distracting occurred 37% of procedure duration. Infant distress was positively related to parent reassuring and negatively related to parent praising. Parent chronic pain was related to increased parent distracting, but not to reassuring. Parent psychological problems were not associated with parent behavior and infant distress. **Conclusion:** Parent behavior, rather than psychological traits, is related to increased venipuncture distress in young infants. This finding suggests that the focus should be on interventions based on behavior modification.

INTRODUCTION

Parent behavior is an important factor that is associated with child distress during medical procedures (Blount, Bunke, Cohen, & Forbes, 2001; Blount et al., 1997; Blount, Corbin, Sturges, & Wolfe, 1989; Frank, Blount, Smith, Manimala, & Martin, 1995; Manimala, Blount, & Cohen, 2000; Manne et al., 1992; Schechter et al., 2007). Reassurance, criticism, empathy, and apologies are related to higher distress levels in children (Blount et al., 1997; Blount, Sturges, & Powers, 1990; Schechter et al., 2007). Distraction and humor, on the other hand, encourage children to cope and these behaviors are inversely related to child distress (Blount et al., 1997; Blount et al., 1990; Schechter et al., 2007).

Most research has been carried out in school-aged children, whereas less research has investigated these associations in children under the age of 3. Infant distress and pain due to medical procedures have been understudied and undertreated for many years (Anand & Craig, 1996; Blount, Piira, Cohen, & Cheng, 2006).

Studying infants during immunizations, Sweet & McGrath (1998) found that parent reassurance, empathy, and apologies were associated with increased facial pain expression. Furthermore, parent reassurance during immunizations was related to infant distress, whereas parent efforts to distract their infant were associated with infant play and distraction, but not with lower infant distress (Cohen, Bernard, McClellan, & MacLaren, 2005). In an experimental study, conducted by the same research group, infants in an experimental 'distraction' condition (i.e. parents were instructed to distract the infant) showed fewer distress behaviors during immunization than infants in a control condition (Cohen et al., 2006). A study by Blount et al. found that non-procedural talk to the infant was associated with lower levels of cry, although parent reassurance and empathizing were not related to infant cry (Blount, Devine, Cheng, Simons, & Hayutin, 2008). Overall, results regarding associations of reassurance and empathizing with infant immunization behavior are inconsistent, and it is unclear whether parent distraction has a negative or no relationship with infant distress. Furthermore, as far as associations between parent and infant behavior seem to exist, Cohen et al. (2005) noted that it is still unknown whether these associations can be generalized to infants in other medical procedures, such as venipuncture.

More salient parent factors, such as the presence of chronic pain, may also shape the way parents behave in their infant's medical procedure. It is thought that parent chronic pain can be 'transferred' to their child, i.e. when parents experience pain, their children are more likely than other children to also experience pain. Many studies have found a positive association between parent chronic pain and child chronic pain (Garber, Zeman, & Walker, 1990; Jamison & Walker, 1992; Levy, Whitehead, Von Korff, & Feld, 2000; Mikail & von Baeyer, 1990; Schanberg et al., 2001). Besides a biological component, reinforcement and modeling are two important constructs from social learning theory that have been used to explain these findings. It is thought that children learn from their parents how to behave when distressed or in pain, via

imitation or because certain illness behaviors are rewarded (i.e. reinforced) by the parents. It is possible that these constructs also play a role in explaining parent behavior during their infants' medical procedure or in explaining how distressed their infants become, based on previous experiences with their parents in similar situations. However, to our knowledge, no research has yet investigated the influence of parent chronic pain on infant distress in a medical procedure.

Parents' psychological problems can also affect parenting, resulting in a compromised development of the child. For instance, it has been shown that maternal postpartum depression is associated with impaired parenting (e.g. being less responsive and affectionate, and displaying less verbal and playing interaction) and compromised infant development (e.g. insecure attachment, behavioral problems, and delayed cognitive development such as language and IQ; Grace, Evindar, & Stewart, 2003; Josefsson & Sydsjo, 2007; Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Righetti-Veltima, Bousquet, & Manzano, 2003). Perhaps parent symptoms of depression, anxiety or somatization not only affect children in their daily life, but also during medical procedures. It has already been shown that parent state anxiety in a medical procedure is related to infant pain (Bernard & Cohen, 2006). Parent *traits* of psychological symptoms might also be related to parent and infant behavior. Some researchers have investigated parent psychological problems in relation to child behavior during medical procedures, but results to date remain inconsistent. For example, depressed mood in mothers was related to increased infant pain response (Moscardino, Axia, & Altoe, 2006), whereas maternal trait anxiety was not significantly related to school-aged children's distress (Frank et al., 1995). In yet another study, maternal psychological problems were related to her subjective assessment of infant pain, but were not associated with observed infant pain reactivity (Pillai Riddell, Stevens, Cohen, Flora, & Greenberg, 2007). Most of these studies used cross-sectional designs and small numbers of participants.

The aim of this study is to examine the association of parent behavior with infant distress behavior during a venipuncture, and the prospective association of parent chronic pain and psychological problems with parent and infant behavior. We hypothesize that (1) infant distress behaviors are positively related to parent reassurance and empathic comments, and negatively related to distraction, (2) parent chronic pain and symptoms of depression, anxiety, and somatization are related to parent reassurance and empathic comments, and inversely related to parent distraction, and (3) these parent characteristics are related to infant distress.

METHODS

Setting

The Generation R Study is a prospective population-based study investigating growth, development and health from fetal life into young adulthood in Rotterdam, the Netherlands. All pregnant women in Rotterdam with expected delivery dates between April 2002 and January 2006 were eligible to participate in the Generation R Study. Midwives and obstetricians informed eligible mothers about the study at their first prenatal visit in routine care and handed out the information package. The research staff contacted these mothers by phone and in person at the first ultrasound examination, to provide additional information about the study and to obtain informed consent. Mothers and children with diseases and/or developmental delays were not excluded. The Generation R Study has been described in detail elsewhere (Jaddoe et al., 2006). The current investigation was conducted in a subgroup within the Generation R Study: the Generation R Focus Study, which is carried out to obtain detailed measurements of children's development. The children participating in the Generation R Focus Study were eligible if they were born between February 2003 and August 2005. Only children of Dutch national origin were included, meaning that the children, their parents, and their grandparents were all born in the Netherlands. The children visited the research center at 1.5, 6, 14, 24, and 36 months of age for somatic and behavioral assessments. Written informed consent was obtained from all participants. The study has been approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam.

Study population

In the current investigation, data are presented of the 14 month visit of the Generation R Focus Study. A total of 882 infants and their parents came for this visit between June 2004 and November 2006. Of the 882 participating infants, 407 (46%) parents gave informed consent for blood sampling of their child. Because the venipuncture was performed purely for research purposes (e.g. research into risk factors for immunological diseases and diabetes), the reasons for not giving consent are not asked for, out of respect for the parents' decisions. Due to practical problems (e.g. no good vein could be located, infant removed anesthetic patch), venipunctures were performed in 361 infants (89% of infants whose parents consented). In a further 80 infants no video recordings were available, due to a late start of this current investigation and some technical problems with the equipment. Six infants were excluded from data analyses because someone other than (one of) the parents accompanied the infant (e.g. grandmother). Thus, data from 275 infants and their parent were available for analyses.

Venipuncture procedure

The infant received a patch of the anesthetic eutectic mixture of prilocaine and lidocaine (EMLA) on the skin of the venipuncture site, one hour before venipuncture. Recordings started from the moment the research nurse began preparing the venipuncture site by removing the EMLA patch, and continued until after the infant's recovery. The infant was positioned on the parent's lap or on the examination table. During the venipuncture procedure one nurse and one assistant performed the blood sampling. Always, at least one parent was present. Twenty-five infants (9.1%) were accompanied by both parents; only the behaviors of the parent on whose lap the child was sitting, were coded for analyses. The other parent often was not visible in the video recording, as the focus was on the parent and infant involved in the procedure. Parents did not receive instructions on how to behave.

Measures

Infant and parent behavior

Behavior of the infant and parent during the venipuncture was coded using an observation instrument, which has been developed for the purpose of this study. It includes a selection of behaviors from various existing observation scales of parent and child/infant behavior during medical procedures (e.g. CAMPIS-R, CAMPIS-SF, CAMPIS-IV, MAISD, MBPS) that are suitable for one-year-old infants and their parents. The instrument includes both non-verbal and verbal behaviors of parent and infant, and will be referred to as the Generation R Infant Distress Scale (GRIDS). We will use the following terminology: the *behavior codes* (e.g. parent reassurance) reflect certain *behaviors* (e.g. saying "It will be over soon"). To develop the instrument, detailed transcriptions of several video recordings were used to obtain a saturated list of all behaviors. Behaviors were either assigned to existing behavior codes from the available observation scales mentioned above or assigned to new behavior codes. We used clinical judgment to place observed behaviors into codes, for example, our infant behavior code 'soothing' includes sucking on a pacifier or thumb, as in other measures, but was also coded when the infant was gently rocking him/herself. A previously existing code 'playing/engaging in distraction' was extended to include engaged looking at toys or looking at him/herself on the video camera screen. A new code is the parent behavior code 'restraint': the parent's (re)action to restrict the infant's movement (other than the arm in which the needle was inserted). The following parent behavior codes were coded: reassuring (including patting and stroking), empathic comments, restraint of movement, restraint of sight, apologizing, distracting, praising, non-procedural talk to infant, procedural talk to infant, non-procedural talk to adults, procedural talk to adults, behavioral commands to infant, and laughing at adults. Infant behavior codes included: crying, resisting (including flailing), requesting emotional support, looking sad or angry, verbal pain reports, information seeking (i.e. looking at, point-

ing to, reaching for, or touching the venipuncture site, tourniquet, or band-aid, or closely observing the nurses handling the procedure equipment), playing/engaging in distraction, soothing, eating, non-procedural talk, and laughing/smiling. Behaviors codes were coded as present or absent for every 5-second interval, which is a less time consuming way than producing written transcripts of the behaviors in each procedure and then coding these (Blount, 2005, personal communication). The proportion (i.e. percentage) for each behavior code was calculated by dividing the number of intervals in which that behavior code occurred by the total number of intervals (Cohen et al., 2005; Cohen et al., 2006; Frank et al., 1995). This scoring metric is easy to understand and reflects the amount of behaviors shown as a percentage of procedure duration. Scores range from 0 to 1. Parent and infant behavior were never coded by the same rater, and all raters were blind to results on all other measurements. Five raters were trained to code the recordings, and after this training all raters coded a random selection of recordings to calculate inter-rater reliability ($N = 11$). Intraclass correlation coefficients (using an absolute agreement definition) ranged from .65 to .99; these are shown in Table 2.2.

Validity infant distress measure

To validate the infant behavior codes, nurses completed a Visual Analog Scale (VAS) of infant distress, immediately after the venipuncture. A VAS is a horizontal line ranging from 0 cm (*no distress*) to 10 cm (*worst distress possible*).

Parent chronic pain

Parent chronic pain was determined from questionnaires on parent physical health prenatally. Mothers completed the questionnaire of physical health at 12 weeks gestation and fathers at 20 weeks gestation. Fathers completed the questionnaire at a later date due to later enrollment in the study. The questionnaire contained a checklist of chronic illnesses and diseases. The illnesses included in the current study as conditions of chronic pain were migraine, other types of headaches, intestinal disorders, back disorders, and rheumatoid arthritis. In addition, parents were asked whether they had any other chronic illness not listed in the checklist. Answers were reviewed by one of the authors (NW) and a second rater with a medical degree to extract chronic illnesses that involve pain. Inter-rater agreement was 86%. Differences were discussed to reach consensus. One dichotomous variable of any versus no pain was created.

Parent symptoms of psychological problems

Parent psychological problems were assessed using the Dutch version (De Beurs, 2006) of the Brief Symptom Inventory (BSI; Derogatis, 1993; Derogatis & Melisaratos, 1983). The BSI is a 53-item questionnaire, which was developed as a shorter version of the SCL-90. The BSI contains six subscales, of which three subscales were used: depression, anxiety, and somatization. The BSI was assessed at 20 weeks gestation (mother as well as father) and two

months after the child's birth (mother). Respondents indicated how much the symptom or problem distressed or bothered them in the past two weeks, on a scale of 0 (*not at all*) to 4 (*extremely*). Mean scores were calculated. The BSI has shown good test-retest reliability (.68 to .91) and good construct, criterion and convergent (with the SCL-90) validity (Derogatis & Melisaratos, 1983). Internal reliability in the current study, measured by Cronbach's alpha, was: .76, .81, and .62 respectively for depression, anxiety, and somatization of the mother during pregnancy; .81, .70, and .67 respectively for depression, anxiety, and somatization of the father during the mother's pregnancy; and .84, .85, and .59 respectively for depression, anxiety, and somatization of the mother two months after her child's birth.

Covariates

We considered demographics, obstetric and neonatal variables, variables regarding previous medical experiences, and covariates of the venipuncture and of the 14 month visit as possible confounders. These included infant sex, birth dates of the infant and of the parents, parity (i.e. number of children in the family who are older than the child participating in this study), and infant medical history during the first year of life (multiple visits to the general practitioner, visit to the specialist, hospitalization), which were obtained from the midwife and hospital records, and from questionnaires. Parent education was classified as primary education (elementary school), secondary education (high school, vocational training), or higher education (university degree). Covariates of the venipuncture procedure were the following: sex of the accompanying parent, site of the venipuncture, and whether the infant had been ill in the week preceding the visit. This information was obtained from the video-recordings and from a questionnaire. The covariates were considered potential confounders because they might theoretically be related to how infants and parents behave in the venipuncture procedure. For example, parents that have previous experience with a child growing up and experiencing daily pains (i.e. parity > 0), might react differently to the index infant than parents for whom this is their first child.

Data analyses

To examine whether non-response was selective, missing data analyses were carried out, comparing (1) the parents who participated in the 14 month visit of the Generation R Focus Study to those who were eligible but did not participate, (2) the parents who gave consent for blood sampling to the parents who did not consent.

We performed a principal components analysis to see if the infant behavior codes in the GRIDS could be combined into an infant distress component variable. A solution with one component was found, including crying, resisting, requesting emotional support, information seeking, and playing/engaging in distraction (all item loadings > .45 and internal reliability by Cronbach's alpha = .65). As information seeking and playing/engaging in distraction

loaded negatively on the component, they were reverse-coded. The component variable was termed *infant distress*. The component score was calculated by summing the percentages of occurrence of the five behavior codes. Due to the possibility of simultaneous occurrence of two or more behavior codes, the component score no longer reflects a percentage. It is a measure of severity of distress, with a possible range of 0 to 5 (i.e. the sum of the percentages of five behavior codes with range 0 to 1).

Because the scoring unit of the component score infant distress may be less intuitively easy to understand than the scoring units of the infant behavior codes (i.e. percentages), results will be presented of both the infant distress component and the most frequently occurring behavior codes. Many parent and infant behavior codes had low occurrences; we only considered variables with a mean occurrence > 10% as outcome variables in the analyses, to include meaningful analyses only. Before linear regression analyses were carried out, the assumptions of linearity, normality and homoscedasticity were tested and confirmed. The covariates were selected as a result of exploratory analyses, and were included in the analyses if one or more effect estimates changed meaningfully (defined as more than 5%). The analyses were adjusted for infant age and sex, parent age and sex, and parity. Other variables, like parent education, infant medical history, infant illness, or infant sleep quantity or quality did not confound any of the associations. In the analyses in which parent behavior codes were the determinants, we used multivariate models, entering the behavior codes in the analyses through stepwise selection. Further, separate analyses were run for the parent psychological determinants, due to the strong correlation between them. An a-priori concern was familywise error due to multiple hypothesis testing, therefore Bonferroni corrections were applied. Analyses were performed on data of the accompanying parent. Analyses were repeated on the subsample of mothers, yet results did not materially change and will therefore not be presented here. There were not enough fathers in our sample to carry out meaningful analyses in this subsample. First, models were fitted using the prenatally measured psychological problems, and then we repeated the analyses using the maternal psychological problems that were assessed two months after delivery. Analyses were carried out using SPSS version 15.

Non-response analyses

Results of missing data analyses indicated that the mothers of infants who did not participate in the 14 month visit were on average 1.38 years younger, $t(579.5) = 5.0, p < .001$ (two-tailed), and were educated at a lower level (high education 53.4% vs. 65.7% respectively), $\chi^2(4, N = 1161) = 29.2, p < .001$. Similar results were found for fathers. Although statistically significant, these differences are small. The non-participating infants were more likely to have visited a medical specialist in the first year of life than infants that participated (44.7% vs. 37.4% respectively), $\chi^2(1, N = 1102) = 4.4, p = .037$, but were not more likely to have visited a general

practitioner or to have been hospitalized. The groups of participating and non-participating families did not differ on any of the other variables.

Missing data analyses concerning data on consent for blood sampling showed that infants of non-consenting parents were more likely to be the firstborn in their family than infants of consenting parents (66.2% vs. 55.2% respectively), $\chi^2(3, N = 879) = 12.1, p = .007$. Also, these infants were more likely to have visited a general practitioner twice or more times in the first year of life than infants of consenting parents (71.6% vs. 62.1% respectively), $\chi^2(1, N = 845) = 8.5, p = .004$. There were no differences on all other variables.

RESULTS

Validity of infant distress measure

The infant distress component score as measured by the GRIDS was positively associated with the nurses' VAS rating of infant distress ($r_s = .72, p < .001$).

Parent and infant characteristics

Table 2.1 displays the descriptive statistics for the covariates and for parent chronic pain and parent psychological symptoms. Infants were aged between 13.1 and 17.5 months (mean 14.6 months). A total of 235 mothers (85.5%) and 40 fathers participated in the blood sampling procedure. Thirty-three percent of parents had chronic pain. Mean levels of symptoms of depression, anxiety, and somatization of the accompanying parents were 0.10, 0.19, and 0.23 respectively. Table 2.2 displays the descriptive statistics for parent and infant behavior during the venipuncture procedure. Infant distress scores were on average 2.36 (range 0.66-4.10). The most commonly occurring infant behavior was crying ($M = 58\%$ of procedure duration, $SD = 30\%$). Parents reassured their infants on average during a third of the procedure ($M = 34\%$, $SD = 22\%$). Parent distraction also occurred during roughly a third of the procedure ($M = 37\%$, $SD = 23\%$).

Parent behavior associated with infant behavior

Table 2.3 presents the results of the linear regression analyses of parent behavior and infant distress and crying. Parent reassuring was significantly associated with infant distress ($B = 1.704, 95\% \text{ CI} = 1.404, 2.005, p < .001$) and explained 35% of the variance (ΔR^2) in infant distress. According to Cohen's criteria for R^2 , the association is large (Cohen, 1988). Parent praising was inversely associated with infant distress ($B = -3.012, p < .001, \Delta R^2 = 3\%$). Infant crying was related to parent reassuring ($p < .001$) and inversely related to praising ($p < .001$).

Table 2.1. Infant and parent characteristics ($N = 275$)

Characteristic	M (SD) or %	Range
Infant characteristics		
Sex (% boy)	52.4%	
Age (in months)	14.55 (0.79)	13.06 – 17.49
Venipuncture site (% inside elbow, versus hand)	77.8%	
Illness in previous week (% yes)	57.5%	
Contacted general practitioner (% twice or more) ^a	60.1%	
Contacted medical specialist (% once or more) ^a	38.4%	
Hospitalized (% once or more) ^a	15.4%	
Parent characteristics		
Sex (% mother)	85.5%	
Age (in years)	33.70 (4.22)	20.08 – 52.26
Educational level		
No or primary	0.7%	
Secondary	33.0%	
High	66.3%	
Parity (% of infants being firstborn)	56.0%	
Parent chronic pain (% yes) ^b	32.7%	
Parent depression - during pregnancy ^c	0.10 (0.25)	0.00 – 1.83
Parent anxiety - during pregnancy ^c	0.19 (0.34)	0.00 – 2.67
Parent somatization - during pregnancy ^c	0.23 (0.29)	0.00 – 1.57
Mother depression - 2 months after delivery ^d	0.13 (0.32)	0.00 – 2.17
Mother anxiety - 2 months after delivery ^d	0.16 (0.38)	0.00 – 2.50
Mother somatization - 2 months after delivery ^d	0.15 (0.24)	0.00 – 1.71

^a Assessments of infant medical history spanned the period of 0 to 12 months of age.

^b $N = 260$.

^c $N = 252$.

^d $N = 216$.

Furthermore, infant resisting was associated with parent reassuring ($B = 0.205, p < .001$), empathic comments ($B = 1.713, p < .01$), and restraint of infant's movements ($B = 0.376, p < .01$). Also, infant information seeking was associated with parent reassuring ($B = -0.360, p < .001$). Lastly, infant playing was associated with parent reassuring ($B = -0.254, p < .001$) and with parent distracting ($B = 0.218, p < .001$). No other associations having $p < .01$ were found between parent and infant behaviors. After Bonferroni corrections, the results presented in Table 2.2 regarding infant distress and parent empathic comments ($p = .012$) and regarding infant crying and parent non-procedural talk to adults ($p = .033$) were not significant.

Table 2.2. Mean occurrences and Intraclass Correlation Coefficients (ICCs) of behavior codes

Behavior codes	<i>M (SD)</i> of the percentage of procedure duration	Range	ICC ^a
Parent			
Reassuring	.34 (.22)	0-1	.98
Empathic comments	.01 (.02)	0-.15	.89
Restraint of movement	.04 (.11)	0-1	.84
Restraint of sight	.01 (.04)	0-.34	-
Apologizing	.00 (.00)	0-.04	-
Distracting	.37 (.23)	0-1	.97
Praising	.03 (.04)	0-.23	.98
Non-procedural talk to infant	.03 (.04)	0-.19	.65
Non-procedural talk to adults	.09 (.08)	0-.41	.97
Procedural talk to adults	.04 (.05)	0-.34	.92
Procedural talk to infant	.02 (.03)	0-.18	.91
Behavioral commands to infant	.01 (.02)	0-.12	.83
Laughing at adults	.04 (.05)	0-.34	.94
Infant			
Distress ^b	2.36 (0.66)	0.66-4.10	.99
Crying	.58 (.30)	0-1	.99
Resisting	.20 (.17)	0-.82	.97
Information seeking	.24 (.20)	0-.93	.98
Requesting emotional support	.07 (.13)	0-1	.93
Looking sad	.01 (.03)	0-.17	.67
Looking angry	.00 (.00)	0-.06	-
Verbal reports of pain	.00 (.00)	0-.04	-
Playing	.24 (.19)	0-.86	.98
Soothing	.05 (.10)	0-.65	.94
Eating	.05 (.14)	0-1	.99
Non-procedural talk/verbal utterances by the infant	.02 (.05)	0-.48	.89
Laughing / smiling	.00 (.02)	0-.18	-

Note. Dashes signify that the ICC for that behavior was not calculated due to very low occurrence of the behavior. ICC = Intraclass Correlation Coefficient.

^a ICCs were calculated using an absolute agreement definition.

^b Infant distress is the sum of crying, resisting, requesting emotional support, information seeking (reverse-coded), and playing (reverse-coded); the value does not reflect a percentage of procedure duration, but is the sum of these five codes and indicates severity of distress.

Table 2.3. Relation between parent behavior and infant distress during venipuncture

Parent behavior	Infant distress ^a		Infant crying	
	B (95% CI)	ΔR^2	B (95% CI)	ΔR^2
Reassuring	1.704 (1.404; 2.005) ***	34.6%	0.747 (0.614; 0.880) ***	30.8%
Empathic comments	3.997 (0.882; 7.112) *	1.4%	-	-
Praising	-3.012 (-4.567; -1.458) ***	3.1%	-1.160 (-1.871; -0.449) **	2.6%
Non-procedural talk to adults	-	-	-0.421 (-0.807; -0.035) *	1.1%

Note. Hierarchical multiple regression analyses were performed in which infant sex and age, parent sex and age, and parity were entered first. Parent behavior codes were tested for entry and included in the model if they were significant predictors of the infant behavior. Dashes signify non-significant associations. B values represent unstandardised regression coefficients; CI = confidence interval; ΔR^2 = explained variance by that determinant (i.e. after subtraction of explained variance by covariates or other determinants).

^a Infant distress is the sum of crying, resisting, requesting emotional support, information seeking (reverse-coded), and playing (reverse-coded).

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Parent pain and psychological problems as predictors of parent behavior

Parent chronic pain was prospectively associated with increased parent distracting ($B = 0.098$, $p = .001$, $\Delta R^2 = 4.1\%$), but not with parent reassuring ($p = .69$). None of the parent symptoms of psychological problems (symptoms of depression, anxiety, and somatization) were associated with parent behavior. Essentially the same results were found when repeating the analyses using the postnatal assessment of maternal psychological problems, two months after delivery.

Parent pain and psychological problems as predictors of infant distress

There was a trend towards an association of parent chronic pain with infant information seeking, but due to the Bonferroni correction it was no longer statistically significant. Parent chronic pain was not related to the infant distress component score or the behavior codes crying, resisting, or playing. Parent symptoms of anxiety, depression, and somatization were not related to the infant distress component score, crying, resisting, playing, or information seeking. Essentially the same results were found for maternal psychological problems measured two months after delivery.

DISCUSSION

The current study demonstrates that parent reassuring was related to 14-month-old infant venipuncture distress and that parent praising was inversely related to infant distress. When investigating the infant behavior code crying, this code was also positively associated with parent reassuring and negatively associated with parent praising. Further, reassuring was negatively related to infant information seeking and playing. Infants, whose parents distracted them, played more. Parent behavior and infant distress were not related to parent symptoms of depression, anxiety, or somatization. Interestingly, parent chronic pain was associated with higher levels of parent distraction, but not with infant playing. Parent chronic pain also was not related to parent reassurance, or any of the other parent or infant behavior codes. These findings support the notion that behavior in this medical procedure context, rather than parent psychological traits, is related to distress in young infants.

Our main findings regarding the association of parent reassuring with infant distress behaviors are in line with results of other observational studies in infants (Cohen et al., 2005; Sweet & McGrath, 1998). However, Blount et al. (2008) found that reassuring was not related to infant crying. Perhaps the difference in results is due to the difference in mean age and age range of the infants. The current study investigated infants aged between 13.1 and 17.5 months, with a mean age of 14.6 months, whereas Blount et al. investigated a much wider age range: 1.6 to 20.6 months, with a mean age of 8.7 months. Also, the sample used by Blount et al. consisted of a mixture of African American, Caucasian, and Hispanic ethnicities, whereas in our sample all children and parents were Dutch natives. Possibly, there are cultural or ethnical differences regarding parent reassurance, which could have led to the differential findings. Furthermore, a lack of power due to small sample size in the Blount et al. study may have caused the differential findings as well, as they have investigated 49 infants, whereas our sample consisted of 275 infants. Findings of the association of parent reassurance with infant distress have also not been consistently replicated in experimental studies. One experimental investigation in preschool children showed causal associations of parent reassurance with child verbal fear and need for restraint during immunization (Manimala et al., 2000). However, these associations were quite small, and another experimental investigation during immunizations did not find any effect of reassurance on child behavioral distress when compared to a control condition (Gonzalez, Routh, & Armstrong, 1993). More experimental research into effects of parent reassurance is necessary. The relationship we found between parent distraction and infant playing during the procedure has previously been reported by the research group of Cohen et al. (Cohen et al., 2005; Cohen et al., 2006) and by Blount et al. (2008). Furthermore, studies in older children have reported associations of distress behaviors with both parent reassuring and distracting as well (Blount et al., 2001; Blount et al., 1997; Blount et al., 1989; Frank et al., 1995; Manne et al., 1992). Our finding that parent distraction was not related to decreased infant distress behaviors was consistent with

an observational study (Cohen et al., 2005), but not with three experimental studies (Cohen et al., 2006; Gonzalez et al., 1993; Manimala et al., 2000). Lastly, our result that parent praising was related to infant distress and crying, has not previously been found: this parent behavior was not included in the MAISD (Cohen et al., 2005) or CAMPIS-IV (Blount et al., 2008). The behavior was included in the CAMPIS versions for older children, in which it was not related to child distress (Blount et al., 1989).

A large part of parent behavior consisted of reassuring. There are several possible mechanisms that can explain the relationship between parent reassuring and infant distress behaviors, because it might seem counterintuitive that reassuring is associated with higher levels of distress and lower levels of playing. One of the possible explanations is that usually when the infant is in distressing situations, the parent tries to end the situation, whereas in a medical procedure the parent may explicitly communicate an understanding of the infant's feelings, yet does nothing to stop the procedure. This confusion may lead to increasing distress. Other possible mechanisms are that reassurance may function as an acknowledgement and confirmation of distress (McMurtry, McGrath, & Chambers, 2006). For example, reassurance can act as a warning that the parent is anxious or knows something bad is going to happen. Reassurance may also reward and thus reinforce distress behavior. Or reassurance may implicitly give permission to the infant to express distress openly. However, it could also be the case that parents start to reassure their infant *because* the infant is showing signs of distress. Regarding a potential mechanism of the association between parent distracting and infant playing / engaging in distraction, possibly reinforcement of coping behaviors is playing a role, as operant conditioning takes place when infant behavior is rewarded with parent attention (Cohen, 2002). Another mechanism is that when infants take the initiative to start playing, that parents react to this behavior by joining in the play and thereby distracting the infant. A mechanism explaining the negative association of parent praising with infant distress behaviors could be that when infants are less distressed, the parents react with praising to try to reinforce this behavior, possibly resulting in even less distress behavior shown by the infant.

Another hypothesis of this paper concerned the influence of parent symptoms of depression, anxiety, or somatization on parent and infant behavior during a venipuncture. We demonstrated that none of the psychological problems were prospectively related to parent or infant behaviors. This is consistent with some studies that also used observational measures of infant reactivity and parent behavior (Frank et al., 1995; Pillai Riddell et al., 2007). Yet our findings are inconsistent with results from two studies, of which one found that mothers' psychological problems were associated with her subjective ratings of infant pain (Pillai Riddell et al., 2007), and the other that mothers' depressed mood was related to increased infant pain response (Moscardino et al., 2006). The levels of psychological problems in our sample were low, which may account for the lack of findings.

Regarding parent chronic pain, there were no relationships with parent or infant behavior, except for parent distraction. Our expectancy was that parents with chronic pain would be more likely to reassure their infant, yet parent chronic pain was actually associated with increased distracting. Perhaps this finding represents an awareness in these parents of the influence of distraction when in pain, but we cannot infer this from our data. Further research is necessary to find out more about possible positive effects of parent chronic pain and about mechanisms. Notwithstanding, parents with chronic pain were not found to display more reassurance or empathic comments than parents without chronic pain. However, this does not rule out that these parents still can act as a model and/or reinforce their infant's expressions of pain or distress in day-to-day situations, as previous researchers have found relationships between the existence of parent and child chronic pain (Garber et al., 1990; Jamison & Walker, 1992; Levy et al., 2000; Mikail & von Baeyer, 1990; Schanberg et al., 2001). Further research on this topic is necessary as well.

Strengths of this study are the large number of participants in comparison to other studies in the field and the availability of information on many potential confounders. We chose to use an empirical approach to select behaviors from previous observation instruments and from our observations. We feel confident that the GRIDS has adequate reliability and validity. The absolute inter-rater agreement was good to excellent, although a somewhat small number of video recordings were coded for reliability analyses. Further, the correlation of the GRIDS infant distress component variable with the nurse VAS rating of infant distress was high. A further strength of our study is that objectivity in terms of behavior ratings was ensured by coding the behaviors of parents and infants in very small intervals and by only coding presence or absence of behaviors instead of interpreting behaviors. Moreover, there were different coders for infant behavior and for parent behavior, to avoid contamination. Furthermore, to our knowledge, we were the first to study the association of parent chronic pain with infant distress during a medical procedure. Another strength is the prospective design when investigating the associations of parent chronic pain and psychological problems with parent and infant behavior. Also, by designing our study to include measurements of parent chronic pain and psychological problems *before* the birth of the child, we have ensured that we could not only show prospective relationships, but also that there could not be a causal path leading from early infant distress to parent problems.

A limitation of our study is that causality of the association of parent behavior with infant distress behavior cannot be inferred. Experimental investigations studying the effects of parent reassurance on infant distress are needed. Another limitation is that caution is required when generalizing our findings, as selection bias may have influenced the results. The majority of parents in our study was educated at university level (66%) when compared to the eligible but non-participating families (53%), and especially when compared to the general population in Rotterdam (32%; Statistics Netherlands, 2007). Further, the sample of infants

whose parents consented to blood sampling is selective in terms of medical history in the first year of life. This suggests that the healthier infants were more likely to participate.

Our study was conducted in a homogeneous sample of indigenous Dutch infants and excluded infants with other national origin. Many of the previous studies in the field have investigated samples who were predominantly (76% to 89%) of European origin (Blount et al., 1997; Cohen et al., 2005; Cohen et al., 2006; Frank et al., 1995; Sweet & McGrath, 1998). However, whether U.S. samples of European descent and a European (Dutch) sample differ culturally with respect to the association between parent and infant behavior during a medical procedure has not yet been investigated.

In conclusion, this study demonstrates that parent behaviors, especially reassurance, are related to young infants' distress behaviors. Many other studies have shown that higher levels of child distress, anxiety, and/or pain in medical procedures are predictive of distress, pain, and fear in subsequent medical procedures (Blount et al., 2006). Parent behavior modification interventions might be a way to minimize pain and distress in medical procedures. Especially because some potential mechanisms imply a causal path from parent reassurance to infant distress. Moreover, reassurance is probably a natural parent behavior to display in a distressing situation for infants and children and it has been shown to occur a large percentage of the time. Behavior modification could consist of teaching parents and staff to distract the child and discouraging them from reassuring the child (Schechter et al., 2007). These recommendations can now be generalized to 1-year-old infants and to venipuncture procedures. As parent chronic pain and psychological problems were not related to increased parent reassurance and infant distress in this study, for now this behavioral advice applies to all parents with respect to medical procedures in their infant.

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Chapter 3

Children's attachment and temperament as risk factors for venipuncture distress



ABSTRACT

Objective: This study examined the effects of attachment and temperament on infant distress during venipuncture. **Method:** The study was embedded in the Generation R Study, a prospective population-based study. Two different research procedures (i.e. blood sampling and the Ainsworth Strange Situation Procedure) yielded measures of venipuncture distress and attachment security and disorganization in 246 infants aged 14 months. Four temperament traits (distress to limitations, fear, recovery from distress, and sadness) were assessed using the maternally reported Infant Behavior Questionnaire – Revised, at the age of 6 months. **Results:** There were no differences between mean levels of distress during venipuncture in infants classified as having insecure attachment, but there was a trend for disorganized attachment. The temperament traits were not related to distress. However, children with a disorganized attachment and higher temperamental fear had more venipuncture distress. **Conclusion:** When different risk factors are present simultaneously, infant distress is heightened.

INTRODUCTION

Medical procedures are a distressing experience for children. It is important to gain understanding of what determinants might affect differences in children's distress, as both the assessment and treatment of pain and distress may improve from basic knowledge about determinants underlying the experience and expression of pain (Lilley, Craig, & Grunau, 1997). Moreover, reactions to a painful medical procedure might be seen as an indicator of how children react to all types of acute pain, including everyday pains (Goodenough, Perrott, Champion, & Thomas, 2000). Thus, the medical procedure can be used to study which factors affect how children react to and deal with acute pain in general. Many variables have been found to influence procedural distress of infants and children, such as parent and staff behavior during the procedure (Blount, Corbin, Sturges, & Wolfe, 1989; Blount, Devine, Cheng, Simons, & Hayutin, 2008; Cohen, Bernard, McClellan, & MacLaren, 2005; Frank, Blount, Smith, Manimala, & Martin, 1995; Manne et al., 1992; Schechter et al., 2007; Wolff et al., 2009), children's fear and anxiety during the procedure (Blount, Piira, Cohen, & Cheng, 2006), and previous medical experiences (Blount et al., 2006; Rocha, Prkachin, Beaumont, Hardy, & Zumbo, 2003). Child variables such as attachment or temperament may also shape the child's reactions to acute pain and distress. Temperament and attachment are two distinct constructs that both impact on individual differences in cognition, affect, and behavior especially in stressful situations (Vaughn, Bost, & Van IJzendoorn, 2008). Moreover, the interaction effects of attachment and temperament affect responses to stress as well (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Vaughn et al., 2008). These two constructs therefore seem ideal candidates to relate to acute pain. Further, the reactions to a venipuncture not only indicate reactions to other types of acute pain, but high levels of pain and distress during medical procedures also increase the fear, pain and distress in future procedures (Blount et al., 2006; Rocha et al., 2003). If the fear and pain accumulate over procedures, it may prevent people from getting regular health or dental check-ups or from seeking help in early stages of disease. In particular if symptoms are not severe enough to weigh up to the fear of undergoing a medical procedure. A consequence may be that health care costs rise in the long term. To be able to reduce acute pain and distress (both during procedures and in everyday life), it is important to gain understanding of what determinants might affect differences in children's acute pain and distress reactions. As mentioned above, the venipuncture procedure can serve as a paradigm to study relations of child acute pain and distress with other variables.

Theory and previous findings on distress in relation to attachment, temperament, and the interaction between attachment and temperament will now be discussed. The quality of infants' attachment to their parent defines which attachment behaviors are elicited in situations that are stressful or fear-inducing for the infant (Weinfield, Sroufe, Egeland, & Carlson, 2008). Infant attachment quality can be classified as secure, insecure avoidant, insecure ambivalent/resistant (organized strategies; Ainsworth, Blehar, Waters, & Wall, 1978), or as

disorganized (Main & Solomon, 1990). Based on attachment theory, infants with insecure or disorganized attachment to their parent may experience increased distress or pain behavior in a medical procedure. To our knowledge, only a few studies have investigated the relationship between attachment and procedural distress. Observed behavioral reactivity due to inoculations in infants aged two, four, and six months was not related to their attachment (in)security at 18 months (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996). Walsh et al. determined both attachment and immunization reactivity in five-year-old children using three assessment methods: observational ratings, self-report, and maternal report (Walsh, McGrath, & Symons, 2008). For attachment, scores from the three assessment methods were combined. The commonly used mutually exclusive attachment categories (secure, insecure-avoidant, insecure-ambivalent/resistant, and disorganized) were regarded as four separate dimensions on which each child received a score. They found that children with a higher score on ambivalent or disorganized attachment showed stronger pain reactions and took more time to calm down; there were no associations of attachment security or avoidance with pain reactivity (Walsh et al., 2008). It is difficult to draw conclusions from the results of these two studies, because they used different study designs and different methods for assessing attachment. For example, Walsh et al. did not use the four mutually exclusive attachment categories coded from the gold standard Strange Situation Procedure by Ainsworth et al. (1978), and the study by Gunnar et al. (1996) did not investigate attachment disorganization. And although attachment disorganization seems to be related to behavioral pain reactivity in 5-year-old children (Walsh et al., 2008), it is still unclear whether this association exists in infants. In the current study, we hypothesize, based on the model of Walsh et al. (2008), that infants rely on their parents to regulate stress. Based on daily experiences with their parent, infants have expectations of the parent's availability and responsiveness in times of stress. These expectations are generalized to internal working models (Bowlby, 1969/1982) that will guide the infant's behavior in a medical procedure.

Temperament is conceptualized by Rothbart and colleagues as the constitutionally based individual differences in reactivity and self-regulation (Gartstein & Rothbart, 2003; Rothbart, Ahadi, & Evans, 2000). Temperament is relatively stable over time and in different contexts (Frick, 2004; Komsis et al., 2006). A situation that is distressing for infants, such as a medical procedure, can lead to different distress intensities depending on the temperamental traits. In children older than 3 years, the association of temperamental difficulty with behavioral reactivity to medical procedures has been shown (Bournaki, 1997; Helgadottir & Wilson, 2004; Lee & White-Traut, 1996; Rocha et al., 2003; Schechter, Bernstein, Beck, Hart, & Scherzer, 1991; Young & Fu, 1988). A few studies have also reported on the association of infant temperament with procedural pain or distress. No relationship was found between temperamental negative emotionality and infant pain reactivity (Lilley et al., 1997) or between temperamental fear and behavioral distress (Gunnar et al., 1996). However, infant 'difficultness' was related to pain behavior at age 6 months, whereas difficultness at 18 months of age was not cross-

sectionally associated with pain behavior (Sweet, McGrath, & Symons, 1999). More recent studies found that infants having more difficult temperament displayed higher behavioral reactivity (Klein, Gaspardo, Martinez, Grunau, & Linhares, 2009), cried longer (Piira, Champion, Bustos, Donnelly, & Lui, 2007), but did not show greater facial pain responses (Piira et al., 2007). The results are inconsistent, perhaps because different studies used different dimensions and definitions of temperament, and different measures of pain/distress.

Some investigators have studied interaction effects of attachment and temperament to explain adaptive responses to stress. Temperament theory assumes that reactivity and regulation of affect and behavior are broad trait-like characteristics of a person. Attachment theory assumes that arousal and regulation of affect and behavior in stressful situations are guided by the infants' internal working models. To our knowledge, only one study has examined the interaction of attachment and temperament on behavioral reactivity in a medical procedure; the interaction of insecure attachment and fearful temperament was not significantly associated with behavioral distress (Gunnar et al., 1996). These authors did not investigate disorganized attachment in relation to temperament and distress. Although they did not find a significant interaction of secure-insecure attachment and temperament in predicting behavioral distress, there was some evidence of an interaction effect on other distress measures, such as the stress hormone cortisol (Gunnar et al., 1996). Other researchers also found an interaction effect of attachment insecurity and temperamental inhibition on cortisol stress reactivity (Nachmias et al., 1996).

In the current study, we examined the associations of attachment and temperament with infants' venipuncture distress behavior. We hypothesized that insecure attachment is related to increased venipuncture distress in infants. We also expected disorganized attachment to be related to increased distress. Further, we hypothesized that temperamental fear, distress to limitations, recovery from distress, and sadness predict infant venipuncture distress, as these temperamental dimensions specifically concern the reactivity to and regulation of stressful events. Moreover, we expect that infants with both highly reactive temperament and insecure or disorganized attachment are more distressed than other infants.

METHODS

Setting

The Generation R Study is a prospective population-based study investigating growth, development and health from fetal life into young adulthood in Rotterdam, the Netherlands. All pregnant women living in Rotterdam with expected delivery dates between April 2002 and January 2006 were eligible to participate in the Generation R Study. Mothers and children with diseases and/or developmental delays were not excluded. The Generation R Study has been

described in detail elsewhere (Jaddoe et al., 2008). The current investigation was conducted in a subgroup within the Generation R Study: the Generation R Focus Study, which is carried out to obtain detailed measurements of children's development. The children participating in the Generation R Focus Study were eligible if they were born between February 2003 and August 2005. Only children of Dutch national origin were included, meaning that the children, their parents, and their grandparents were all born in the Netherlands. The children visited the research center at 14 months of age for somatic and behavioral assessments. Written informed consent was obtained from all participants. The study has been approved by the Medical Ethical Committee of the Erasmus Medical Center, Rotterdam.

Study population

The 14-month visit of the Generation R Focus Study included optional blood sampling. There was no medical indication for blood sampling, but 407 parents consented to the procedure. In 361 infants of these parents, venipunctures were actually performed. The main reason for not performing a venipuncture was practical, for example if no good vein could be located. Video recordings of the venipuncture were available for 275 (68%) infants, due to a late start of this current investigation and some technical problems with the equipment. For 8 infants, no video recordings of the Strange Situation Procedure were available (mainly because of technical problems), while in another 18 infants, the parent accompanying the infant during the venipuncture was not the parent accompanying the infant during the Strange Situation procedure. Furthermore, there were three pairs of siblings participating in the investigations; we randomly excluded data from one infant. After exclusion of these 29 infants, analyses were performed on the data of 246 infants (60% of eligible infants).

The characteristics of parents and infants are provided in Table 3.1. Infants were aged between 13.1 and 17.5 months ($M = 14.5$, $SD = 0.8$), 51% were boys. A total of 221 mothers (90%) and 25 fathers participated in the blood sampling procedure. Of these parents, 94% was the primary caregiver of the infant. Sixty-seven percent of parents had attained a form of higher education.

Non-response analyses

To examine whether non-response was selective, missing data analyses were carried out. Infants who were eligible but for whom there was no video recording of the venipuncture, were compared to the infants for whom we did have a recording. Infants were compared on covariates such as age, sex, parental age, gestational age at birth, birth weight, parity, medical history during first year of life, parental education, family functioning, and parental psychological problems, and on the study determinants attachment security, attachment disorganization, and temperament. Families of eligible, non-participating infants were

Table 3.1. Infant and parent characteristics (*N* = 246)

Characteristic	<i>M</i> (<i>SD</i>) / %	Range
Infant		
Sex (% boy)	50.8%	
Age (months)	14.5 (0.8)	13.1 – 17.5
Gestational duration (weeks)	40.1 (1.6)	28.9 – 43.0
Illness / teething discomfort in week preceding visit (% yes)	58.9%	
Days spent in daycare per week		
0	15.2%	
1.0 to 2.5	43.5%	
3.0 or more	41.3%	
Contacted general practitioner (% twice or more) ^a	60.4%	
Contacted medical specialist (% once or more) ^a	39.1%	
Hospitalized (% once or more) ^a	14.2%	
Parity (% of infants being firstborn)	56.5%	
Infant venipuncture behavior		
Infant distress scale	2.37 (0.67)	0.68 – 4.10
Infant crying (% of procedure duration)	0.58 (0.30)	0.00 – 1.00
Infant resisting (% of procedure duration)	0.20 (0.18)	0.00 – 0.82
Infant requesting emotional support (% of procedure duration)	0.07 (0.13)	0.00 – 1.00
Infant information seeking (% of procedure duration)	0.25 (0.20)	0.00 – 0.93
Infant playing / engaging in distraction (% of procedure duration)	0.24 (0.18)	0.00 – 0.86
Infant attachment classification		
A (Avoidant; % of ABCD)	10.6%	
B (Secure; % of ABCD)	52.4%	
C (Resistant; % of ABCD)	13.4%	
D (Disorganized; % of ABCD)	23.6%	
Infant temperament (<i>N</i> = 136)		
Distress to limitations	0.63 (0.31)	0.00 – 1.77
Fear	0.30 (0.26)	0.00 – 1.40
Recovery from distress	0.43 (0.26)	0.00 – 1.25
Sadness	0.63 (0.25)	0.00 – 1.33
Parent		
Sex (% mother)	89.8%	
Caregiver accompanying child (% primary)	93.8%	
Age (years)	33.6 (4.2)	20.1 – 52.3
Educational level		
No or primary	0.8%	
Secondary	32.1%	
High	67.1%	
Psychological problems	0.18 (0.24)	0.00 – 1.90
Family functioning (% unhealthy)	5.7%	

^a Assessments of the infant's medical history spanned the period of 0 to 12 months of age.

experiencing less family difficulties than families of participating infants (1.3% versus 6.1% respectively), $\chi^2(1, N = 379) = 5.12, p = .02$. There were no differences on any other variable.

Procedure of 14-month visit

One hour before venipuncture, the infant received a patch of the anesthetic eutectic mixture of prilocaine and lidocaine (EMLA) on the skin of the venipuncture site, to reduce pain from this procedure. After the application of EMLA, the parent and infant participated in the Strange Situation Procedure (SSP; described later) to assess attachment; the SSP was videotaped. After the SSP, the infant and parent participated in various non-stressing measurements, such as a playful assessment of motor development. At the end of the 14-month visit, blood sampling (venipuncture) took place, which was videotaped. The nurse and assistant, who sampled blood, were blind to the infant's behavior during the SSP. When both parents accompanied the infant to the visit, we asked the parent who spent the most time with the infant to take part in the SSP; but for blood sampling, the choice of who participated was left to the parents. Twenty-five infants (9.1%) were accompanied by both parents; only the behaviors of the parent on whose lap the child was sitting during the venipuncture were coded for analyses.

Measures

Infant temperament

Temperament was assessed using mother-reports of four scales of the Infant Behavior Questionnaire – Revised (IBQ-R; Gartstein & Rothbart, 2003), six months after birth. The IBQ-R asks mothers to rate the frequency of specific behaviors observed over the past week. We chose four scales that directly refer to infant reactivity and regulation of stress: distress to limitations, fear, recovery from distress, and sadness. Distress to limitations refers to negative emotionality and reactions to caretaking activities. Fear includes startle or distress to new objects and persons. Recovery from distress refers to rate of recovery from peak distress or frustration and ease of falling asleep. Finally, sadness relates to general low mood. In contrast to the other three scales, higher original scores on recovery from distress denoted less problems. They were reversed, for ease of interpretation. Thus, higher scores on all of the scales indicate more reactive behavior. The scores for each scale were calculated by dividing the sum of the items by the number of endorsed items. Internal consistencies for the four scales of the IBQ-R in the current sample were $\alpha = .73$ for distress to limitations, $\alpha = .82$ for fear, $\alpha = .70$ for recovery from distress, and $\alpha = .67$ for sadness, which is comparable to the internal consistencies reported by Gartstein and Rothbart (2003). Data on the temperamental traits was available for 155 infants. Of the 91 infants without temperament data, most mothers never received the 6-month questionnaire on temperament due to technical problems with

the database (Roza et al., 2008). This missingness is probably completely at random, which implies there is a loss of power, but this is unlikely to introduce bias.

Strange Situation Procedure and measures of infant attachment

Infant attachment was assessed using the Strange Situation Procedure (SSP; Ainsworth et al., 1978). The SSP is a widely used and well-validated procedure to measure the quality of the attachment relationship. The procedure consists of seven episodes of three minutes each and is designed to evoke mild stress in the infant to trigger attachment behavior evoked by the unfamiliar lab environment, a female stranger entering the room and engaging with the infant, and the parent leaving the room twice. The SSP used in the current study included all these stimuli but to make it fit into a tight time schedule, we shortened the (pre-)separation episodes with one minute, keeping the critical reunion episodes intact. Infant behavior was observed to code organized (avoidant [A], secure [B], or resistant [C]) and disorganized (D) attachment. Attachment security (ABC) was coded according to the Ainsworth coding system (Ainsworth et al., 1978) and attachment disorganization (D) according to the system of Main and Solomon (Main & Solomon, 1990). We calculated two dichotomous variables to be used in the analyses. The attachment security variable was defined as B versus A, C, and D. The attachment disorganization variable was defined as D versus A, B, and C. A reliable coder carried out coding of the infants' behavior; she was trained and qualified to code infant behavior from SSPs at the University of Minnesota. This coder was blind to results on all other measurements. One of two expert coders was consulted for inconclusive cases, which were discussed to reach consensus (6.5% of the cases). Inter-coder agreement was calculated on 70 SSPs that were coded by a second reliable coder. For ABCD classification, inter-coder agreement was 77% ($\kappa = .63$), agreement on security was 83% ($\kappa = .66$), and agreement on disorganization was 87% ($\kappa = .64$).

Infant distress

The distress behavior of the infant during the venipuncture was coded using the Generation R Infant Distress Scale, as described in an earlier study by our group (Wolff et al., 2009). The 'infant distress' scale score combined the following behavior codes, based on factor analysis: crying, resisting, requesting emotional support, the reverse-coded information seeking, and the reverse-coded playing/engaging in distraction (Wolff et al., 2009). These five behavior codes were coded as present or absent for every 5-second interval of the video recordings. The proportion for each behavior code was calculated by dividing the number of intervals in which that behavior code occurred by the total number of intervals. Scores of the codes ranged from 0 to 1. The infant distress scale score was calculated by summing the proportions of occurrence of the five behavior codes. Due to the possibility of simultaneous occurrence of two or more behavior codes, this composite distress measure was not calculated as a proportion as the individual measures were, but rather it is a severity measure with a possible

range of 0 to 5. The Cronbach's alpha for this measure was .67. The five raters who coded infant venipuncture distress were different persons than the rater who coded attachment. Raters were blind to results on all other measurements. The raters were trained to code the recordings; after this training all raters coded a random selection of recordings to calculate inter-rater reliability ($N = 11$). The intraclass correlation coefficient (using an absolute agreement definition) was .99 for the infant distress scale. The intraclass correlation coefficients for the five separate behavior codes were .99 for crying, .97 for resisting, .93 for requesting emotional support, .98 for information seeking, and .98 for playing/engaging in distraction.

Covariates

Demographics were obtained from the midwife and hospital records and from questionnaires: infant sex, age, gestational age at birth, birth weight, parity, infant medical history during the first year of life (contact with general practitioner, contact with medical specialist, hospitalization), and parent age. We considered several situational variables as possible confounding variables, such as whether the infant had been ill in the week preceding the visit or whether and how much time the infant spent in day-care. Parent education was classified as primary education (elementary school), secondary education (high school, vocational training), or higher education (university degree). As overall measures of family functioning and parent psychological problems, we used the subscale General Functioning of the Family Assessment Device (Byles, Byrne, Boyle, & Offord, 1988; internal consistency in our study was $\alpha = .94$) and the Global Severity Index of the Brief Symptom Inventory (De Beurs, 2006; internal consistency in our study was $\alpha = .90$), both assessed in mid-pregnancy.

Data analyses

We carried out multiple imputation of the missing values on the temperament traits, to increase power (Schafer, 1997, 1999). As mentioned in the Measures Section, the missing values resulted from technical difficulties in sending out questionnaires, which means a loss of power, but no bias being introduced. Moreover, non-response analyses revealed that missingness of the data was not dependent on child age, child sex, child attachment classification, gestational age at birth, birth weight, parity, parent age, parent sex, parent education, parent psychological problems, or family difficulties. We were thus confident that the assumption for multiple imputation techniques, 'missing at random', was being met. We also tested the assumptions of linearity, normality, homoscedasticity, and collinearity, and we checked for outliers. A log-transformed temperamental fear variable was used in the imputation model; the back-transformed variable was used in the actual analysis models. Other assumptions were not violated. As the rate of missing data on temperament was fairly high (37%), we generated 10 imputed datasets to still achieve a relative efficiency of at least .97 (Rubin, 1987). Multiple imputation using a quite high number of imputed datasets is a

statistically valid approach, showing adequate results in the presence of high rates of missing data (Schafer & Graham, 2002; Wayman, 2003). To perform the multiple imputation, we used the Markov Chain Monte Carlo method in Proc MI as implemented in SAS 9.2. Imputed values of dichotomous variables were not rounded after imputation, to avoid introducing bias (Horton, Lipsitz, & Parzen, 2003). Both the imputation model and the actual analysis models were fitted using standard deviation (SD) scores of temperament, for ease of interpretation of the parameter estimates. After fitting linear regression models, we used Proc MIANALYZE in SAS 9.2 to combine the parameter estimates generated from each of the 10 imputed datasets, and to obtain adjusted standard errors by incorporating between- and within-imputation variance. The results of analyses including participants with missing data on temperament were similar to the results in participants with completely observed data.

ANOVA's were carried out in SAS 9.2 to derive mean distress levels for attachment security and attachment disorganization. Then, we carried out linear regression analyses to test the association of venipuncture distress with attachment security (B versus non-B), disorganization (D versus non-D), and the four temperament scales distress to limitations, fear, recovery from distress, and sadness. Next, we calculated interaction terms for each of the two dichotomous attachment variables with each of the four temperament variables. A linear regression analysis was carried out to test whether there were interaction effects of highly reactive temperament and insecure or disorganized attachment on venipuncture distress after controlling for their main effects. We did not adjust for multiple testing.

The linear regression analyses were adjusted for infant sex. Further covariates were selected as a result of exploratory analyses, and were included in the linear regression analyses if one or more effect estimates changed meaningfully (defined as more than 10%). Consequently, the regression analyses were also adjusted for parent education, parent reported family functioning, and infant visits to a medical specialist in the first year of life.

A power analysis showed that a sample of 246 participants, with $\alpha = .05$, a conservative $\beta = .90$, and 10 predictors (i.e., 6 main effect variables and 4 covariates), yields the ability to detect a small to medium effect size of at least $f^2 = .09$ (i.e., $R^2 = .08$; Soper, 2010).

RESULTS

Infant distress, attachment, and temperament descriptives

The infant distress score in the venipuncture procedure ranged from .68 to 4.10 with a mean of 2.37 (Table 3.1). Of the 246 infants, 129 (52%) infants were classified as securely attached (B) to their parent and 58 (24%) infants were classified as displaying disorganized attachment (D). The mean of temperament traits ranged from .30 for fear to .63 for sadness and for distress to limitations.

Mean infant distress per attachment category

The unadjusted ANOVA of attachment and venipuncture distress showed that infants with a secure attachment classification (B) showed a mean distress level of 2.34 ($SD = .67$) during the venipuncture procedure. Infants with insecure attachment (A, C, and D) showed a mean distress level of 2.41 ($SD = .67$). These mean distress levels did not differ significantly. Infants with disorganized attachment (D) showed a somewhat higher distress level ($M = 2.49$, $SD = .70$) than infants without a disorganized attachment classification (A, B, and C; $M = 2.33$, $SD = .66$). However, the difference again was not significant.

Main effects of infant attachment and temperament on distress

Next, we performed linear regression analyses, adjusted for infant sex, parent education, parent reported family functioning, and infant visits to a medical specialist in the first year of life (called 'covariates' from now on). Insecure attachment predicted a .10 higher mean distress level than secure attachment. Disorganized attachment was associated with a .18 higher mean distress level, after adjustment for covariates. These main effects were not significant, although there was a trend for disorganized attachment ($p = .08$).

There was a .10 decrease in mean infant distress for every standard deviation (SD) increase in distress to limitations, a .02 increase in distress per SD increase in fear, a .09 increase in distress per SD increase in recovery from distress, and a .12 increase in distress per SD increase in sadness, after adjustment for covariates. All of these associations were not significant.

Interaction of attachment and temperament on infant distress

Table 3.2 presents the linear regression model including the interaction effects. The interaction between disorganized attachment and fearful temperament significantly predicted distress, after adjustment for the covariates and the main effects of attachment and temperament. For infants classified as disorganized, each SD increase in fear was associated with a .56 higher score on distress ($p = .035$). The explained variance of this model was 13.5%. Figure 3.1 shows the significant positive relation between infant distress and temperament among infants with disorganized attachment, and shows that there was no relation between infant distress and temperament among infants with organized attachment.

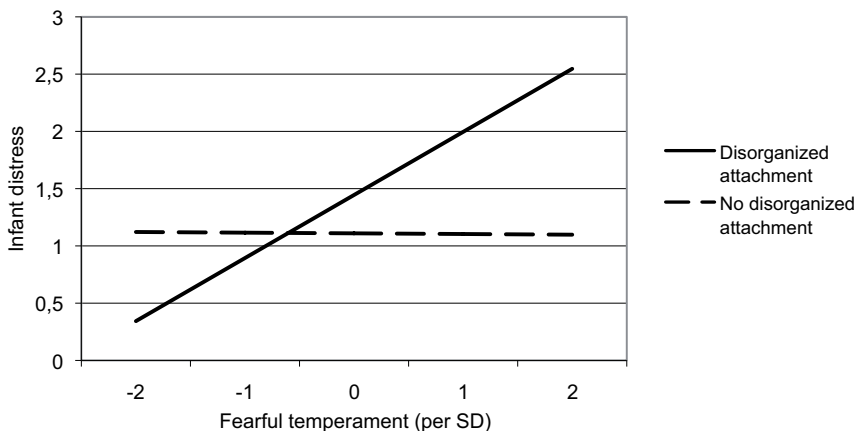
Table 3.2. Interaction effects of attachment and temperament on infant distress

Determinant	Infant distress
	B (95% CI)
Attachment	
Insecurity (ACD versus B)	0.073 (-0.175; 0.321)
Disorganization (D versus ABC)	0.335 (-0.024; 0.694) #
Temperament	
Distress to limitations (per SD)	-0.147 (-0.353; 0.060)
Fear (per SD)	-0.006 (-0.199; 0.187)
Recovery from distress (per SD)	0.121 (-0.072; 0.313)
Sadness (per SD)	0.149 (-0.088; 0.387)
Interaction terms	
Insecurity x distress to limitations	0.301 (-0.047; 0.649) #
Insecurity x fear	-0.068 (-0.425; 0.289)
Insecurity x recovery from distress	-0.059 (-0.316; 0.197)
Insecurity x sadness	-0.084 (-0.461; 0.293)
Disorganization x distress to limitations	-0.173 (-0.610; 0.264)
Disorganization x fear	0.557 (0.038; 1.075) *
Disorganization x recovery from distress	-0.016 (-0.413; 0.381)
Disorganization x sadness	-0.241 (-0.716; 0.234)

Note. The B-values of attachment and temperament are not the main effects, but come from the linear regression model including the interaction terms. Main effects of attachment and temperament are presented in the text only. Standard deviation (SD) scores of the temperament scales were used. The model was adjusted for infant sex, infant visits to a medical specialist in the first year of life, parent education, and family difficulties.

$p < .10$.

* $p < .05$.

**Figure 3.1.** Interaction effect of attachment and temperament on venipuncture distress

DISCUSSION

The current study showed that there was a trend for attachment disorganization to predict higher levels of venipuncture distress in 14-month-old infants. Furthermore, the interaction of disorganized attachment and fearful temperament was significantly associated with distress; fear predicted an increase in distress only in infants with a disorganized attachment classification. The main effects of attachment insecurity and temperament were not associated with increased infant distress.

The trend we found for a main effect of attachment disorganization is consistent with the findings by Walsh et al. (2008), who found that children with higher scores on disorganized attachment had a stronger reaction to the immunization procedure. Our non-significant finding for the main effect of the attachment insecurity classification is in line with the study by Gunnar et al. (1996), who found that previous pain experiences were not related to infants' secure-insecure attachment. Also Walsh et al. (2008) found no relationship for their secure and avoidant attachment dimensions with 5-year-old children's immunization reactivity. It seems that attachment insecurity does not affect a child's distress reactions, whereas attachment disorganization does impact on a child's distress. An explanation as to why we only found a trend, is that the effect of disorganized attachment on procedural distress may become stronger as the child grows older, explaining both our result and the result found by Walsh et al. (2008). Further research is necessary.

Regarding the prospective mother-reported temperament ratings, we found no main effects of any of the temperamental traits, measured at 6 months of age, with venipuncture distress at 14 months of age. Our measure of distress included both behaviors indicative of high reactivity as well as low regulation of distress. Perhaps the hypothesized main effects were non-significant because we used this composite measure. However, our non-significant result is consistent with many previous infant studies (Gunnar et al., 1996; Lilley et al., 1997; Sweet et al., 1999), but not all (see Klein et al., 2009; Piira et al., 2007). It is interesting that a hypothesized association that comes from a clear theoretical background and that has been consistently found in children older than 3 years (Bournaki, 1997; Lee & White-Traut, 1996; Rocha et al., 2003; Schechter et al., 1991), yields inconsistent results in infant samples. Perhaps temperament might be associated with learning effects in the first years of life, explaining why a clear relationship has been found between temperament and procedural distress in children older than 3 years but not in infants.

Although there were no main effects of attachment or temperament on infant venipuncture distress, we found an interaction effect. Infants classified as having disorganized attachment, who also have higher levels of fear, showed more distress during the venipuncture. In view of the number of tests performed in this study, this result must be interpreted carefully. Yet, the association is consistent with the theoretical frameworks of attachment and temperament and with the breadth of related areas of research investigating the interaction effects of

attachment and temperament on stress reactivity and regulation (Vaughn et al., 2008). As the venipuncture procedure was used as a paradigm investigating infants' reactions to distress and acute pain in general (Goodenough et al., 2000), we argue if disorganized attachment and fearful temperament interact to determine the risk of increased acute pain and distress, this can be generalized to other situations of acute pain, such as falling during play. A likely explanation of this relation is that infants with disorganized attachment fail to develop effective strategies to regulate negative emotion. When these infants also have a fearful temperament trait, this will result in higher distress (more negative emotion, less regulation) during stressful or painful situations. Future research is necessary to replicate this result.

The interaction effect (.56 increase in infant distress) may not seem clinically relevant, but it is almost the size of the standard deviation of the distress measure (.67). An increase of almost a standard deviation is quite large. It means that a child with both disorganized attachment and fearful temperament always scores one distress-quartile higher than another child without both disorganized attachment and fearful temperament but with otherwise exactly the same characteristics. Thus, for a small proportion of the population, a fearful temperament combined with disorganized attachment triggers or is a necessary component of the occurrence of high distress. Furthermore, the strength of this interaction effect is important for etiological reasons, on a population level. This finding provides knowledge on mechanisms. It seems that not individual characteristics of child (or parent) influence the amount of acute pain or distress, but that characteristics of parent and child interact and that this relational aspect has an impact on children's acute pain and distress. Future research on acute pain and distress should consider relational aspects. An implication for parenting a child with acute pain (both in everyday situations and during medical procedures) is that parents of fearful infants can help their infant regulate acute pain and distress, in particular if their infant shows a disorganized reaction to stress. However, parents of infants who display a disorganized attachment, often also have unresolved/disorganized attachment representations themselves. Van IJzendoorn performed a meta-analysis and found a combined effect size of $d = 0.65$, $r = .31$ (Van IJzendoorn, 1995) for parent's unresolved attachment predicting infant's disorganized attachment. It is thought that parents' unresolved state of mind causes these parents to interact with their infant in a frightening/frightened way, which then leads to the development of infant disorganized attachment (Lyons-Ruth & Jacobvitz, 2008). Thus, these parents might find it particularly hard to help regulate their infant's acute pain and distress. A short screening at child health centers and the offer of psycho-education might be a solution. Moreover, during medical procedures, behavioral coaching of the parent is found to be effective (Cohen et al., 2006), as well as the staff's distraction aimed directly at the infant (Cohen, 2002).

One limitation of the current study is that we found a higher proportion of attachment disorganization (23.6%) than was reported in a meta-analysis for US normal low risk samples (15%; Van IJzendoorn, Schuengel, & Bakermans-Kranenburg, 1999). It could be argued that

selection bias affected our results. However, the proportion of attachment disorganization in our sample was similar to that in other infants in the Generation R Study who did not have venipuncture distress data available. Moreover, selection bias is probably stronger in the small convenience samples used in other studies, leading to an under-representation of families with problems, in which insecure and disorganized attachments are assumed to occur more frequently. This could have led to a previous underestimation of the prevalence of disorganized attachment in the general population. Further, we only had mother reports of the temperament measure. An aggregated variable using assessments from multiple informants (i.e. mother and father) would be more robust. Another limitation is that the Generation R Study was not designed to investigate the current research question. Had we found significant main effects of attachment classification on venipuncture distress, we would not have been able to rule out a carry-over effect of distress from the SSP to the venipuncture procedure. However, we did not find main effects, so the non-significant main results as well as the interaction effect remain informative.

A strength of this study is the fact that we used observational measurements of attachment and venipuncture distress. Further, the observations that yielded the assessments of attachment and distress originated from different lab procedures (i.e. different video recordings) and the actual behavior ratings were performed by different raters and using a double-blind design. The relationship between mother-reported temperament and venipuncture distress was investigated prospectively from 6 to 14 months of age. Moreover, we had information available on a large number of potential confounding variables. Another strength of this study is the relatively large number of participants in comparison to the other studies in the field. Furthermore, by multiply imputing the missing values, we reduced any possible selection bias and increased power. Power calculations showed that we had enough power to detect small to medium effect sizes.

This underpins our conclusion that there are no main effects of temperament or attachment on children's acute pain and distress. The distress of infants is thus not increased dependent on the sensitivity of the parent (i.e. sensitivity is a precursor of attachment classification), but on interaction of child and parent factors. When different risk factors are present simultaneously, acute pain and distress are heightened.

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Part 2

Child chronic pain and somatic complaints



Chapter 4

Parental and children's risk factors for somatic complaints



ABSTRACT

Objective: To investigate the effect of child temperament, maternal psychological symptoms, maternal chronic pain, and parenting stress on children's somatic complaints.

Methods: The study was embedded in the Generation R Study, a population-based cohort study. Child somatic complaints were assessed via mother-report in 5,171 children, at 18 months. Questionnaires assessed maternal somatic symptoms, symptoms of depression, and anxiety during pregnancy and two months after delivery, maternal chronic pain during pregnancy, parenting stress 18 months after birth, and mother-reported child temperament 6 months after birth, as the determinants. **Results:** Fearful temperament, temperamental falling reactivity, maternal somatic symptoms, anxiety symptoms, and parenting stress each independently and prospectively increased the likelihood of children's somatic complaints at 18 months of age. **Conclusions:** In toddlers, temperament, maternal stress, and maternal somatic symptoms seem particularly important for the development of somatic complaints, but long-term research is needed to establish causality and predictive value of these factors.

INTRODUCTION

Somatic complaints, particularly recurrent pain complaints, are common in childhood (Campo & Fritsch, 1994). Somatic symptoms or complaints in children include abdominal pain, headaches, musculoskeletal pain, fatigue, nausea, loss of appetite, and dizziness, among others (Eminson, 2007). Medically unexplained somatic symptoms are a heterogeneous group of conditions characterized by persistent physical symptoms that cannot be explained by medical illness (Brown, 2007). One study found that 56% of children reported one or more symptoms during the preceding two weeks, as assessed with the Children's Somatization Inventory, a self-report instrument which asks children to rate the frequency of 36 symptoms (Garber, Walker, & Zeman, 1991). Overall, the exact prevalence of somatic symptoms in children, however, cannot easily be derived from the literature, because of inconsistent definitions between studies (some definitions include only pain, others also include symptoms like dizziness or nausea) and the use of different measurement instruments (see review of Campo & Fritsch, 1994). Moreover, because prevalence studies mostly investigated school-aged children, the frequency of somatic symptoms in toddlers is not known.

Children often express distress through somatic symptoms (Craig, Cox, & Klein, 2002; Garralda, 1996). Most symptoms are preceded by psychosocial stress and are of short duration, involving little functional impairment (Eminson, 2007). Nevertheless, medically unexplained somatic symptoms can be a burden on the child, the family, and the health care system (Campo & Fritsch, 1994; Eminson, 2007). Somatic complaints in toddlers have also been associated with behavior problems in adolescence, such as increased externalizing and internalizing problems (Pihlakoski et al., 2006). Moreover, somatic symptoms frequently become chronic and lead to the development of somatization disorder later in life (Rocha, Prkachin, Beaumont, Hardy, & Zumbo, 2003), which is a defined psychiatric condition involving a large number of symptoms, often coinciding with psychological stress (American Psychiatric Association, 2000).

In terms of causes of somatic symptoms, several aspects have been identified, among which are psychosocial factors, such as family tension or child worry about parents, child temperament, and parent physical and mental health complaints. Studies to date have investigated one factor at a time, which makes developing a comprehensive theoretical model in order to explain somatic symptoms not straightforward. In addition, somatic symptoms do not constitute a unitary phenomenon (Eminson, 2007). Eminson thus suggests a simple model which aims to identify 'within child factors,' 'within parent factors,' and 'health care professional factors.' At each level of factors, there will be processes that either increase or maintain a child's symptoms and associated impairment, or that decrease the symptoms and impairment. Interactions between the child and the parent and between the parent and the health care system may also exacerbate or maintain symptoms (Eminson, 2007). In the current study, many potential factors will be investigated; the focus is on the 'within child factors' and 'within parent factors'.

The present study will focus on temperament as a primary child factor. Previous research suggests that temperament impacts the presence of somatic symptoms. 'Emotionality' at age three positively determined somatic symptoms at four years of age (Grunau, Whitfield, Petrie, & Fryer, 1994). Rocha and Prkachin (2007) investigated negative mood, withdrawal and adaptable behavior, combined into a temperament trait 'adjustment'. They found that lower 'adjustment' at age five was related to increased somatic symptom reports at age 12. Yet, there is a lack of knowledge about these associations in children younger than three years.

When it comes to parent factors, research has focused on parent somatic symptoms. A study by Craig et al. investigated children of mothers suffering from chronic somatization (i.e. medically unexplained physical symptoms of at least 2 years duration), mothers with chronic ill health (i.e. medically diagnosed symptoms of at least 2 years duration), and mothers who never suffered from chronic physical symptoms. They found that mothers with chronic somatization reported more headaches, stomach-aches, other types of pain, fatigue, and eating difficulties in their children than chronically ill or healthy mothers (Craig et al., 2002). Livingston, Witt, and Smith (1995) studied a sample of parents with somatic symptoms and the number of parental somatic symptoms significantly predicted the presence of more than two unexplained somatic symptoms in the child. Further, in a sample of children with recurrent abdominal pain, an association was found between parental somatic symptoms and children's somatic symptoms (Walker, Garber, & Greene, 1994). Results from all these studies are consistent, yet all studies investigated children aged four or older.

Keeping with 'within parent factors', anxiety and depression have also been found to be more common in mothers of children with somatic complaints (Campo & Fritsch, 1994) or specific pain complaints (Campo et al., 2007; Garber, Zeman, & Walker, 1990). However, most research concerning this association has investigated children with pain, which means these findings cannot be generalized to children with other somatic symptoms.

Finally, parenting stress is another potential parent factor. It is theorized that compromised parenting reduces the ability of the child to deal with common childhood aches (Grunau et al., 1994). To our knowledge, no research has investigated parenting stress as a predictor of children's somatic symptoms. However, parenting stress has been investigated in relation to internalizing problems, a higher order classification of behavior problems, which include somatic complaints (Achenbach & Edelbrock, 1978; Achenbach & Rescorla, 2000). Parenting stress measured at one, two, and three years of age predicted internalizing problems of four-year-old children (Goldberg et al., 1997). Parenting stress has also been related to the persistence of internalizing problems in preschool children (Briggs-Gowan, Carter, Bosson-Heenan, Guyer, & Horwitz, 2006). These findings point to a possible contribution of parenting stress to somatic symptoms.

There is a lack of knowledge about parental determinants of somatic complaints in children younger than four years. Yet in the first few years of life, the development of children is strongly influenced by the parents. If a parent experiences physical or psychological

symptoms, the child's development can easily be affected, possibly precipitating somatic symptoms. Child and parent factors may precipitate the development of somatic complaints independently and also in interaction. The aim of the present study was to prospectively investigate several potential determinants of medically unexplained somatic symptoms in young children. Both within child factors and within parent factors were investigated. Based on Eminson's model and previous research, we hypothesized that child temperament, maternal chronic pain, somatic symptoms, depressive symptoms, anxious symptoms, and current parenting stress each independently and prospectively predict increased somatic symptoms in 18-month-old children.

METHODS

Setting

The current investigation was conducted within the Generation R Study, a population-based cohort study from 12 weeks gestation into young adulthood in Rotterdam, the Netherlands. The Generation R Study, designed to investigate determinants of health, development, and growth, has been described previously in detail (Jaddoe et al., 2006). At inclusion in the study, written informed consent was obtained from all participants. The Medical Ethical Committee of the Erasmus Medical Center, Rotterdam, approved of the study.

Participants and procedures

All pregnant women living in Rotterdam with expected dates of delivery between April 2002 and January 2006 were invited to participate. A total of 7,295 women with live born children gave consent for postnatal follow-up. When the children were 18 months old, 7,096 questionnaires were sent out (3% not sent out due to logistical problems) and 5,342 questionnaires were returned (response rate 75%). A total of 5,171 parents completed the questions concerning child somatic complaints. The mean age of the children was 18.4 months ($SD = 1.0$ month) and 49.6% were boys. The mothers were on average 33.3 years old. The national origin of the children was 66.7% Dutch, 9.0% other Western, such as European or American, and 24.3% other non-Western, such as Moroccan, Turkish, or Surinamese.

To examine whether non-response was selective, missing data analyses were carried out, comparing the parents who completed the 18 months questionnaire on somatic complaints with those who did not return or complete that questionnaire. We conducted Student's *t*-tests for normally distributed continuous variables, Mann-Whitney U-tests for continuous variables that were not normally distributed, and χ^2 -tests for categorical variables. There was a higher percentage of children of non-Western origin among the families who did not

complete the questionnaire of child somatic complaints (53.3% vs. 24.3% respectively), $\chi^2 (2, N = 6817) = 530.0, p < .001$. Parents who did not complete the questionnaire were less likely to take their child to the general practitioner in the first year of the child's life (64.3% vs. 69.0% respectively), $\chi^2 (1, N = 5627) = 7.77, p < .005$, were educated at a lower level (27.1% vs. 56.6% university education), $\chi^2 (2, N = 6633) = 534.1, p < .001$, and were also more likely to report chronic pain (38.9% vs. 35.4%), $\chi^2 (1, N = 6278) = 6.3, p = .012$, symptoms of depression (Mann Whitney $Z [Z] = -11.0, p < .001$), symptoms of anxiety ($Z = -9.3, p < .001$), somatic symptoms ($Z = -12.2, p < .001$), and more temperamental difficulties with respect to the child's activity level (mean 0.91 vs. 0.78), $t(4113) = 8.7, p < .001$, distress to limitations (mean 0.79 vs. 0.68), $t(4117) = 7.1, p < .001$, fear ($Z = -7.6, p < .001$), and falling reactivity ($Z = -6.6, p < .001$).

Measures

Over the course of the Generation R Study parents completed many questionnaires at different assessment moments. Due to convenience and methodological issues, specific measures were administered at different time points over the course of the study. During pregnancy, we assessed maternal chronic pain at 12 weeks gestation and maternal psychological symptoms at 20 weeks gestation. Maternal psychological symptoms were assessed again two months after the child's birth. Child temperament was assessed six months after birth. Parenting stress and child somatic complaints were measured when the children were 18 months old.

Child temperament

Child temperament was assessed using an adapted version of six scales of the Infant Behavior Questionnaire – Revised (IBQ-R; Gartstein & Rothbart, 2003). The IBQ-R asks parents to rate the frequency of specific behaviors observed over the past week (Gartstein & Rothbart, 2003). The six scales in our adapted version included Activity Level, Distress to Limitations, Fear, Duration of Orienting, Falling reactivity, and Sadness (Roza et al., 2008). Activity level relates to gross motor activity and squirming. Distress to limitations refers to negative emotionality and reaction to frustrating situations. Fear includes rejection of new objects and persons. Duration of orienting comprises items on attention and distractibility. Falling reactivity refers to rate of recovery from peak distress or frustration. Finally, sadness relates to lowered mood due to personal suffering or object loss. In contrast to the other five scales, the original scores on falling reactivity denoted less problems. They were reversed, for ease of interpretation. Thus, higher scores on all of the scales indicate more difficult behavior. Similar to Gartstein and Rothbart (2003), the scores for each scale were calculated by dividing the sum of the items by the number of completed items. The IBQ-R has adequate reliability and validity (Gartstein & Rothbart, 2003). Internal consistencies, measured by Cronbach's alpha, for the adapted IBQ-R in the current study were .71 for activity level, .74 for distress to limitations,

.85 for fear, .72 for duration of orienting, .75 for falling reactivity, and .75 for sadness, which is comparable to the internal consistencies of the original IBQ-R.

Maternal chronic pain

Maternal chronic pain was determined from questions regarding general physical health. Various kinds of illnesses and diseases were listed and mothers were asked to indicate whether they were chronically suffering from the illness or not. We tried to minimize misclassification of pregnancy-related symptoms as chronic pain, by asking for specific conditions (i.e. diagnoses instead of symptoms) and clearly indicating in the questionnaire instructions that the questions were about general health. The following conditions were categorized as chronic pain: migraine, other types of headaches, intestinal disorders, back disorders, and rheumatoid arthritis. In addition, mothers were asked whether they had any other (not listed) chronic illness or condition. This essay question was reviewed by one of the authors (NW) and a second rater with a medical degree to extract chronic illnesses that involve pain. Answers included ulcerative colitis, Crohn's disease, specific types of arthritis, sarcoidosis, whiplash, repetitive strain injury (i.e. cumulative trauma disorder), dystrophy, or dysplasia. Inter-rater agreement was 86%. Differences were discussed to reach consensus. We created a dichotomous variable indicating the presence of a chronic pain condition.

Maternal psychological symptoms

Maternal psychological symptoms were assessed using the Dutch translation (De Beurs, 2006) of the Brief Symptom Inventory (BSI; Derogatis, 1993; Derogatis & Melisaratos, 1983). The BSI is a 53-item questionnaire and contains six subscales, of which three subscales were used: depression, anxiety, and somatization. Also, the total score of all endorsed symptoms was calculated (General Symptom Index, GSI) and used as a general measure of maternal psychological symptoms. Respondents indicated how much each listed symptom or problem distressed or bothered them in the past two weeks, on a five-point scale. In accordance with the procedure outlined in the manual (De Beurs, 2006), scores for each subscale from each measurement moment were summed and divided by the amount of completed items. The Dutch BSI has shown good test-retest reliability (.71 to .89), good internal consistencies (.88, .85, .85, and .96 for depression, anxiety, somatic symptoms, and general symptoms respectively) and good criterion, discriminant, and convergent validity (De Beurs, 2006). In the current sample, internal consistencies for depression, anxiety, somatic symptoms, and general symptoms, as measured by Cronbach's alpha's, were .85, .81, .73, and .96 at the prenatal measurement moment, and .83, .81, .72, and .95 at the postnatal measurement moment.

Parenting stress

The level of stress in the parent-child dyad was measured by the Nijmeegse Ouderlijke Stress Index – Kort (NOSIK; De Brock, Vermulst, Gerris, & Abidin, 1992), the Dutch version of the

Parenting Stress Index – Short Form (Abidin, 1983). The NOSIK comprises 25 questions on two domains: parenting stress due to parent factors and parenting stress due to child factors. Only the 11 items of the parent domain were used in the present analyses. Examples of questions are: ‘Parenthood of this child is harder than I thought’ or ‘I often do not understand my child’. Items were assessed on a four-point Likert scale. Analogous to the manual (De Brock et al., 1992), scores were summed and divided by the number of completed items. Higher scores indicate greater levels of stress. The NOSIK has good reliability (Cronbach’s alpha = .95) and validity (De Brock et al., 1992). Internal reliability for the 11 items in the current study, measured by Cronbach’s alpha, was .72.

Outcome measure: child somatic complaints

The children’s somatic complaints were measured using a subscale from the Child Behavior Checklist 1½-5 (CBCL; Achenbach & Rescorla, 2000). The CBCL consists of 99 problem items; parents indicated whether their child did not (0), sometimes (1), or often (2) experience this problem. Scores of 11 items concerning somatic complaints without a known medical cause were summed to create a summary score of the subscale Somatic complaints, with a possible range of 0 to 22, as described in the manual (Achenbach & Rescorla, 2000). Examples of items are: “Headaches, without medical cause,” “Constipation, without being ill,” “Nauseous, without medical cause”. Dutch norm groups provided cut-off scores (based on 83rd percentile in norm group) to differentiate between subclinical/clinical problems and non-clinical problems (Tick, 2007). The CBCL has good reliability and validity; the internal consistency of the somatic complaints scale, measured by Cronbach’s alpha was .80 (Achenbach & Rescorla, 2000). The internal consistency of the somatic complaints subscale in the current study was .49.

Covariates

Demographics, such as the child’s sex, age, ethnicity, gestational duration, birth weight, medical history during the first year of life (multiple visits to the general practitioner, visit to the specialist, hospitalization), maternal education, age, and parity were obtained from questionnaires and from the midwife and hospital records. Maternal education was categorized as no or primary (elementary school or less), secondary (high school, lower vocational training), or high (higher vocational training and university). The child’s ethnicity was classified by the countries of birth of the parents, according to the Dutch standard classification criteria of Statistics Netherlands (2004).

Data analyses

Due to non-response, not all data on determinants was available for the 5,171 participants. The proportion of missing data for the determinants ranged between 1% and 33%. For example, the maternal chronic pain variable had a missing value in 12% of participants. If only

the cases without missing data would be analyzed, statistical power is reduced, selection bias increases, and information retained in the incompletely observed cases is lost (Schafer, 1997). This might affect the strength and significance of effect estimates as well as the generalizability to the whole population. Therefore, we carried out multiple imputation of the missing data (Schafer, 1997, 1999). The results when including participants with missing data confirmed Shafer's reasoning, but were still very similar to the results in participants with completely observed data. We generated 10 imputed datasets, to achieve a relative efficiency of at least 0.97 with these percentages of missing values (Rubin, 1987). Because of the non-monotone missing pattern of the data, we used the Markov chain Monte Carlo method in Proc MI as implemented in SAS version 9.1 (SAS Institute Inc., 2004). Variables with skew distributions were transformed to meet the procedure's assumption of a multivariate normal distribution of the data. Imputed values of dichotomous variables were not rounded after imputation, to avoid introducing bias (Horton, Lipsitz, & Parzen, 2003). Both the imputation model and the actual analysis models were fitted using standard deviation (*SD*) scores of the determinants, for ease of interpretation of the parameter estimates. After fitting logistic regression models, we used Proc MIANALYZE in SAS version 9.1 to combine the parameter estimates generated from each of the 10 imputed datasets, and to obtain adjusted standard errors and confidence intervals by incorporating between- and within-imputation variance.

To test our hypotheses, we carried out logistic regression analyses in SAS version 9.1. First, we fitted models to test the effect of each determinant on child somatic complaints. These models were adjusted for demographics (i.e. child's age, sex, ethnicity, and maternal education) and the child's medical history. Other potential confounders (e.g. maternal age) did not significantly change any effect estimates and were not included in the analyses. Then, models were fitted to test whether the observed effects were independent effects or whether attenuation of effects indicated that some variables were indicators of one underlying construct. These models were thus additionally adjusted for child temperament, parenting stress, maternal chronic pain, and prenatal somatic symptoms. Maternal somatic, anxious, and depressive symptoms were not adjusted for each other due to collinearity and comorbidity of the respective symptom scores. Interaction effects between determinants and confounders and among determinant pairs were investigated, but will not be reported, as none were significant.

RESULTS

There were 265 (5%) children who scored above the cut-off score on somatic complaints on the CBCL, meaning they had (sub)clinical levels of symptoms.

Associations of child somatic complaints with demographics

Table 4.1 shows the associations of somatic complaints with demographics. Non-Western children were more likely to have (sub)clinical levels of somatic complaints. Also, mothers of children with (sub)clinical levels of symptoms were on average 1.6 years younger and were educated at a lower level than mothers of children with nonclinical symptoms.

Prediction of child somatic complaints by determinants

Table 4.1 presents the unadjusted associations of the determinants with child somatic complaints. Children with (sub)clinical levels of somatic complaints differed significantly from children without somatic complaints on all investigated determinants.

Results of model I in which the determinants were adjusted for demographics (Table 4.2) show that children with somatic complaints at 18 months of age were more likely to have a parent who reported more temperamental difficulties in their child (for example, more fearful temperament, more sadness, and more difficult temperament regarding falling reactivity [i.e. the rate of recovery from distress]). Mothers of children with somatic complaints also reported more psychological symptoms. For example, these mothers reported more somatic symptoms during pregnancy and two months after the child's birth. Further, parents of children with somatic complaints experienced more parenting stress. Unlike the unadjusted associations shown in Table 4.1, maternal chronic pain did not predict child somatic symptoms after adjusting for demographic characteristics.

When the determinants were additionally adjusted for each other (model II, Table 4.2), child somatic complaints were still significantly influenced by fearful temperament and by the temperamental trait falling reactivity. None of the other temperamental traits predicted

Table 4.1. Child and parent characteristics ($N = 5,171$)

Characteristic	Child somatic complaints, non-clinical ($N = 4,906$) <i>M (SD) or %</i>	Child somatic complaints, (sub)clinical ($N = 265$) <i>M (SD) or %</i>	Odds ratio
Child gender (% boy)	49.5%	51.3%	1.08
Child age in months	18.40 (0.97)	18.66 (1.25)	1.23***
Gestational duration in weeks	39.85 (1.77)	39.91 (1.61)	1.02
Birth weight in kilograms	3.439 (0.571)	3.377 (0.534)	0.83
Child ethnicity			
Dutch	68.0%	41.5%	reference
Non-Dutch, Western ^a	9.1%	8.1%	1.47
Non-Dutch, non-Western ^a	22.9%	50.4%	3.61***

Continued

Table 4.1. (continued)

Characteristic	Child somatic complaints, non-clinical (N = 4,906) M (SD) or %	Child somatic complaints, (sub)clinical (N = 265) M (SD) or %	Odds ratio
Contacted general practitioner (% twice or more) ^b	68.8%	73.4%	1.25
Contacted medical specialist (% once or more) ^b	38.7%	45.6%	1.33*
Hospitalized (% once or more) ^b	14.9%	15.5%	1.05
Child temperament - 6 months			
Activity level	0.77 (0.33)	0.93 (0.32)	1.57***
Distress to limitations	0.68 (0.32)	0.82 (0.31)	1.52***
Fear	0.37 (0.30)	0.55 (0.39)	1.61***
Duration of orienting	0.99 (0.37)	1.04 (0.39)	1.15
Falling reactivity	0.47 (0.29)	0.64 (0.33)	1.68***
Sadness	0.66 (0.29)	0.78 (0.31)	1.48***
Maternal age in years	33.34 (4.64)	31.65 (5.45)	0.93***
Maternal educational level			
No or primary	4.9%	19.8%	5.84***
Secondary	37.6%	40.5%	1.56**
High	57.4%	39.7%	reference
Parity (% of children firstborn)	58.7%	62.1%	1.16
Maternal chronic pain - prenatal (% yes)	35.1%	42.3%	1.35*
Maternal psychological symptoms - prenatal			
Somatic symptoms	0.32 (0.39)	0.59 (0.62)	1.61***
Depression	0.17 (0.41)	0.34 (0.52)	1.32***
Anxiety	0.23 (0.39)	0.48 (0.61)	1.48***
General symptoms	0.23 (0.31)	0.44 (0.48)	1.51***
Maternal psychological symptoms - 2 months			
Somatic symptoms	0.23 (0.35)	0.48 (0.58)	1.53***
Depression	0.19 (0.40)	0.41 (0.54)	1.41***
Anxiety	0.20 (0.38)	0.45 (0.57)	1.45***
General symptoms	0.21 (0.31)	0.44 (0.49)	1.53***
Parenting stress - 18 months	0.30 (0.29)	0.59 (0.51)	1.73***

Note. Children with non-clinical and (sub)clinical somatic complaints were compared on the listed characteristics using logistic regression analyses.

^a Non-Dutch Western ethnicities include European and American origin, non-Western ethnicities include all other countries of origin, such as Morocco, Turkey, or Surinam.

^b Assessments of the infant's medical history spanned the period of 0 to 12 months of age.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

Table 4.2. Association of child somatic complaints with parental and child determinants

Determinants	Child somatic complaints – model I ^a	Child somatic complaints – model II ^b
	OR (95% CI)	OR (95% CI)
Child determinants		
Temperament - 6 months		
Activity level (per SD)	1.33 (1.13; 1.57) ***	1.15 (0.95; 1.40)
Distress to limitations (per SD)	1.30 (1.08; 1.56) **	0.87 (0.68; 1.12)
Fear (per SD)	1.40 (1.21; 1.63) ***	1.24 (1.04; 1.48) *
Duration of orienting (per SD)	1.09 (0.93; 1.28)	1.07 (0.89; 1.28)
Falling reactivity (per SD)	1.43 (1.23; 1.67) ***	1.27 (1.02; 1.58) *
Sadness (per SD)	1.39 (1.18; 1.64) ***	1.02 (0.83; 1.24)
Parental determinants		
Maternal chronic pain - prenatal	1.19 (0.91; 1.57)	1.01 (0.75; 1.35)
Maternal psychological symptoms - prenatal		
Somatic symptoms (per SD)	1.44 (1.28; 1.63) ***	1.25 (1.09; 1.43) **
Depression (per SD)	1.19 (1.06; 1.34) **	1.00 (0.86; 1.15)
Anxiety (per SD)	1.37 (1.24; 1.52) ***	1.20 (1.07; 1.35) **
General symptoms (per SD)	1.39 (1.25; 1.55) ***	1.17 (1.03; 1.33) *
Maternal psychological symptoms - 2 months		
Somatic symptoms (per SD)	1.40 (1.26; 1.56) ***	1.24 (1.10; 1.39) ***
Depression (per SD)	1.30 (1.16; 1.44) ***	1.10 (0.96; 1.25)
Anxiety (per SD)	1.37 (1.25; 1.52) ***	1.21 (1.08; 1.35) ***
General symptoms (per SD)	1.40 (1.26; 1.56) ***	1.19 (1.05; 1.34) **
Parenting stress - 18 months (per SD)	1.58 (1.44; 1.73) ***	1.47 (1.33; 1.63) ***

Note. Hierarchical logistic regression analyses were performed on standardized scores. OR = odds ratio; CI = confidence interval; SD = standard deviation.

^a Model I was adjusted for child's sex, age, ethnicity, medical history, and maternal education.

^b Model II encompassed model I and was additionally adjusted for all temperamental traits, maternal chronic pain, maternal somatic symptoms during pregnancy, and parenting stress. Due to collinearity and comorbidity of the respective psychological symptom scores, all maternal psychological symptoms were not adjusted for each other.

* $p < .05$.

** $p < .01$.

*** $p < .001$.

somatic complaints. Maternal prenatal somatic symptoms significantly predicted a 25% increased risk of the child having somatic complaints. The same held for maternal somatic symptoms measured two months after the child's birth. Also maternal anxiety and general symptoms, both during pregnancy and two months after the child's birth predicted a greater likelihood of a child having somatic complaints. Maternal depression did not predict child somatic symptoms in model II (i.e. after adjustment for maternal chronic pain, parenting

stress, and child temperament). Parenting stress remained a strong risk factor for child somatic complaints in model II, it predicted a 47% increase in risk. The Nagelkerke R^2 for model II that included maternal somatic symptoms during pregnancy, maternal chronic pain, all child temperament traits, and parenting stress was 16.5%.

DISCUSSION

Our findings underpin the basis of the theoretical model by Eminson, that there are many different etiological factors for somatic symptoms in children. Our study showed that when a child had a more fearful temperament or needed more time to recover from distress (i.e. falling reactivity) at six months of age, there was a greater likelihood of the child having somatic complaints one year later. Moreover, more maternal somatic symptoms and symptoms of anxiety during pregnancy, and shortly after the child's birth increased the likelihood of a child having somatic complaints at 18 months of age. Parenting stress was strongly associated with child somatic symptoms as well. These are independent determinants of child somatic complaints. Maternal depression and chronic pain also predicted child somatic complaints, but after adjusting for demographic characteristics, parenting stress, and child temperament, effects on child somatic complaints were attenuated and non-significant.

Child temperament was the most proximal factor investigated as a determinant of child somatic symptoms. Children who react with fear to new persons or situations, or who need more time to recover from distressing experiences were more prone to experience somatic symptoms. Every standard deviation increase in each of these temperamental traits was associated with approximately 25% increase in the likelihood of child somatic symptoms. Our findings are consistent with other studies that showed that temperamental differences in reactivity of school-aged children are prospectively associated to somatic symptoms (Grunau et al., 1994; Rocha & Prkachin, 2007). Our findings support the notion that the development of somatic symptoms often starts with anxious or emotionally reactive children who perceive more threat and danger in the environment (Beck, 2008).

Maternal somatic symptoms and anxiety were highly significant risk factors, predicting a 20% to 25% increase in risk of somatic complaints in very young children for every standard deviation increase in maternal symptoms. There are several mechanisms that can explain the 'transfer' of somatic symptoms or anxiety from mother to child. First, children might learn by imitation (i.e. modeling) to be anxious, or to have a heightened sensitivity to various bodily symptoms, and attribute harmful meaning to them. Also, children might imitate parental behavior of expressing distress as somatic complaints. Previous studies have indeed found that specific pain behavior of parents is often modeled by their children, affecting the occurrence of somatic symptoms (Osborne, Hatcher, & Richtsmeier, 1989; Rickard, 1988). Second, children's somatic complaints could be reinforced by the extra attention from a mother with

somatic symptoms. Previous studies found that children's symptoms are influenced by parental reinforcement (Walker, Garber, & Greene, 1993; Whitehead et al., 1994). Third, children may experience stress because their mother is displaying anxiety or somatic symptoms. As children have not yet fully developed cognitive abilities and verbal skills to express emotional stress and difficulties, many children may manifest distress or difficulties through somatic symptoms (Garralda, 1996). However, this same line of reasoning could apply to the hypothesized relationship between maternal depression and child somatic symptoms, yet our data did not show such an association. Fourth, children might inherit specific genetic variations and thus the susceptibility to respond to environmental stress with physiological changes or psychological symptoms (Walker et al., 1994). Fifth, bias might influence our results: mothers who have high somatic concerns or are anxious, might project the same feelings regarding their children's health and thus could *report* more symptoms. Although the last assessment of maternal somatic symptoms took place 16 months before the measurement of child somatic complaints, information bias may exist and result in an overestimation of the associations. Future research should try to disentangle real associations from information bias. Possibilities are to assess children's symptoms by other informants' reports (i.e. fathers) or to use observational data. Future investigations should also attempt to find out which mechanisms provide the best explanation for the associations between maternal and children's somatic symptoms.

We found that parenting stress was strongly related to child somatic complaints; each standard deviation increase in parenting stress was associated with a 47% increase in the likelihood of somatic complaints. This result is consistent with studies finding parenting stress being related to internalizing problems (Briggs-Gowan et al., 2006; Goldberg et al., 1997). Parenting stress was measured at the same time as child somatic complaints. Prospective research is needed to gain insight into the temporal relationship and predictive value of the factor.

Maternal chronic pain did not predict children's somatic complaints after adjusting for demographic characteristics. This is not consistent with previous studies, that found that children who have more somatic complaints or concerns were more likely to have a parent with a physically painful illness (Craig et al., 2002; Jamison & Walker, 1992). However, these studies investigated children aged four years and older, while our sample consisted of 18-month-old children.

The internal consistency of the somatic complaints scale was moderate ($\alpha = .49$). This coefficient was calculated using the original item assignment of the CBCL (Achenbach & Rescorla, 2000). Numerous populations have been studied using these CBCL item assignments and it is not desirable to have multiple scoring systems unless we know that the factor structure differs for a well-defined subgroup. Our moderate internal consistency suggests that the factor structure could be less robust across settings, cultures, age groups, etc. The alpha in our Dutch sample was similar to the alpha in the Dutch normative sample studied

by Tick et al. (2007); their alpha for somatic complaints was .52 (personal communication). However, a formal evaluation of the factor structure is only possible with a confirmatory factor analysis. Such an analysis is beyond the scope of the present study.

A limitation of this study is the fact that there still might be selection effects in our data, as the outcome variable 'somatic complaints' was not imputed. Amongst the families who did not complete the outcome measure, there was a higher percentage of children of non-Western origin, the mothers were educated at a lower level, and reported more chronic pain, psychological symptoms, and child temperamental difficulties. Eminson's (2007) theoretical model describes lower socio-economic status and family's mental and physical health as risk factors for higher somatic symptom scores in children. Therefore, we expect that results from a more representative sample will yield similar or stronger effects than the effects that we found in the current sample. Another limitation is that we do not have data regarding maternal chronic pain post pregnancy. One aspect that also deserves attention in future research is the role of fathers in the development of somatic symptoms. Further, our study lacks information about the health care professional factors in Eminson's model, as we used a population-based sample instead of a clinical sample. Examples of professional factors, which could be investigated in the future, include the communication about the child's and the parents' feelings and experiences, and how a trusting working relationship is established (Eminson, 2007).

In conclusion, our study indicated that both parental psychological health and child temperament are risk factors for a child having (sub)clinical levels of somatic symptoms. Many of these risk factors were measured more than one year before the assessment of somatic symptoms, yet predicted 20% to almost 50% greater risks of somatic symptoms for every standard deviation increase in the risk factor. The risk factors thus have prolonged and substantial effects during the first 18 months of children's lives. Our findings suggest that the first months of children's development are a critical period. Physicians and other health care professionals, who are consulted for the somatic symptoms of children, should be aware of both the existence of relationships of these symptoms with psychosocial factors and also the longitudinal aspects of the relationships. Professionals can provide care not only directed at the child's complaint, but should also specifically address these psychosocial issues in their conversations with parents. Moreover, it is important to realize that the temperamental difficulties, maternal somatic symptoms, symptoms of anxiety, and parenting stress are all *independent* risk factors, meaning that, ideally, all of these issues should be addressed. When the risk factors are detected early in the child's life, it is possible to start early interventions to prevent children's somatic symptoms from aggravating.

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Chapter 5

Parental mental health and somatic symptoms as risk factors for chronic pain



Chapter 6

Children's mental health and its relationship with chronic pain



Chapter 7

General discussion



INTRODUCTION

The main aims of this thesis were: 1) to examine whether adverse parental and child factors are associated with infants' distress levels during a venipuncture, as proxy for acute pain, 2) to investigate if early parental and child risk factors affect somatic complaints and the occurrence of chronic pain, in toddlers. Based on the theoretical model described in the General introduction, we hypothesized that risk factors such as parental behavior in response to child pain, parental anxiety, parental depression, parental somatic symptoms, parental chronic pain, parenting stress, child attachment, child temperament, and child behavioral and emotional problems impact on the child's procedural distress level and on the occurrence of chronic pain and somatic complaints.

We had an exciting opportunity to investigate this hypothesis in very young children. All studies in this thesis were embedded in the Generation R Study, a multi-ethnic population-based study among approximately 5,000 families in Rotterdam, the Netherlands. In this chapter, I discuss our major findings, address methodological issues, and conclude with implications for clinical practice and recommendations for future research.

MAIN FINDINGS

The studies in this thesis investigated a number of risk factors for the development of children's pain. Several of these factors have already been associated with the development of chronic pain in older children and adolescents in previous studies, but few studies have been carried out in samples of very young children. This thesis extends the knowledge on risk factors for pain in infants and toddlers.

Infants' venipuncture distress

In the first part of this thesis, we studied the associations between parent and child factors and venipuncture distress. It is known that parental behavior affects infants' behavior. However, most research was performed in immunization settings and little was known about generalizability of the findings to other medical procedures. Moreover, knowledge was limited about more distal parent and child factors, such as parental anxiety or child temperament. Chapter 2 describes that parent reassuring was related to 14-month-old infant venipuncture distress and that parent praising was inversely related to infant distress. Parent distracting was not related to infant distress. Parent symptoms of depression, anxiety, or somatic symptoms were not related to parent procedural behavior or infant distress. Parent chronic pain was not related to parent reassurance or infant distress behaviors either. It seems that behavior in this medical procedure context, rather than parent psychological traits or physical health, is

related to distress in young infants. In chapter 3, we showed that the child factors temperament and insecure attachment were not associated with infant distress in the venipuncture procedure. We found a trend for attachment disorganization to predict higher levels of distress. Infants with both disorganized attachment and fearful temperament had significantly increased levels of distress.

Parental behavior during the venipuncture

The observed association of parental reassuring with infant distress behaviors during venipuncture (chapter 2) is in line with results of immunization studies in infants, both observational (Cohen, Bernard, McClellan, & MacLaren, 2005; Sweet & McGrath, 1998) and experimental (Manimala, Blount, & Cohen, 2000). Furthermore, studies in older children have reported associations of parental reassuring with child distress behaviors as well (Blount, Bunke, Cohen, & Forbes, 2001; Blount et al., 1997; Blount, Corbin, Sturges, & Wolfe, 1989; Frank, Blount, Smith, Manimala, & Martin, 1995; Manne et al., 1992). We have thus added further confirmation to the accumulating evidence that reassurance is negatively related to infant and child distress, across medical settings (i.e. different procedures). It seems counterintuitive that reassuring is associated with higher levels of distress, but there are several possible mechanisms that can explain the relationship between parental reassuring and infant distress behaviors. As these were cross-sectional data, we cannot know the direction of the association. Thus, a likely mechanism could be that parents start to reassure their infant *because* the infant is showing signs of distress. There are also several explanations assuming a causal path of reassuring to distress. One of these explanations is that usually when the infant is in distressing situations, the parent tries to end the situation, whereas in a medical procedure the parent may explicitly communicate an understanding of the infant's feelings, yet does nothing to stop the procedure. This confusion may lead to increasing distress. Other possible mechanisms are that reassurance may function as an acknowledgement and confirmation of distress (McMurtry, McGrath, & Chambers, 2006). For example, if parents reassure their distressed child, this attention might implicitly reward the behavior that the child is currently showing. The distress behaviors may thus be reinforced and the child continues to show these behaviors. Furthermore, reassurance may implicitly give permission to the infant to express distress openly (McMurtry et al., 2006). These mechanisms assume one causal direction. Yet, I suspect that this is probably not the case. I think there is a behavioral loop that starts with infant distress caused by the frightening procedure situation. If the infant is slightly distressed or apprehensive, parents start to reassure their infant, because they think that this will be beneficial in relieving their infant's distress (Walker et al., 2006). However, the reassurance leads to more infant distress via the mechanisms mentioned above. Previous research in older children also showed that children perceived parental attention (i.e. reassurance) as not being beneficial in relieving their discomfort (Walker et al., 2006). The increased distress then leads to more parental reassuring, and so on.

Our result that parental praising reduced distress and crying (chapter 2), has not previously been found, as very little research investigated this relation (even in older children). A likely mechanism is that praise reinforces the infant's behavior. If the infant is showing some coping behavior or is crying less hard than the parent expected, the parent praises the child for being such a good boy/girl. This in turn reinforces the coping behavior and diminishes the distress behavior of the child.

More distal parental risk factors

Previous studies found mixed results regarding the influence of parental factors outside the specific procedure context, such as psychological traits or chronic pain, on a child's procedural distress. For instance, one study found that mothers' psychological problems were associated with observed infant pain (Moscardino, Axia, & Altoe, 2006). Yet, associations of maternal psychological problems with procedural reactivity were not found in other studies (Frank et al., 1995; Pillai Riddell, Stevens, Cohen, Flora, & Greenberg, 2007). Our results are in line with these latter studies, as infant distress was not influenced by parental depression or anxiety (chapter 2).

Concerning parental chronic pain, only two studies of young adults investigated the relation between parental pain and their adult children's experimental pain response. One study found that a higher number of family members with pain was related to lower pain intensity in a lab procedure (Zeichner, Widner, Loftin, Panopoulos, & Allen, 1999); the other study found that parental pain was related to increased sensitivity to lab-induced pain in women, but not in men (Fillingim, Edwards, & Powell, 2000). As far as we know, no studies were performed on the impact of parental chronic pain on acute pain responses in child or infant samples. We showed that parental chronic pain did not affect the infants' venipuncture distress behavior (chapter 2).

Children's risk factors

We also studied child factors as risk factors for venipuncture distress. Temperament and attachment are two distinct constructs that both impact on individual differences in cognition, affect, and behavior especially in stressful situations (Vaughn, Bost, & Van IJzendoorn, 2008). These variables can thus be expected to shape the child's reactions to a distressing medical procedure. Moreover, the interaction effects of attachment and temperament also affect responses to stress (Nachmias, Gunnar, Mangelsdorf, Parritz, & Buss, 1996; Vaughn et al., 2008). There was little previous research on attachment classifications. The attachment security classification was not related to children's distress reactions in two previous studies (Gunnar, Brodersen, Nachmias, Buss, & Rigatuso, 1996; Walsh, McGrath, & Symons, 2008), but attachment disorganization was related to more reactivity to a medical procedure in five-year-old children (Walsh et al., 2008). Our results corroborate these findings; we found no relation between attachment insecurity and distress and we found a trend for attachment

disorganization to predict higher distress levels (chapter 3). Perhaps, the effect of disorganized attachment on procedural distress becomes stronger as the child grows older. This might explain why we only found a trend.

We also found that temperament by itself did not influence the amount of distress expressed during venipuncture (chapter 3). Many previous studies also did not find relations between temperament and procedural distress in infants (Gunnar et al., 1996; Lilley, Craig, & Grunau, 1997; Sweet, McGrath, & Symons, 1999). Yet this relation was hypothesized based on a clear theoretical background (Rothbart, Ahadi, & Evans, 2000) and it has been consistently shown in children older than 3 years (Bournaki, 1997; Lee & White-Traut, 1996; Rocha, Prkachin, Beaumont, Hardy, & Zumbo, 2003; Schechter, Bernstein, Beck, Hart, & Scherzer, 1991) and also in two infant studies (Klein, Gaspardo, Martinez, Grunau, & Linhares, 2009; Piira, Champion, Bustos, Donnelly, & Lui, 2007). Perhaps the impact of temperament is dependent on learning effects in the first years of life. For example, infants may still differ somewhat in their responses to and regulation of stress across situations, as they are 'trying out' what behavior is best suitable for them. Older children may have established a consistent behavior pattern. This is consistent with earlier observations that rank-order stability of temperamental reactivity over the first 3 years is modest (Roberts & DelVecchio, 2000), that reactivity of some physiological and psychological systems underlying temperament are relatively labile during the first years of life (e.g. Crockenberg & Leerkes, 2006; Hane & Fox, 2006; Jahromi, Putnam, & Stifter, 2004; for overview see Vaughn et al., 2008), and the suggestion that social forces can modify initial levels of reactivity (Rothbart & Bates, 2006). This can explain why a clear relationship has been found between temperament and procedural distress in children older than 3 years but very inconsistently in infants.

Some investigators have studied interaction effects of attachment and temperament to explain adaptive responses to stress in medical procedures. Temperament theory assumes that reactivity and regulation of affect and behavior are broad trait-like characteristics of a person. Attachment theory assumes that arousal and regulation of affect and behavior in stressful situations are guided by the infants' internal working models. Some studies found that attachment and temperament interacted to predict higher levels of the stress hormone cortisol (Gunnar et al., 1996; Nachmias et al., 1996). To our knowledge, only one study has examined the interaction effect of attachment and temperament on behavioral reactivity; the interaction of insecure attachment and fearful temperament was not significantly associated with behavioral distress in a medical procedure (Gunnar et al., 1996). Yet Gunnar et al. did not investigate attachment disorganization in relation to distress. We did and we showed a significant interaction effect of disorganized attachment and fearful temperament on infant distress (chapter 3). This is consistent with the theoretical frameworks of attachment and temperament, with the research of effects on cortisol responses to distress in medical procedures (Gunnar et al., 1996; Nachmias et al., 1996), and with related areas of research investigating the interaction effects of attachment and temperament on stress reactivity and regulation (e.g.

physiological stress responses to fear-inducing film clips; (Gilissen, Bakermans-Kranenburg, Van, & Van der Veer, 2008; Gilissen, Koolstra, van IJendoorn, Bakermans-Kranenburg, & Van der Veer, 2007). Probably, the combination of fearful temperament and disorganized attachment lead to a baseline level of psychological vulnerability, which resulted in peak distress reactions when the child was placed in the very stressful venipuncture situation.

Conclusion on risk factors for infants' venipuncture distress

Parental behaviors during the painful procedure and children's psychological vulnerability (due to the simultaneous presence of multiple risk factors), rather than parental psychological traits or chronic pain were related to procedural distress.

I speculate that parental behavior shown during a medical procedure is very similar to the parental reactions to the child's everyday pains: some parents will comfort briefly and then encourage their child to go play again, while others may spend much time comforting and reassuring their child and talking extensively about the pain and about how the child feels. This behavior probably affects how the child copes with everyday pains, but if this is a non-optimal coping, these parental reactions and the associated non-optimal child coping may also influence the development or persistence of chronic pain. I suspect that the parental reactions to their child in pain are very similar across situations. Thus, the same parental behavior of giving attention, comforting, and reassuring might affect how children cope with everyday pains, how they deal with medical procedure pains, and how they cope with chronic pain as well. A finding that corroborates this line of reasoning is that adolescents who did not cope well with their chronic pain in daily life (i.e. had a school absence problem), also showed non-optimal coping and expressed more pain during lab-induced painful exercises than children with chronic pain who coped well in daily life (Dunn-Geier, McGrath, Rourke, Latter, & D'Astous, 1986). The mothers of 'non-copers' frequently discouraged coping behavior during the exercises. It seems that mothers' behavior interacts with child coping both during a lab procedure and in daily life.

Toddlers' somatic complaints and chronic pain

In the second part of this thesis, we investigated whether various parent and child factors were associated with somatic complaints or pediatric chronic pain. These studies were performed in a large sample of approximately 4,000 to 5,000 children and their parents. Chapter 4 describes that children with a more fearful temperament or who score high on the temperamental dimension 'recovery from distress' (i.e. needing more time to recover from distress) had a greater risk of developing somatic complaints. Moreover, maternal somatic symptoms, symptoms of anxiety, and parenting stress also increased the likelihood of a child having somatic complaints. Maternal chronic pain was not related to children's somatic complaints. In chapter 5, we showed that mothers' and fathers' somatic symptoms and fathers' anxiety

and depression were longitudinally related to child chronic pain. Parental chronic pain was not associated with child chronic pain. In chapter 6 we reported that children who already showed somatic complaints at 1.5 years, had an increased likelihood of having chronic pain at 3 years, whereas other behavioral and emotional problems in 1.5-year-old toddlers did not increase the risk of incident chronic pain during follow-up. Likewise, chronic pain in toddlers without behavioral and emotional problems did not increase the risk of newly developed behavioral and emotional problems. However, at the time children had chronic pain, they were more likely to have concurrent internalizing problems, such as symptoms of anxiety and depression, somatic complaints other than pain, sleep problems, or being withdrawn.

Parental risk factors

Although the first part of this thesis showed that parental factors did not affect an infant's acute venipuncture distress (chapter 2), parental anxiety and somatic symptoms had a strong and significant influence on the development of chronic symptoms, such as somatic complaints (chapter 4) and chronic pain (chapter 5). Relations for parental depression were present, but less strong and they sometimes did not reach statistical significance. For example, the mothers' depression was related to children's somatic complaints (chapter 4), but not to children's chronic pain (chapter 5), whereas the fathers' depression was significantly associated with children's chronic pain (chapter 5). Previous studies, performed mainly in clinical samples and investigating children aged 4 and older, already showed that anxiety and depression are more common in mothers of children with somatic complaints (Campo & Fritsch, 1994) or chronic pain complaints (Campo et al., 2007; Garber, Zeman, & Walker, 1990; Ramchandani, Stein, Hotopf, Wiles, & Alspac Study Team, 2006; Walker & Greene, 1989) and also that mothers' and fathers' somatic symptoms increased the likelihood of the child to experience somatic symptoms or pain (Craig, Cox, & Klein, 2002; Livingston, Witt, & Smith, 1995; Walker, Garber, & Greene, 1994; Walker & Greene, 1989). Our studies added to this previous knowledge as we now know that associations are similar in a population-based sample and in children younger than 3 years. Furthermore, we showed that fathers' psychological symptoms also have an effect on their children's chronic pain. Some potential mechanisms explaining these results stem from social learning theory (Bandura, 1977; Craig, 1983), which states that parents may influence pain experience in children via modeling or reinforcement.

Modeling can likely explain the relation between parental anxiety, depression and somatic symptoms and the development of child somatic complaints and chronic pain. Children may imitate their parent's illness-related behavior. Another type of modeling may occur when the parents' physical symptoms or the parents' attention and concern and harmful attribution of their symptoms (i.e. theory of Pennebaker, 1982) are imitated by the child. The child may learn that it is normal behavior to pay much attention to your body's sensations and to consider these sensations as potentially harmful. Previous studies have indeed found that modeled pain behavior of parents is often imitated by their children, affecting the occurrence

of pain or other somatic symptoms (Osborne, Hatcher, & Richtsmeier, 1989; Rickard, 1988). One might ask how likely it is that children as young as 2 years are influenced by this kind of parental behavior and imitate it. Yet it is widely known that toddlers imitate many other parental behaviors, such as during pretend play. Also, even children aged 1 or younger use social referencing to get a clue about how to behave, for example in situations involving pain. These kinds of parental behaviors teach the older infant or young toddler how to react to pain. I think that modeling thus is a highly likely mechanism explaining how parental mental health and somatic symptoms can affect children's pain.

A second plausible mechanism playing a role in explaining how parental anxiety and somatic symptoms are related to the development of somatic and pain complaints is reinforcement. The parents, who experience symptoms themselves, might think 'I know how miserable my child must feel'. This empathy may cause parents to direct extra attention or more attention to the child's complaints or pain behavior, when compared to parents without symptoms. Also, anxious parents may give more attention to their child's pain complaints, because they are anxious about the severity or duration or cause of the complaints and keep asking their child how he/she feels, or if the pain is getting worse or not. Previous studies found that parental reinforcement (e.g. giving special treats or gifts) influenced children's symptoms (Walker, Garber, & Greene, 1993; Whitehead et al., 1994).

Besides the two mechanisms from social learning theory, a third mechanism that may explain the association of parental depression, anxiety, and somatic symptoms with child somatic complaints and chronic pain is that the parental factors have an indirect effect on children, via the young children's ability to express stress. Children have not yet fully developed cognitive abilities and verbal skills to express emotional stress and difficulties, so many children may manifest distress or difficulties through physical symptoms (Garralda, 1996). Anecdotes of children having abdominal pain on their first day at school are known by almost everyone. Some children only suffer from these kinds of pain during very stressful times, but others may have a lower threshold for stress to be expressed as somatic symptoms. Also, some children may be more susceptible to stress or have more stress experiences in their young lives than others, for example if one of their parents has mental health issues affecting the family environment. As the young children in our studies probably experienced stress when they had a parent displaying depression, anxiety, or somatic symptoms, there might be an increased risk for these children to express this stress as pain or somatic symptoms (chapters 4 and 5).

We have shown in this thesis that parental chronic pain was not associated with somatic complaints (chapter 4), and chronic pain (chapter 5). This result is in line with the results from the only other prospective population-based study in young children by Ramchandani et al. (2005, 2006). Yet, many studies using pediatric clinic samples of older children showed that parental chronic pain is associated with children's chronic pain (Garber et al., 1990; Jamison &

Walker, 1992; Levy, Whitehead, Von Korff, & Feld, 2000; Mikail & von Baeyer, 1990; Schanberg et al., 2001; Walker et al., 1994). There are several reasons for this difference in results between clinical studies and population-based studies. Perhaps as adult chronic pain is quite prevalent, it might seem related to children's pain in clinical samples, but is not an etiological factor if investigated in the general population. Clinical and population-based studies have different samples, so the children will have different severity of pain complaints and the two types of studies differ methodologically (e.g. there might be selection effects in the clinical studies that reduce generalizability). Also, many of the clinical samples involved children aged 8 or older; a certain duration of exposure to the parent's pain may be necessary before the effect manifests itself as the experience of pain symptoms in the child. Another explanation of the difference between population-based studies and clinical studies can be at the determinant side: parental pain may need to reach a certain threshold or level of salience before children are affected, as suggested by Evans et al. (2008). This means that a dose-response relation might exist. The parental chronic pain in population-based samples may be lower or less salient than in samples in which children are recruited in clinics. It also may be less salient than the burden of various somatic symptoms. This hypothesized difference in salience might explain why we found strong associations for parental somatic symptoms with the outcome measures, but not for parental chronic pain.

Parenting stress has previously been related to internalizing problems (Briggs-Gowan, Carter, Bosson-Heenan, Guyer, & Horwitz, 2006; Goldberg et al., 1997). We showed that it is also strongly related to somatic complaints (chapter 4). However, parenting stress was measured at the same time as child somatic complaints, so we do not know the temporal relationship and predictive value of the factor. Both directions of the association are plausible. A parent may find it stressful to raise a child who has a number of physical symptoms which impact on the parent-child relationship. Or parenting stress may lead to stress in the child which then may be expressed as somatic symptoms, because of the earlier mentioned young developmental level of the child.

Children's risk factors

Not only parental factors, but also characteristics of the child itself may lead to a baseline level of vulnerability that influences how much stress the child experiences when something unusual happens. In school-aged children, research has already shown that temperamental differences in reactivity are prospectively associated to somatic symptoms (Grunau, Whitfield, Petrie, & Fryer, 1994; Rocha & Prkachin, 2007). We proved that temperament of children as young as 6 months predicts somatic complaints one year later (chapter 4). Our findings support the notion that the development of somatic symptoms often starts with anxious or emotionally reactive children who perceive more threat and danger in the environment (Beck, 2008). Children with a so-called 'difficult' temperament may be more vulnerable to

experience much stress from life events or even from daily situations like meeting a stranger. Many parents mentioned the birth of a new sibling as 'cause' of chronic pain complaints in their child, other parents noted anxiety or stress as cause (unpublished results from our data). These children may be vulnerable to experience high stress levels than others would in similar situations. Or they may be more vulnerable to express stress as physical symptoms instead of using other expression methods like acting out, perhaps because of their physiological make-up.

Although temperament was related to somatic complaints in toddlers, we found that another child factor, behavioral and emotional problems at 1,5 years, did not precede chronic pain complaints at 3 years (chapter 6). Evans et al. (2008) described that the child psychological vulnerability for pain construct includes child temperament and anxiety sensitivity. Other psychological characteristics do not seem to influence pain. Anxiety sensitivity refers to the specific tendency to interpret anxiety-related bodily sensations (e.g. rapid heartbeat) as dangerous (Reiss, Peterson, Gursky, & McNally, 1986). This construct is correlated with but conceptually distinct from trait anxiety (McNally, 1996). It could be that only this specific anxiety sensitivity construct affects a child's pain experience and that other types of anxiety or emotional problems do not impact on pain. This would explain our finding that the CBCL scales of trait anxiety and other broad constructs of behavioral and emotional problems were not longitudinally related to the development of chronic pain. The reason that child chronic pain was strongly related to internalizing problems in cross-sectional analyses is possibly that these problems are a direct consequence of the pain. This is confirmed in a theoretical model by Palermo et al., in which the child's emotional symptoms are seen as moderators or mediators in the causal pathway from pain to functional disability, i.e. they are a consequence of the pain (Palermo & Chambers, 2005).

METHODOLOGICAL CONSIDERATIONS

Definition

We defined pediatric chronic pain as 'continuous or recurrent pain that exists for three months or more,' in accordance with Perquin et al. (2000). However, this may have meant that children who had pain on one day in each of these three months were included in the 'chronic pain group,' whereas children who had pain every day for only two months were excluded. However, there is no indication that this potential misclassification was related to any of the investigated determinants, so it will not have led to bias in the effect estimates found in our studies.

We included children with pain from a diagnosed disease as well as children whose pain etiology was not (yet) known. However, we excluded everyday pains, such as pain from teeth-

ing, or from falling or bumping into people or objects. Children aged 2 and 3 experience many of these everyday pains. These pains are a normal part of toddlerhood and their frequency decreases as the child grows older. Moreover, these everyday pains are not the kind of pain leading to possible absence from preschool or frequent health care use. However, other researchers using the three months criterion in studies of preschool aged samples have not excluded the everyday pains. This may make it more difficult to compare results from different studies.

Prevalence

The prevalence rates of chronic pain in our studies were 1.5% in 2-year-old children (chapter 5) and 2.3% in 3-year-old children (chapter 6). This is lower than prevalence estimates reported in other population samples, for example the 12% in 0 to 3-year-old children in the much-cited study by Perquin and colleagues (Perquin et al., 2000). Their very high prevalence estimate has not been replicated in the preschool age group. The differences may partly be attributed to the context in which the questions were asked. Respondents use the instructions prior to completing a questionnaire and the context in which the questions are asked, to interpret what they should report (Passchier, Hunfeld, Jelicic, & Verhage, 1993; Schwarz, 1999). The questions on child chronic pain in our studies were embedded in a large questionnaire booklet including a wide variety of questions on normal development, growth, and health, whereas Perquin et al only asked questions about pain. Our approach is less likely to bias parent reports of their child's pain by pain focused response tendencies, leading to a more valid prevalence estimate. Further, everyday pains were excluded as 'chronic pain' in our studies, as mentioned above. Perquin et al do not mention such exclusion criteria in their study, which might also have resulted in an unrealistically high prevalence estimate.

Persistence

The chronic pain definition we used did not discriminate between medically diagnosed pain and medically unexplained pain. Both 'types' of pain could have been present in the chronic pain group in different proportions at the different measurement moments. An indication for this can be found in chapter 6, in which we presented data on the persistence of chronic pain from 2 to 3 years of age. Only 7 children of the 49 who had chronic pain at 2 years also experienced chronic pain at 3 years. A reason for the low pain persistence could be the regression to the mean effect. Yet, this methodological issue can probably account for only a part of the very high percentage of discontinuance. Another explanation might be found in the children's abilities to express pain in toddlerhood. When we looked at the parent's idea of the cause of the pain at 2 years (unpublished data), many medically diagnosed causes were mentioned, such as recurrent otitis media. It seems that most of these medical problems

were adequately treated one year later, as almost all children's pain disappeared. At the 2 years measurement, very few parents listed psychological causes like anxiety or stress (5.9% of cases), whereas these were more common at the 3 years measurement (15.4% of cases). Perhaps many parents had difficulty judging pain due to non-medical causes in their 2-year-old children, as many of these children do not have a large enough vocabulary and cognitive abilities to express pain adequately and indicate where the pain is located in the body. So parents mostly had to guess whether their child is crying or feeling miserable because of pain or because of other negative emotions, whereas a medical problem in a clear location (such as the ear that the child keeps rubbing) and with other symptoms (such as fever and/or excessive ear wax coming out of the ear) can be diagnosed and parents can be quite certain that the child has pain. So at 2 years, there might have been under-reporting of not medically explained pain. As children develop cognitively, they are better capable of communicating pain and pain locations and parents will be better able to adequately judge their child's symptoms and reasons for it and be confident enough to mention it in a survey. This difference may explain why we found such low pain continuity from 2 to 3 years. It would be very interesting to see pain persistence from 3 years onward. I hypothesize that such a persistence estimate will be higher than the 2 to 3 years figure, because the language and cognitive abilities of children advance so much from 2 to 3 years.

Selection bias

Selection bias occurs when there is a difference in a relation between determinant and outcome among those who participate in a study and those who were eligible for the study, but did not participate (Rothman & Greenland, 1998). Selection bias can result from selective non-participation at intake in the study or selective loss to follow-up.

The initial response rate for the Generation R Study was 61% (Jaddoe et al., 2008). Non-participation was not random; there were fewer families with lower socio-economic status and from ethnic minorities and fewer children with medical complications among the participants than expected from the population figures in Rotterdam (Van Lith, 2004). This indicates that the healthier and wealthier families participated in our study, which could have resulted in a selection bias in the results of our studies on pain within the Generation R Study, if these selection effects were related to both determinants and outcome in our studies.

The studies described in this thesis also may have suffered from selective loss to follow-up. In most of our studies, non-response analyses showed that the following types of families were more likely to be lost to follow-up: families of non-Western origin, with parents who had more psychological symptoms, were younger, were lower educated, and sought more medical care for their child, and with children who were more likely to have temperamental difficulties and behavioral and emotional problems. This selective follow-up resulted in an under-representation of families from the most disadvantaged groups, who are at risk for

physical and mental health problems. In the study where missing data on determinants was most prominent, we applied multiple imputation of missing values to overcome part of the selection bias. In all studies, missing data on covariates was imputed. However, in other studies we did not impute missing values on determinants and we never imputed missing data of the outcome measures. This could mean that selection effects remained in the data.

If indeed the healthier and wealthier families were more likely to participate, then possibly the results we found for this group are an underestimation of the effects in the general population. The assumption is that families, who scored higher on many of the investigated determinants, such as parental anxiety, also had the greatest risks of chronic pain. If they would have participated, the effect estimates of the study would thus have been higher. However, as we cannot know the relation between determinant and outcome in the non-participating and non-responding families, any statement on the direction or strength of the effect of selection bias would be speculation.

Information bias

If there are errors in the measurement of participants, information bias can occur (Rothman & Greenland, 1998). Particularly if misclassification of the outcome is associated with the determinant, or vice versa, the effects of information bias are difficult to predict (Rothman, 2002). In the majority of associations studied in this thesis, the determinants were measured a long time before assessment of the outcome. Because the determinants were not measured at the same time as the outcome, differential misclassification of the determinants is highly unlikely. Moreover, in the studies on venipuncture distress, the measurement method for a number of determinants was a questionnaire, whereas the outcome was assessed by coding behavioral observations. The coders were blind to determinant data of the participants. In these studies, differential misclassification of the outcome is unlikely as well. However, in the studies using parent-reported determinants and parent-reported outcome data, information bias was rather likely, for example if mothers reported more pain in their child *because* they themselves were worried and anxious (and also reported higher anxiety scores when asked about their symptoms). We tried to overcome this problem by using longitudinal data: we measured the determinants many months, even years, before we assessed the outcome. However, if a mother reported high anxiety shortly after the child's birth, she may still be anxious when the child is 2 years old and thus still report more pain due to her own anxiety, instead of the actual pain the child experiences. In one study, an extra effort to overcome possible information bias was done by including mothers as well as fathers in the study (chapter 4). Cross-comparisons yielded similar results as mother-reported data, indicating that information bias was not substantial.

Confounding bias

Confounding is seen as a confusion of effects, in which the apparent effect of the determinant on the outcome is distorted due to an extraneous factor that influences both determinant and outcome (Rothman & Greenland, 1998). For an extraneous factor to fulfill the criteria of a confounding factor, two conditions must be met. First, the extraneous variable is related to the determinant without being the consequence of the determinant. Second, the same extraneous variable is related to the outcome independent of the exposure. A confounding factor is thus not an intermediate in the causal path from determinant to outcome (Rothman & Greenland, 1998). One of the strengths of the Generation R Study is the multidisciplinary setting and extensive and ongoing data-collection. This means that there is a large dataset including many potential confounding variables. In all of our studies, we tested many covariates to see if they were confounding the effect estimates and if so, we adjusted the analyses for these variables. For example, parity (defined as being firstborn or not), confounded the relations of parent factors with infant venipuncture distress and child chronic pain. It is very plausible that having older children means that parenting the index child differs from parenting a firstborn child. One can imagine that parents are more experienced and relaxed when they already have older children, affecting both their own anxiety or somatic complaints (relation with determinants) and how they cope with their child's everyday pains, resulting in an altered pain experience in their child (relation with outcome). Both biological and psychosocial factors can confound relations of parent and child factors with children's pain experience. For example, child age and sex, parent age and sex, and parity attenuated the association of parent factors with child venipuncture distress, see chapter 2, and child ethnicity, child sex, and maternal and paternal anxiety attenuated the relation between child factors and child chronic pain, see chapter 6.

However, one must be careful not to overadjust the analyses. That is, the true effect is underestimated if analyses are adjusted for an intermediate in the causal pathway from a determinant to an outcome, or if analyses are controlled for a variable that is a consequence of the outcome. Therefore, our analyses on child chronic pain (chapter 5 and 6) were not adjusted for the child's medical history, as the child's medical history (i.e. multiple visits to general practitioner or specialist) can be a consequence of the chronic pain. Also, one might speculate that we should not have adjusted the relation of parental psychological symptoms with child somatic complaints for other study variables such as parenting stress, as parenting stress could very well have been an intermediate in the pathway from parental depression and anxiety to child somatic complaints (chapter 4). This can be seen in the large attenuation of effect estimates after adjustment, e.g. the odds ratio of maternal depression to predict somatic complaints was 1.30 ($p < .001$) after adjustment for demographics and 1.10 ($p > .05$) after additional adjustment for parenting stress and child temperament (chapter 4). In hindsight, I think it would have been better to use the effect estimate that was not adjusted for these intermediate variables.

Although we were able to evaluate many variables to test if they were potential confounders of the associations under study, we also may have missed some confounders. Residual confounding remains likely in epidemiological studies. For example, we were not able to control for parental chronic pain measured after the child's birth. It might be possible that residual confounding of this factor influenced the relations we found between child factors and child distress, somatic complaints or chronic pain.

Causality

In epidemiological studies, causality cannot be proven. The nine criteria for causal inference of observed associations are temporality, strength, consistency, specificity, biological gradient, plausibility, coherence, experimental evidence, and analogy (Hill, 1965). These causal criteria can be considered as viewpoints or standards that may provide positive support to inferences about causality (Hill, 1965). However, each criterion has its own problems; consistency, specificity, biological gradient, plausibility, coherence, and analogy are rather vague, misleading, or subjective criteria (Rothman, 2002) and will not be discussed here.

According to Rothman (2002), temporality is possibly the most important criterion to determine whether an association found in an observational study is causal. The determinant has to precede the outcome in time, to allow causal inference (Rothman & Greenland, 1998). The majority of studies in this thesis had a longitudinal design, except for the association between parental venipuncture behavior and infant venipuncture distress, that was part of the study in chapter 2, and the association between parenting stress and child somatic complaints, that was part of the study described in chapter 5. These had cross-sectional designs. Also, the infant's attachment and venipuncture distress were measured at the same time, as described in chapter 3, but the attachment of the child to the parent was established long before it was measured. Thus, we feel confident that the analyses of attachment and distress can be considered longitudinal as well. In cross-sectional designs, the directionality of the association is not clear. This means, for example, that we cannot know whether a certain parental behavior (e.g. reassuring) caused infant distress, or vice versa.

Strength of an association depends on the prevalence of other causal factors and on the effects of confounders (Rothman, 2002). In our studies, the effect sizes were only small to moderate. Our small to moderate effect sizes suggest that the total burden of chronic pain and somatic complaints on a population level is not caused by variations in parental mental health. However, in a small proportion of cases with pain or somatic complaints, a high parental anxiety may trigger or may be a necessary but in itself insufficient causal component of the occurrence of somatic or pain complaints.

The last causality criterion to discuss is experimental evidence. The experimental evidence, however, is very limited or unavailable, as it is unethical to induce or manipulate anxiety or somatic symptoms or chronic pain in parents to see whether their children will have a greater

risk of developing chronic pain. For determinants of procedural distress, one experimental study has shown that parental reassuring indeed increases child distress (Manimala et al., 2000). Similarly, parental attention (i.e. reassuring) during lab-induced gastrointestinal pain led to more symptom complaints in both well children and chronic pain patients when compared to a no instruction condition or a distraction condition (Walker et al., 2006).

In conclusion, it is hard to determine causality in an association coming from an observational study. Although we took great care of the most important 'causality' criterion by studying (and showing) temporal relations in our studies, we cannot assert causality of the associations.

Yet, it is tempting to speculate that parental anxiety causes child chronic pain and somatic complaints. Indeed, a child's character or behavior cannot have influenced the level of anxiety the parent had before the child was born (the opposite direction of effects, i.e. reversed causality). As experimental studies in this area are unethical, the best that research can do is observational research. Studies thus need to replicate our findings, so that evidence can be built up and conclusions can (hopefully) be corroborated.

CLINICAL IMPLICATIONS

The burden of having chronic pain as a child is high and there is a strong negative influence of the chronic pain on the child's daily functioning and quality of life, the family's lives, and on the health care system (Berger, Gieteling, & Benninga, 2007; Eccleston, Bruce, & Carter, 2006; Hunfeld et al., 2001; Merlijn et al., 2003; Roth-Isigkeit, Thyen, Stoven, Schwarzenberger, & Schmucker, 2005). Therefore, it is important to prevent chronic pain from developing, persisting, or getting worse. The risk factors we found can provide guidance on issues that need to be addressed in clinical care or in public health activities.

Before I give specific recommendations, the clinical relevance concerning the strength of the associations needs to be mentioned. Many of the relations we found in our studies were highly statistically significant and are important on a group level. However, some may argue that the clinical relevance of some associations for an individual patient is low, as the effect sizes were only small to moderate. However, even effects of this magnitude are informative about the etiology of child pain and may be important for prevention or treatment efforts. In medical science, effect sizes of a magnitude of $r = .04$ are sometimes considered to be of high practical importance (Rosenthal, 1990). He describes that a medical experiment was prematurely terminated based on an effect size of $R^2 = .0011$, with a corresponding $r = .034$, for the effect of aspirin in reducing heart-attacks, because it was considered unethical to continue to give a placebo to the patients in the control group. For comparison, the odds ratio of 1.29 that we found for the effect of fathers' anxiety on child chronic pain (chapter 5), corresponds with an effect size of Nagelkerke $R^2 = .035$ (unpublished data), which is a small

to medium effect size according to Cohen's criteria (Cohen, 1988). Of course, the chronic pain that we studied is not a severe, life threatening disease such as heart-attacks are, but Rosenthal (1990) also states that even small effect sizes of for example $r = .04$ ($R^2 = .0016$) implicate that 4% of people can be helped. From this perspective, parent and child factors, such as parental anxiety and child temperament may be valid targets for interventions to reduce children's pain or somatic complaints.

Not all children's pain in our studies seemed severe and in need of treatment. Therefore, I suggest that intervention and prevention should not target all children with pain longer than 3 months, but only those presenting to health care. In those cases, parents actively ask for help and the perceived severity can be assumed to be high. Thus, I recommend professionals in clinical practice who are consulted for somatic or pain complaints, to also consider the psychological wellbeing of both parents and children. Especially parents' anxiety and somatic symptoms may increase their toddler's risk of developing somatic or pain complaints by 20% to 30% for each standard deviation increase in the parental symptom. These associations exist, even though the parents in our studies did not have extremely high levels of psychological symptoms. Rather, the distribution of parental psychological symptoms in our studies on chronic pain and somatic complaints is very similar to the distribution in the adult Dutch norm population (De Beurs, 2006). Further, parenting stress increased the toddlers' somatic complaints by almost 50%. Health care professionals should thus ask about parental and child mental health in children presenting with physical symptoms or pain. If short screening questions by the physician or pediatrician point to above-average symptoms or stress in (one of) the parents, a 'difficult' child temperament, or comorbid internalizing symptoms in the child, a so-called 'two-track policy' can be followed and the family may be referred to a psychologist who can work with the family members on psychological problems parallel to the medical track.

The clinical implication described above stems from the high-risk approach to prevention: screen and treat those individuals that have the highest risk of a certain symptom or disease. However, a population approach to prevention can also be adopted. A population approach tries to improve all individuals' health a little bit (i.e. move the whole distribution of the determinant in a favorable direction), which aims to diminish the incidence of the associated disease or outcome (Rose, 1985). This approach has a large potential for the population as a whole. As one standard deviation increase relative to the population average of parental anxiety and somatic symptoms can already affect children's chronic pain and somatic complaints, I recommend that prevention activities are targeted towards all parents. An important tool to prevent the persistence or recurrence of pain or somatic complaints can be to educate parents about the effect of their mental health on their child's health and to advise them to seek help if they experience symptoms. This education might be incorporated in the care that prevention-focused health care centers offer, for example in municipal child health centers (the Dutch 'consultatiebureau' and 'GGD'). Another option is to teach parents the effect of

their behavior in response to child pain, explain that this might be influenced by their mental health, and teach them how to behave in a favorable way. An idea could thus be to make and test the effectiveness of a short movie clip for parents on how to deal with everyday pains or immunization distress in their child. This can provide parents with the knowledge of reinforcement and modeling mechanisms and teaches them how best to behave in such situations. The new knowledge may put a halt to the hypothesized causal path from parental risk factors via social learning mechanisms to children's pain experiences, and thereby hopefully preventing pain and pain complaints to reoccur or become chronic. If such a movie clip proves to be effective in preventing new-onset or recurrence of pain, the cost-effectiveness of this prevention tool is expected to be high, because it can be distributed easily via child health centers or the internet.

To prevent high levels of pain and distress during medical procedures, the causal loop of reassuring and distress both increasing each other's occurrence should be prevented from occurring or continuing. This may be done by explaining to parents what the negative effect is of reassuring and providing them with a short distraction training that teaches them how to distract their child. Experimental evidence has shown this strategy to be successful in diminishing infants' pain and distress during a painful procedure when compared to a typical care condition (Cohen et al., 2006), although there was no reassurance condition in that study. In an experimental study in older children, it has been shown that parental distraction led to fewer complaints when compared to a no instruction condition, whereas parental attention led to more complaints (Walker et al., 2006).

FUTURE RESEARCH

Now that we know that many parent and child factors influence the development of chronic pain already at a very young age, future research should study interaction effects. Structural equation modeling can be used to study all factors simultaneously and in interaction with each other. This can help uncover which factors are interacting with which other factors, how many factors are 'necessary' before chronic pain will develop, and which factors have the strongest effect on the development of chronic pain.

Studies on pain using the biopsychosocial model may adopt new techniques for investigating risk factors and correlates of chronic pain. Imaging studies of the child's brain are a relatively new area of research. Studies are now being performed in young children in the Generation R Study to find out whether changes in the brain affect child psychiatric symptoms, such as ADHD, via altered processing of information. Pain research may also benefit from these techniques, for example to find out whether pain and distress signals are being processed differently in children with or without chronic pain or in children who showed high or average distress during a medical procedure.

Future research may also try to find out more about the mediating effects of modeling and reinforcement in the relation between parental factors and young children's pain. Questionnaires may ask for parental responses to child pain and the parents' own illness behaviors to test if (one of) these can explain the association of parental mental health with children's chronic pain. Research may also try to investigate the proposed mechanism of a pathway via the expression of stress as physical symptoms in children who have not yet fully developed cognitive and verbal skills. This may be done by asking the other parent without mental health issues to report on the level of stress in family interactions and on his/her opinion about whether the child might be affected by this family stress. Also, the parent might be asked if the child is complaining of pain shortly after a stress peak or during times of heightened family stress, or whether pain complaints seem unrelated to events happening in the family. Diaries can also be used to record such information on a day-to-day basis.

Since we found low persistence of chronic pain from 2 to 3 years, it would be important to know whether persistence from 3 years onwards is higher. As hypothesized, parents might be better able to interpret and report on their 3- or 4-year-old-child than on their less verbally and cognitively advanced 2-year-old child. Therefore, follow-up studies of pain prevalence and persistence in young children are necessary. Researchers might also add a question to parental questionnaires as to how difficult it was to judge their child's pain, so interpretation of the results will be easier.

Further, I hypothesize that parental behavior in reaction to child pain is similar across situations. This would mean there is a relation between parental behavior during an acute pain situation, such as a venipuncture, and the later development of chronic pain in the child. Future studies should collect data regarding acute pain responses in children who later develop chronic pain. One way to achieve this is to set up a case-control study embedded in an ongoing cohort study. All children might be videotaped during a laboratory pain situation and then followed-up to see who develops chronic pain. Of the children with chronic pain (and a control group) the videos of the acute pain procedure can be coded for analyses. Our research group is currently performing such a data collection in the Generation R Study's measurement wave at 5 years. If the hypothesized relation between parental behavior during a procedure and the development of chronic pain indeed exists, acute pain situations might be used as intervention opportunity to prevent new-onset or persistence of chronic pain.

To minimize information bias, future studies should try to use independent informants of determinants and of the child's pain complaints. For example, research can study the relation of father-reported determinants with mother-reported outcomes and vice versa. Moreover, as our studies were among the first to explore early predictors of pediatric pain in toddlers, future population-based studies need to replicate our findings.

Randomized controlled trials (RCT) need to be carried out to test if the prevention and intervention activities I proposed in the clinical implications section will indeed be successful in preventing future pain and distress during medical procedures in infants, and in prevent-

ing toddlers' chronic pain to occur or persist. For example, an RCT could investigate whether a movie clip about dealing with their children's pain is effective in having parents react to their child's pain with distraction or praise rather than reassurance and (reinforcing) attention. It could be that an extensive skills training for parents is not even necessary. Previous research showed that a short instruction on distraction techniques to parents prior to an immunization already resulted in significantly more parental distracting behavior and also in significantly more infants being engaged in distraction than a 'typical care' control condition (Cohen et al., 2006). Another RCT could be performed on the effect of treating parents with above average levels of psychological symptoms and how this may prevent chronic pain in their children or prevent a pain problem from persisting many months.

CONCLUSION

The causal model of pediatric pain described in the General introduction, which is based on the models by Eminson (2007), Evans et al. (2008), Palermo and Chambers (2005), describes several risk factors for children's pain. We investigated these risk factors in a large sample of very young children from the general population.

We found that parental mental health, especially somatic symptoms, anxiety, and depression had a significant influence on the development of symptoms of longer duration (i.e. somatic complaints and chronic pain). However, children's distress from a medical procedure was not influenced by parental factors outside the specific procedure context, such as psychological traits. Another theorized factor in the causal model is parental chronic pain. In our studies, parental chronic pain neither influenced venipuncture distress, nor impacted on somatic complaints and chronic pain. Child temperament was found to be a longitudinal risk factor for (sub)clinical levels of somatic complaints, but was only related to procedural distress in interaction with disorganized attachment. Behavioral and emotional problems were no longitudinal risk factors for chronic pain, but the cross-sectional association with chronic pain proved to be strong.

My theory is that many mechanisms described above are playing a role in increasing a young child's risk of developing chronic pain. Each mechanism is an independent contributor, but I propose that the combination (or interaction) of a psychologically vulnerable child and modeling or reinforcement behaviors by a parent who has anxiety or somatic symptoms might pose an even greater risk for a child to develop chronic pain complaints. For example, if a child has a fearful temperament or is prone to react to stress by experiencing somatic symptoms and also has a parent who suffers from anxiety or somatic symptoms, which puts stress on the family relations, then this child may be particularly likely to develop chronic pain. Evans et al. (2008) reiterates this notion by asserting that it is likely that complex, bidirectional influences operate in the parent-child environment that make the child prone to developing chronic pain.

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Chapter 8

Summary / Samenvatting



SUMMARY

In **Chapter 1**, the topic of pain in young children is introduced. Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, 1979). Chronic pain of at least 3 months duration is quite common in children and even in toddlers. Levels and duration of acute pain and distress during medical procedures are high as well. Furthermore, there are significant consequences of both acute and chronic pain, such as an altered pain perception after high acute pain that increases fear and pain in future procedures, and impaired daily functioning and quality of life in children with chronic pain. Thus, it is important to gain understanding of what determinants might affect differences in children’s procedural distress and chronic pain. Theoretical models and previous evidence show various parent factors, such as anxiety, depression, and chronic pain, and child factors, such as temperament, as determinants of pediatric acute and chronic pain. Most studies so far have investigated children aged 3 or older and many have used clinical samples and/or cross-sectional designs. As a consequence, it is not clear what the early longitudinal risk factors are for toddlers’ pain.

The general aim of this thesis was to extend existing knowledge on prenatal and early postnatal determinants of young children’s acute pain and chronic pain. The studies presented in this dissertation were carried out within the Generation R Study, a prospective multi-ethnic population-based study investigating growth, development and health from fetal life onwards in Rotterdam, the Netherlands.

In **Part 1**, we studied the effects of several parent and child factors on infants’ venipuncture distress (as proxy of acute pain). **Chapter 2** presents the study of various parent factors in association with infants’ distress during venipuncture. Parent behavior and infant distress were examined in this potentially painful medical procedure. Further, the associations of parent chronic pain and psychological problems with parent behavior and infant distress during the procedure were investigated. Video recordings of 275 parents and their 14-month-old infant undergoing venipuncture were coded with an observational instrument to yield measures of infant distress behaviors and parent behaviors, such as reassuring, showing empathy, praising, and distracting. Parent chronic pain and psychological problems were assessed by questionnaires. Infants cried 58% of procedure duration. Parent reassuring occurred 34% of procedure duration, parent distracting occurred 37% of procedure duration. Infant distress was positively related to parent reassuring and negatively related to parent praising. Parent chronic pain was related to increased parent distracting, but not to reassuring or infant distress. Parent psychological problems were not associated with parent behavior and infant distress. We conclude that parent behavior, rather than psychological traits, is related to increased venipuncture distress in young infants. In **Chapter 3**, the effects of two child factors, attachment and temperament, on infant distress during venipuncture were

studied. Two different research procedures (i.e. blood sampling and the Ainsworth Strange Situation Procedure) yielded measures of venipuncture distress and attachment security and disorganization in 246 infants aged 14 months. Four temperament traits (distress to limitations, fear, recovery from distress, and sadness) were assessed with the Infant Behavior Questionnaire – Revised, at the age of 6 months. There were no differences between mean levels of distress during venipuncture in infants classified as having insecure attachment, but there was a trend for disorganized attachment. The temperament traits were not related to distress. However, children with both a disorganized attachment and higher temperamental fear had more venipuncture distress. We conclude that when different risk factors are present simultaneously, distress in the venipuncture procedure is heightened.

In **Part 2**, we investigated whether parent and child risk factors affect the development of more chronic symptoms, i.e. somatic complaints and chronic pain, in toddlers. The study in **Chapter 4** investigated the longitudinal effects of parent and child factors on toddlers' somatic complaints at 1.5 years. Child somatic complaints at 1.5 years were assessed by the Somatic Complaints subscale of the Child Behavior Checklist (CBCL). Some examples of items in this scale are abdominal pain without medical cause, headaches without medical cause, constipation, nausea, painful defecation, and skin rashes or other skin problems without medical cause. Data on child somatic complaints were available in 5,171 children. Questionnaires assessed the following parent factors: maternal chronic pain, somatic symptoms, symptoms of depression, and anxiety during pregnancy and two months after delivery, and parenting stress 1.5 years after birth, and assessed the child factor temperament via mother-report six months after birth. Our study showed that when a child had a more fearful temperament or needed more time to recover from distress at six months of age, there was a greater likelihood of the child having somatic complaints one year later. Moreover, heightened maternal somatic symptoms and symptoms of anxiety during pregnancy and shortly after the child's birth increased the likelihood of a child having somatic complaints at 1.5 years. Parenting stress was strongly associated with child somatic symptoms as well. These are independent determinants of child somatic complaints. In conclusion, both maternal mental health and child temperament are risk factors for (sub)clinical levels of somatic symptoms in toddlers. In **Chapter 5** the effects of various parent factors on toddlers' chronic pain at 2 years were examined. Child chronic pain was measured by parent-reported questionnaire in 4,596 children. Mothers and fathers completed questionnaires on their own chronic pain and mental health, such as depression, anxiety, and somatic symptoms, during pregnancy and again when their child was 2 months old. The prevalence of child chronic pain was 1.5%. The most common pain locations were the ear and abdomen. Mothers' somatic symptoms predicted a greater likelihood of the child having chronic pain at age 2. Fathers' depression, anxiety, and somatic symptoms also predicted increased occurrence of chronic pain in toddlers. Mothers' or fathers' chronic pain was not associated with child chronic pain. It is remarkable

that fathers' mental health has such an impact on child chronic pain. It is remarkable that fathers' mental health has such an impact on child chronic pain. Psychological and somatic symptoms in the parent(s) may lead to child chronic pain via modeling or reinforcement of illness behavior. The low prevalence should be seen in context of this large population-based study not focused purely on pain. Health care professionals consulted for children's chronic pain should also carefully consider both mothers' and fathers' mental and physical health. The study in **Chapter 6** addressed the cross-sectional and temporal associations of chronic pain with behavioral and emotional problems in toddlers. Parents of 3,751 toddlers completed questionnaires of their child's health and development. Behavioral and emotional problems were measured at 1.5 and 3 years, chronic pain was measured at 2 and 3 years. Cross-sectional associations between chronic pain and internalizing mental health problems were considerable. Chronic pain did not precede the development of new behavioral and emotional problems. Behavioral and emotional problems did not precede incident (i.e. new-onset) chronic pain, but many children who developed chronic pain at 3 years already had somatic symptoms other than pain at 1.5 years. Chronic pain is associated with concurrent mental health problems. There were no longitudinal relations of chronic pain and mental health. When professionals in medical care are consulted for a child's pain complaints, the child's mental health should be considered simultaneously.

Finally, **Chapter 7** provides a general discussion of the main findings, addresses methodological considerations of the studies presented in this thesis, and states recommendations for clinical practice and future research.

Reference

IASP. (1979). Pain terms: A list with definitions and notes on usage: recommended by the IASP Subcommittee on Taxonomy. *Pain*, 6(3), 249.

SAMENVATTING

In **Hoofdstuk 1** wordt het onderwerp pijn bij jonge kinderen geïntroduceerd. Pijn is gedefinieerd als “een onaangename sensorische en emotionele ervaring die wordt geassocieerd met werkelijke of mogelijke weefselschade, of wordt beschreven in termen van zulke schade” (IASP, 1979). Chronische pijn die minstens 3 maanden duurt, komt vrij vaak voor bij kinderen en zelfs bij peuters. Het niveau en de duur van acute pijn en ‘distress’ tijdens medische procedures zijn ook hoog. Daarnaast zijn er significante gevolgen van zowel acute als chronische pijn, zoals een veranderde pijnperceptie na intense acute pijn, die zorgt voor meer angst en pijn in toekomstige procedures en een aangetast dagelijks functioneren en kwaliteit van leven bij kinderen met chronische pijn. Het is dus belangrijk om inzicht te krijgen in welke determinanten de verschillen tussen kinderen kunnen verklaren in procedurele distress en chronische pijn. Theoretische modellen en wetenschappelijk bewijs laten zien dat diverse ouderfactoren, zoals angst, depressie en chronische pijn, en kindfactoren, zoals temperament, determinanten zijn van pediatrische acute en chronische pijn. De meeste onderzoeken tot nu toe hebben kinderen van 3 jaar of ouder bestudeerd en veel onderzoeken hebben klinische steekproeven gebruikt en/of een cross-sectionele studie-opzet. Als gevolg daarvan is het nog niet duidelijk wat de vroege lange-termijn risicofactoren zijn voor pijn bij peuters.

Het algemene doel van dit proefschrift is om de reeds bestaande kennis uit te breiden over prenatale en vroeg postnatale determinanten van acute en chronische pijn bij jonge kinderen. De studies die in dit proefschrift worden gepresenteerd, zijn uitgevoerd in het Generation R Onderzoek, een prospectief, multi-ethnisch populatie-gebaseerd onderzoek naar groei, ontwikkeling en gezondheid vanaf de zwangerschap, in Rotterdam.

In **Deel 1** bestudeerden we de effecten van verschillende ouder- en kindfactoren op distress (als proxy van acute pijn) bij bloedprikken in 14 maanden oude kinderen. **Hoofdstuk 2** presenteert de studie van verschillende ouderfactoren in relatie tot distress bij kinderen tijdens bloedprikken. Het gedrag van ouders en de distress van het kind werden bestudeerd in deze mogelijk pijnlijke procedure. Ook werden de relaties onderzocht van chronische pijn en psychologische problemen bij de ouders met distress van het kind tijdens de procedure. Video opnames van 275 ouders en hun 14 maanden oude kind die een bloedprik onderging, werden gecodeerd met een observatie-instrument om distress gedragingen van het kind en gedragingen van de ouder te meten. Voorbeelden van gedragingen van de ouder zijn geruststellen, empathisch reageren, prijzen en afleiden. Chronische pijn en psychologische problemen bij de ouder werden gemeten met vragenlijsten. Kinderen huilden gemiddeld gedurende 58% van de procedure. Ouders stelden hun kind gerust gedurende 34% van de procedure en zij leidden hun kind af gedurende 37% van de procedure. Distress van het kind was positief gerelateerd aan geruststellen door ouders en had een negatief verband met prijzen door ouders. Chronische pijn bij ouders was gerelateerd aan een toename van

afleiden door ouders, maar hing niet samen met geruststellen of distress bij het kind. Psychologische problemen van ouders waren niet gerelateerd aan gedrag van ouders en distress van het kind tijdens de bloedprik. We concluderen dat gedragingen van ouders, en niet hun psychologische karaktertrekken, samenhangen met een toename van distress bij bloedprikken in jonge kinderen. In **Hoofdstuk 3** onderzochten we de effecten van twee kindfactoren, gehechtheid en temperament, op distress bij kinderen tijdens bloedprikken. Twee verschillende onderzoeksprocedures (d.w.z. bloedprikken en de Vreemde Situatie Procedure van Ainsworth) leidden tot metingen van bloedprik-distress en van (on)veilige gehechtheid en gedesorganiseerde gehechtheid in 246 kinderen van 14 maanden. Vier temperament schalen uit de Infant Behavior Questionnaire – Revised (Distress to limitations, Fear, Recovery from distress en Sadness) werden afgenomen toen de kinderen 6 maanden oud waren. Er waren geen verschillen in distress niveaus tijdens bloedprikken bij kinderen die werden geclassificeerd als onveilig gehecht in vergelijking met veilig gehechte kinderen, maar er was een trend voor gedesorganiseerde gehechtheid om tot hogere niveaus van distress te leiden. De temperament karakteristieken hingen niet samen met distress. Echter, kinderen die zowel een gedesorganiseerde gehechtheid als een angstig temperament hadden, hadden meer distress tijdens het bloedprikken. We concluderen dat wanneer verschillende risicofactoren gelijktijdig aanwezig zijn, dat de distress tijdens medische procedures verhoogd is.

In **Deel 2** bestudeerden we of ouder- en kindfactoren invloed hadden op de ontwikkeling van meer chronische symptomen, zoals somatische klachten en chronische pijn, bij peuters van 1,5 tot 3 jaar. **Hoofdstuk 4** beschrijft de lange termijn effecten van ouder- en kindfactoren op somatische klachten bij peuters van 1,5 jaar. De somatische klachten werden gemeten met de Somatische Klachten schaal van de Child Behavior Checklist (CBCL). Voorbeelden van items in deze schaal zijn buikpijn zonder medische oorzaak, hoofdpijn zonder medische oorzaak, obstipatie, misselijkheid, pijnlijke ontlasting en huiduitslag of andere huidproblemen zonder medische oorzaak. Er waren van 5.171 kinderen gegevens bekend over somatische klachten. Met behulp van vragenlijsten werden de volgende ouderfactoren gemeten: maternale chronische pijn, somatische symptomen, symptomen van depressie en angst en ouderschapsstress. De kindfactor temperament werd ook gemeten met een vragenlijst, die door moeder werd ingevuld. Ons onderzoek toonde aan dat als een kind op de leeftijd van 6 maanden een angstig temperament had of relatief veel tijd nodig had om bij te komen van een stressvolle gebeurtenis, dat er dan een grotere kans was dat dat kind een jaar later somatische klachten had. Bovendien verhoogden ook maternale somatische symptomen en symptomen van angst tijdens de zwangerschap en vlak na de geboorte van haar kind, de kans dat het kind somatische klachten had op 1,5-jarige leeftijd. Ouderschapsstress was ook sterk geassocieerd met somatische klachten. Deze factoren zijn onafhankelijke determinanten van somatische klachten bij kinderen. Concluderend, zowel maternale mentale gezondheid en temperament van het kind zijn risicofactoren voor het bestaan van somatische klachten bij

peuters. In **Hoofdstuk 5** staat het onderzoek naar de effecten van verschillende ouderfactoren op chronische pijn bij peuters van 2 jaar. Chronische pijn bij het kind werd gemeten met een vragenlijst die door de ouders werd ingevuld, in 4.596 kinderen. Tijdens de zwangerschap en toen het kind 2 maanden oud was, vulden moeders en vaders vragenlijsten in over hun eigen chronische pijn en mentale gezondheid, zoals depressie, angst en somatische symptomen. De prevalentie van chronische pijn bij kinderen was 1,5%. De meest voorkomende pijnlocaties waren het oor en de buik. Somatische symptomen bij moeder voorspelden een grotere kans op chronische pijn bij het kind op tweejarige leeftijd. Depressie, angst en somatische symptomen bij vaders voorspelden ook een toegenomen kans op chronische pijn bij peuters. De chronische pijn bij zowel moeders als vaders was niet gerelateerd aan chronische pijn bij het kind. Het is opvallend dat de mentale gezondheid van vaders zo'n impact heeft op chronische pijn bij het kind. Psychologische en somatische symptomen bij de ouder(s) kunnen leiden tot chronische pijn bij het kind via 'modeling' (model staan) of 'reinforcement' (bekrachtiging) van ziektegedrag. De lage prevalentie moet gezien worden in de context van dit grote populatie-gebaseerde onderzoek dat niet alleen op pijn is gefocust. Professionals in de gezondheidszorg die geraadpleegd worden voor chronische pijn bij kinderen, zouden ook zorgvuldig aandacht moeten besteden aan de mentale en fysieke gezondheid van zowel moeders als vaders. Het onderzoek in **Chapter 6** behandelt de cross-sectionele en longitudinale relaties van chronische pijn met gedrags- en emotionele problemen bij peuters. Ouders van 3.751 peuters vulden vragenlijsten in over de gezondheid en ontwikkeling van hun kind. Gedrags- en emotionele problemen werden gemeten op 1,5 en 3 jaar, chronische pijn werd gemeten op 2 en 3 jaar. Cross-sectionele verbanden tussen chronische pijn en internaliserende problemen waren sterk. Chronische pijn ging niet vooraf aan het ontstaan van nieuwe gedrags- en emotionele problemen. Gedrags- en emotionele problemen gingen niet vooraf aan het ontstaan van nieuwe pijnklachten, maar veel kinderen die chronische pijn hadden ontwikkeld op de leeftijd van 3 jaar, hadden al somatische klachten (exclusief pijn) op 1,5-jarige leeftijd. Chronische pijn en problemen met de mentale gezondheid treden tegelijkertijd op. Er waren geen longitudinale relaties tussen chronische pijn en mentale gezondheidsproblemen. Als professionals in de gezondheidszorg geconsulteerd worden voor chronische pijn bij een kind, zou ook de mentale gezondheid van dat kind moeten worden nagegaan.

Als laatste geeft **Hoofdstuk 7** een algemene discussie van de belangrijkste bevindingen, behandelt methodologische aspecten van de onderzoeken die in dit proefschrift staan beschreven en benoemt aanbevelingen voor de klinische praktijk en toekomstig onderzoek.

Referentie

IASP. (1979). Pain terms: A list with definitions and notes on usage: recommended by the IASP Subcommittee on Taxonomy. *Pain*, 6(3), 249.

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ABOUT THE AUTHOR

Noor Wolff was born on March 10, 1980 in Eindhoven, the Netherlands. From 1992 to 1998 she attended secondary school in Eindhoven at the Van Maerlantlyceum. In 1998 she went to the University of Tilburg to study Psychology. In 2000 she spent a semester studying Psychology at the University of Alberta in Edmonton, Canada. She completed a clinical internship at the Catharina Hospital in Eindhoven. Next, she conducted research on abdominal pain in children at the Catharina Hospital, specifically studying whether children's pain and anxiety diminished after completing an autogenic relaxation training. She graduated in 2003, having specialized in Child and Adolescent Psychology. In 2004, she started a PhD project, the research of which is presented in this thesis, at the Erasmus Medical Center, Rotterdam. This PhD project was a collaboration of the Department of Medical Psychology & Psychotherapy and the Department of Child & Adolescent Psychiatry. During her PhD studies, she obtained a Master of Science degree in Epidemiology from the Netherlands Institute for Health Sciences (Nihes) in 2007. She also worked part-time as a lecturer in communication skills and professional behavior in the medical school of the Erasmus Medical Center. From January 2008 she worked half-time as a lecturer and coordinator/developer of communication skills education and half-time on her PhD research. After finishing her PhD project, she continued to work at the Department of Medical Psychology & Psychotherapy combining education and research.

Noor Wolff is married to Rick Janssen and they are the proud parents of Bas (born May 12, 2009) and Job (born October 29, 2010).

PHD PORTFOLIO

Name PhD student: N.J. Wolff

Erasmus MC department: Medical Psychology & Psychotherapy

Research school: NIHES

PhD period: 2004-2011

Promotors: Prof. dr. J. Passchier & Prof. dr. F.C. Verhulst

Supervisors: dr. A.S.E. Darlington & dr. H. Tiemeier

1. PhD training	Year	Workload (ECTS)
Research skills		
<i>MSc Epidemiology, NIHES:</i>	2006-2007	
Principles of research in medicine	2004	0.7
Methods of public health research	2006	0.7
Topics in meta-analysis	2006	0.7
Health economics	2006	0.7
Case-control studies	2006	0.7
Introduction to public health	2006	0.7
Prevention research	2006	0.7
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
Study design	2006	4.3
Methodologic topics in epidemiologic research	2006	1.4
Modern statistical methods	2006	4.3
In-depth courses		
Structural Equation Modeling, Erasmus MC, Rotterdam	2005	1
Basiscursus didactiek universitair onderwijs, Erasmus University Rotterdam	2005	1
<i>MSc Epidemiology, NIHES:</i>		
Psychiatric epidemiology	2007	1.1
Repeated measurements in clinical studies	2007	1.4
Missing values in clinical research	2007	0.7
Analysis of time-varying exposures	2007	0.7
Maternal and child health	2007	0.9
National and international conferences – participation and presentations		
7th International Symposium on Pediatric Pain (ISPP), Vancouver, Canada. Poster presentation: <i>Maternal chronic pain and behavior, and acute pain and distress in infants</i>	2006	2
Invitational conference on chronic pain 2007, Rotterdam, the Netherlands. Oral presentation: <i>Invloed gedrag ouders op distress in kinderen van 1 jaar</i>	2007	0.5
Voorjaarscongres van de Nederlandse Vereniging voor Psychiatrie (NVVP), Amsterdam, the Netherlands. Oral presentation: <i>Vroege predictoren van somatische klachten bij peuters</i>	2008	0.5

Invitational conference on chronic pain 2008, Rotterdam, the Netherlands. Oral presentation: <i>Invloed gedrag ouders op distress in kinderen van 1 jaar</i>	2008	0.5
Congres Nederlandse Vereniging voor Medisch Onderwijs (NVMO), Egmond aan Zee, the Netherlands.	2008	0.6
Congres Hoofdzaken: 10 jaar Innovatiefonds Zorgverzekeraars, Utrecht, the Netherlands. Oral presentation: <i>Invloed gedrag ouders op distress bij kinderen van 1 jaar</i>	2009	0.5
Interacademiale Dag Medische Psychologie, Rotterdam, the Netherlands. Oral presentation: <i>Dreumes-drama? Somatische klachten zonder medische oorzaak</i>	2009	0.5
8th International Symposium on Pediatric Pain (ISPP), Acapulco, Mexico. Two poster presentations: <i>Determinants of venipuncture distress in infants and Determinants of somatic complaints in toddlers</i>	2010	2

Seminars and workshops

PhD day, Erasmus MC, Rotterdam	2005	0.3
Minicursus Methodologie van patiëntgebonden onderzoek en voorbereiding van subsidieaanvragen, Erasmus MC, Rotterdam	2005	0.3
Workshop TRAILS – Generation R, Erasmus MC, Rotterdam	2006	0.6

Reviewing papers

Reviewed a paper for Journal of Child Psychology and Psychiatry	2010	0.2
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2. Teaching activities

Year

Workload
(ECTS)

Supervising practicals

Supervising and developing education in communication skills and attitude in the medical curriculum; 0.1 fte in 2004-2007, 0.44 fte in 2008-2010, 0.67 fte in 2011	2004 - present	
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Supervising Master's theses

Supervised Nadia van den Berg, student Developmental and Educational Psychology, Leiden University. Thesis title: <i>De invloed van het gedrag van moeder op coping, distress en pijn bij 14-maanden oude kinderen tijdens venapunctie</i>	2007	3
Supervised Sandra Kuiters, student Developmental and Educational Psychology, Leiden University. Thesis title: <i>Verschillen in de gedragingen van moeders en hun kinderen bij het bloedprikken op 14 en 24 maanden oude leeftijd</i>	2007	3
Supervised Marijana Milosavljevic, student Clinical and Health Psychology, Erasmus University Rotterdam. Thesis title: <i>Distress en pijn bij zeer jonge kinderen: Invloed van het gedrag van de moeder op de pijnervaringen en distresservaringen van het kind in een acute pijnsituatie</i>	2006	3
Supervised Elsbeth Zandee, student Clinical and Health Psychology, Erasmus University Rotterdam. Thesis title: <i>Distress en pijn bij kinderen: Het gedrag van de ouder en verpleegkundige tijdens een bloedafnameprocedure</i>	2007	3

1 ECTS (European Credit Transfer System) is equal to a workload of 28 hours.

1 fte (full time equivalent) is equal to a working week of 36 hours.
