Characteristics of autism spectrum disorder in preterm born children

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Proefschrift ingediend tot het behalen van de academische graad
van Doctor in de Psychologie

2016

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

This first chapter starts with a definition of preterm birth and the developmental risks that are related to it. We also provide a definition of autism spectrum disorder (ASD), give an overview of signs of ASD in the first years of life and stress the importance of early detection of the disorder. Consequently, the association between preterm birth and ASD is demonstrated with a short overview of the literature concerning this topic. Finally, the objectives of this dissertation are formulated and an overview of the different chapters is provided.

PRETERM BIRTH

Prematurity is a complex condition with multiple risk factors (Allen, 2008) and it results from countless socioenvironmental and genetic factors (Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007). Preterm birth occurs when a child is born before 37 weeks of gestational age (GA), more than three weeks before the estimated date of birth. The limit of viability in Flanders, defined as the stage of foetal maturity that ensures a reasonable chance of extra-uterine survival, lies currently around 24 weeks' gestational age and a birth weight of 500 g, with a "grey zone" between 24 and 26 weeks (Finoulst, Vankrunkelsven, & Gyselaers, 2013).

Separate categories in defining preterm birth are used, based on gestational age and birth weight. Children born before 28 completed weeks of gestation are born extremely preterm, a birth between 28 weeks and 31 weeks and 6 days is defined very preterm. Moderately preterm is when a child is born between 32 and 33 weeks, 6 days and late preterm birth occurs when delivery occurs between 34 weeks and 36 weeks 6 days (March of Dimes, PMNCH, Save the Children, & World Health Organization, 2012). Post-term birth is defined as birth at 42 weeks' gestation or more (Campbell, Ostbye, & Irgens, 1997). Birth weight rather than gestational age is also used to subdivide preterm children into categories (< 1000 g: extremely low birth weight, 1000 - 1500 g: very low birth weight, 1500 - 2500 g: low birth weight; World Health Organization, 2011). Infants whose birth weight is below the 10th percentile for the gestational age, are born small for gestational age (SGA).

For this dissertation, it was decided to use the corrected age, computed by subtracting the weeks a child is born too early from the chronological age of the child, in the first two years of life. Correcting for prematurity when comparing preterm children with children born at term is common practice in developmental assessment (Wilson & Cradock, 2004).

Prevalence

Prematurity is an important perinatal health problem across the world (Beck et al., 2010). In 2010, a worldwide estimate of 14.9 million preterm births was registered, 11%

of all livebirths worldwide (Blencowe et al., 2012). Spontaneous preterm births which are idiopathic account for 45–50% of all preterm births, while 30% are related to preterm rupture of membranes. Indicated preterm delivery happens in 15–20% of all preterm births (Beck et al., 2010). Reasons for the rising incidence of preterm births over the past decades in Western developed countries are advancing maternal age, increasing indicated preterm births mainly due to maternal illness and the higher rate of multiple pregnancies, linked to the increase of assisted reproduction technologies (Goldenberg, Culhane, Iams, & Romero, 2008). Importantly, the rate of preterm delivery in singletons in the United States had declined consistently since 2005 (Gyamfi-Bannerman & Ananth, 2014). In Belgium, and more specifically in the geographically defined region of Flanders, 7.4% of all births occur before 37 weeks of gestation, among which 0.4% are extreme preterm births, 0.7% are very preterm births and 6.2% are moderately to late preterm births. Children with low birth weight (< 1500 g) represent 6.9% of all new-borns. Multiple pregnancy is also in Flanders a clear risk factor for prematurity, resulting in a ten-fold increased rate of prematurity in multiple pregnancies (Devlieger, Martens, Martens, Van Mol, & Cammu, 2015).

Mortality

Worldwide, about 40% of deaths in children younger than 5 years in the year 2010 occurred in the neonatal period, most often because of preterm birth complications (Lawn, Gravett, Nunes, Rubens, & Stanton, 2010; Liu et al., 2012). In addition, a large proportion of deaths after preterm birth are associated with the decision to withhold or withdraw intensive care (Larroque, 2004). However, the survival rates for very early preterm born children have increased due to improved neonatal management, because of technological advances and the collaborative efforts of obstetricians and neonatologists (Lemola, 2015). The abovementioned increase in medically indicated preterm births is also associated with a decrease in perinatal morbidity (Ananth, Joseph, Oyelese, Demissie, & Vintzileos, 2005). In Belgium, the mortality rate of babies with a birth weight of at least 500 g was 6.1‰ in 2014 (Devlieger et al., 2015).

Morbidity

Although the increased survival rate of extremely and very preterm born children is a positive evolution, prematurity leads to neonatal complications and preterm born children are often confronted with several developmental problems throughout childhood, adolescence and even into adulthood. Outcome studies are numerous, investigating various domains of functioning.

Acute and chronic complications of preterm birth result from immaturity of a wide range of organ systems: lungs and respiratory systems (Respiratory Distress Syndrome (RDS) and Chronic Lung Disease (CLD)), gastrointestinal systems (Necrotizing enterocolitis (NEC)), cardiovascular systems (patent ductus arteriosus), and central nervous systems (Intraventricular haemorrhage (IVH), white matter injury and periventricular leukomalacia (PVL)). Many of these complications have life-long consequences for the preterm child (Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007; De Kleine et al., 2007; Gibson, 2007).

Sensory disabilities are also associated with preterm birth, with an increasing prevalence of mild to severe visual and auditory deficits with decreasing birth weight or gestational age (Jarjour, 2014; Saigal & Doyle, 2008).

On the neuromotor domain, cerebral palsy (CP) is diagnosed in many preterm born children, being the major disabling neuromotor outcome following preterm birth (Bracewell & Marlow, 2002). Children who do not meet criteria for CP, often show milder motor impairments (gross or fine motor developmental delay, mild neuromotor disabilities, motor planning problems and sensorimotor integration problems; Allen, 2008). When a very preterm born baby is compared with a full term born baby, the preterm born child is more visually active and demonstrates less flexion and more extensor activity (Bracewell & Marlow, 2002).

There is also substantial evidence for cognitive impairments in a broad range of domains. The most consistent finding concerns general intelligence, with lower levels of general intelligence in preterm children being demonstrated throughout childhood (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Wilson-Costello, Friedman, Minich, Fanaroff, & Hack, 2005). Kerr-Wilson, MacKay, Smith, and Pell (2012) demonstrated a dose-response relationship between intelligence and gestational age.

The degree of prematurity is also linearly related to worse academic outcomes (Lemola, 2015). Academic underachievement in preterm born children in reading, writing and mathematics was demonstrated by Aarnoudse-Moens, Weisglas-Kuperus, van Goudoever, and Oosterlaan (2009) and Moster, Lie, and Markestad (2008) provided evidence for less successful academic trajectories in preterm born children. Learning disabilities are also more prevalent in preterm born children (Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007).

Next to the incidence of major disabilities such as CP, cognitive and sensory impairments, there is raising awareness for more subtle developmental issues. The more subtle disorders of central nervous system function include language disorders, attention deficits, behavioural problems and social-emotional difficulties (Anderson & Doyle, 2003; Barre, Morgan, Doyle, & Anderson, 2011; Charkaluk, Truffert, Fily, Ancel, & Pierrat, 2010; Clark, Woodward, Horwood, & Moor, 2008; Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007; Johnson & Marlow, 2014; Samara, Marlow, & Wolke, 2008). Problems with peers were prevalent in more than 25% of a cohort of extremely preterm born 6-year-old children (EPICURE), compared to in 5% of the term born controls (Samara et al., 2008). Parents of very low birth weight male adolescents scored their children significantly higher on a social syndrome scale, but the adolescents themselves rated similar scores for this subscale (Dahl et al., 2006).

Moreover, there is substantial evidence for a greater risk of psychiatric symptoms and diagnoses in childhood and adolescence (e.g., Indredavik et al., 2004, 2005; Treyvaud et al., 2013), but also in infancy (Janssens et al., 2009). In the past years, research in several cohorts of preterm born individuals of different ages also suggested a link between prematurity and autism spectrum disorder (ASD).

AUTISM SPECTRUM DISORDER

This neurodevelopmental disorder, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; APA, 2013, p. 50), is characterised by developmental difficulties in social communication and social interaction. These

symptoms are supplemented with repetitive behaviour, interests or activities, such as stereotyped movements or speech, insistence on sameness and routines, fixated interests of an unusual intensity or topic, or unusual sensory interests. The DSM-5 specifies that symptoms should be present in the early developmental period, but they may not become fully manifest until social demands exceed limited capacities or the symptoms may be masked by learned and compensating strategies. Specifiers can be applied to indicate possible accompanying intellectual or language impairment, the association with a known medical or genetic condition, or the comorbidity with other neurodevelopmental, mental or behavioural disorders (APA, 2013, p. 50-51).

The prevalence of ASD is usually estimated at 60-70 per 10,000 children, which indicates that it is one of the most prevalent childhood neurodevelopmental disorders. The overall prevalence estimate in a study of 8-year-old children was even higher, 11.3 per 1000 or 1 in 88 (ADDMN, 2012). The diagnosis of ASD is overrepresented in males with four times as many cases of ASD than in females in individuals with average cognitive abilities. The sex ratio found in children with intellectual disability is 2:1 (Elsabbagh et al., 2012; Fombonne, 2009). In a minority of cases, ASD is associated with a known medical condition or syndrome (Chakrabarti & Fombonne, 2005). The disorder often results in lifelong impairments and puts a burden on the family of the child and on society.

A recent review summarised the possible causes for ASD in four lines of thought: ASD can be seen as a disorder of the social brain, as resulting from general neuro-cognitive factors, such as attention or sensory processing, as a result of the additive effect of social and domain-general atypicalities and lastly, as resulting from brain-wide neural impairments (Gliga, Jones, Bedford, Charman, & Johnson, 2014).

Screening and diagnostic measures

Since Filipek and colleagues (1999) suggested the use of screening instruments for ASD suitable for infants and toddlers, great efforts have been put into the development of screening instruments for early detection of ASD during the past decades within two models of early detection: systematic population screening and a two-stage screening procedure (Oosterling et al., 2009). In the second model, a specific screening instrument for ASD is only applied to children showing a deviant developmental path at a routine

developmental surveillance. Screening instruments that can be used for screening in the general population or in high-risk populations are the Checklist for Autism in Toddlers (CHAT; Baron-Cohen, Allen, & Gillberg, 1992; Baron-Cohen et al., 1996), the Modified Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001), the First Year Inventory (FYI; Reznick, Baranek, Reavis, Watson, & Crais, 2007), and the Early Screening for Autistic Traits Questionnaire (ESAT; Dietz, Swinkels, van Daalen, van Engeland, & Buitelaar, 2006; Swinkels et al., 2006). A major revision of the CHAT resulted in the Quantitative CHAT (Q-CHAT; Allison et al., 2008).

'Gold standard' diagnosis of ASD is today a lengthy and time consuming process, which involves a multidisciplinary team (MDT) to assess the functioning of the child and collect behavioural and historic information and to provide consensus clinical judgement (Falkmer, Anderson, Falkmer, & Horlin, 2013). Two of the most well-validated measures that are used in the diagnostic procedure for ASD are the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, Dilavore, & Risi, 1999) or the ADOS-2 (Lord et al., 2012) and the Autism Diagnostic Interview – Revised (ADI-R; Rutter, LeCouter, & Lord, 2003). Both instruments are considered the 'gold standard' tools in research protocols. In a recent literature review both instruments stood out with the largest evidence base and the highest sensitivity and specificity. For an ASD diagnosis, the combined use of the ADOS and the ADI-R had equal correct classification rates as diagnosis by a MDT, indicating a very good accuracy in diagnosing ASD (Falkmer et al., 2013).

Early signs of ASD and the importance of early detection

As explained above, one of the diagnostic conditions of ASD is the presence of symptoms early in life. Although the scientific knowledge about the signs or symptoms of ASD early in life is increasing progressively, children are on average at least three years old by the time they receive a diagnosis (Barbaro & Dissanayake, 2009; Steiner, Goldsmith, Snow, & Chawarska, 2012). Results from retrospective studies with coding of home videos (Adrien et al., 1993; Baranek, 1999; Osterling, Dawson, & Munson, 2002; Osterling & Dawson, 1994; Teitelbaum, Teitelbaum, Nye, Fryman, & Maurer, 1998) or parent report (Lord, 1995; Wimpory, Hobson, Williams, & Nash, 2000), prospective population screening studies and prospective studies with high-risk infant siblings of children with

ASD (Yirmiya & Charman, 2010), enabled several researchers in the past decades to identify early markers of a later diagnosis of ASD. Results clearly indicated that ASD symptoms emerge in the first two years of life, with behavioural symptoms being overt by the end of the first year (Elsabbagh & Johnson, 2009).

During the first six months of life, studies suggest relatively typical development in social engagement and motivation (Dawson, Osterling, Meltzoff, & Kuhl, 2000; Jones, Gliga, Bedford, Charman, & Johnson, 2014; Rozga et al., 2011; Wan et al., 2013) and no differences in several domains of social and communicative functioning (e.g., Bedford et al., 2012; Elsabbagh et al., 2013, 2014; Hudry et al., 2014; Ozonoff et al., 2010). However, dyadic and intersubjective abnormalities have been detected in some studies, as well as reduced amounts of time paid to social stimuli (Yirmiya & Charman, 2010). Moreover, other studies did find differences around the age of 6 months in the domain of temperamental development (Clifford, Hudry, Elsabbagh, Charman, & Johnson, 2013; Del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2014; Zwaigenbaum et al., 2005). Although overt behavioural symptoms mainly emerge around the end of the first year of life, studies using laboratory brain function measures have reported differences between high-risk siblings and low-risk controls already during the first year of life (Elsabbagh & Johnson, 2009). Betting beneath behavioural and overt indicators and symptoms of ASD goes beyond the scope of this doctoral dissertation, so we will not go into detail with respect to this topic.

By 12 months of age, mainly social behaviour impairments, such as ignoring people, lower frequency of eye contact and gazing to a person (Feldman et al., 2012; Maestro et al., 2002), deficits in social attention (Ozonoff et al., 2010) no or poor imitation of others (Dawson et al., 2000; Feldman et al., 2012; Macari et al., 2012) and poor social responsiveness (Maestro et al., 2002) and communication deficits, such as delays in receptive and expressive language development (Mitchell et al., 2006; Zwaigenbaum et al., 2005), lack of appropriate facial expressions, and lack of social smiles (Maestro et al., 2002), were identified as infant signs of ASD.

A low frequency of orienting to name call (Feldman et al., 2012; Nadig et al., 2007; Osterling et al., 2002; Osterling & Dawson, 1994; Werner, Dawson, Osterling, & Dinno, 2000), absence of showing of objects and a lack of pointing (Osterling & Dawson, 1994;

Rozga et al., 2011), poor use of gestures (Landa, Holman, & Garrett-Mayer, 2007) and deficits in initiating (Landa et al., 2007) and responding to joint attention (Rozga et al., 2011), are also early behavioural indicators within the domains of social interaction and communication. Lack of interest in other children and no amusement in playing social games like peek-a-boo or in cuddles, were also reported by parents as concerns in the first years of life (Barbaro & Dissanayake, 2009).

Given the appropriateness of certain repetitive behaviours at specific ages and their contribution to motor development, the study of repetitive behaviours as risk indicators for ASD is an important challenge (Rogers, 2009). Repetitive and stereotyped behaviours at the age of 12 months were mainly found to differentiate between children with ASD and children with typical development, but not between children who go on to develop ASD and children with intellectual impairment (Barbaro & Dissanayake, 2009). Atypical movement patterns during object play, rather than repetitive behaviours, such as spinning toys, unusual visual regard and rotation, were found to differentiate the outcome group with ASD from the outcome group without (Damiano, Nahmias, Hogan-Brown, & Stone, 2010; Ozonoff et al., 2008), as did repetitive movements involving arms and hands (Loh et al., 2007).

Next to the social and communication impairments and the repetitive behaviours that are consistently reported in infants who go on to be diagnosed with ASD, deficits in executive functioning, behavioural reactivity, difficulties with transitions and impaired motor control (Bryson et al., 2007; Flanagan, Landa, Bhat, & Bauman, 2012) have also been found to be indicators of ASD early in life. There is also general consistency about differences on standardised developmental tests by 12 months of age (Rogers, 2009) and later on at 14 and 24 months of age (Landa & Garrett-Mayer, 2006). The above reported temperamental characteristics are another early sign that falls outside the range of core symptoms of ASD (Elsabbagh & Johnson, 2009; Rogers, 2009).

Understanding how ASD unfolds from birth onwards and early identification of signs of ASD is critical to start understanding the developmental mechanisms of the disorder. Most abovementioned studies focused on isolated measures predicting later outcome and evidence from a combination of measures is necessary to establish the underlying mechanisms of ASD (Gliga et al., 2014). Also reducing the age at which ASD is diagnosed,

is crucial. This way, children who require early intervention can be identified and appropriate intervention targets can be found (Barbaro & Dissanayake, 2009; Jones et al., 2014). Also implementing interventions to lessen the burden of early emerging developmental perturbation, thus preventing secondary neurodevelopmental disturbances, is an important aspect (Yirmiya & Charman, 2010). Finally, reducing the burden on concerned parents is an important research target (Zwaigenbaum, Bryson, & Garon, 2013). Findings of the different studies that got a look into early signs of ASD, indicated that various behavioural indices of attention, perception, communication, temperament, social behaviour and sensory-motor development characterise children who later on develop ASD. Yet not a single developmental trajectory has been identified (Yirmiya & Charman, 2010).

Perinatal risk factors

As summarised by Jones, Gliga, Bedford, Charman and Johnson (2014), symptoms of ASD likely emerge from a complex interaction between pre-existing neurodevelopmental vulnerabilities and the child's environment, modified by compensatory skills and protective factors. There is increasing recognition that environment in addition to genes needs to be considered since environmental factors likely modulate genetic vulnerabilities responsible for the manifestation of ASD (Yirmiya & Charman, 2010).

Several large-scale studies focused on risk factors in the neo- and perinatal period and various factors were identified as being associated with a higher risk for ASD. Two of those factors are low birth weight and gestational age below 37 weeks of gestation, indicating the importance of considering prematurity as a risk factor for ASD (Yirmiya & Charman, 2010).

ASD IN PRETERM BORN CHILDREN

Prematurity as a risk factor for ASD

Already halfway through the past century, Pasamanick, Rogers, and Lilienfeld (1956) and Knobloch and Pasamanick (1975), demonstrated an association between low birth

weight and autism. These studies were followed by a great number of epidemiological, population-based, cross-sectional and case-control studies that indicated that prematurity, low birth weight and lower gestational age, play a role in the aetiology of ASD (Nelson, 1991).

Case-control studies and large population studies demonstrated lower birth weights (Brimacombe, Ming, & Lamendola, 2007; Burd, Severud, Kerbeshian, & Klug, 1999; Glasson et al., 2004; Lampi et al., 2012; Larsson et al., 2005; Maimburg & Vaeth, 2006; Mann, McDermott, Bao, Hardin, & Gregg, 2010; Molly, Esserman, Anckarsäter, Sullivan, & Lichtenstein, 2012; Wier, Yoshida, Odouli, Grether, & Croen, 2006; Wilkerson, Volpe, Dean, & Titus, 2002; Zhang et al., 2010) and lower gestational ages (D'Onofrio et al., 2013; Larsson et al., 2005; Mamidala et al., 2013; Movsas & Paneth, 2012; Schendel & Bhasin, 2008; Williams, Helmer, Duncan, Peat, & Mellis, 2008) in children diagnosed with autism or ASD, compared to case-controls. A review of seven epidemiological studies indicated that the main neonatal conditions significantly associated with ASD, were birth weight and gestational age, along with intrapartum hypoxia (Kolevzon, Gross, & Reichenberg, 2007). A more recent review with 85 included studies also identified preterm birth as a risk factor for ASD (Guinchat et al., 2012). In a register-based study, Eaton, Mortensen, Thomsen, and Frydenberg (2001) demonstrated that the effect of prematurity on the risk for hospitalisation for ASD is substantially larger than the risk for other psychiatric disorders. Moreover, recent evidence demonstrated a clear gradually increased risk for ASD with shorter gestation (Kuzniewicz et al., 2014; Leavey, Zwaigenbaum, Heavner, & Burstyn, 2013; Movsas & Paneth, 2012).

However, some studies failed to replicate the association between low birth weight (Bilder, Pinborough-Zimmerman, Miller, & McMahon, 2009; Croen, Grether, & Selvin, 2002; Cryan, Byrne, O'Donovan, & O'Callaghan, 1996; Glasson et al., 2004; Stein, Weizman, Ring, & Barak, 2006) or low gestational age (Bilder et al., 2009; Buchmayer et al., 2009; Glasson et al., 2004; Hultman et al., 2002; Maimburg & Vaeth, 2006; Mason-Brothers et al., 1990) with a higher risk for autism or ASD.

Two other issues related to this topic, but not primordial for the content of this doctoral dissertation, are the association between small for gestational age (SGA) status and ASD demonstrated in several population-based studies (Buchmayer et al., 2009;

Hultman et al., 2002; Lampi et al., 2012; Larsson et al., 2005; Maimburg & Vaeth, 2006; Moore, Kneitel, Walker, Gilbert, & Xing, 2012) and the association between post-term birth and ASD (Movsas & Paneth, 2012; Sugie, Sugie, Fukuda, & Ito, 2005; Zhang et al., 2010). Movsas and Paneth (2012) stated that normal gestational age at birth appears to mitigate the severity of autistic social impairment in children with ASD.

Screening studies

Most screening studies investigating the prevalence of ASD symptomatology in preterm born children were conducted in early childhood, around the (corrected) age of 24 months. They all revealed that features of ASD have a disproportionally higher prevalence in preterm toddlers compared to toddlers in the general population (Dudova et al., 2014; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Kuban et al., 2009; Limperopoulos, 2009; Moore, Johnson, Hennessy, & Marlow, 2012; Stephens et al., 2012; Wong, Huertas-Ceballos, Cowan, & Modi, 2014).

Screening for ASD in late childhood and adolescence also revealed higher screening rates (Hack et al., 2009; Indredavik et al., 2010; Williamson & Jakobson, 2014).

Diagnostic studies

Since several studies indicated that the high frequency of neurological, cognitive, and sensory difficulties in the functioning of preterm born children may give rise to false-positive screening classifications for ASD (Johnson & Marlow, 2009; Kuban et al., 2009; Moore et al., 2012; Stephens et al., 2012), a diagnostic evaluation to confirm true rates of ASD in preterm born children seemed to be indicated. Two studies at the age of 2 (Dudova, Kasparova, et al., 2014; Dudova, Markova, et al., 2014; Gray et al., 2015) and two studies in late childhood and adolescence (Johnson et al., 2010; Pinto-Martin et al., 2011), confirmed a positive ASD screen with a further diagnostic assessment.

What factors contribute to the higher prevalence of ASD in preterm born children?

Several studies provided possible explanations for the association between preterm birth and ASD. Johnson and colleagues (2010) suggested that ASD in preterm born

children is associated with altered brain development. Lampi and colleagues (2012), for example, suggested that NICU infants may experience intraventricular haemorrhages and white matter injuries, which may mediate the relationship between prematurity and ASD. The association between cerebellar haemorrhagic injury and ASD screening rates was demonstrated in a study of Limperopoulos and colleagues (2007). Buchmayer and colleagues (2009) showed that the association between ASD and preterm birth is mediated by neonatal complications, such as intracranial bleeding, cerebral oedema or seizures in the neonatal period. In a study of Kuzniewicz and colleagues (2014), intracranial haemorrhage was also associated with ASD in infants born before 34 weeks of gestation. Another hypothesis is that improvements in obstetric and neonatal management have led to an increased rate of survivors with pre-existing brain damage (Guinchat et al., 2012). Preterm born children and children who go on to develop ASD may also share similar neurodevelopmental antecedents (Lampi et al., 2012). Maternal risk factors that were found to mediate the relation between prematurity and ASD are preeclampsia (Buchmayer et al., 2009) and maternal infection or inflammation (Meldrum et al., 2013).

In general, considering preterm birth as an individual risk factor, independent from other neonatal and perinatal risks is difficult. It remains unclear if prematurity as a risk factor plays a causal role and is strictly environmental or if prematurity plays a secondary role in shaping clinical expression of a genetic vulnerability (Guinchat et al., 2012). As demonstrated, the research literature considering explanations for the above reported association is extensive and this doctoral dissertation does not have the intention to provide additional answers considering this topic.

RESEARCH OBJECTIVES AND OVERVIEW OF THE CHAPTERS

Studies about the link between prematurity and ASD features and diagnoses are very disparate and results are inconsistent, dependent on the degree of prematurity and impairment of the children, the measures used, and the age of assessment. Nevertheless, the general finding is that features of ASD are significantly more common in the preterm

population than in the general population. Already at the (corrected) age of 24 months, ASD symptomatology seems to be more prevalent in preterm born children with differing gestational ages. We might wonder if precursors indicative for ASD are already more prevalent in the course of the second year of life, as is the case in younger siblings of children with ASD, another group at-risk for developing ASD (Elsabbagh & Johnson, 2009; Jones et al., 2014; Zwaigenbaum et al., 2013).

Karmel and colleagues (2012) retrospectively investigated behavioural characteristics of NICU graduates who went on to be diagnosed with ASD. Those children had persistent neurobehavioural abnormalities, a higher incidence of asymmetric visual tracking and arm tone deficits at the corrected age of 1 month. At 4 months, children with later ASD preferred higher amounts of visual stimulation. Declining mental and motor performance was found between the ages of 7 and 10 months. These results indicate that differences in specific behaviour between preterm children who go on to be diagnosed with ASD and those who are not, can be identified already early in life. However, early developmental pathways to the emergence of ASD symptoms in the group of very preterm born children are so far not well characterised. Drawing on the model of prospective studies of infant siblings of children with ASD, longitudinal investigations of children born prematurely, employing multiple measures and methods at multiple time-points are needed to identify early markers and early developmental trajectories and to make comparisons between high- and low-risk groups.

Prospective research has several advantages, when compared with retrospective studies and screening studies. Behaviours of interest can be elicited at particular ages or time points early in life and the behaviours can be compared between different groups of children. The development of behaviours can also be assessed across different time points, enabling to investigate relations between early deficits, following behavioural manifestations and diagnostic status (Barbaro & Dissanayake, 2009).

The main goals of this dissertation are: (1) to evaluate the prevalence of ASD in extremely and very preterm born children in Flanders (Chapters 2 and 3) and (2) to prospectively study developmental characteristics of preterm born children at risk for ASD (Chapters 4 and 5).

Chapter 2

In this chapter, we aim to provide a more comprehensive picture of the prevalence of ASD in a geographic cohort of extremely preterm born adolescents by using established diagnostic instruments in addition to screening instruments. In the Extremely Preterm Infants in BELgium (EPIBEL) cohort, perinatal data of all the children born before 27 weeks of gestation in a two-year period (1999 and 2000) were collected (Vanhaesebrouck et al., 2004). At 3 years of age, the cognitive and motor development of the Flemish (Dutch-speaking) children was assessed (De Groote et al., 2007). For the current study, this group was tested again at the age of 11 - 15 years. Participants passed a screening procedure with two screening instruments and a diagnostic evaluation with a semi-structured assessment and a parent interview.

Chapter 3

Chapter 3 aims to investigate the prevalence of ASD features in very preterm born infants at the early corrected age of 18 months. In a prospective follow-up study, ASD symptomatology in very preterm born children was estimated by using an internationally established diagnostic instrument in addition to two validated screening tools. This provides us with both parent-reported measures as well as with a direct observation measure of ASD symptoms. Children were followed from birth onwards, so developmental characteristics in early life that are possibly associated with higher rates of ASD symptomatology are also discussed. Neo- and perinatal characteristics are considered, but also results of possible associations with motor, cognitive, and language development, adaptive functioning, joint attention skills and behavioural problems are presented.

Chapter 4

As was stated by Wan and colleagues (2012), the early presence of social and other difficulties in children who go on to develop ASD, might suggest that specificities in caregiver-infant interaction are an important aspect to investigate in developmental trajectories. Given the increased risk for ASD in preterm born children and the specific characteristics of the interactions between mothers and their preterm born children,

along with the specifics of the interactions between mothers and their children at-risk for or with ASD, this chapter investigates the link between early mother-child interaction (MCI) and ASD symptomatology. Studying MCI in extremely and very preterm born children early in life, in the context of ASD, offers the potential for earlier detection of possible emerging symptoms of ASD in those children and may provide us with more insights into the developmental pathways through which preterm born children develop ASD.

Chapter 5

As reported above, temperamental specificities already are apparent in children at developmental risk for ASD in the first years of life. Given the increased risk for ASD in preterm born children and the specific temperamental profiles in individuals with (an increased risk for) ASD, this chapter investigates the link between preterm temperamental profiles and ASD symptomatology. This study assesses early temperamental profiles of the cohort of very preterm born children at consecutive time points in the first years of life (corrected ages of 5, 10 and 18 months), in the light of ASD symptomatology at the corrected age of 18 months.

Chapter 6

In the final chapter, a summary of the most important findings is provided, limitations are discussed and implications for future practice and research are given.

It should be noted that this dissertation consists of several research papers, which are submitted for publication, are currently under review, or have been published. Since each of the manuscripts should be able to stand on its own, their contents may partially overlap.

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CHAPTER 2

EXTREMELY PRETERM BORN CHILDREN AT VERY HIGH RISK FOR DEVELOPING AUTISM SPECTRUM DISORDER[1]

ABSTRACT

This study aimed to provide a more comprehensive picture of the prevalence of autism spectrum disorder (ASD) in a geographic cohort of extremely preterm born adolescents by using established diagnostic instruments in addition to screening instruments. Fifty-three participants passed a screening procedure with two screening instruments and a diagnostic evaluation with a semi-structured assessment and a parent interview. Of the adolescents, 28% had a community based clinical diagnosis of ASD. When research diagnoses were also taken into account, this rate increased to 40%. Intellectual disability, language impairment and behavioural difficulties are characteristic for these children with ASD. This study is to our knowledge the first to use ASD-specific diagnostic instruments to confirm ASD diagnoses in extremely preterm born children in early adolescence. The study expands findings of previous research and raises the need for follow-up into late childhood and early adolescence.

INTRODUCTION

In the past decades, major advances in perinatal care have increased the survival rate of extremely preterm born children, born before 27 weeks of gestation (Wilson-Costello, Friedman, Minich, Fanaroff, & Hack, 2005). Follow-up studies have shown that these children are often confronted with developmental problems and psychiatric diagnoses in late childhood and early adolescence (Farooqi, Hägglöf, Sedin, Gothefors, & Serenius, 2006, 2007; Indredavik, Vik, Heyerdahl, Kulseng, & Brubakk, 2005; Johnson et al., 2009, 2010b; Saigal & Doyle, 2008; Saigal, Hoult, Streiner, Stoskopf, & Rosenbaum, 2000; Saigal, Pinelli, Hoult, Kim, & Boyle, 2003). Studies also suggest a link between extreme prematurity and autism spectrum disorder (ASD), characterised by persistent deficits in social communication and social interaction, and restrictive and repetitive patterns of behaviours, interests or activities (American Psychiatric Association, 2013). Prematurity and low birth weight are considered to be risk factors for ASD (Johnson & Marlow, 2011; Kolevzon, Gross, & Reichenberg, 2007; Lampi et al., 2012; Larsson et al., 2005; Mamidala et al., 2013; Schendel & Bhasin, 2008; Williams, Helmer, Duncan, Peat, & Mellis, 2008). Two recent studies even found a gradual increased risk of traits of ASD with shorter gestation (Kuzniewicz et al., 2014; Leavey, Zwaigenbaum, Heavner, & Burstyn, 2013). Screening studies in early childhood revealed that features of ASD have a disproportionally higher prevalence in the preterm compared to the general population (Kuban et al., 2009; Limperopoulos et al., 2008; Moore, Johnson, Hennessy, & Marlow, 2012; Wong, Huertas-Ceballos, Cowan, & Modi, 2014). Studies with the Modified-Checklist for Autism in Toddlers (M-CHAT; Robins & Dumont-Mathieu, 2006; Robins, Fein, Barton, & Green, 2001) found screening percentages between 21 and 41% (Kuban et al., 2009; Limperopoulos et al., 2008; Moore et al., 2012). The use of multiple screening instruments resulted in comparable percentages (Dudova et al., 2014; Stephens et al., 2012).

Screening in late childhood and early adolescence revealed similar results. Hack and colleagues (2009) examined a group of 8-year-old children (birth weight < 1000 g) and found higher symptom severity scores in these children compared with term peers. In another study, scores on the Autism Spectrum Screening Questionnaire (Ehlers, Gillberg,

& Wing, 1999) were higher for very preterm adolescents (gestational age < 32 weeks), compared with their term-born counterparts (Indredavik et al., 2010).

Since several studies indicated that the high frequency of neurological, cognitive and sensory difficulties may give rise to false-positive screening classifications for ASD (Johnson & Marlow, 2009; Kuban et al., 2009; Moore et al., 2012; Stephens et al., 2012), a diagnostic evaluation to confirm true rates of ASD is indicated. To our knowledge, only one study confirmed a positive ASD screen with a further assessment in late childhood: of the 15.8% children with a positive screen on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003), 8% was diagnosed with ASD following a psychiatric evaluation at 11 years (Johnson et al., 2010a). However, clinical assessment involving direct observation by a clinician was not performed (Stephens et al., 2012). The only studies that did include a direct observation measure were conducted with infants (2 years; birth weight < 1500 g; Dudova et al., 2014) and older adolescents (16 - 21 years; birth weight < 2000 g; Pinto-Martin et al., 2011) and resulted in prevalence rates of 13% (Dudova et al., 2014) and 5% (Pinto-Martin et al., 2011), respectively.

To conclude, a detailed observation of the prevalence of ASD using both parent report and direct observation is not yet available for the age group between 11 and 15 years. The current study therefore aims to provide a more substantiated picture of ASD prevalence in extremely preterm born children in their early adolescence by using internationally established diagnostic instruments in addition to screening tools. IQ, language and behavioural characteristics of children with and without ASD are compared.

METHODS

Participants

Participants in this study belonged to the Extremely Preterm Infants in BELgium (EPIBEL) cohort. In this cohort, perinatal data of all the children born before 27 weeks of gestation in a two-year period (1999 and 2000) were collected (Vanhaesebrouck et al., 2004). At 3 years of age, the cognitive and motor development of the Flemish (Dutch-

speaking) children (n = 91) was assessed (De Groote et al., 2007) with the Bayley Scales of Infant Development – II (van der Meulen, Ruiter, Spelberg, & Smrkovsky, 2004). For the current study, this group was tested again at the age of 11 - 15 years.

All 91 children included in the 3-year follow-up study were eligible. However, five (5%) of the families moved abroad and seven (8%) were excluded because Dutch was not their mother tongue. The remaining 79 families were contacted by the developmental centres who were responsible for the follow-up of the children in the first years of life, because according to the Belgian privacy law, their home addresses were not available to the authors. Of these 79 families, 66 (84%) replied. The other families could not be reached due to changed contact information (11%) or no response (5%). Of the 66 responding families, 13 (20%) chose not to participate. As such, data of 53 children of the Flemish part of the EPIBEL cohort (67%) were collected.

Participants were 32 (60%) boys and 21 (40%) girls with a mean age of 12.60 years (SD = 1.03; range: 11 - 15); mean birth weight was 791.75 g (SD = 179.08; range: 400 - 1210). Mean age of mothers at birth was 27.81 years (SD = 4.18, range: 20 - 38). Nine children (17%) suffered from cerebral haemorrhage grade III or IV and three children from cystic leukomalacia (6%). At the age of three, nine children (17%) were diagnosed with a central motor deficit. Currently, eight children showed major motor impairments (e.g., cerebral palsy) and eight suffered from major visual impairment or blindness. Another three children had auditory difficulties. Eighteen children were part of a twin and four children formed a quadruplet.

Birth weight (t(89) = -.09, p = .930), gestational age (U = 933.50, p = .901) and age of mother at birth (U = 913.50, p = .582) were not significantly different between participants and drop-outs (n = 38). The percentage of drop-outs with cerebral haemorrhage grade III or IV (n = 7, 18%) or cystic leukomalacia (n = 3, 9%) did not differ significantly from the percentage in the participating group (χ^2(1) = 0.03, p = .859, χ^2(1) = 0.18, p = .672). Nine drop-outs were diagnosed with a central motor deficit at the age of three, which is not significantly different from the number in the participating group (χ^2(1) = 1.48, p = .223). The difference in psychomotor developmental index was marginally significant (drop-outs M = 66.60, SD = 14.76; participating M = 74.87, SD = 19.09; t(62) = -1.84, p = .070). However, drop-outs had a significantly lower mental

developmental index (M = 72.29, SD = 17.27; $t(69)$ = -2.60, p = .010) at the age of 3 than participating children (M = 83.81, SD = 18.86).

Materials

Two validated questionnaires were used to estimate ASD symptoms. Firstly, the SCQ lifetime version (Rutter, Bailey, et al., 2003), a 40-item parent questionnaire, was used. Total scores were compared with the established cut-off to screen for ASD (i.e., 15). External validity of the SCQ as a first-level screen for ASD in at-risk samples was demonstrated (sensitivity .88 - .96, specificity .72 - .80; Berument, Rutter, Lord, Pickles, & Bailey, 1999; Chandler et al., 2007) and sufficient internal validity was also established (Wei, Chesnut, Barnard-Brak, & Richman, 2015). Also the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005; Roeyers, Thys, Druart, De Schryver, & Schittekatte, 2011), a 65-item questionnaire, was administered. A total T-score above the established cut-off of 60 indicates mild to severe shortcomings in social functioning, characteristic for children with mild to severe autistic symptomatology. The SRS is characterised by good internal consistency (Roeyers et al., 2011), good concurrent validity (Constantino et al., 2003; Roeyers et al., 2011) and high sensitivity (.90) and specificity (.88; Roeyers et al., 2011). Parents were asked to complete both questionnaires.

The diagnostic evaluation included the Autism Diagnostic Observation Schedule (ADOS; Lord, Rutter, Dilavore, & Risi, 2008) and the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003). The ADOS is a semi-structured assessment of communication, social interaction and play. In this study, module 3 was used and ADOS2-algorithms were applied (Gotham, Risi, Pickles, & Lord, 2007). There is significant evidence for sensitivity and specificity for the ADOS in differentiating children with ASD from children with non-spectrum disorders (Gotham et al., 2007). Inter-rater agreement for diagnostic classification ranged from 81% to 93% and internal consistency for all domains and modules ranged from .47 to .94 (Lord et al., 2008). We aimed to assess the functioning of all participating children with the ADOS.

The ADI-R, a semi-structured interview in which parents are questioned about their child's social and communication development, was administered when children had a community based clinical diagnosis of ASD or when ADOS-scores were above the cut-off

for ASD. Test-retest and interrater reliabilities of the ADI-R are excellent (most intraclass correlation coefficients > .90). Internal consistencies of domain scores ranged from .54 to .84. Concurrent validity was very good and criterion validity was excellent. Discrimination between ASD versus non-ASD subjects is very good (sensitivity 1.00; specificity > .97; Rutter, Le Couteur, et al., 2003).

Higher scores on both diagnostic instruments are indicative for more autistic traits. Both ADOS and ADI-R were administered by the first author, who was trained to research reliability. Inter-rater reliability was obtained by scoring of a number of administrations by three other trained researchers (MD, PW and HR).

Intelligence was assessed using an abridged version of the Wechsler Intelligence Scale for Children-III (WISC-III; Grégoire, 2000; Wechsler, 1991). With four subscales (Similarities, Picture Concepts, Block Design and Vocabulary), an intelligence quotient was obtained (M = 100, SD = 15). In addition, language development was examined by means of the Dutch version of the Clinical Evaluation of Language Fundamentals (CELF-IV(-NL); Kort, Schittekatte, & Compaan, 2008; Semel, Wiig, & Secord, 2003), a test for evaluation and diagnosis of language difficulties. Testing with four subtests provided us with a core score for language development (M = 100, SD = 15).

Information about medical and psychological diagnostic and treatment history and scholastic achievement was obtained using a self-designed questionnaire. Parental, teacher and self-ratings of behavioural problems were collected, using the Child Behaviour Checklist (CBCL), the Teacher Report Form (TRF) and the Youth Self Report (YSR; Achenbach, 1991). In addition, the Disruptive Behaviour Disorders Rating Scales (Pelham, Gnagy, Greenslade, & Milich, 1992; VvGK (Oosterlaan et al., 2008)) was used to screen for disruptive behaviour disorders. Higher scores on these questionnaires indicate higher symptom prevalence.

Statistical analyses

Data were analysed using the Statistical Package for the Social Sciences software version 19 (SPSS Inc., Chicago, Il, USA). In the first part of the results section, descriptive analyses (e.g., cross tabulations) were performed to provide information about the ASD

clinical diagnostic status, the ASD diagnostic status based on assessment with the diagnostic instruments and the ASD screening status of the preterm born children. Four groups of children were formed. Children with a community based clinical diagnosis of ASD form the *clinical ASD*-group. Children with a score above the cut-off for ASD on one or both diagnostic instruments (ADOS and/or ADI-R), but without a former community based clinical diagnosis form the *research ASD*-group. The children from these two diagnostic groups are together considered as the *ASD*-group. A third group is defined as the *ASD concern*-group. This group comprises the children with a positive screen for ASD, on one or both screening questionnaires, but without a clinical or research diagnosis of ASD. Children without a screen for or a diagnosis of ASD are considered as children without ASD (*no ASD*-group).

Independent samples t-tests, chi-square analyses and (one-way) ANOVA's were performed to compare developmental characteristics of the different groups of children. Analyses are labelled 'four groups' when children with a community based clinical diagnosis and children with a research diagnosis are considered separately and 'three groups' when they are considered as one group. Bonferonni post-hoc analyses were applied. For all analyses, the overall significance level was set at .05. Significance levels below .10 were considered marginally significant.

Ethics

This study was approved by the local ethical committee. Both children and parents gave written informed consents.

RESULTS

Suspicion of ASD

Based on the scores on the screening questionnaires and diagnostic measures, the participating children were divided in four groups reflecting a different grade of suspicion of ASD diagnosis. The first group (*clinical ASD*-group) consisted of 15 (28%) children with a community based clinical diagnosis of ASD, received prior to our

evaluation. The second group (*research ASD*-group) consisted of another six (11%) children with a clinical score on one or both diagnostic measures, who never received a clinical diagnosis. Of the total sample, 21 children (40%) thus had a clinical or research diagnosis of ASD. The two groups of children together are considered as the ASD-group. A third group (*ASD concern*-group) comprises the children with a positive screen on the SCQ and/or the SRS (*n* = 12, 23%), but without a clinical diagnosis or a clinical score on one or both diagnostic measures. The remaining 20 children (38%) belonged to the fourth group of children without any suspicion of ASD.

Information about diagnostic status was retrieved from clinical diagnostic reports. In the first group of 15 (28%) children with a community based clinical diagnosis of ASD, received prior to our evaluation, diagnosis was confirmed by a clinical score on the ADOS in nine of these children. The other six children had severe (cognitive and motor) impairments and behavioural difficulties that made an assessment with the ADOS impossible. Assessments with modules 1 or 2 of the ADOS were considered, but it was clear that the children who were unable to be assessed with the module 3, due to insufficient testability or severe intellectual or motor impairments, were also unable to be tested with another module. Complementary to the ADOS, clinical diagnosis was confirmed with the ADI-R in 10 of these 15 children. Two additional children had a subclinical score on the part of the algorithm that measures communication deficits, but scored clinically on the other parts. Two parents were not willing to participate in this part of the study and the interview was not proposed to the parents of one boy, given the severe impairments of their child. The clinical diagnosis of this boy was the only one which was not confirmed by ADOS or ADI-R. The total percentage of confirmed community based clinical diagnoses was thus 26%.

The second group consisted of six (11%) children with a clinical score on one or both diagnostic measures, who never received a clinical diagnosis. Two children had a clinical score on both the ADOS and the ADI-R, three children only had a clinical score on the ADOS, but not on the ADI-R and one boy had a clinical score on the ADI-R, but was not assessed with the ADOS, due to severe impairments. These children are labelled as children with a research diagnosis of ASD.

A third group of children, which consisted of a substantive part of the children without a clinical or research diagnosis, also warrant our concerns, when considering their positive screen on the SCQ and/or the SRS (n = 12, 23%). Ten SRS screens were found and on the SCQ, parents of five children reported a score above the threshold for ASD.

The remaining 20 children (38%) belonged to the fourth group of children without any suspicion of ASD.

The screening results of the total clinically evaluated group and the different subgroups are shown in Table 1. As depicted, the children in the *clinical ASD*-group all screened positive on at least one of both screeners. In the *research ASD*-group, the results are less clear. Four children screened positive on the SRS, but only two children had a positive screen on the SCQ. Significant differences were found between the children with a clinical diagnosis and a research diagnosis when considering total T-scores on the SRS (t(19) = 2.63, p = .017) but not the SCQ (t(18) = 1.83, p = .085). ADOS and ADI-R scores are also presented in Table 1. Children with a clinical or research diagnosis of ASD were more likely to be male (χ^2(1, n = 53) = 6.12, p = .013). Of those children diagnosed with ASD, 17 were boys (81%) and 4 were girls (19%). However, no significant gender differences were found for scores on the screening instruments (SCQ t(43) = 1.16, p = .251; SRS t(45) = 0.46, p = .650).

Intelligence, language development and scholastic achievement

One sample t-tests revealed that the total group of assessed preterm born children scored significantly below population average (M = 100, SD = 15) for intelligence (M = 80.74, SD = 18.49; t(46) = -7.13, p < .001) and language development (M = 88.92, SD = 19.71, t(48) = -3.94, p = .001). Children who were not able to complete the test (n = 3) were assigned the minimum score (being 50 for the WISC-III, and 55 for the CELF-IV-NL) on both tests for these analyses. When the children who were not able to complete the

Table 1

Total scores on the SRS, the SCQ, the ADOS and the ADI-R (M(SD))

| | SRS | | | | SCQ | | | | ADOS | | | | ADI-R | | | |
	n	Total T-score	Range	% screens	n	Total score	Range	% screens	n	Social Affect	Restricted repetitive behaviours	Total score	n	Reciprocal social interaction	Communication	Restricted repetitive behaviours
Total	47	72.19 (24.11)	37 - 123	62%	45	11.33 (9.76)	0 - 30	33%	43	3.16 (3.82)	0.98 (1.18)	4.14 (4.20)				
*ASD-*group	21	89.95[1] (20.44)	47 - 123	90%	20	16.45[1] (9.83)	0 - 30	50%	14	7.43[1] (3.44)	1.79[2] (1.31)	9.21[1] (3.04)	18	16.39 (8.51)	10.94 (5.96)	5.11 (3.05)
Clinical *ASD*	15	96 .47[1] (16.69)	68 - 123	100%	14	18.93[1] (7.87)	7 - 30	57%	9	6.44[1] (2.51)	2.22[1] (1.09)	8.67[1] (3.04)	12	18.75 (6.69)	12.50 (5.12)	6.17 (3.07)
Research *ASD*	6	73.67[1] (21.12)	47 - 108	67%	6	10.67 (12.19)	0 - 28	33%	5	9.20[1] (4.44)	1.00 (1.41)	10.20[1] (3.11)	6	11.67 (10.37)	7.83 (6.77)	3.00 (1.67)
ASD concern	12	71.75[1] (12.43)	58 - 98	83%	11	13.18[2] (7.44)	1 - 25	45%	11	1.27 (1.35)	0.82 (1.08)	2.09 (1.51)				
No ASD	14	45.93 (5.58)	37 - 55	0%	14	2.57 (3.61)	0 - 14	0%	18	1.00 (1.91)	0.44 (0.78)	1.44 (1.85)				
Three groups		$F_{(2,44)} = 34.25^{**}$				$F_{(2,42)} = 13.43^{**}$			$F_{(2,40)} =$	32.38^{**}	6.54^{*}	53.29^{**}				
Four groups		$F_{(3,43)} = 32.23^{**}$				$F_{(3,41)} = 11.57^{**}$			$F_{(3,39)} =$	25.02^{**}	6.34^{*}	36.49^{**}				

Note. SRS Social Responsiveness Scale (Constantino & Gruber, 2005); *SCQ* Social communication Questionnaire (Rutter, Bailey, et al., 2003); *ADOS* Autism Diagnostic Observation Schedule (Lord et al., 2008); *ADI-R* Autism Diagnostic Interview-Revised (Rutter, Le Couteur, et al., 2003); *ASD* autism spectrum disorder; *ASD-group* children with a clinical or research diagnosis of autism spectrum disorder; *ASD concern* children with one or two positive screens for autism spectrum disorder; *no ASD-group* children without a clinical or research diagnosis of ASD or positive screen for ASD; [1]significantly different (*p* < .001) from *no ASD-group*, based on post hoc Bonferonni tests; [2]significantly different (*p* < .01) from *no ASD-group*, based on post hoc Bonferonni tests; * *p* < .01, ** *p* < .001

intelligence and the language tests (*clinical ASD*-group *n* = 2, *research ASD*-group *n* = 1) were excluded, very similar results were obtained.

Two one-way ANOVA's showed that the groups of children with or without a positive screen or a research or clinical diagnosis of ASD differed significantly in their level of intelligence (Table 2; *F*(2,44) = 5.84, *p* = .006; *F*(3,43) = 4.45, *p* = .008). Bonferonni post hoc analyses revealed that the *clinical ASD*-group separately (*p* = .005) and the total *ASD*-group (*p* = .005) differed significantly from the *no ASD*-group. Of the children in the *ASD*-group, 47% had an intellectual disability (WISC-III score < 70).

A significant difference was also found for language development (Table 2; *F*(2,45) = 4.55 , *p* = .016; *F*(3,45) = 4.71, *p* = .006). The *no ASD*-group scored significantly higher than both the *ASD concern*-group (*p* = .044) and the total *ASD*-group (*p* = .025). The *clinical ASD*-group separately also scored significantly lower (*p* = .009) than the *no ASD*-group. Over 50% of the children in the total *ASD*-group had language difficulties, as did 64% of the children in the *ASD concern*-group (CELF-IV-NL score < 85). Children with a clinical diagnosis did not differ significantly from children with a research diagnosis in intelligence level (*p* = 1.000) and language level (*p* = .371).

Table 2

Intelligence and language in children with a different grade of suspicion of ASD

		WISC-III			CELF-IV-NL	
	n	M*(SD)*	Range	*n*	M*(SD)*	Range
Total	47	80.74*(18.49)*	42 - 113	48	88.92*(19.71)*	55 - 124
ASD-group	19	72.53*(20.45)*[1]	42 - 105	19	82.84*(21.89)*[2]	55 - 124
Clinical *ASD*	13	69.31*(20.03)*[1]	42 - 105	13	77.54*(19.26)*[1]	55 - 106
Research *ASD*	6	79.50*(21.40)*	50 - 103	6	94.33*(24.56)*	55 -124
ASD concern	11	78.36*(12.44)*	61 - 97	11	81.64*(15.37)*[2]	62 - 106
NoASD-group	17	91.47*(14.47)*	65 - 113	19	99.21*(15.58)*	71 - 121
Three groups		*F*(2,44) = 5.84[**]			*F*(2,46) = 4.94[*]	
Four groups		*F*(3,43) = 4.45[**]			*F*(3,45) = 4.71[**]	

Note. WISC-III Wechsler Intelligence Scale for Children – *III* (Grégoire, 2000; Wechsler, 1991)*; CELF-IV-NL* Clinical Evaluation of Language Fundamentals (Kort et al., 2008; Semel et al., 2003); *ASD* autism spectrum disorder; *ASD-group* children with a clinical or research diagnosis of autism spectrum disorder; *ASD concern* children with one or two positive screens for autism spectrum disorder; *NoASD-group* children without a clinical or research diagnosis of or positive screen for autism spectrum disorder; [1]significantly different (*p* < .01) from *no ASD-group*, based on post hoc Bonferonni tests; [2]significantly different (*p* < .05) from *no ASD-group*, based on post hoc Bonferonni tests; [*] *p* < .05; [**] *p* < .01

The percentage of children in special education was higher in the *ASD*-group and in the *ASD concern*-group than in the *no ASD*-group [*ASD* 67%, *ASD concern* 67%, *no ASD* 30%; $\chi^2(2) = 6.72$, *p* = .035)].

Behavioural characteristics

Mean T-scores on the different scales of the Achenbach questionnaires (CBCL *n* = 45, TRF *n* = 31 and YSR *n* = 40) can be found in Table 3. Analyses revealed a significantly higher level of behavioural difficulties in children in the total *ASD*-group, in comparison with the *no ASD*-group. Mainly children from the *clinical ASD*-group showed elevated T-scores (Bonferroni post hoc analyses). Compared to the *no ASD*-group, significantly more children in the *clinical ASD*-group scored above the clinical cut-off of the CBCL internalising scale ($\chi^2(1) = 10.76$, *p* = .005), the CBCL externalising scale ($\chi^2(1) = 6.61$, *p* = .037), the CBCL total problem scale ($\chi^2(1) = 16.13$, *p* < .001), the TRF internalising scale ($\chi^2(1) = 6.12$, *p* = .047) and the YSR total problem scale ($\chi^2(1) = 6.72$, *p* = .035). Significantly more children of the *ASD concern*-group scored above the clinical cut-off of the CBCL total problem scale ($\chi^2(1) = 7.78$, *p* = .021) compared to the *no ASD*-group.

Similar results can be found for behavioural disorder symptoms (*n* = 47). Analyses revealed a higher level of attention deficits, hyperactivity/impulsivity, oppositional defiant disorder problems and conduct disorders symptoms in children with a clinical diagnosis of ASD (Table 4).

Table 3

Mean total scale T-scores and percentage of children scoring above the clinical cut-off score (i.e., 70) on the CBCL, TRF and YSR

	CBCL				TRF				YSR			
	n	Internal.	External.	Total	*n*	Internal.	External.	Total	*n*	Internal.	External.	Total
Total group	45	56.93 (36%)	50.53 (16%)	55.62 (33%)	31	57.81 (32%)	51.00 (16%)	55.77 (19%)	40	51.53 (15%)	43.80 (5%)	47.00 (8%)
ASD-group	19	61.58[1] (53%)	55.68[1] (20%)	62.21[1] (53%)	13	65.00[2] (54%)	56.54[3] (31%)	63.00[2] (38%)	15	55.53[3] (27%)	49.73[2] (13%)	54.60[2] (20%)
Clinical *ASD*	13	65.31[1] (62%)	60.15[1] (31%)	66.46[1] (69%)	8	68.00[2] (63%)	59.50[3] (38%)	64.75[2] (50%)	10	56.90[3] (30%)	53.20[1] (20%)	58.50[2] (30%)
Research *ASD*	6	53.50 (33%)	46.00 (0%)	53.00 (17%)	5	60.20 (40%)	51.80 (20%)	60.20 (20%)	5	52.80 (20%)	42.80 (0%)	46.80 (0%)
ASD concern	12	61.42[2] (42%)	53.50[2] (25%)	59.58[1] (42%)	8	54.88 (25%)	47.25 (0%)	52.25 (0%)	11	52.00 (18%)	41.36 (0%)	43.09 (0%)
No ASD-group	14	46.79 (7%)	41.00 (0%)	43.28 (0%)	10	50.80 (10%)	46.80 (10%)	49.20 (10%)	14	46.86 (0%)	39.36 (0%)	41.86 (0%)
Three groups	$F_{(2,42)} =$	9.58***	9.48***	14.79***	$F_{(2,28)} =$	7.09**	4.27*	8.69**	$F_{(2,37)} =$	3.97*	5.88**	6.10**
Four groups	$F_{(3,41)} =$	9.07***	11.04***	14.29***	$F_{(3,27)} =$	5.69**	3.78*	6.08**	$F_{(3,36)} =$	2.91*	6.21**	5.87**

Note. CBCL Child Behaviour Checklist (Achenbach, 1991)*; TRF* Teacher Report Form (Achenbach, 1991); *YSR* Youth Self Report (Achenbach, 1991)*; ASD-group* children with a clinical or research diagnosis of autism spectrum disorder; *ASD concern* children with one or two positive screens for autism spectrum disorder; *no ASD-group* children without a clinical or research diagnosis of or positive screen for autism spectrum disorder; [1]significantly different (*p* < .001) from *no ASD-group*, based on post hoc Bonferonni tests; [2]significantly different (*p* < .01) from *no ASD-group*, based on post hoc Bonferonni tests; [3]significantly different (*p* < .05) from *no ASD-group*, based on post hoc Bonferonni tests; * *p* < .05, ** *p* < .01, *** *p* < .001

Table 4

Mean(SD) scores on the VvGK

	n	Attention deficits	Hyperactivity/ Impulsivity	Oppositional defiant disorder	Conduct disorder
	n		M*(SD)*		
Total group	47	12.34*(2.32)*	12.00*(2.29)*	12.21*(2.82)*	11.70*(2.09)*
ASD-group	21	13.48*(2.18)*[1]	13.10*(2.19)*[1]	13.52*(2.60)*[1]	12.43*(2.23)*[3]
Clinical *ASD*	15	13.67*(1.99)*[2]	13.73*(1.83)*[1]	13.87*(2.47)*[1]	12.67*(2.19)*[3]
Research *ASD*	6	13.00*(2.76)*	11.50*(2.35)*	12.67*(2.94)*	11.83*(2.40)*
ASD concern	12	12.17*(2.33)*	12.33*(2.46)*[3]	12.33*(2.46)*	11.83*(2.41)*
No ASD-group	14	10.79*(1.53)*	10.07*(0.27)*	10.14*(0.53)*	10.50*(0.76)*
Three groups	*F*(2,44)	7.28**	10.58***	8.69**	4.07*
Four groups	*F*(3,43)	4.94**	10.09***	6.18**	2.96*

Note. ASD-group children with a clinical or research diagnosis of ASD; *ASD concern* children with one or two positive screens for ASD; *no ASD-group* children without a clinical or research diagnosis of or positive screen for ASD; *VvGK* Vragenlijst voor Gedragsproblemen bij Kinderen (Oosterlaan et al., 2008); [1]significantly different (*p* < .001) from *no ASD-group*, based on post hoc Bonferonni tests; [2]significantly different (*p* < .01) from *no ASD-group*, based on post hoc Bonferonni tests; [3]significantly different (*p* < .05) from *no ASD-group*, based on post hoc Bonferonni tests; * *p* < .05, ** *p* < .01, *** *p* < .001

DISCUSSION

This follow-up study expands findings of previous research that demonstrated elevated scores on ASD screeners in preterm born children. In this Flemish cohort of children born before 27 weeks of gestation, the prevalence of community based clinical and/or research diagnoses of ASD was found to be 40%. When only taking into account community based clinical diagnoses made before our evaluation, which were confirmed with a clinical score on the ADOS and/or the ADI-R, and thus applying a stricter rule to estimate the prevalence rate, the percentage of ASD diagnoses was still 26%. If we would assume that none of the drop-outs has a clinical diagnosis of ASD, which is very unlikely, the prevalence rate in the total Flemish EPIBEL group would still be 16%.

This study is to our knowledge the first to use ASD-specific diagnostic instruments to confirm ASD diagnoses in early adolescence. We made use of two well-validated instruments which are considered the gold standard in the diagnostic process for ASD,

namely the ADOS and the ADI-R. They are considered to be the instruments with the highest specificity and sensitivity in the diagnostic assessment for ASD (Falkmer, Anderson, Falkmer, & Horlin, 2013). Use of both instruments and the inclusion of clinical diagnostic information, resulted in an extensive coverage of the ASD prevalence in this at-risk group.

This high prevalence rate is remarkable and it obviously exceeds prevalence rates in the general population (Elsabbagh et al., 2012) and in other studies that did not use ASD specific instruments. The prevalence rates are also considerably higher than those reported in the EPICure study, which found a prevalence rate of 8%, based on assessment with a general diagnostic parent interview (Johnson et al., 2010a).

In addition to the children with a diagnosis of ASD, our study also discovered a significant rate of elevated scores on both screening instruments. Parents rated clinically significant social-communicative difficulties in an additional 23% of the children. Especially the rate of impairments in social responsiveness, based on data collected with the SRS, is notable. These screening results confirm findings of previous research, in which diagnosed ASD was considered to be the extreme end of a distribution of symptoms that are generally increased in extremely preterm born children (Johnson et al., 2010a). These numbers also point out again the importance of the use of diagnostic instruments in research as well as in the clinical field.

Extremely preterm born boys were more likely to be diagnosed with ASD than girls. However, the sex ratio in the ASD groups in this study was only 2.79:1. Moreover, no gender differences were found for screening results. Children with ASD were also characterised by a lower IQ. Not only were their IQ scores significantly below the mean intelligence score of the children without any suspicion of ASD, almost half of the children with a diagnosis of ASD were intellectually disabled. These results are in line with results of prevalence studies that reported average intelligence in 16 - 56% of all ASD cases (Elsabbagh et al., 2012). In addition, impaired language development was also characteristic. Language problems were however not only detected in children with a diagnosis of ASD but also in other children who screened positive for ASD. Moreover, applying basal scores for both intelligence and language measurements (being 50 for the WISC-III, and 55 for the CELF-IV-NL) to estimate the intelligence level and language

development of the children who could not be tested with the instruments we used, may have inflated the mean intelligence and language level of the participating children in both the *clinical* and the *research ASD*-groups, suggesting that the current number may still be an overestimation of their overall cognitive and language capacities. However, omitting these children from the analyses would have overestimated the overall language and cognitive levels even more.

Data also revealed that parents, teachers and the children themselves with a community based clinical diagnosis of ASD reported a significantly higher prevalence of internalising and externalising problems than those of children without any suspicion of ASD. A higher rate of disruptive behaviour disorder symptoms was also pinpointed. These results are comparable with results of full term born children with ASD, in which the majority of parents report their child with ASD as having internalising or externalising problems (Skokauskas & Gallagher, 2012).

All these findings confirm suggestions from previous studies, in which ASD is thought to represent part of a preterm phenotype (Wong et al., 2014) which resembles more the pattern seen in children with syndromic ASD (Kuban et al., 2009) and thought to have a different pathogenic pathway involving global impairment in brain development (Johnson et al., 2010a).

This study contributes also in other ways to the research field in this area. Firstly, population studies focusing only on children born before 27 weeks of gestation are scarce. This group of children with an extremely low gestational age made its appearance only in some studies, with the EPICure study as the main example. However, caution in applying the evidence to the development of recently born extremely preterm children is warranted, since medical and neonatal intensive care have developed in the past decade. Moreover, this was only the second study to investigate the prevalence of ASD in late childhood and early adolescence. Most ASD studies in preterm born children were conducted in infancy, a period of childhood in which under- or overestimation of the prevalence of ASD cannot be ruled out. To our knowledge, this was also the first study to include the SRS to screen for ASD symptomatology in extremely preterm born children and this instrument seems to cover a great deal of the difficulties experienced by ex-preterm born children.

Nevertheless some limitations need to be acknowledged. Although we succeeded in reaching 58% of the children of a complete birth cohort (67% of the children who qualified for participation) in an area (Flanders) with a population of more than 6 million inhabitants, the number of participants is still modest. Generalising the results to the entire EPIBEL-cohort thus needs caution. However, when comparing developmental characteristics of participating and non-participating children, a significantly lower mental developmental index at the age of 3 was found in the non-participating children. Given the strong association that was found between intelligence and diagnostic status of ASD, this finding could suggest an underestimation of the prevalence of ASD in this extremely preterm born cohort. On the other hand, we should acknowledge the possible increased participation of parents of children with a known ASD or with concerns considering the atypical social communicative development of their child. However, the study was not announced as focusing on ASD, but as a general developmental assessment. Secondly, we were not able to assess all children with both the ADOS and the ADI-R because not all the families were willing to take part in both parts of the research. Moreover, several children had severe impairments which made an assessment with the ADOS impossible. In addition, although we compared the results within the extremely preterm born sample with norm scores and prevalence rates in the general population, not including a full term control sample to compare with the preterm results, limits the robustness of the findings. Lastly, the high rate of twins in the assessed sample may have influenced the results. However, the prevalence of ASD in singletons was somewhat higher, but comparable. Mean intelligence and language scores were similar when twins were excluded.

Summary

This study aimed to provide a more comprehensive picture of the prevalence of autism spectrum disorder in a geographic cohort of extremely preterm born children in late childhood and early adolescence by using established ASD-specific diagnostic instruments in addition to screening instruments. Fifty-three children passed a screening procedure with two screening instruments (SCQ and SRS) and a diagnostic evaluation with a semi-structured assessment (ADOS) and a parent interview (ADI-R). 28% of the

adolescents had a community based clinical diagnosis of ASD. When research diagnoses were also taken into account, this rate increased to 40%. Intellectual disability, language impairment and behavioural difficulties are characteristic for these children with ASD. The study confirms and further documents the elevated risk for ASD symptomatology and diagnosis in extremely preterm born children. The high prevalence rate in late childhood and early adolescence that exceeds previously reported rates, raises the need for early screening and diagnostic follow-up during the first years of life to improve opportunities for extremely preterm born children to benefit from early intervention. It also raises the need for follow-up into late childhood and early adolescence, considering the suspected age-related increase in prevalence rates.

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THE PREVALENCE OF AUTISM SPECTRUM DISORDER SYMPTOMS IN VERY PRETERM INFANTS AT 18 MONTHS OF CORRECTED AGE

ABSTRACT

This prospective study aimed to investigate the prevalence of symptoms of autism spectrum disorder (ASD) at 18 months of corrected age in very preterm born infants (gestational age < 30 weeks). In addition to screening instruments we used the Autism Diagnostic Observation Schedule-2 (ADOS-2). Parents reported clinical rates of ASD symptomatology in 9% of the infants and concerning ASD symptoms on the diagnostic measure were observed in 11% of the children. None of the children with a positive screen was also assigned a concern score on the ADOS-2 and vice-versa. The results indicate a high rate of false-positive and false-negative classifications and force us to consider the value of existing instruments to assess ASD symptomatology in very preterm born infants.

INTRODUCTION

In the past years, research in several cohorts of preterm born individuals of different ages suggested a link between prematurity and autism spectrum disorder (ASD), a neurodevelopmental disorder characterised by persistent deficits in social communication and social interaction, and restrictive and repetitive patterns of behaviours, interests or activities (American Psychiatric Association, 2013).

Based on results of retrospective studies, prematurity and low birth weight were clearly found to be risk factors for ASD (e.g., Johnson & Marlow, 2011; Kolevzon, Gross, & Reichenberg, 2007; Lampi et al., 2012; Larsson et al., 2005; Mamidala et al., 2013; Schendel & Bhasin, 2008; Williams, Helmer, Duncan, Peat, & Mellis, 2008). Moreover, recent evidence demonstrated a gradually increased risk of ASD with shorter gestation period (Kuzniewicz et al., 2014; Leavey, Zwaigenbaum, Heavner, & Burstyn, 2013; Movsas & Paneth, 2012).

Most screening studies investigating the prevalence of ASD symptomatology were conducted in early childhood, around the (corrected) age of 24 months. They all revealed that features of ASD have a disproportionally higher prevalence in preterm toddlers compared to toddlers in the general population (Dudova et al., 2014; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Kuban et al., 2009; Limperopoulos, 2009; Moore, Johnson, Hennessy, & Marlow, 2012; Stephens et al., 2012; Wong, Huertas-Ceballos, Cowan, & Modi, 2014). For example, studies with the Modified-Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001) found positive screening percentages between 19 and 41% (Dudova et al., 2014; Kuban et al., 2009; Limperopoulos, 2009; Moore, Johnson, Hennessy, et al., 2012) while in the general population, a positive screen rate between 1 and 2% on the M-CHAT has been found (Kleinman et al., 2008; Robins et al., 2014). However, to our knowledge, none of the above reported studies made use of the recommended follow-up interview of the M-CHAT (Kleinman et al., 2008; Lipkin, 2012). A more recent study in very preterm born two-year-olds with a gestational age (GA) below 30 weeks did use the follow-up interview. They found an initial screening rate of 13% on the M-CHAT, but when the follow-up interview was applied, only 3% of the preterm infants remained positive (Gray et al., 2015). Q-CHAT (Quantitative-Checklist for Autism

in Toddlers; Allison et al., 2008) scores of a preterm cohort (GA < 30 weeks, *M* = 33.7, *SD* = 8.3) in the study of Wong and colleagues (2014) were significantly higher than published general population scores (*M* = 26.7, *SD* = 7.8). Of the participants, 16% had a score higher than 2 *SD* above the general population mean. A study that used multiple screening instruments in children with a GA < 27 weeks found comparable elevated percentages: 20% of the children had one or more positive screens. However, screening percentages of the individual screeners in this study were less elevated; 10% had a positive Pervasive Developmental Disorders Screening Test, second edition (Siegel, 2004), 6% failed the response to name task and 9% failed response to joint attention (Stephens et al., 2012; see Table 1 for an overview).

Screening for ASD in late childhood and adolescence also revealed elevated rates of ASD symptomatology. Hack et al. (2009) examined a group of 8-year-old extremely low birth weight children (birth weight < 1000 g) and found higher scores for autistic and Asperger traits in these children compared with term peers. In another comparable study, scores on the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers, Gillberg, & Wing, 1999) were also higher for a group of very low birth weight adolescents at the age of 14 (birth weight < 1500 g; *M* = 5.7, *SD* = 0.7) than for controls (*M* = 1.9, *SD* = 0.3; Indredavik et al., 2010). Lastly, parents of 8-to-11-year-old children born at very low birth weight rated their children as displaying significantly more symptoms of a developmental social disorder (*M* = 52.5) than controls (*M* = 47.2; BASC-2; Reynolds & Kamphaus, 2004) and the mean Autism Quotient - Child version (Auyeung et al., 2009) total score for the children in this preterm sample (*M* = 60.3) was significantly higher than that of full-term controls (*M* = 53.8; Williamson & Jakobson, 2014).

Since several studies demonstrated that the high frequency of neurological, cognitive and sensory difficulties in the functioning of preterm born children may give rise to false-positive screening classifications for ASD (Johnson & Marlow, 2009; Kuban et al., 2009; Moore, Johnson, Hennessy, et al., 2012; Stephens et al., 2012), a diagnostic evaluation to confirm true rates of ASD in preterm born children seemed to be indicated.

Table 1

Overview of recent studies investigating prevalence of ASD symptoms and ASD in infancy

Authors	Publication year	GA (weeks)	Birth weight	Exclusion criteria	n =	Age	Screening measure(s)	Prevalence	Prevalence after correction for impairment	Diagnostic measure(s)	Diagnostic prevalence
Limperopoulos et al.	2008		< 1500 g	cerebral dysgenesis, dysmorphic syndromes or chromosomal disorder	91	18 - 24 m (corrected)	*M-CHAT*	26%		*NA*	*NA*
Kuban et al.	2009	< 28		children who could not complete BSID-II	988	2 years (corrected)	*M-CHAT*	21%	10%	*NA*	*NA*
Moore et al.	2012	< 26		*NA*	523	2 years (calendar)	*M-CHAT*	41%	17%	*NA*	*NA*
Stephens et al.	2012	< 27		hearing impairment, blindness, severe *CP*	554	18 - 22 m (corrected)	*PDDST-II* RJA (*ADOS*) Response to name (*ADOS*)	10% 6% 9% 20%		*NA*	*NA*
Wong et al.	2014	< 30		*CP*, severe neurosensory impairments	141	24 m (corrected)	*Q-CHAT*	16%		*NA*	*NA*
Dudova et al.	2014		< 1500 g	substantial disabilities major vision or hearing impairments	101	2 years (corrected)	*M-CHAT* *CSBS-DP-ITC* *ITSP*	19% 26% 11% 43%		*ADOS* and best estimate clinical diagnosis	13%
Gray et al.	2015	< 30		twins, major congenital abnormality	97	24 m (corrected)	*M-CHAT* + follow-up interview	13% 3%		best estimate clinical diagnosis	1%

Note. GA gestational age; *CP* cerebral palsy*; M-CHAT* Modified Checklist for Autism in Toddlers (Robins et al., 2001)*; PDDST-II* Pervasive Developmental Disorders Screening Test, second edition (Siegel, 2004)*; RJA* Response to Joint Attention*; ADOS* Autism Diagnostic Observation Schedule (Lord, Rutter, Dilavore, & Risi, 1999); *Q-CHAT* Quantitative Checklist for Autism in Toddlers (Allison et al., 2008); *CSBS-DP-ITC* Communication and Symbolic Behaviour Scales - Developmental Profile - Infant/Toddler Checklist (Wetherby & Prizant, 2001); *ITSP* Infant/Toddler Sensory Profile (Dunn, 2002)

Dudova and colleagues (2014) assessed a group of extremely and very low birth weight (birth weight < 1500 g) children at the corrected age of 2 years. Of the children, 43% screened positive on at least one of three screening questionnaires. The prevalence rate based on diagnostic assessments with the Autism Diagnostic Observation Schedule (ADOS; Lord et al., 2000), however, was only 13%. In the abovementioned study by Gray and colleagues (2015), only one infant (1%) was diagnosed with ASD after an evaluation by a developmental paediatrician at the age of 2.

Two studies evaluated the positive ASD screens with a further diagnostic assessment in late childhood. In the EPIcure cohort (GA < 26 weeks), there were 16% positive screens with the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003) and 8% of these 11-year-old children were diagnosed with ASD following a psychiatric evaluation with the Development And Wellbeing Assessment (DAWBA; Goodman, Ford, Richards, Gatward, & Meltzer, 2000; Johnson et al., 2010). Clinical assessment involving direct observation or assessment of the children by a clinician was not performed (Stephens et al., 2012). In a recent study by Verhaeghe and colleagues (2015) with extremely preterm born children (GA < 27 weeks) in late childhood and early adolescence (age M = 12.60, SD = 1.03), 28% of the participating children had a community based clinical diagnosis of ASD. When research diagnoses, based on assessments with the ADOS (Lord et al., 2000) and/or the Autism Diagnostic Interview-Revised (ADI-R; Rutter, LeCouter, & Lord, 2003) were also taken into account, this rate increased to 40%. Parents rated clinically significant social-communicative difficulties on the SCQ (Rutter, Bailey, et al., 2003) and the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005) in an additional 23% of the children. Those classifications can be considered as false-positive. Another study that did include a direct observation measure to confirm ASD screens with the SCQ or the ASSQ, was conducted with older adolescents (16 - 21 years) with a birth weight of less than 2000 grams. The estimated prevalence rate of ASD based on assessments with the ADOS or the ADI-R was 5% (Pinto-Martin et al., 2011).

Several of the abovementioned studies in preterm born children reported associations with neonatal and perinatal factors. Severity of prematurity (lower birth weight, lower GA, illness severity, more hospital days) and associated medical difficulties (abnormal MRI studies, severe bronchopulmonary dysplasia (BPD), administration of postnatal steroids,

and late-onset bacteraemia), were found to be related with measures of ASD symptomatology (Limperopoulos et al., 2008; Moore, Johnson, Hennessy, et al., 2012; Stephens et al., 2012). Pregnancy related factors, such as chorioamnionitis and acute intrapartum haemorrhage, were also found to be associated with a positive autism screening (Limperopoulos et al., 2008) and other maternal characteristics such as ethnicity, education and emotional problems as well (Gray et al., 2015; Stephens et al., 2012; Wong et al., 2014). Buchmayer and colleagues (2009) argued that the link between preterm birth and ASD most likely is explained by the higher rates of obstetric and neonatal complications that influence early brain development, resulting in abnormal neurologic development.

Next to the neonatal associations, being male was also reported as a clear risk factor in several studies (Limperopoulos et al., 2008; Moore, Johnson, Hennessy, et al., 2012; Stephens et al., 2012).

As mentioned above, the elevated screening rates in preterm children with motor, cognitive, visual and hearing impairments are striking (Gray et al., 2015; Kuban et al., 2009; Moore, Johnson, Hennessy, et al., 2012; Stephens et al., 2012; Wong et al., 2014). Lastly, evidence was found for significant associations between positive screens for ASD and abnormal behavioural scores and more internalising and externalising problems (Gray et al., 2015; Stephens et al., 2012).

Summarising, studies about the link between prematurity and ASD features and diagnoses are very disparate and results are inconsistent, dependent on the degree of prematurity and impairment of the children, the measures used and the age of assessment. Nevertheless, the general finding is that features of ASD are significantly more common in the preterm population than in the general population. Already at the (corrected) age of 24 months, ASD symptomatology seems to be more prevalent in preterm born children with differing gestational ages. We might wonder if precursors indicative for ASD are already more prevalent in the course of the second year of life, as is the case in younger siblings of children with ASD, another group at-risk for developing ASD (Elsabbagh & Johnson, 2009; Jones, Gliga, Bedford, Charman, & Johnson, 2014; Zwaigenbaum, Bryson, & Garon, 2013).

A second general finding is the high rate of false-positive screens for ASD, confirmed by the lower prevalence rates when diagnostic measures are introduced. Moreover, subclinical but impairing rates of social-communicative difficulties in preterm children need to be recognised. Dimensional measures to assess ASD symptomatology can provide us with information about possible clinically significant social-communicative difficulties below the diagnostic threshold for ASD, as put forward by Wong and colleagues (2014).

The current study aims to investigate the prevalence of ASD features in preterm born children at the early corrected age of 18 months. In a prospective follow-up study, ASD symptomatology in very preterm born children was estimated by using an internationally established diagnostic instrument in addition to two validated screening tools. This provides us with both parent reported measures as well as with a direct observation measure of ASD features.

Children were followed from birth onwards, so developmental characteristics in early life possibly associated with higher rates of ASD symptomatology are also discussed. Neo- and perinatal characteristics are considered, next to possible associations with motor, cognitive and language development, adaptive functioning, joint attention skills and behavioural problems.

METHODS

Participants

The study population included all children born before 30 completed weeks of gestation in two hospitals in a geographically defined region in Belgium with 2.65 million inhabitants during a 13 month period (May 2012 - June 2013, *N* = 97). The development of these very preterm born children is systematically assessed by specialised clinical centres at defined moments in the first years of life. A first follow-up assessment is scheduled at the corrected age of 4 months, approximately 4 months after discharge from the hospital. At this moment, parents were invited to participate in our study, which was presented as an additional follow-up of the social-communicative and behavioural development of their children, next to the standardised follow-up of medical and neuro-

motor development. Families who did not show up at the 4-month follow-up could not take part in our research (*n* = 6). Parents and children were excluded from the study when the responsible paediatrician judged that the parents would not be able to participate in the study due to limited cognitive abilities (*n* = 2), when they were no native Dutch speakers (*n* = 13) or when children were under supervision of the juvenile court (*n* = 2). As such, parents of 74 children were invited to participate in the current study. Seven families did not wish to participate, resulting in a participation rate of 91% (*n* = 67; 33 boys). We decided not to exclude those children with major impairments, to provide a heterogeneous, representative sample of preterm born children.

Participants had a mean birth weight of 1036.90 grams (*SD* = 267.71; range: 480 - 1548). Thirty-three children were born extremely preterm (GA < 28 weeks) and the other 34 children were born very preterm (28 weeks < GA < 30 weeks). Thirty-two children were twins, 26 of whom were still in twin pairs. Mean age of mothers at birth was 30.79 years (*SD* = 4.75, range: 21.78 - 46.08) and fathers were on average 32.89 years old (*SD* = 7.10, range: 23.83 - 64.12). Children spent on average 78.73 days (*SD* = 26.81, range: 24 - 180) in the hospital after birth.

Several reasons resulted in non-participation of a number of families in the assessment moment at the corrected age of 18 months (moved abroad *n* = 1, no longer reachable *n* = 3, illness *n* = 2, parents too busy *n* = 2 and participation discontinued *n* = 3). Of the original sample of 67 families of very preterm children, 56 participated in the third assessment moment (84%).

Procedure

The reported data were collected in the course of a prospective follow-up study conducted in the first years of life. Children were assessed at the corrected ages of 5, 10 and 18 months. Families were invited at the University lab but, if necessary for logistic reasons, observations were conducted at home. This was the case for *n* = 33, *n* = 33, and *n* = 11 children, at the three different assessment moments, respectively. The different observations of each research moment were planned in a fixed order and afterwards parents were given a series of questionnaires, to be completed at home. They were

encouraged to complete and return the questionnaires within a one-month framework after the assessment.

Materials

Developmental characteristics. Information about neonatal and perinatal medical history of the preterm born children was collected from Neonatal Intensive Care Unit (NICU) reports. The cognitive development was assessed with the Bayley Scales of Infant Development - II (BSID-II; van der Meulen, Ruiter, Spelberg, & Smrkovsky, 2002) at each research moment, providing us with a developmental index (M = 100, SD = 15) and a developmental age. The Alberta Infant Motor Scale (AIMS; Piper, Pinnell, Darrah, Maguire, & Byrne, 1992) was assessed to measure gross motor maturation at the ages of 5 and 10 months; percentiles were obtained. Language development (word counts for Word Comprehension (WC) and Word Production (WP)) was assessed at the corrected ages of 10 and 18 months, by means of Dutch versions of the short form Mac-Arthur Bates Communicative Development Inventories (N-CDI; Fenson et al., 1993; Zink & Lejaegere, 2003). In addition, joint attention behaviours (Initiating of Joint Attention IJA, Responding to Joint Attention RJA and Initiating of Behavioural Request IBR) were assessed at the age of 10 months by means of an abridged version of the Early Social Communication Scales (Mundy et al., 2003). Frequencies of the joint attention behaviours were used in the analyses (rates per minute). The Vineland Screener (Van Duijn, Dijkxhoorn, Noens, Scholte, & Van Berckelaer-Onnes, 2009), a measure of adaptive functioning, provided us with adaptive age scores for the developmental domains of communication, daily living skills, socialisation, motor skills and the total adaptive functioning. Parental ratings of behavioural problems were collected at the third research moment, using the Child Behaviour Checklist (CBCL 1.5-5; Achenbach, 1991); T-scores were used for further analyses.

ASD symptomatology at the corrected age of 18 months. At the third research moment, ASD symptomatology was assessed. A major revision of the Checklist for Autism in Toddlers (CHAT; Baron-Cohen et al., 1996; Baron-Cohen, Allen, & Gillberg, 1992) resulted in the Quantitative CHAT (Q-CHAT; Allison et al., 2008). This questionnaire contains 25 items, which need to be scored on a 5-point scale. The Q-CHAT

dimensionalises each item with a total higher score indicating more autistic traits. It takes parents about 5 to 10 minutes to complete.

A second screening instrument for young children which was administered, is the Early Screening of Autistic Traits Questionnaire (ESAT; Dietz, Swinkels, van Daalen, van Engeland, & Buitelaar, 2006; Swinkels et al., 2006). The ESAT is a 14-item screening instrument and was developed to prospectively identify autism as early as at 14 months of age in a general population (Oosterling et al., 2010). Children with 3 or more negative answers are considered screen-positive and thus at high risk for developing ASD (Dietz et al., 2006).

The diagnostic evaluation for ASD included the Toddler module (Luyster et al., 2011) of the Autism Diagnostic Observation Schedule - 2 (ADOS-2; Lord et al., 2012). The ADOS-2 is a semi-structured assessment of communication, social interaction and play, and consists of five modules, each of which is appropriate for children and adults of differing developmental and language levels. The Toddler module (ADOS-T) comprises 15 activities, each of which aim to elicit different aspects of social-communicative behaviour in children with a developmental age between 12 and 30 months and a nonverbal mental age of at least 12 months. Scores were used for the subscales Social Affect (SA) and Restricted Repetitive Behaviours (RRB) and a Total score was also used. Higher scores are indicative for more ASD symptomatology. Based on the Total score, a range of concern was determined ('little-to-no concern', 'mild-to-moderate-concern', and 'moderate-to-severe-concern'). In addition, Total scores were also compared with the established cut-off for research use (i.e., 12; Luyster et al., 2009). All assessments were performed and scored by ADOS trained psychologists (LV and JV).

Statistical analyses

Data were analysed using the IBM Statistical Package for the Social Sciences software version 19 (IBM Corp, 2010). Descriptive characteristics of the children are presented. Bivariate analyses were applied to compare characteristics of non-responding and responding participants. Descriptive analyses provided us with information about the three ASD instruments. Bivariate and correlational analyses were applied to investigate the associations between neonatal and perinatal variables and ASD symptomatology, and

between developmental characteristics and ASD symptomatology. Linear stepwise regression models are presented, that investigate the possible predictive value of the associated developmental measures. Spearman correlations and logistic regression models were used when applicable. For all analyses, the overall significance level was set at .05.

Ethics

This study was approved by the local ethical committee. Parents gave written informed consents.

RESULTS

Clinical characteristics

Parents of 44 preterm born children (79%) completed the Q-CHAT and parents of 39 children (70%) completed the ESAT within a two-month framework after the research moment. Not all the parents were willing to complete the extensive set of questionnaires and unfortunately, some of the bundles of questionnaires were lost in the mail. Fifty-four children (96%) were formally assessed with the Toddler-module of the ADOS-2. One child could not be assessed due to visual problems and one child was too tired to be assessed. Descriptives of the three different samples of children are provided in Table 2. An overview of all the participating children with their available ASD measures is provided in Table 3. Families of children who were not assessed with the ADOS-T (M = 35.19, SD = 16.64) had a significantly lower SES than families of

Table 2

Descriptives, characteristics of pregnancy and neonatal morbidities of preterm participants

	Q-CHAT (*n* = 44)		ESAT (*n* = 39)		ADOS-T (*n* = 54)	
	n	%	*N*	%	*n*	%
Gender ratio M/F	25/19	57/43	22/17	56/44	28/26	52/48
Number of twins	23	52	21	54	29	53
First born/later born	30/14	68/32	27/12	69/31	38/16	70/30
Extremely preterm/very preterm	23/21	52/48	19/20	49/51	25/29	46/54
	M(*SD*)	Range	M(*SD*)	Range	M(*SD*)	Range
SES	43.23(*11.56*)	12.00 - 63.50	42.09(*11.75*)	12.00 - 63.50	43.70(*12.06*)	12.00 - 63.50
Birth weight (g)	1030.23(*263.02*)	605.00 – 1548.00	1016.92(*265.78*)	605.00 - 1548.00	1023.13(*265.70*)	480.00 - 1548.00
GA (weeks)	27.09(*1.46*)	24 -29	27.08(*1.55*)	24 - 29	27.31(*1.49*)	24 - 29
Apgar score 1 min	5.95(*2.36*)	1 - 9	5.85(*2.25*)	1 - 9	5.96(*2.49*)	1 - 10
Apgar score 5 min	7.82(*1.51*)	2 - 10	7.85(*1.20*)	3 - 10	7.67(*1.79*)	2 - 10
Hospitalisation days	77.61(*22.33*)	24 - 124	78.31(*23.34*)	24 - 124	77.85(*23.94*)	24 - 147
Age mother at birth	30.92(*4.09*)	23.04 - 41.38	30.23(*3.61*)	23.04 - 38.69	31.24(*4.59*)	23.04 - 46.08
Age father at birth	32.34(*5.64*)	23.83 - 55.79	31.50(*3.72*)	25.22 - 39.89	32.80(*6.14*)	23.83 - 55.79
	n	%	*N*	%	*n*	%
RDS	13	30	12	31	14	26
CLD	9	21	9	23	12	22
IVH grade III/IV	5	11	5	13	5	9

Note. Q-CHAT Quantitative Checklist for Autism in Toddlers (Allison et al., 2008); *ESAT* Early Screening of Autistic Traits Questionnaire (Dietz et al., 2006; Swinkels et al., 2006); *ADOS-T* Autism Diagnostic Observation Schedule - 2, Toddler module (Lord et al., 2009; Luyster et al., 2009); *GA* gestational age; *SES* socio-economic status (Hollingshead, 1975); *CLD* Chronic Lung Disease; *RDS* Respiratory Distress Syndrome; *IVH* Intraventricular Haemorrhage

participating children (M = 43.70, SD = 12.06, t(64) = -2.11, p = .039). No other differences in characteristics between responding/participating and non-responding/participating participants could be found.

Q-CHAT screening results

Mean corrected age of participants at the moment of completion of the Q-CHAT was 19.04 (SD = 0.50) months. Internal consistency was satisfactory (α = .66) and reported scores were normally distributed (K-S(44) = 0.9, p = .200; skewness = 0.31 (SD = 0.36); kurtosis = -0.07 (SD = 0.70)). Q-CHAT scores of this group of very preterm born children ranged between 18 and 53, with a mean score of 32.75 (SD = 7.87). In comparison with the mean general population score (M = 26.7, SD = 7.8) as reported in Allison et al. (2008), very preterm born children in this sample scored significantly higher (t(43) = 5.10, p < .001). The sample mean also differed significantly from the reported mean ASD sample score (M = 51.8, SD = 14.3; t(43) = -16.05, p < .001; Allison et al., 2008). A third one-sample t-test showed that the mean score in this sample of very preterm born children did not differ significantly from a previously reported very preterm sample mean score (M = 33.7, SD = 8.3; t(43) = -0.80, p = 428; Wong et al., 2014). Since no cut-off is available to determine a score indicative for ASD, scores higher than 2 SD above the mean general population score (as applied in Wong et al., 2014) were considered deviant. Four preterm children (9%) scored above this threshold (see Table 3).

Item-score distributions and median scores are presented in Table 4. Median scores were highest for items 8 ('How many words can your child say?'), 16R ('Does your child do the same thing over and over again (e.g., running the tap, turning the light switch on and off, opening and closing doors)?') and 18R ('Does your child echo things s/he hears (e.g., things that you say, lines from songs or movies, sounds)?'). In our sample, some of the items did not correlate significantly with the total Q-CHAT sum score. This was the case for items 1, 3R, 5, 7R, 10, 12R, 18R and 22R (see Table 4).

Table 3

Overview of ASD assessments with according scores, and screening results and concern scores in preterm participants (n = 56)

	Q-CHAT (n = 44)			ESAT (n = 39)			ADOS-T (n = 54)				
	Completed	Score	Screen	Completed	Score	Screen	Completed	SA	RRB	TOTAL	Concern score
1	1	24	0	0			1	5	0	5	0
2	1	33	0	1	1	0	1	3	0	3	0
3	1	34	0	1	2	0	0				
4	1	30	0	1	0	0	1	0	0	0	0
5	1	34	0	1	2	0	1	1	1	2	0
6	1	28	0	1	0	0	1	1	0	1	0
7	1	18	0	1	0	0	1	1	1	2	0
8	1	32	0	1	0	0	1	9	0	9	0
9	1	35	0	1	0	0	1	4	1	5	0
10	**1**	**48**	**1**	1	1	0	1	3	1	4	0
11	1	27	0	1	0	0	1	2	0	2	0
12	1	24	0	1	0	0	1	6	1	7	0
13	1	40	0	1	0	0	1	2	1	3	0
14	0			0			1	2	1	3	0
15	1	23	0	1	1	0	1	5	0	5	0
16	1	34	0	1	0	0	1	5	0	5	0
17	0			0			1	5	1	6	0
18	1	35	0	0			1	7	0	7	0
19	1	32	0	0			1	0	0	0	0
20	1	30	0	0			1	3	0	3	0
21	1	34	0	1	1	0	**1**	**12**	**0**	**12**	**1**
22	0			0			1	3	0	3	0
23	1	27	0	0			1	0	0	0	0
24	1	23	0	1	0	0	1	0	0	0	0
25	**1**	**47**	**1**	**1**	**3**	**1**	1	3	1	4	0
26	1	25	0	0			**1**	**7**	**3**	**10**	**1**
27	0			0			1	3	1	4	0
28	0			0			1	6	0	6	0
29	1	37	0	1	1	0	1	3	1	4	0
30	1	37	0	1	1	0	1	6	2	8	0
31	1	26	0	1	0	0	1	2	0	2	0
32	1	24	0	1	0	0	1	0	2	2	0
33	1	35	0	1	1	0	1	4	3	7	0
34	1	35	0	1	0	0	**1**	**9**	**3**	**12**	**1**
35	1	37	0	1	1	0	1	2	3	5	0
36	**1**	**53**	**1**	1	3	1	1	3	2	5	0
37	0			0			1	2	1	3	0
38	0			0			1	2	1	3	0
39	0			0			1	7	1	8	0
40	0			0			1	5	1	6	0
41	1	27	0	1	0	0	1	4	2	6	0
42	**1**	**45**	**1**	1	1	0	1	2	2	4	0
43	0			0			1	**12**	**3**	**15**	**1**
44	1	39	0	1	0	0	1	6	1	7	0
45	1	41	0	1	0	0	1	**9**	**2**	**11**	**1**
46	1	35	0	1	0	0	1	2	4	6	0
47	1	41	0	1	0	0	1	6	2	8	0

48	0		0				1	6	1	7	0
49	1	31	0	1	1	0	1	4	1	5	0
50	0		1	1	0	0					
51	1	26	0	1	0	0	1	0	0	0	0
52	**1**	**36**	**0**	**1**	**1**	**0**	**1**	**9**	**2**	**11**	**1**
53	1	40	0	1	0	0	1	3	1	4	0
54	1	39	0	1	1	0	1	5	2	7	0
55	1	20	0	1	0	0	1	5	1	6	0
56	1	20	0	1	0	0	1	4	1	5	0

Note. Q-CHAT Quantitative Checklist for Autism in Toddlers (Allison et al., 2008); ESAT Early Screening of Autistic Traits Questionnaire (Dietz et al., 2006; Swinkels et al., 2006); *ADOS-T* Autism Diagnostic Observation Schedule - 2, Toddler module (Lord et al., 2009; Luyster et al., 2009); *SA* social affect; *RRB* restricted and repetitive behaviour; Positive screens or concern scores are indicated in bold; missing values are marked in grey

Table 4

Item-score distribution (% responses) Q-CHAT, median scores and item-total score correlations (n = 44)

|		0	1	2	3	4	*Mdn*	*r*(44)
1	Look when call name	25	57	18	0	0	*1.00*	.20
2	Eye contact	41	55	2	0	2	*1.00*	.46**
3R	Line objects up	25	25	36	12	2	*1.50*	.11
4	Understand child's speech	0	35	37	9	19	*2.00*	.53***
5	Proto-imperative pointing	43	43	9	5	0	*1.00*	.15
6	Proto-declarative pointing	34	34	21	9	2	*1.00*	.44**
7R	Interest maintained by spinning object	25	57	14	4	0	*1.00*	.24
8R	Number of words	2	7	39	45	7	***3.00***	.37*
9	Pretend play	25	50	16	7	2	*1.00*	.27†
10	Follow a look	32	43	18	5	2	*1.00*	.24
11R	Sniff/lick unusual objects	25	23	14	25	13	*2.00*	.63***
12R	Use of hand as tool	27	23	11	32	7	*1.50*	.15
13R	Walk on tiptoes	45	18	30	7	0	*1.00*	.32*
14	Adapt to change in routine	25	71	4	0	0	*1.00*	.43**
15	Offer comfort	2	35	37	12	14	*2.00*	.36*
16R	Do same thing over and over again	11	9	30	41	9	***2.50***	.40**
17	Typicality of first words	61	32	2	0	5	*0.00*	.53***
18R	Echolalia	0	7	20	50	23	***3.00***	.02
19	Gestures	63	30	7	0	0	*0.00*	.42**
20R	Unusual finger movements	89	2	2	5	2	*0.00*	.51***
21	Check reaction	18	48	32	2	0	*1.00*	.34*
22R	Maintenance of interest	30	36	25	7	2	*1.00*	.09
23R	Twiddle objects repetitively	7	18	39	25	11	*2.00*	.38*
24R	Oversensitive to noise	30	41	27	2	0	*1.00*	.31*
25R	Stare at nothing with no purpose	46	18	25	9	2	*1.00*	.38**

Note. † *p* < .10 * *p* < .05 ** *p* < .01 ***p* < .001; *Q-CHAT* Quantitative Checklist for Autism in Toddlers (Allison et al., 2008) - for a detailed description of the different item scores, see questionnaire; Items indicated with 'R' were scored reversed

ESAT screening results

Mean corrected age of participants at the moment of completion of the ESAT was 19.02 (*SD* = 0.52) months. The non-normal distribution of negative scores is presented in Figure 1 (K-S(39) = 0.33, *p* < .001; skewness = 1.52 (*SD* = 0.38); kurtosis = 2.14 (*SD* = 0.74)).

Figure 1

Distribution of number of negative ESAT-scores (n = 39)
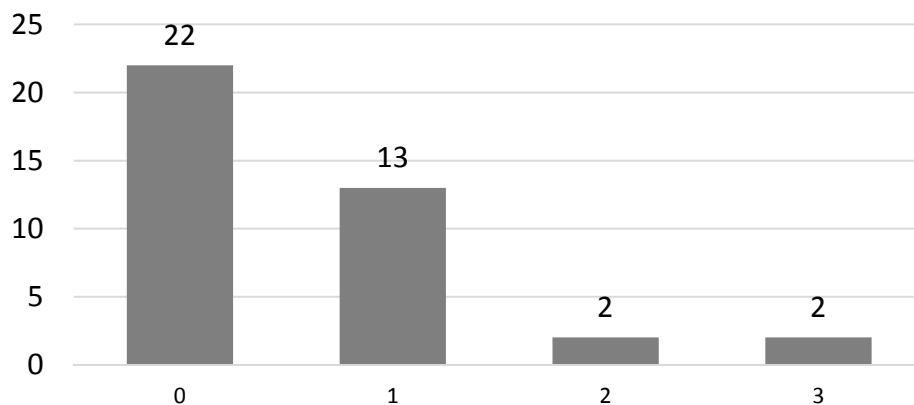
Application of the cut-off of three or more negative items, resulted in a positive screening percentage of 5%. Parents of two children reported negative answers on three items.

Detailed item-level analyses showed that all items were answered by all parents. Table 5 provides an overview of the number of negative answers per item. Seven items were responded positively by all the parents. The highest number of negative answers (*n* = 8, 21%) was found for item 8 ('Is the behaviour of your child free of stereotyped movements like banging his/her head or rocking his/her body?'), followed by five (13%) negative answers for item 7 ('When your child has been left alone for some time, does he/she tries to attract your attention, for instance by crying or calling?').

Table 5

Number (%) of negative answers per item ESAT (n = 39)

		n	*%*
1	Interested different toys	0	0
2	Varied play	3	8
3	Emotions understanding	2	5
4	Reaction to sensory stimuli	0	0
5	Facial expression	0	0
6	Eye contact	2	5
7	**Attracts attention**	**5**	**13**
8	**Stereotypical movements**	**8**	**21**
9	Brings/shows objects	0	0
10	Interest people	0	0
11	Likes cuddling	2	5
12	Smiles directly	0	0
13	Enjoys social play	1	3
14	Reacts when spoken to	0	0

Note. ESAT Early Screening of Autistic Traits Questionnaire (Dietz et al., 2006; Swinkels et al., 2006)

ADOS-T Range of concern

Children were on average 18.68 (*SD* = 0.42) months old (corrected age) when they were assessed with the ADOS-T. Mean scores for SA and RRB were 4.07 (*SD* = 2.93; range: 0 - 12) and 1.07 (*SD* = 1.03; range: 0 - 4), respectively, and the mean Total score was 5.15 (*SD* = 3.33; range: 0 - 15). There were no significant differences in scores between assessments that were conducted in the lab (*n* = 44) or in the home setting (*n* = 10; SA *U* = 192.00, *p* = .530; RRB *U* = 172.50, *p* = .265; Total *U* = 188.00, *p* = .474) and between assessments with (*n* = 50) or without (*n* = 4) the parent present in the room (assessments of twins and only one parent present); SA *U* = 90.50, *p* = .762; RRB *U* = 98.50, *p* = .962; Total *U* = 93.50, *p* = .836).

Applying 'range of concern'-criteria resulted in a percentage of 89 (*n* = 48) of the scores indicating 'little-to-no concern', 9% (*n* = 5) 'mild-to-moderate concern', and 2% (*n* = 1) 'moderate-to-severe concern'. 11% (*n* = 6) of the preterm children thus had concern scores on the ADOS-T. Implementing the cut-off score for research (i.e. 12) resulted in a percentage of 6% (*n* = 3) of the children scoring above the cut-off.

When considering the proportions of the different scores on the algorithm items of the ADOS-T (see Table 6) in both groups of children with or without a concern score, only six algorithm items showed clear distinct distributions, with higher percentages for higher scores in the concern sample (A2 $p <$ .001; B5 $p =$ .001; B12 $p =$ .026; B15 $p <$ .001; A3 $p =$ .014; D2 $p =$ .004). One additional item scores distribution was marginally significantly different (B6, $p =$ .066).

Item score distributions for other ADOS-T items with significant distinct distributions in both groups of children are also displayed in Table 6. All children with a concern score, used less than five words or word approximations during the assessment, while this was the case in only 65% of the non-concern children (A1 $p =$ .012). A higher percentage of children in the non-concern sample used several undirected vocalisations, because a high number of children in the concern group rarely or never vocalised (A9 $p =$ .002).

A higher percentage of children with a concern score showed no response to both unable toy play trials or moved hands of the experimenter in both trials (B2 $p =$ .012). In addition, the amount of social overtures was significantly lower in the concern sample (B16a $p =$ .002), and the overall quality of rapport during the interaction was significantly lower (B18 $p =$ .024).

Table 6

Score distributions (%) ADOS-T algorithm items for preterm children with or without a concern score and other ADOS-T non-algorithm items with significantly different score distributions (%) in preterm children with or without a concern score (n = 54)

		No concern (*n* = 48)						Concern (*n* = 6)						
Item	Item description	0	1	2	3	8	*Mdn*	0	1	2	3	8	*Mdn*	*U*
A2	**Spontaneous vocalisation directed to others**	**85**	**15**	**0**	**0**		***0.00***	**17**	**0**	**66**	**17**		***2.00***	**27.50*****
A8	Use of gestures	23	52	23	2	0	*1.00*	17	33	50	0	0	*1.50*	111.00
B1	Unusual eye contact	85	15	0	0	0	*0.00*	67	33	0	0	0	*0.00*	117.00
B4	Facial expressions directed to others	81	13	6	0		*0.00*	33	67	0	0		*1.00*	81.00
B5	**Integration of gaze and other behaviours**	**90**	**10**	**0**	**0**		***0.00***	**17**	**33**	**50**	**0**		***1.50***	**31.50*****
B6	Shared enjoyment in interaction	77	15	6	2		*0.00*	33	33	17	17		*1.00*	77.00†
B12	**Showing**	**48**	**21**	**8**	**23**		***1.00***	**17**	**0**	**0**	**83**		***3.00***	**64.00***
B13	Spontaneous initiation of joint attention	85	15	0	0		*0.00*	83	0	17	0		*0.00*	137.50
B14	Response to joint attention	83	11	6	0		*0.00*	100	0	0	0		*0.00*	120.00
B15	**Quality of social overtures**	**98**	**2**	**0**	**0**		***0.00***	**17**	**83**	**0**	**0**		***1.00***	**27.00*****
A3	**Intonation of vocalisations**	**50**	**10**	**0**	**0**	**40**	***0.50***	**0**	**0**	**0**	**0**	**100**	***8.00***	**57.00***
D1	Unusual sensory interest	92	6	2	0		*0.00*	83	17	0	0		*0.00*	132.50
D2	**Hand and finger movements**	**73**	**25**	**2**	**0**		***0.00***	**17**	**33**	**33**	**17**		***1.50***	**45.50****
D5	Unusually repetitive interests or stereotyped behaviours	65	29	6	0		*0.00*	50	33	17	0		*0.50*	119.00
Item	Item description	0	1	2	3	4/8	*Mdn*	0	1	2	3	4/8	*Mdn*	*U*
A1	Overall level of spoken language	2	8	25	48	17	*3.00*	0	0	0	33	67	*4.00*	55.00*
A9	Frequency of undirected vocalisation	69	27	0	0	4	*0.00*	17	0	0	0	83	*8.00*	36.50**
B3	Unable toy play	63	23	8	6	0	*0.00*	17	17	17	50	0	*2.50*	55.00*
B16a	Amount of social overtures examiner	83	17	0	0		*0.00*	17	33	50	0		*1.50*	36.00**
B18	Overall quality of rapport	73	27	0	0		*0.00*	17	83	0	0		*1.00*	63.00*

Note. † *p* < .10 * *p* < .05 ** *p* < .01 *** *p* < .001; *ADOS-T* Autism Diagnostic Observation Schedule - 2, Toddler module (Lord et al., 2009; Luyster et al., 2009) – for a detailed description of the different item scores, please see ADOS-T protocol booklets; Significant differences score distributions algorithm items between children with or without a concern score are indicated in bold

Convergence between screening and diagnostic measures

As mentioned above, an overview of the scores on the three different instruments is available in Table 3. Valid data for both screening questionnaires and the ADOS-T were available for 37 preterm born children. Of the group of children with complete data, 78% (*n* = 29) did not screen positive on one of the screeners and was not assigned a concern score on the ADOS-T. Eight (22%) children were assigned a positive screen or a concern score for the presence of ASD symptomatology. However, none of the children with a screen on one or both screening instruments was also assigned a concern score on the ADOS-T ($\chi^2(1)$ = 0.54, *p* = 1.00; $\chi^2(1)$ = 0.26, *p* = 1.00). Vice-versa, children with a concern score on the ADOS-T, did not screen positive on the Q-CHAT or the ESAT. Moreover, two of the children with a positive Q-CHAT screen, did not screen positive on the ESAT but two other children did ($\chi^2(1)$ = 17.44, *p* = .009).

Since no associations were found between both screening measures and the ADOS-T, the different instruments were considered separately in the subsequent analyses.

Associations between neonatal and perinatal characteristics and ASD symptomatology

Associations between neonatal and perinatal characteristics and ASD symptomatology were considered. To correct for multiple analyses, Bonferonni-Holm corrections (Holm, 1979) were applied. Given the non-normal distribution of RRB scores, a binary variable was computed, differentiating children without any observed RRB symptomatology (score 0, *n* = 18, 33%) from children with observed RRB symptomatology (scores 1 - 4; *n* = 36, 67%). The following characteristics were taken into account: sex, gestational age, birth weight, length at birth, head circumference at birth, number of hospitalisation days, APGAR scores 1 and 5, suffering from Respiratory Stress Syndrome (RDS), Chronic Lung Disease (CLD) and intraventricular haemorrhage (IVH) grade III or IV, and age of mother and father at birth.

No significant associations between characteristics and Q-CHAT and ADOS-T scores were found. A significant negative correlation between ESAT scores and birth weight (*r*(39) = -.44, *p* = .005) could be found.

Associations between developmental characteristics and ASD symptomatology

No significant correlations between developmental measures assessed at the corrected ages of 5 and 10 months, and ASD symptomatology at 18 months were found.

Word Comprehension count at 18 months was correlated negatively with Q-CHAT scores ($r(40)$ = -.46, p = .003), and SA ($r(42)$ = -.47, p = .002) and Total ADOS-T scores ($r(42)$ = -.56, p < .001). Word Production count only correlated negatively with SA ($r(42)$ = -.32, p = .039) and Total ADOS-T scores ($r(42)$ = -.36, p = .019). The adaptive age component for communication (Vineland Screener) at 18 months correlated negatively with the ADOS-T SA and Total scores ($r(39)$ = -.41, p = .009 and $r(39)$ = -.45, p = .004, respectively). Developmental Index (BSID-II) at 18 months of age, correlated negatively with both Q-CHAT and ADOS-T scores (Q-CHAT $r(42)$ = -.59, p < .001; and ADOS-T (SA $r(51)$ = -.32, p = .024; Total $r(51)$ = -.36, p = .010), as did the obtained developmental age (Q-CHAT $r(42)$ = -.52, p < .001; and ADOS-T (SA $r(51)$ = -.31, p = .032; Total $r(51)$ = -.32, p = .023). When considering DSM-scales of the CBCL 1.5-5, one positive correlation between the ADHD-scale with the ESAT scores could be found ($r(35)$ = .51, p = .002).

When entered in different stepwise regression models with Q-CHAT scores, ESAT scores, ADOS-T SA, ADOS-T RRB, and ADOS-T Total scores, respectively, as dependent variables, Word Comprehension and the developmental index of BSID-II were found to be significant predictors. Word Comprehension at 18 months count was found to be a significant predictor for the ADOS-T SA score ($β$ = -.36, R^2 = .11, $F(1,39)$ = 6.03, p = .019) and for the ADOS-T Total score ($β$ = -.46, R^2 = .19, $F(1,39)$ = 10.20, p = .003). The developmental index 18 months (BSID-II) was found to be predictive for Q-CHAT scores ($β$ = -.53, R^2 = .26, $F(1,38)$ = 14.64, p < .001) and Total ADOS-T score ($β$ = -.37, R^2 = .11, $F(1,36)$ = 5.63, p = .023). ESAT scores were significantly predicted by the DSM ADHD-scale ($β$ = -.58, R^2 = .32, $F(1,33)$ = 16.63, p < .001).

DISCUSSION

As stipulated in the introduction section of this paper, studies about the link between prematurity and ASD features and diagnoses are very disparate and results are inconsistent. Even when only considering those studies that were conducted around the age of 2 (see Table 1), very conflicting results were found. Screening rates varied between 3% and 43% and the hardly available diagnostic prevalence rates between 1% and 13%. Notwithstanding the variety in measures, informants and inclusion criteria, the general finding is that features of ASD are significantly more common in the preterm population than in the general population. The current study assessed the social-communicative functioning of very preterm born children in more detail using both parent screening instruments as well as a well-established direct observation diagnostic measure, the ADOS-2 at the corrected age of 18 months. The results confirm the elevated prevalence rate of ASD features but at the same time they underscore the importance of caution in interpreting results of currently available measures.

When simply considering the results of the individual screening instruments, positive screening rates on both the Q-CHAT (9%) and the ESAT (5%) are below screening figures in preterm samples reported elsewhere. However, the mean Q-CHAT score in this very preterm born sample was not statistically different from the one reported in another very preterm sample, assessed at the corrected age of 24 months (Wong, Huertas-Ceballos, Cowan, & Modi, 2014), although in this study, children with severe neurosensory disabilities and cerebral palsy were excluded. Our results also confirm the shift to the right in the distribution of the scores, as mentioned in the work of Wong and colleagues (2014). The ESAT was originally developed as a population screener, with focus on children aged 14-15 months and has not been used as a screener in a preterm population before. Screening with the ESAT did not provide additional value since all children with a positive screen on the ESAT were also detected by the Q-CHAT.

In addition to the use of two screening instruments, we also observed the social and communicative development of the children by means of the ADOS-T. 11% of infants were assigned a concern score on the ADOS-T, with 2% of the children having a score that represents 'moderate-to-severe-concern'. Implementing the cut-off score for research

purposes resulted in a percentage of 6% of the children scoring above the cut-off for ASD. The only previous studies that made use of a diagnostic procedure to confirm positive screens in infants (Dudova et al., 2014; Gray et al., 2015), found two very disparate prevalence rates (13% versus 1%). Samples of the different studies varied with respect to the inclusion of children with major impairments and with respect to age of assessment.

In the study of Stephens and colleagues (2012), two items of the ADOS were used as screeners based on observation of infant behaviour. 6% of the extremely preterm born children (GA < 27 weeks) failed the response to name task and 9% of the children failed the response to joint attention task (fail = score 2 or 3). Since the ADOS-T was administered in our sample, a comparison with the results of these specific items is also possible. For both items, 6% of the very preterm born children in our sample screened positive. None of these children, however, had a concern score on the ADOS-T, indicating that these items not seem to discriminate between the groups of children with or without a concern score for ASD in this very preterm sample.

Interestingly, none of the children who had a positive screen for ASD based on parent report, was assigned a concern score on the ADOS-T, performed by a trained clinician, who was blind for the screening status of the children. Previous studies often reported a high rate of possible false-positive classifications in very preterm born children, probably due to co-morbid impairments (Johnson et al., 2011; Kuban et al., 2009; Moore, Johnson, Hennessy, et al., 2012). Likewise in our sample, most of the children with a positive screen on the Q-CHAT or the ESAT were children with comorbid impairments, within the cognitive, visual or motor domain.

Previous studies that included a diagnostic procedure to confirm positive screens only assessed those infants with a positive screen (Dudova et al., 2014; Gray et al., 2015), which implies that children who were not detected with the screener were not assessed with a diagnostic procedure, providing no information about possible false-negative classifications. The results of this study tell us that some of the preterm born children who were not detected by their parents as showing clinically significant social-communicative impairments, did show some abnormalities in this domain of functioning, along with peculiarities in the domain of restrictive and repetitive patterns of behaviours, interests or activities. Two studies that did provide information about very low rates of false-

negative classifications assessed older preterm born children (Johnson et al., 2011; Pinto-Martin et al., 2011). Only one of the children who was assigned a concern score on the ADOS-T was severely impaired, both in the motor and cognitive domain of functioning. No other specific aspects of functioning characterised the children who were assigned a concern score.

Our results confirm the limited predictive value of ASD screeners in preterm born children. Moreover, since no clinical diagnostic information was available because of the young age of the children, we also need to be cautious in the interpretation of the results of the ADOS-T. The abovementioned findings force us to consider the value and specificity of existing instruments to assess ASD symptomatology in populations of very preterm born children, with their specific characteristics, difficulties and impairments.

In any case, the higher vulnerability in preterm infants for deficits in the social and communicative domain and some aspects of repetitive patterns of behaviours, interests or activities, was already demonstrated in a wide range of studies and was now again confirmed in our sample. Whether these difficulties reflect autistic traits or are indicative of impaired social and communicative skills associated with the preterm phenotype (Moore, Johnson, Hennessy, et al., 2012), the importance of early clinical assessment of social-communicative development and the possible presence of repetitive patterns of behaviours, interests or activities from an early age onwards, stays. Furthermore, research into the early developmental pathways to the emergence of ASD symptoms in this group is necessary. As was highlighted by Williamson and Jakobson (2014), understanding the core deficits that underlie the social difficulties and other symptoms, displayed by certain preterm born children, is very important. Reducing the age at which ASD symptoms are identified, is crucial. This way, children who require early intervention can be identified and appropriate intervention targets can be found (Barbaro & Dissanayake, 2009; Jones et al., 2014). Implementing interventions to lessen the burden of early emerging developmental perturbation, thus preventing secondary neurodevelopmental disturbances, is also an important aspect (Yirmiya & Charman, 2010). Finally, reducing the burden on concerned parents is an important research target (Zwaigenbaum et al., 2013).

Although previous studies reported numerous and varying associations between neonatal and perinatal characteristics of preterm born children and ASD symptomatology, our results revealed only a small amount of single associations. Birth weight was negatively correlated with ESAT scores, but not with Q-CHAT or ADOS-T scores. A recent study of Gray and colleagues (2015) with very preterm born children also reported that no perinatal or neonatal factors were associated with a positive screen on the M-CHAT. Assessments of domains of functioning at the age of 18 months though, were associated with rates of ASD symptoms at the same age. Children with more ASD features showed lower Word Comprehension counts and cognitive development. We found not a single association with cognitive, motor social-communicative and adaptive functioning at the ages of 5 and 10 months.

No relationship with gender was demonstrated. Other studies did find that being male was a clear risk factor for ASD in preterm born children (Limperopoulos et al., 2008; Moore, Johnson, Haider, Hennessy, & Marlow, 2012; Stephens et al., 2012) but it was also pointed out that the sex ratio in preterm populations was significantly lower than the ratio in full term ASD populations (Kuban et al., 2009; Wong et al., 2014). Possible explanations for the lack of significant associations are the small sample size and the heterogeneity of our preterm sample. In addition, other studies may not have corrected for multiple testing, which can artificially have augmented the associations that were found.

The findings need further investigation in larger samples of preterm born children. Additional domains of functioning during the first year of life need to be considered as possible predictors for later ASD features. Temperamental development and interactional competencies during the first year of life need to be considered. Likewise, social preference and social abilities, such as eye gaze, response to name and interest in others, need to be investigated from birth onwards.

Study limitations and future research

Some limitations of the study need to be acknowledged, along with some additional suggestions for future research. The main limitation of the study is the relatively small sample size and the poor rate of return of the questionnaires. However, extensive efforts were made to collect as many completed questionnaires as possible and return rates were

comparable to those in other studies (e.g., Wong et al., 2014). A related issue is the small sample size of the ASD concern group. This flaw is however inherent to the prospective follow-up study design which was applied, in which we expect only a small percentage of the children to show symptoms of ASD. Because of the high rate of attrition, caution in generalisation of the findings is needed. Additionally, the early age of ASD symptomatology assessment should be mentioned, which may have influenced the rate of reported and observed ASD symptomatology. Further follow-up of the groups of children until the ages of 2 and 3 years is planned and diagnostic ASD groups will be formed, based on ASD assessment at the two later assessment moments.

Conclusions

This study again demonstrated the higher prevalence rate of ASD symptoms in a very preterm sample, already at the early corrected age of 18 months, based on assessment with two parent questionnaires and a direct observation measure. The clear disagreement between screening results and diagnostic measures again emphasises the caution in interpreting results of screening questionnaires when used in a preterm population. In this study, no associations between motor, cognitive, adaptive and communicative functioning in the first year of life and ASD symptomatology at the age of 18 months were found. The functioning of infants with higher rates of ASD features was characterised by slower cognitive development and word comprehension problems at the age of 18 months.

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CHAPTER 4

QUALITY OF INTERACTION BETWEEN PRETERM INFANTS AND THEIR MOTHER IN THE FIRST YEAR OF LIFE IS ASSOCIATED WITH ASD SYMPTOMATOLOGY AT 18 MONTHS[1]

ABSTRACT

This study assessed aspects of mother-preterm child interaction (MCI; n = 67; gestational age < 30 weeks), in the light of later autism spectrum disorder (ASD) symptomatology. At 5 months, there were no differences in MCI between preterm and full term dyads but at 10 months, mothers of preterm infants were less sensitive and preterm infants were less involved. The preterm dyadic patterns were less reciprocal and more negatively charged. Within the preterm sample, maternal Intrusiveness 10 months significantly predicted parent-reported ASD symptoms. Observed ratings of ASD symptomatology were predicted by lower rates of infant Involvement at both 5 and 10 months. The findings suggest that characteristics of MCI can be considered as early indicators of later ASD symptomatology.

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[1] Based on Verhaeghe, L., Vermeirsch, J., Demurie, E., & Roeyers, H. (2015). *Quality of interaction between preterm infants and their mother in the first year of life is associated with ASD symptomatology at 18 months.* Manuscript submitted for publication.

INTRODUCTION

In the past decades, major advances in neonatal and perinatal care have increased the survival rate of extremely (gestational age (GA) < 27 weeks) and very preterm (28 < GA < 32 weeks) born infants. Although this is a positive evolution, there is growing concern for their developmental outcome, since follow-up studies have shown that these children are often confronted with developmental problems in various domains of functioning (e.g., Moore, Hennessy, et al., 2012; Woodward et al., 2009). Screening studies in cohorts of preterm born children of different ages have suggested a link between prematurity and autism spectrum disorder (ASD), a neurodevelopmental disorder characterised by persistent deficits in social communication and social interaction, and restrictive and repetitive patterns of behaviours, interests, or activities (American Psychiatric Association, 2013). Several screening studies conducted in early childhood, around the (corrected) age of 24 months (Dudova et al., 2014; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Kuban et al., 2009; Limperopoulos et al., 2008; Moore, Johnson, Hennessy, & Marlow, 2012; Stephens et al., 2012; Wong, Huertas-Ceballos, Cowan, & Modi, 2014) and a few screening studies conducted in late childhood and adolescence (Hack et al., 2002; Indredavik et al., 2010; Williamson & Jakobson, 2014) indicated that ASD symptoms are significantly more prevalent in preterm children than in children in the general population.

Additional diagnostic evaluations were included in a number of studies in early childhood (Dudova et al., 2014; Gray et al., 2015), late childhood (Johnson et al., 2010), early adolescence (Verhaeghe et al., 2015), late adolescence (Pinto-Martin et al., 2011) and adulthood (Moster, Lie, & Markestad, 2008). They all confirmed the elevated prevalence of ASD in the preterm population and more specifically in extremely and very preterm born individuals.

The specific causes for the higher prevalence of ASD and ASD symptoms in these preterm children are still unclear. In addition, early developmental pathways to the emergence of ASD symptoms in this group of children are not well characterised. Drawing on the model of prospective studies of infant siblings of children with ASD, longitudinal investigations of children born prematurely, employing multiple measures and methods

at multiple time-points, are needed to identify early markers and early developmental trajectories and to make comparisons between high- and low-risk groups.

The development of a child is known to be a product of the continuous dynamic interactions of the child and the experiences provided by his or her family and context (Sameroff, 2009). The primary relationship between a mother and her child plays a primordial role in this early development (Bozzette, 2007). Moreover, high quality of the mother-child interaction (MCI) is known to facilitate the child's developmental outcomes as well as its competence (Muller-Nix et al., 2004). As was stated by Wan and colleagues (2012) concerning the early follow-up of at-risk siblings of children with ASD, the early presence of social and other difficulties in children who go on to develop ASD, might suggest that specificities in caregiver-infant interaction are an important aspect to investigate in developmental trajectories of children who are at-risk for developing ASD.

Mother-infant interaction and preterm birth

Preterm infants are found to be less alert and focused (e.g., Minde et al., 1985), more passive (Crnic, Greenberg, Ragozin, Robinson, & Basham, 1983; Lester, Hoffman, & Brazelton, 1985; Muller-Nix et al., 2004) and less responsive social partners than their full term born counterparts (Barnard, Bee, & Hammond, 1984; Crnic et al., 1983; Schmücker et al., 2005; Singer et al., 2003). Several studies demonstrated that preterm infants can have a diminished ability to provide cues that promote proximity and contact to the parent (L. Davis, Edwards, & Mohay, 2003), they show for example less positive affect (Korja et al., 2008) or initiate less eye contact (Malatesta, Grigoryev, Lamb, Albin, & Culver, 1986).

Preterm infants thus provide less initiations to be followed by their parents. Moreover, preterm birth is a stressful event, firstly because the preparation time of the parents until the birth of the child is suddenly interrupted. In addition, intensive care of the child and prolonged hospital stays inevitably cause some separation between mother and child. Parents often feel anxious, stressed or even depressed, being oblivious of the child's developmental outcomes (Korja, Latva, & Lehtonen, 2012). As was summarised by Evans et al. (2014), this could lead to withdrawal of the mother and therefore decrease her ability to be sensitive for the cues that her child provides. Next to being less sensitive,

mothers of preterm born children were also found to be more controlling of the interaction at the age of 6 months. However, behaviour of mothers of preterm and full term infants was comparable at the later age of 18 months (Muller-Nix et al., 2004). In contrast, a study of Agostini, Neri, Dellabartola, Biasini, and Monti (2014) showed adequate sensitivity in preterm infants' mothers and higher involvement with their infants, compared to full term mothers at the age of 3 months. On the other hand mothers of extremely low birth weight infants in this sample exhibited an intrusive interactive behaviour pattern. A recent review (Korja et al., 2012) summarised that differences in maternal behaviour between mothers of preterm and full term infants are most evident during the first six months of life and mostly concern controlling of the interaction (Montirosso, Borgatti, Trojan, Zanini, & Tronick, 2010).

Next to individual infant and maternal behaviours, dyadic patterns also seem to differ between mother-preterm and mother-full term dyads (Harrison & Magill-Evans, 1996). In a study by Forcada-Guex et al. (2006), two specific patterns of interactions that could play a protective (cooperative pattern) or a risk-precipitating (controlling pattern with a controlling mother and a compulsive-compliant infant) role on developmental outcome were found. The controlling pattern was found to be much more prevalent among preterm than among full term dyads.

Preterm birth has thus been shown to be a significant factor in affecting the behaviour of the preterm child and the mother during interaction and accordingly in affecting the quality of the mother-child interaction. However, results are not always consistent. Although several studies reported differences between preterm and full term dyads, some studies did not (Greenberg & Crnic, 1988; Korja et al., 2008; Montirosso et al., 2010; Schermann-Eizirik, Hagekull, Bohlin, Persson, & Sedin, 1997). A recent meta-analysis by Bilgin and Wolke (2015) clearly showed no differences in sensitivity and responsiveness between mothers of preterm children and full term children and some studies even reported a better quality of mother-child interaction in preterm dyads (Greene, Fox, & Lewis, 1983).

Both neonatal and perinatal characteristics of the functioning of the child, such as neurobiological risk (Greene et al., 1983; Muller-Nix et al., 2004; Schmücker et al., 2005) and severity of illness (Karabekiroglu et al., 2015; Minde et al., 1985), seem to play a role

in the association between preterm birth and quality of the mother-child interaction. Maternal characteristics, such as depression and anxiety (Feeley, Gottlieb, & Zelkowitz, 2005; Feldman & Eidelman, 2007; Poehlmann & Fiese, 2001; Schmücker et al., 2005; Singer et al., 2003), traumatic experience (Muller-Nix et al., 2004), maternal attachment representations (Coppola, Cassibba, & Costantini, 2007), or the perceived support (Feeley et al., 2005) have also been found to influence the association between preterm birth and quality of the mother-child interaction. Maternal use of coping strategies, both in the hospital and at home, were found to be important factors in predicting quality of MCI (L. Davis et al., 2003).

Previous studies clearly demonstrated the importance of certain characteristics of dyadic interaction for later development in preterm samples. For example, a study by Poehlmann and Fiese (2001) demonstrated that reciprocal and engaging interactions at 6 months moderated the relationship between neonatal risk and cognitive outcome at 12 months. The results indicated that engaging in early positive interactions can have a positive influence on cognitive outcome in low birth weight children, even when at high neonatal risk. In a study by Treyvaud and colleagues (2009), cognitive development of very preterm born children at the age of 2 was found to be associated with most parenting domains, with synchrony emerging as the most predictive. Unexpectedly, more parental negative affect was associated with more optimal psychomotor development. In a sample of extremely preterm born two-year-olds, higher quality of dyadic relationship and maternal sensitivity were associated with positive neurocognitive outcome (Rahkonen et al., 2014). In contrast, language skills at 24 months were only weakly predicted by features of early MCI at the age of 6 months (Stolt et al., 2014).

Mother-infant interaction and ASD

Raising a child at-risk for ASD or diagnosed with ASD can be highly stressful (N. O. Davis & Carter, 2008; Estes et al., 2013). The impairments in social and communicative functioning, core symptoms of ASD, have a considerable impact on the daily interactions between parents and their child with or at-risk for ASD. Evidence from studies that got a look into the interaction between parents and their children with ASD or at-risk for ASD, pointed out clear differences in the behaviours of both mothers and their children with

ASD, compared to mothers and typically developing children or children with other disabilities.

Older children with ASD were found to be less compliant and more avoidant than typically developing children and children with other disabilities during interactions with their mother (Lemanek, Stone, & Fishel, 1993). In a recent home-video study, children with ASD showed less orienting towards people during interactions in the first semester of life. Thereafter they exhibited a much smaller increase of seeking people behaviours than typically developing children (Saint-Georges et al., 2011). A recent prospective follow-up study of high- and low-risk siblings collected data of parent-infant interaction between the ages of 6 and 10 months. High-risk infants were rated as less lively (Wan et al., 2012). Furthermore, at 12 months of age, infant positive affect and attentiveness predicted ASD outcome at age 3 (Wan et al., 2013). However, in another prospective follow-study of siblings at-risk who went on to be diagnosed with ASD or not, and low-risk controls, no differences in frequency of gaze, smiles and vocalisations were found at the age of 6 months during a short period of interaction (Rozga et al., 2011).

Older studies were indicative for higher frequencies of control strategies used by mothers of children with ASD and more directive parenting, compared with mothers of typically developing children (e.g., Kasari, Sigman, Mundy, & Yirmiya, 1988; Lemanek, Stone, & Fishel, 1993). More physical contact, more high-intensity behaviours and fewer social verbal approaches were also evident in interactions between mothers and their toddler with ASD in a more recent study of Doussard-Roosevelt et al. (2003). In the abovementioned studies of Wan and colleagues (2012;2013), parents of siblings at-risk showed higher directiveness at the ages of 6 and 12 months. These results suggest that parents may be compensating for the lack of social interactions of their child and thus for their child's disability (El-Ghoroury & Romanczyk, 1999; Saint-Georges et al., 2011; Spiker, Boyce, & Boyce, 2002).

Although most studies found clear differences in controlling and directive patterns of parenting in infancy and toddlerhood, only some studies with infants found differences in sensitivity (Wan et al., 2012; 2013), a key determinant of early attachment, between parents of children with or at-risk for ASD and parents of typically developing children. A pilot study with a small sample of 18-months-old high- and low-risk children subsequently

diagnosed with ASD or not, found no differences in maternal sensitivity in function of emergent ASD status. However, maternal sensitivity did predict expressive language growth only in children who were diagnosed with ASD (Baker, Messinger, Lyons, & Grantz, 2010). In a study of Kasari and Sigman (1997), responsiveness to the child's nonverbal communication bids of caregivers of older preschool children with ASD was similar to that of other caregivers. A within-family study investigated whether mothers adapted their behaviour when interacting with their preschool child with ASD or with the younger sibling. Results indicated that mothers were less responsive towards the child with ASD (Meirsschaut, Warreyn, & Roeyers, 2011).

In MCI research in families with a child with ASD, not only individual characteristics of both mother and child were assessed, but also characteristics of the dyadic interaction were subject of some studies. Saint-Georges and colleagues (2011) suggested that the study of the emergence of autism should focus on characteristics of the interaction rather than on behaviours of each member of the dyad. Synchrony, a characteristic that has been found to be influential in the development of social-communicative skills and language development of children with ASD (Siller & Sigman, 2002), was found to be weaker in infant-led interactions between mothers and their child at-risk for ASD (Yirmiya et al., 2006). Siller and Sigman (2002) however, found no differences between synchrony of mothers and children with ASD, and mothers and their typically developing children around the age of 4.5 years.

The current study

Given the increased risk for ASD in preterm born children and the specific characteristics of the interactions between mothers and their preterm born children, along with the specifics of the interactions between mothers and their children at-risk for or with ASD, this study will investigate the association between maternal, infant and dyadic characteristics of the early MCI and ASD symptomatology in a very preterm sample. Studying MCI in extremely and very preterm born children early in life, in the context of ASD, offers the potential for earlier detection of possible emerging symptoms of ASD in these children and may provide us with more insights into the developmental pathways through which preterm born children develop ASD.

We expect that quality of mother-child interaction in the first year of life will differ between preterm and full term born dyads, mainly with regard to maternal intrusiveness and infant involvement. In the light of later ASD symptoms, we hypothesise that higher rates of ASD symptomatology at 18 months will be associated with less infant involvement, higher maternal intrusiveness and lower maternal sensitivity, along with lower quality of the dyadic interaction in preterm born dyads at 5 and 10 months.

METHODS

Participants

The study population included all the children born before 30 weeks of gestation in two hospitals in a geographically defined region in Belgium during a 13-month period (May 2012 - June 2013, $N = 97$). In Belgium, the development of these very preterm born children is systematically assessed by specialised clinical centres at fixed age points, starting from the corrected age of 4 months, approximately 4 months after discharge from the hospital. During that first visit, parents were invited to participate in the current study, which was presented as an additional follow-up of the social-communicative and behavioural development of their child, next to the standardised follow-up of medical and neuro-motor development. Families who did not show up at the 4-month follow-up were not invited to take part in the current study ($n = 6$). Families were excluded from the study when the responsible paediatrician judged that the parents would not be able to participate in the study due to limited cognitive abilities ($n = 2$), when not mastering the Dutch language ($n = 13$) or when the children were under supervision of the juvenile court ($n = 2$). As such, the parents of 74 children were invited to participate in the current study. Seven families did not wish to participate, resulting in a participation rate of 91% ($n = 67$). Through leaflets distributed in well-baby clinics, 38 full term children and their parents were recruited.

Table 1

Sample characteristics of the preterm and full term participants included in the group comparisons at the (corrected) ages of 5 and 10 months

	5 months					10 months				
	Preterm (*n* = 54)		Full term (*n* = 31)			Preterm (*n* = 57)		Full term (*n* = 33)		
	n =	%	*n* =	%	χ²(1) =	*n* =	%	*n* =	%	χ²(1) =
Gender ratio M/F	25/29	46/54	16/15	52/48	.64	29/28	51/49	19/14	58/42	.38
Number of twins	22	41	0	0	17.04***	25	44	0	0	20.04***
First born/later born	39/15	72/28	2/29	6/94	34.12***	41/16	72/28	2/31	6/94	36.34***
	M(*SD*)	Range	M(*SD*)	Range	F =	M(*SD*)	Range	M(*SD*)	Range	F =
SES	40.20(*13.27*)	12 - 66	50.37(*9.38*)	30 - 66	77.13***	42.71(*13.32*)	12 - 66	50.71(*7.83*)	32.5 - 66	12.87***
Birth weight (g)	1026.94(*282.28*)	480 - 1548	3614.17(*526.56*)	2600 - 4400	272.31***	1000.56(*245.85*)	480 - 1548	3602.67(*472.90*)	2600 - 4400	424.00***
GA (weeks)	27.17(*1.58*)	23 - 29	39.50(*1.17*)	37 - 41	1254.37***	27.28(*1.47*)	24 - 29	39.58(*1.15*)	37 - 41	1542.07***
(Corrected) age (months)	5.56(*0.32*)	4.63 - 6.27	5.13(*0.47*)	4.00 - 6.57	24.58***	10.48(*0.34*)	9.73 - 11.17	10.10(*0.53*)	9.00 - 11.30	13.18***
Apgar score 1 min	6.08(*2.28*)	1 - 9				6.13(*2.40*)	1 - 10			
Apgar score 5 min	7.92(*1.40*)	3 - 10				7.82(*1.81*)	2 - 10			
Hospitalisation days	80.53(*27.69*)	24 - 180				82.19(*26.67*)	45 - 180			
Age mother at birth	30.33(*4.44*)	21.78 - 41.38	31.73(*2.63*)	27.42 - 36.91	3.28***	31.22(*4.62*)	23.04 - 46.08	31.84(*2.93*)	27.42 - 40.44	0.60
	n =	%				*n* =	%			
CLD	11	20				12	21			
RDS	15	28				15	26			
IVH grade III/IV	5	9				5	9			

Note. *** *p* < .001 ; *GA* gestational age; *SES* socio-economic status (Hollingshead, 1975); *CLD* Chronic Lung Disease; *RDS* Respiratory Distress Syndrome; *IVH* Intraventricular Haemorrhage

Due to several reasons (e.g., illness), not all participating children were assessed at the different research contacts. In addition, not all the parents completed the extensive set of questionnaires at each research contact. Furthermore, six preterm born children only started participation at the second research contact and the same applies for two full term children. Table 1 describes the characteristics of the preterm and full term groups of children with valid data at the first two research contacts (5 and 10 months of (corrected) age). Data of MCI were only used when the observation took place within a two-month framework around the target age of assessment (5 and 10 months). Preterm born children were older than full term children at both the first (F(1,83) = 24.59, p < .001) and the second research contact (F(1,47.21) = 13.18, p = .001). Since multiple pregnancy is a clear risk factor for prematurity, the preterm sample also included a significantly higher number of twins (χ^2(1) = 17.04, p < .001; χ^2(1) = 20.04, p < .001). In addition, more children in the preterm group were first born (χ^2(1) = 34.12, p < .001; χ^2(1) = 36.34, p < .001), due to recruitment differences. Families of preterm born children also had a lower SES than families of full term born children (F(1,77.13) = 16.67, p = .001; F(1,87.96) = 12.87, p = .001).

This study was approved by the local ethical committee. All parents included in the study gave written informed consents.

Procedure

The reported data were collected during the first three of five research contacts of a prospective follow-up study conducted in the first years of life. Preterm children were assessed at the corrected ages of 5, 10 and 18 months. Families were invited to the university lab but if necessary, observations were conducted at home. 33, 33 and 11 children at the three different assessment moments were examined at home. Full term infants and their parents were assessed five times in the University lab. In this paper, data of the two first research contacts will be presented (5 and 10 months). Full term infants were not assessed at the age of 18 months, due to protocol differences. Questionnaires were provided to the parents after each research contact, to be completed at home.

Measures

Mother-child interaction (MCI). Each research contact ended with an unstructured play interaction between the infant and the mother, the primary caregiver. Observations were conducted in a standard setting, with a predefined set of age-appropriate toys. At both the ages of 5 and 10 months, the observation started with the child sitting in a commercial seat in front of their mothers but mothers were instructed that they could move their infant if they wanted to and that they could play with the child as they would normally do. The observation lasted for 5 minutes at the (corrected) age of 5 months and for 10 minutes at the (corrected) age of 10 months. Every observation of MCI was digitally recorded to enable coding of the first 5 minutes of every interaction afterwards.

Global aspects of MCI and the functioning of mother and child were evaluated by means of the well-validated Coding Interactive Behaviour (CIB; Feldman, 1998). A number of maternal (22), infant (16) and dyadic behaviours (5; see Table 2) were coded, each behaviour being coded on a 9-point scale (ranging from 1 to 5, with half points allowed). In general, 1 implies a minimal level and 5 implies a maximal level of the specific behaviour or attitude. Based on these behaviours, six constructs at the age of 5 months and seven constructs at the age of 10 months, can be deduced (see Table 2). *Maternal Sensitivity* represents the mother's ability to notice her infant's signals and respond to those appropriately, whereas *Intrusiveness* measures the interruption of the activities of the child by the parent and the attempts of the parent to move the focus of the child. Parents who ignore the signals of their child and control the interaction also score high on this composite. *Infant Involvement* mainly reflects the frequency of vocalisations and the expression of positive affect. Alertness of the child, eye contact and joint attention are also included in the construct, and the composite also measures to what extent the interaction is infant-led. *Negative emotionality* indicates the amount of withdrawal behaviour and negative affect in the infant during the interaction. *Dyadic Reciprocity* refers to synchronous exchanges in which both members contribute to the interaction in an equal way, with turn-taking as an important aspect. In other words, interaction as a game of 'give-and-take'. Dyads that are rated as high with regard to *Negative state* are constricted and poor in terms of emotional expressiveness, content, and level of exploration and enthusiasm (Feldman, 1998).

A number of under-graduate psychology students, trained in the use of the CIB, coded the videotapes. The students had no prior contact with the infant-mother pairs and were blind as to the infants' group status. Training was conducted using training tapes of a number of mother-infant interactions of full term and preterm infants who were not part of the present study, and training continued until 85% agreement was achieved. Interrater reliability (% agreement) was computed by double-coding 20% of the infant-mother interactions at both ages and varied between 87% and 93%. Internal consistency of the different included scales at the different ages varied between .60 and .91 (see Table 2). Constructs without satisfactory internal consistency (maternal Intrusiveness 5 months, infant Negative emotionality 5 months) were excluded from the analyses in question.

Table 2

Coding Interactive Behaviour – Composites

Constructs	Internal consistency (Cronbach's α)	
PARENT	5m	10m
SENSITIVITY	.80	.82
Acknowledging, Imitating, Elaborating, Parent gaze/Joint attention, Positive Affect, Vocal appropriateness, Appropriate range of affect, Resourcefulness, Affectionate touch, Parent supportive presence, Praising [a]		
INTRUSIVENESS	.42	.60
Forcing, Overriding, Parent negative affect/Anger, Hostility, Parent anxiety, Criticising [a]		
PARENT LIMIT SETTING [a]	N/A	.76
Consistency of style, On task persistence, Appropriate structure/Limit setting		(- Consistency of style)
INFANT		
INVOLVEMENT	.64	.64
Child gaze/Joint attention, Child positive affect, Alert, Fatigue (reversed), Child vocalisation, Child initiation, Child affection to parent [a], Competent use of the environment [a]	(- Initiation)	
NEGATIVE EMOTIONALITY	.16	.85
Negative emotionality, Withdrawal, Emotional lability [a]		(- Withdrawal)
DYAD		
RECIPROCITY	.87	.91
Dyadic reciprocity, Adaptation/Regulation, Fluency		
NEGATIVE STATE	N/A	N/A
Constriction		

Note. [a] only applicable at the age of 10 months; Coding Interactive Behaviour (Feldman, 1998).

ASD symptomatology in preterm children at the corrected age of 18 months. A major revision of the Checklist for Autism in Toddlers (CHAT; Baron-Cohen et al., 1996; Baron-Cohen, Allen, & Gillberg, 1992), resulted in the Quantitative CHAT (Q-CHAT; Allison et al., 2008). This questionnaire contains 25 items, which need to be scored by parents on a 5-point scale. It takes about 5 to 10 minutes to complete.

The concern evaluation for ASD included the Toddler module (Luyster et al., 2011) of the Autism Diagnostic Observation Schedule - 2 (ADOS-2; Lord, Luyster, Gotham, & Guthrie, 2012). The ADOS-2 is a semi-structured assessment of communication, social interaction and play and consists of five modules, each of which is appropriate for children and adults of differing developmental and language levels. Scores were computed for the subscales Social Affect (SA) and Restricted Repetitive Behaviours (RRB) and a total score was also computed. All assessments were performed by ADOS trained psychologists (LV and JV). Higher scores on both ASD instruments are indicative for more ASD symptomatology.

Developmental characteristics. The cognitive development of the preterm infants was assessed with the Bayley Scales of Infant Development - II (BSID-II; van der Meulen, Ruiter, Spelberg, & Smrkovsky, 2002) at each research contact, providing us with a developmental index (*M* = 100, *SD* = 15). Information about neonatal and perinatal medical history was obtained from NICU reports.

Psychological wellbeing of the mother. A modification of the Perinatal Posttraumatic Stress Disorder Questionnaire (PPQ; Quinnell & Hynan, 1999) resulted in the PPQ-II (Callahan, Borja, & Hynan, 2006). The questionnaire is a 14-item self-report inventory that identifies symptoms of posttraumatic stress disorder (PTSD) that are related to childbirth experience and the ensuing postnatal period. The items need to be scored on a 5-point Likert scale, with the total score ranging between 0 and 56. A score of 19 or higher is indicative for a higher risk for PTSD. The Dutch translation of the Brief Symptom Inventory (BSI; De Beurs, 2008; Derogatis, 1975) is the short version of the Symptom Checklist - 90 (Derogatis, 1975b). The 53-item self-report questionnaire assesses psychopathology in adults, resulting in scores for 9 scales that measure different dimensions of psychopathology (Somatisation, Obsessive-compulsive, Interpersonal sensitivity, Depression, Anxiety, Hostility, Phobia, Paranoia, Psychoticism), describing both the nature

of the symptoms and the severity. A total score is also obtained, as a severity score for the reported symptoms. Items are rated on a 5-point scale and higher scores are indicative for more psychopathology.

Statistical analyses

Data were analysed using the Statistical Package for the Social Sciences software version 19 (SPSS Inc., Chicago, Il, USA). In the first part of the results section, quality of MCI of preterm and full term children at the ages of 5 and 10 months was compared by means of one-way ANOVA's. When the assumption of homogeneity of variances was violated, Welch corrections were applied. Effect sizes (Cohen's *d)* are also presented.

Second, Pearson correlation analyses and linear stepwise regression models, exploring the possible associations between characteristics of MCI at the ages of 5 and 10 months and ASD symptomatology in preterm born children at the early age of 18 months, are presented. Spearman correlations and logistic regression models were used when applicable.

For all analyses, the overall significance level was set at 0.05. Significance levels below 0.10 were considered marginally significant.

RESULTS

Comparison quality of MCI between preterm and full term infant-mother dyads at the (corrected) ages of 5 months and 10 months

At the (corrected) age of 5 months, there were no differences in quality of MCI between preterm and full term infant-mother dyads, assessed with the CIB. At the age of 10 months, there were significant group differences for one mother-scale, one infant scale and both dyadic scales. Mothers of preterm born children were less sensitive than mothers of full term infants ($F(1,87.98) = 11.45$, $p = .001$; $d = -0.70$) and preterm infants were less involved in the interaction than full term infants ($F(1,88) = 7.73$, $p = .007$; $d = -0.61$). Moreover, preterm infant-mother dyads showed less reciprocity ($F(1,87.85) = 9.73$,

p = .002; d = -0.63) and were characterised by more negativity ($F(1,87.97)$ = 4.59, p = .035; d = 0.44). Table 3 gives an overview of the mean scores on the different composites at the (corrected) ages of 5 and 10 months in both groups of children.

Table 3

Comparison quality of MCI (M(SD)) between preterm and full term infant-mother dyads at the (corrected) ages of 5 months and 10 months as measured with the CIB

	5 months			10 months		
	Preterm (n = 54)	Full term (n = 31)	Cohen's d	Preterm (n = 57)	Full term (n = 33)	Cohen's d
PARENT						
Sensitivity	3.66(*0.53*)	3.73(*0.40*)	-0.15	**3.42(*0.56*)*****	**3.74(*0.33*)**	**-0.70**
Intrusiveness				1.37(*0.37*)	1.30(*0.25*)	0.22
Limit setting				3.38(*0.98*)	3.56(*0.87*)	-0.19
INFANT						
Involvement	3.72(*0.57*)	3.89(*0.45*)	-0.33	**3.50(*0.48*)****	**3.77(*0.40*)**	**-0.61**
Negative emotionality				1.29(*0.53*)	1.22(*0.39*)	0.15
DYAD						
Reciprocity	4.02(*0.75*)	4.22(*0.61*)	-0.29	**3.95(*0.86*)****	**4.40(*0.52*)**	**-0.63**
Negative state	2.00(*0.95*)	1.68(*0.77*)	0.37	**1.87(*1.13*)***	**1.47(*0.64*)**	**0.44**

Note. Bold numbers indicate significant differences between the preterm and the full term sample; $^*p$ < .05, $^{**}p$ < .01, $^{***}p$ < .001; *CIB* Coding Interactive Behaviour (Feldman, 1998).

Quality of MCI in the very preterm sample

Within the very preterm sample, birth weight was significantly associated with infant Involvement at the age of 5 months (r = .31, p = .024) and with maternal Sensitivity at the age of 10 months (r = .28, p = .038). There were no significant associations with gestational age. Apgar scores obtained 1 and 5 minutes after birth correlated both significantly with maternal Limit setting at the age of 10 months (r = .35, p = .010; r = .41, p = .002).

Characteristics of the mother were also associated with some aspects of MCI. Maternal age was significantly associated with maternal Sensitivity at the age of 10 months (r = .27, p = .044). SES correlated (marginally) significantly with dyadic Reciprocity 5 months (r = .27, p = .051), dyadic Negative state 5 months (r = -.26, p = .057) and maternal Sensitivity 10 months (r = .30, p = .021).These correlations can be considered as weak (Cohen, 1988).

Psychological wellbeing of the mother also correlated significantly with quality of MCI. Somatisation symptoms correlated negatively with dyadic Reciprocity 5 months (r = -.31, p = .050), maternal Sensitivity 10 months (r = -.33, p = .028) and dyadic Reciprocity 10 months (r = -.37, p = .012). Rates of Depression symptoms correlated significantly with maternal Intrusiveness 10 months (r = -.40, p = .007) and with dyadic Negative state 10 months (r = -.43, p = .003). Lastly, severity of the reported symptoms correlated significantly with maternal Sensitivity 10 months (r = -.31, p = .036). There were no associations between rates of PTSD as measured with the PPQ-II and quality of MCI.

Does quality of MCI predict ASD symptomatology in a very preterm sample?

In comparison with the mean general population score on the Q-CHAT, as reported in Allison et al. (2008), very preterm born children in this sample scored significantly higher. Applying 'range of concern'-criteria on the scores of the ADOS-T, resulted in a percentage of 89% of the scores indicating 'little-to-no concern', 9% 'mild-to-moderate concern', and 2% 'moderate-to-severe concern'. 11% of the preterm children thus had concern scores on the ADOS-T. Implementing the cut-off score for research (i.e., 12) resulted in a percentage of 6% of the children scoring above the cut-off (see Table 4).

Table 4

ASD symptomatology in the preterm sample at the corrected age of 18 months, as measured with the Q-CHAT and the ADOS-2

	Q-CHAT	ADOS-2 Total	ADOS-2 SA	ADOS-2 RRB
n =	36	39	39	39
M(*SD*)	32.64(*8.35*)	5.33(*3.56*)	4.13(*3.14*)	1.21(*1.06*)
Median	33.50	5.00	3.00	1.00
Range	18 - 53	0 - 15	0 - 12	0 - 4
Skewness	0.39	.80	.94	.70
Kurtosis	-0.17	.36	.44	-.05
Kolmogorov-Smirnov test	.08	.17[**]	.16[**]	.24[***]

Note. [**]p < .01 [***]p < .001; *ASD* autism spectrum disorder; *Q-CHAT* Quantitative Checklist for Autism in Toddlers (Allison et al., 2008); *ADOS-2* Autism Diagnostic Observation Schedule - 2 (Lord et al., 2012); *SA* social affect; *RRB* restrictive and repetitive behaviours.

There were significant correlations between quality characteristics of MCI at the corrected ages of 5 and 10 months, and reported and observed ASD symptomatology at the corrected age of 18 months.

Different stepwise regression models with the measures of ASD features as the dependent variables and the correlated MCI scales as possible predictors, were analysed. The developmental index (DI) of the BSID-II (M = 90.81, SD = 17.09; range: 55.00 - 118.00), measured at the corrected age of 18 months, was also included as a possible predictor when it correlated with the measures of ASD features. There were no significant associations with DI measured at the ages of 5 and 10 months. Table 5 provides an overview of the different stepwise regression analyses.

Does quality of MCI predict reported Q-CHAT scores at the corrected age of 18 months? In a regression analysis, the Q-CHAT score at 18 months was entered as the dependent variable and DI 18 months (step 1; r = -.68, p < .001) and the different correlated MCI characteristics (step 2; maternal Intrusiveness 10 months r = -.39, p = .016; infant Negative emotionality 10 months r = -.32, p = .057) were entered as predictors. In a first model, DI 18 months was a significant predictor ($β$ = -0.68, t = -5.14, p < .001). In the second model, maternal Intrusiveness 10 months was a second significant predictor ($β$ = -0.28, t = -2.16, p = .039) on top of DI ($β$ = -0.61, t = -4.79, p < .001). The first model predicted 44% (adjusted R^2 = .44 , F(1,31) = 26.46, p < .001) and the second model 50% (adjusted R^2 = .50 , F(2,30) = 17.13, p < .001) of the variance in Q-CHAT scores.

Does quality of MCI predict observed ADOS-T total scores at the corrected age of 18 months? The total ADOS-T score correlated significantly with the DI as measured with the BSID-II at 18 months (r = -.41, p = .027). ADOS-T total scores also correlated (marginally) significantly with infant Involvement at the ages of 5 (r = -.30, p = .062) and 10 months (r = -.34, p = .033).

In the regression analysis, DI 18 months was entered as a predictor for ADOS-T total scores in the first step, and infant Involvement 5 months and Involvement 10 months were entered as possible predictors in step 2. In a first model, DI 18 months was a significant predictor for ADOS-T total scores ($β$ = -0.41, t = -2.65, p = .012). Only Involvement 5 months ($β$ = -0.32, t = -2.16, p = .038) was an additional significant predictor in the second

model, on top of DI 18 months ($β$ = -0.40, t = -2.71, p = .012). The DI 18 months in model 1 predicted 15% of the variance in ADOS-T total scores (R^2 = .15, $F(1,34)$ = 6.99, p = .012). DI 18 months along with Involvement 5 months predicted 23% of the variance (R^2 = .23, $F(2,33)$ = 6.22, p = .005).

Table 5

Stepwise multiple linear regression models with DI 18 months as measured with the BSID-II and characteristics of MCI at the corrected ages of 5 and 10 months as possible predictors of ASD symptomatology at the corrected age of 18 months, as measured with the Q-CHAT and the ADOS-2

Linear regression models	Adjusted R^2	B	SE B	$β$
Q-CHAT				
Model 1				
BSID-II DI	.44	-0.31	0.06	-0.68***
Model 2				
BSID-II DI		-0.28	0.06	-0.61***
Maternal Intrusiveness 10 months	.50	-5.54	2.56	-0.28*
ADOS-T total				
Model 1				
BSID-II DI	.15	-0.08	0.03	-0.41*
Model 2				
BSID-II DI	.23	-0.08	0.03	-0.40*
Infant Involvement 5 months		-1.86	0.86	-0.32*
ADOS-T SA				
Model 1				
BSID-II DI	.11	-0.06	0.03	-0.37*
Model 2				
BSID-II DI	.20	-0.06	0.03	-0.36*
Infant Involvement 5 months		-1.71	0.77	-0.33*
Model 3				
BSID-II DI		-0.04	0.03	-0.24
Infant Involvement 5 months	.29	-1.74	0.73	-0.34*
Infant Involvement 10 months		-2.17	0.98	-0.34*

Note *p < .05 ***p < .001; *BSID-II* Bayley Scales of Infant Development - II (van der Meulen et al., 2002); *ASD* autism spectrum disorder; *Q-CHAT* Quantitative Checklist for Autism in Toddlers (Allison et al., 2008); *ADOS-2* Autism Diagnostic Observation Schedule - 2 (Lord et al., 2012); *SA* social affect.

Does quality of MCI predict observed ADOS-T Social Affect scores at the corrected age of 18 months? ADOS-T SA scores also correlated significantly with the DI as measured with the BSID-II at 18 months (r = -.37, p = .027) and with infant Involvement at the age of 5

months (r = -.31, p = .053) and at the age of 10 months (r = -.37, p = .022). In addition, there was a marginally significant correlation between ADOS-T SA scores and dyadic Reciprocity 10 months (r = -.31, p = .059).

When entered in a stepwise regression model, DI 18 months (β = -.37, t = -2.31, p = .027) was a significant predictor for the SA score (R^2 = .11, $F(1,34)$ = 5.35, p = .027). In a second model, Involvement 5 months was a significant predictor (β = -.33, t = -2.21, p = .034), in addition to DI 18 months (β = -.36, t = -2.36, p = .024). This second model predicted 20% of the variance in ADOS-T SA scores (R^2 = .20, $F(2,33)$ = 5.42, p = .009). In the final model, both Involvement 5 months (β = -.34, t = -2.38, p = .024) and Involvement 10 months (β = -.34, t = -2.22, p = .034) significantly predicted ADOS-T SA scores. DI 18 months was no longer a significant predictor (β = -.24, t = -1.55, p = .131). The final model predicted 29% of the variance in ADOS-T SA scores (R^2 = .29, $F(3,32)$ = 5.68, p = .003).

Does quality of MCI predict observed ADOS-T Restrictive and Repetitive Behaviour scores at the corrected age of 18 months? Given the non-normal distribution and limited range of RRB scores, a binary variable was computed, differentiating children without any observed RRB symptomatology (score 0, n = 11, 28%) versus children with observed RRB symptomatology (scores 1 - 4; n = 28, 72%).

DI 18 months correlated marginally significantly with the ADOS-T RRB binary scores (r = -.29, p = .083) and there were two marginally significant Spearman correlations between MCI characteristics and ADOS-T RRB binary scores. Sensitivity at the age of 10 months correlated negatively (r = -.28, p = .080) and Negative emotionality correlated positively (r = .29, p = .079). When entered in a logistic regression, none of the MCI variables, nor the DI 18 months, were significant predictors for the ADOS-T RRB binary scores.

DISCUSSION

The main objectives of this study were to compare characteristics of MCI between preterm and full term born dyads and to explore the association between characteristics of MCI and later ASD symptomatology in very preterm born children. Given the evidence for specificities in quality of MCI from studies with children with ASD (e.g., Wan et al.,

2012, 2013) and high-risk siblings, we expected to find some differences in the quality of mother-preterm infant interactions, related to later ASD symptomatology.

In the first part of the results section, characteristics of MCI were compared between preterm and full term infant-mother dyads, to assess specificities of very preterm MCI. Given findings in previous studies that indicated that maternal differences were mainly found before 6 months of age (Korja et al., 2012), we expected to find differences at the first research contact. However, results indicated no differences in quality of MCI between preterm and full term dyads at the (corrected) age of 5 months.

At the (corrected) age of 10 months, however, differences between behaviour of preterm and full term infants and their mothers and between quality of interaction of preterm and full term dyads were found.

Maternal Sensitivity was rated lower in mothers of preterm born children at the (corrected) age of 10 months. Although findings were quite heterogeneous, a recent meta-analysis including 34 studies, found that mothers of preterm and full term born children on average did not differ in their sensitive behaviour towards their children. Controlling for several moderating factors did not alter results (Bilgin & Wolke, 2015). A possible explanation for the fact that we did find differences in maternal Sensitivity in contrast to the results of the meta-analysis could be that the mean GA in our sample of preterm born children was much below the reported mean GA in the meta-analysis.

Although no associations with maternal symptoms of birth-related PTSD were found, Sensitivity at 10 months was associated with maternal rates of Somatisation and the total severity of reported psychological symptoms. Moreover, SES was also significantly associated with Sensitivity at the age of 10 months, which confirmed earlier findings that mothers with a lower SES appear to be less sensitive (Fuertes, Faria, Soares, & Crittenden, 2009).

Though a difference in Intrusiveness between mothers of preterm and full term children in the first year of life is a consistent finding (Bakeman & Brown, 1980; Crnic et al., 1983; Feldman, 2007; Forcada-Guex et al., 2006; Landry, Chapieski, & Schmidt, 1986; Muller-Nix et al., 2004) we did not find such a difference in our study. This may partly be due to the fact that scores of Intrusiveness were low since mothers were only observed

during a short play interaction. However, when taking a closer look into the subscales that constitute the construct of Intrusiveness, (marginally) significant differences between preterm and full term mothers were found for Hostility ($F(1,70.79) = 2.90$, $p = .093$) and Anxiety ($F(1,85.14) = 7.55$, $p = .007$), with mothers of preterm born children scoring higher. Moreover, while some expression of Negative affect was scored in preterm mothers ($M = 1.09$, $SD = 0.30$), this was not the case in the full term sample ($M = 1.00$, $SD = 0.00$). So although no overall significant difference in maternal Intrusiveness was found, mothers of preterm infants did show more signs of Hostility, Anxiety and Negative affect than mothers of full term born infants.

With regard to infant behaviour during mother-child interaction, our results indicated that preterm born infants were less involved in the interaction than full term born infants at the corrected age of 10 months. These results are in line with previous studies, in which preterm infants were found to be more passive (Crnic et al., 1983; Lester et al., 1985; Muller-Nix et al., 2004) and less responsive social partners than their full term born counterparts (Barnard et al., 1984; Crnic et al., 1983; Malatesta et al., 1986; Schmücker et al., 2005; Singer et al., 2003). The results are also in line with a review of mother-child interaction in preterm born children, that indicated that differences in infant behaviour seem to continue after six months of age (Korja et al., 2012). Although preterm infants were also found to be more fretful during interactions with their mother (Crawford, 1982), our results provided no evidence for more Negative emotionality, when compared to full term infants.

Within the preterm sample, infant Involvement at the age of 10 months correlated significantly with maternal Sensitivity 10 months ($r = .63$, $p < .001$). Within the framework of the Transactional model of development (Sameroff, 2009), we can assume that parents of preterm infants, given the lower frequencies of infant positive affect, communication of affect, initiations and vocalisations, have less infant cues to follow, which could lead to less opportunities to be sensitive. Correspondingly, more maternal Sensitivity can elicit more infant Involvement.

Preterm mother-infant dyads at the corrected age of 10 months were less reciprocal and more constricted than full term dyads. Poorer quality of dyadic interaction in preterm samples was demonstrated in various studies, with dyads being less coherent (Lester et

al., 1985), less synchronous (Feldman & Eidelman, 2007) and with mother and infant being less responsive to one another (Gerner, 1999). Reciprocity was also found to be the poorest in preterm risk groups, when compared with full term control samples and maternal risk groups (Feldman, 2007).

Overall, our results demonstrate significant differences in the interactional behaviour of preterm infants and their mothers, when compared to full term dyads. It has been suggested that these specificities in MCI may be related to developmental outcomes in preterm infants (Feldman, Eidelman, Sirota, & Weller, 2002; Landry, Smith, & Swank, 2003, 2006; Poehlmann & Fiese, 2001; Rahkonen et al., 2014; Stolt et al., 2014; Treyvaud et al., 2009). In typical development, quality of MCI is thought to be an important contributor to social competence (Bozzette, 2007). A study of Miller-Loncar, Landry, Smith, and Swank (2000), for example, demonstrated an association between mother's warm sensitivity at 2 years of age and children's social responsiveness at 4.5 years of age. The second part of the results section took a closer look into the association between MCI-characteristics and ASD symptomatology, within the very preterm born sample. A clear distinction needs to be made between parent-reported rates of ASD symptomatology and observed ASD symptoms, given the differing results.

Parent-reported rates of ASD symptomatology, as measured with the Q-CHAT, at the corrected age of 18 months were significantly predicted by maternal Intrusiveness measured at the corrected age of 10 months, on top of prediction by developmental index at the age of 18 months. More Intrusiveness at the corrected age of 10 months was associated with lower scores on the Q-CHAT, thus with less ASD symptomatology at the corrected age of 18 months.

Studies with children with ASD and infants at-risk for ASD demonstrated the use of more control strategies by mothers of children with ASD and more directive parenting, compared with mothers of typically developing children (Doussard-Roosevelt et al., 2003; Kasari et al., 1988; Lemanek et al., 1993; Wan et al., 2012, 2013). We thus expected that mothers of preterm children with higher rates of ASD symptoms would score higher on the composite of Intrusiveness but the opposite result was found in our very preterm sample. The interpretation of this finding warrants caution and further research into this association is needed. Some studies in infant siblings at-risk for ASD suggested that

intrusive parents may be compensating for the lack of social interactions of their child and thus for their child's disability (El-Ghoroury & Romanczyk, 1999; Saint-Georges et al., 2011; Spiker et al., 2002). We can cautiously hypothesise that in our sample, mothers of children who were anxious or worried about the social-communicative development of their child, may likewise have stimulated their child more, resulting in lower rates of ASD symptomatology.

With regard to observed ASD symptomatology, our results suggest that mainly infant Involvement is predictive for later ASD symptoms. Both total scores and SA scores on the ADOS-T were predicted by less infant Involvement at the corrected age of 5 months, and in addition, SA scores were also predicted by less infant Involvement at the corrected age of 10 months.

The results in our preterm sample are in line with studies that demonstrated that children with autism were found to be less compliant and more avoidant than typically developing children and children with other disabilities (Lemanek et al., 1993), that children who later were diagnosed with ASD showed a lack of interactive initiative and responsiveness (Saint-Georges et al., 2011) and that high-risk infant siblings were also rated as less lively, when compared to typically developing infants at the age of 6-10 months. At 12 months, infant attentiveness to parent and positive affect were lower in the at-risk group later diagnosed with ASD (Wan et al., 2013).

Given the accordance with results of studies with children with or at-risk for ASD and the observation of infant Involvement differing between preterm and full term infants in our sample at the (corrected) age of 10 months, the construct can be an important early indicator to consider when assessing preterm born children, in the light of later observed ASD symptomatology.

A final important result of the study is that the restrictive and repetitive ASD symptoms were not predicted by quality of mother-child interaction.

Previous studies (e.g., Forcada-Guex et al., 2006; Korja et al., 2012; Singer et al., 2003; Treyvaud et al., 2009) assessing the characteristics of MCI in preterm born samples, argued that early assessment of MCI and early intervention to guide parents of preterm born children, seem recommended. Our results also support this recommendation.

Moreover, continued assessment and follow-up at least until the end of the first year of life, is necessary. More robust results are required, before more specific clinical implications can be formulated.

Study limitations

Some limitations of the study need to be acknowledged, along with some additional suggestions for future research. The main limitation of the study is the rather small sample size which reduces the power of the study. Preterm born infants differed from full term infants with respect to SES and age of assessment. Age of assessment was not related to quality of MCI. However, significant correlations between SES and characteristics of MCI in the total sample of children were found, as well as in the preterm sample separately. The possible confounding influence of SES on the reported results thus needs to be acknowledged. In addition, no comparison with respect to developmental index between preterm and full term children could be performed, since cognitive development was measured with two different instruments in both samples. Moreover, the limited time period of the MCI observations and the lack of information about the daily interactions outside the research context, also needs to be acknowledged.

We also need to mention the early age of ASD symptomatology assessment, which may have influenced the rate of reported and observed ASD symptomatology. ADOS-T evaluations need to be considered as a concern evaluation for the presence of ASD, not as a definite diagnostic evaluation. Further follow-up of the groups of children until the ages of 2 and 3 years is planned and diagnostic ASD groups will be formed, based on ASD assessment at the two later research contacts.

Conclusions

This is to our knowledge the first study to assess quality of MCI in a very preterm sample, in the light of later ASD symptomatology. At the age of 10 months results showed that mothers of preterm infants were less sensitive and preterm infants were less involved in the interaction. Moreover, the dyadic patterns between preterm infants and their mothers were less reciprocal and more negatively charged. Regression analyses indicated that characteristics of MCI measured early in life explain a substantial amount of variance

in ASD symptomatology, both when reported by parents as when observed by a trained clinician. Although some of the findings were unexpected and contradicted findings of studies with high-risk siblings, MCI characteristics should be considered as possible early markers of ASD in preterm born children. Given the exploratory nature of the study, replication of the findings is necessary. Moreover, research into the possible underlying transactional mechanisms is required. Follow-up into later childhood is also needed, to investigate the association with ASD symptomatology at a later age.

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CHAPTER 5

EARLY TEMPERAMENT DEVELOPMENT AND SIGNS OF AUTISM SPECTRUM DISORDER IN VERY PRETERM BORN INFANTS[1]

ABSTRACT

This prospective follow-up study assessed early temperamental profiles of very preterm born children (n = 67, gestational age < 30 weeks) at consecutive time points in the first years of life (corrected ages of 5, 10 and 18 months), in the light of later autism spectrum disorder (ASD) symptomatology. Some clear associations between temperament and ASD symptoms were found and regression analyses indicated that temperament measured early in life with the Infant Behavior Questionnaire - Revised (Gartstein & Rothbart, 2003) or the Early Child Behavior Questionnaire (Putnam, Gartstein, & Rothbart, 2006) significantly increased the explained variance in ASD symptomatology, beyond the explained variance accounted for by developmental index. Cuddliness measured at the age of 10 months significantly predicted parent-reported measures of ASD symptoms at the age of 18 months. Observed ratings of total ASD symptomatology at the age of 18 months were predicted by lower rates of Negative Affect and more specifically fear at the age of 5 months. Higher rates of high intensity pleasure at 10 months significantly predicted observed social-communicative symptoms of ASD. Finally, less Negative Affect at 5 months and more perceptual sensitivity at 18

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months, significantly predicted observed restrictive and repetitive behaviours. The findings suggest that temperamental profiles are possible early signs of ASD in preterm born children.

INTRODUCTION

Screening studies in cohorts of preterm born children of different ages have suggested a link between prematurity and autism spectrum disorder (ASD), a neurodevelopmental disorder characterised by persistent deficits in social communication and social interaction, and restrictive and repetitive patterns of behaviours, interests or activities (American Psychiatric Association, 2013). Most screening studies were conducted in early childhood, around the (corrected) age of 24 months (Dudova et al., 2014; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Kuban et al., 2009; Limperopoulos et al., 2008; Moore, Johnson, Hennessy, & Marlow, 2012; Stephens et al., 2012; Wong, Huertas-Ceballos, Cowan, & Modi, 2014). These studies all indicated that ASD symptoms are significantly more prevalent in preterm children than in children in the general population. The few screening studies in late childhood and adolescence arrived at a similar conclusion (Hack et al., 2002; Indredavik et al., 2010; Williamson & Jakobson, 2014). For example, studies with the Modified-Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001) found positive screening percentages between 19 and 41% (Dudova et al., 2014; Kuban et al., 2009; Limperopoulos, 2009; Moore et al., 2012) while in the general population, a positive screen rate between 1 and 2% on the M-CHAT has been found (Kleinman et al., 2008; Robins et al., 2014).

Since screening studies may give rise to a high rate of false-positive screening classifications of ASD, due to the high frequency of neurological, cognitive and sensory difficulties in the development of preterm born children (Johnson & Marlow, 2009; Kuban et al., 2009; Moore et al., 2012; Stephens et al., 2012), additional diagnostic evaluations were included in a number of studies in early childhood (Dudova et al., 2014; Gray et al., 2015), late childhood (Johnson et al., 2010), early adolescence (Verhaeghe et al., 2015), late adolescence (Pinto-Martin et al., 2011) and adulthood (Moster, Lie, & Markestad, 2008). They all confirmed the elevated prevalence of ASD in the preterm population and more specifically in extremely (gestational age (GA) < 27 weeks) and very preterm (28 < GA < 32 weeks) born individuals. The diagnostic prevalence rates in the assessed preterm samples varied between 1% and 40%, while

the prevalence of ASD in the general population is usually estimated at 60-70 per 10,000 children (Elsabbagh et al., 2012; Fombonne, 2009).

The specific causes for the higher prevalence of ASD or ASD symptoms in these preterm children are still unclear. In addition, early developmental pathways to the emergence of ASD symptoms in this group are not well characterised. Drawing on the model of prospective studies of infant siblings of children with ASD, longitudinal investigations of children born prematurely, employing multiple measures and methods at multiple time-points are needed to identify early markers and early developmental trajectories, and to make comparisons between high- and low-risk groups.

Evidence from recent research suggests that behavioural indicators of ASD can be distinguished during the first 2 years of life (e.g., Jones, Gliga, Bedford, Charman, & Johnson, 2014). One of those possible markers is temperament, which is considered to influence behaviour already early in life (Rothbart & Bates, 2006) and which may provide a distinct construct to understand symptom emergence during the course toward ASD outcome (Clifford, Hudry, Elsabbagh, Charman, & Johnson, 2013; Garon et al., 2008).

The psychobiological framework of temperament developed by Rothbart and colleagues (Rothbart, 1981), originally designed to define temperament in the first year of life, is a well-known and widely used theoretical model, in which temperament is defined as constitutionally based differences in reactivity and self-regulation, in the domains of affect, activity and attention. The theoretical model encompasses three broad dimensions which make up for the structure of temperament: Negative Affect, Surgency/Extraversion and Orienting/Effortful Control (Rothbart & Bates, 2006). Table 1 provides an overview of the lower order scales that form the three higher order constructs in the first two years of life (Putnam, Rothbart, & Gartstein, 2008).

Table 1

Higher and lower order structure of temperament within the theoretical framework of Rothbart and colleagues and internal consistency (Putnam et al., 2008)

Constructs	Internal consistency (Cronbach's α)						
	Preterm			Full term		Total sample	
	5m	10m	18m	5m	10m	5m	10m
Negative Affect	.75	.69	.74	.73	.77	.74	.72
falling reactivity/soothability	.87	.88	.75	.87	.78	.88	.85
fear	.92	.87	.76	.81	.91	.90	.90
frustration/distress to limitations	.87	.72	.81	.76	.88	.86	.82
sadness	.78	.78	.60	.72	.73	.81	.76
discomfort [b]			.73				
motor activation [b]			.76				
perceptual sensitivity [b]			.61				
shyness [b]			.79				
Surgency/Extraversion	.61	.71	***.35***	.73	.65	.66	.68
approach/positive anticipation	.78	.86	.90	***-.19***	.84	.70	.85
vocal reactivity [a]	.89	.77		.86	.80	.87	.78
high intensity pleasure	.81	.83	***.56***	.86	.70	.82	.80
smiling and laughter [a]	.78	.73		.68	.77	.81	.76
activity level	.79	.80	.66	.78	.87	.78	.83
perceptual sensitivity [a]	.90	.78		.90	.90	.91	.86
impulsivity [b]			.69				
sociability [b]			***.41***				
Orienting/Effortful Control	***.33***	.68	.71	***.29***	***.40***	***.31***	.63
low intensity pleasure	.79	.91	.76	.70	.72	.74	.86
cuddliness	.79	.92	.77	***.51***	.82	.71	.89
duration of orienting	.66	.93	.88	***.59***	.86	.71	.91
soothability [a]	.86	.87		***.15***	.75	.79	.81
inhibitory control [b]			.85				
attentional shifting [b]			***.47***				

Note. [a] only *IBQ-R* Revised Infant Behavior Questionnaire (Gartstein & Rothbart, 2003), measuring temperament from 3 - 12 months of age; [b] only *ECBQ* Early Childhood Behavior Questionnaire (Putnam et al., 2006), measuring temperament from 18 - 36 months of age; unsatisfactory internal consistencies are indicated in bold italics

Temperament and ASD

The majority of studies on ASD and temperament within the theoretical framework of Rothbart and colleagues (1981) were performed in childhood. Temperamental singularities in children with ASD were mainly found on the scales that constitute the Effortful Control factor, with children with ASD scoring lower than children without ASD. Consistent higher scores on the Negative Affectivity scales, compared to children

without ASD were reported as well. Similar results were found for adolescents and adults with ASD, who also show peculiarities on the scales of the Surgency factor (for a review: Garon et al., 2008). Only few studies have reported on temperamental characteristics in infants with ASD and these studies were mainly based on retrospective observation of temperament and did not make use of parent report (Garon et al., 2008; Zwaigenbaum et al., 2005). One prospective, longitudinal study of early predictors of ASD in a general population sample, reported differences in temperament between children with and without ASD emerging around the age of 24 months (Bolton, Golding, Emond, & Steer, 2012). However, no specifications were provided. A number of studies with high-risk infant siblings of children with ASD reported clear temperamental specificities linked to ASD symptom emergence during infancy. Zwaigenbaum and colleagues (2005), for example, found a clear pattern of singularities at distinct ages in the first year of life on the Infant Behavior Questionnaire (IBQ; Rothbart, 1981). Siblings who went on to have an ASD classification, were distinguished from other siblings and controls by passivity and a decreased activity level at 6 months, followed by extreme distress reactions, a tendency to orient on a specific object for a longer period of time and by decreased expression of positive affect by 12 months of age (Zwaigenbaum et al., 2005). When the same children were followed until the age of 3 in the study of Garon and colleagues (2008), those diagnosed with ASD could be differentiated from non-ASD siblings and controls at the age of 2 by a temperamental profile characterised by lower positive affect and higher Negative Affect, and they also showed difficulties in attentional and behavioural control at the age of 2. The development of nine of the siblings who went on to have a diagnosis of ASD, was described in detail in a prospective case series design, again providing evidence for a specific temperamental profile, marked by distress and dysregulated state (Bryson et al., 2007). In another prospective study of high-risk siblings assessed with both the Infant Behavior Questionnaire - Revised (IBQ-R; Gartstein & Rothbart, 2003) and the Early Childhood Behavior Questionnaire (ECBQ; Putnam, Gartstein, & Rothbart, 2006), Clifford and colleagues (2013) found that siblings later diagnosed with ASD were distinguished from controls by increased perceptual sensitivity at the age of 7 months, and increased Negative Affect and reduced cuddliness in the second year of life, both at the ages of 14 and 24 months.

Based on the few studies that assessed temperamental profiles in infants in the light of later ASD diagnosis, we can summarise that as early as at the age of 6-7 months, high-risk siblings with a later diagnosis of ASD show peculiarities in their temperamental profiles and specificities continue to exist during infant and toddler years. Findings mainly suggest increases in Negative Affect with higher rates of distress, decreases in positive affect, less cuddliness in the first year of life and difficulties in controlling attention and behaviour towards the end of the second year of life.

Temperament in preterm born children

Research into temperamental profiles of preterm born children dates back to the early seventies and eighties. Results of those studies are difficult to interpret due to the large diversity of included and excluded preterm born children, with varying gestational ages and/or birth weights, distinct perinatal histories, the age of assessment of temperament, and foremost because of the different temperament traditions which were applied. While in some studies based on the theoretical framework of Rothbart and colleagues (Rothbart, 1981) preterm born children differed from term born children on several aspects of temperament at different ages of assessment (Cosentino-Rocha, Klein, & Linhares, 2014; Kerešteš, 2005; Klein, Gaspardo, Martinez, Grunau, & Linhares, 2009; Nygaard, Smith, & Torgersen, 2002), other studies failed to replicate these group differences (e.g., Olafsen et al., 2008; Voigt et al., 2013).

Given the increased risk for ASD in preterm born children and the specific temperamental profiles in individuals with (an increased risk for) ASD, this study investigates the link between preterm temperamental profiles and ASD symptomatology. Studying temperamental profiles of extremely and very preterm born children early in life, in the context of ASD, offers the potential for earlier detection of possible emerging symptoms of ASD in these children (Clifford et al., 2013) and may provide us with more insights into the developmental pathways through which preterm born children develop ASD.

Hypotheses can be put forward about the association between temperamental profiles in preterm born children and ASD symptoms. More Negative Affect, less cuddliness, less activity, less positive approach behaviour, and less smiling and laughter

in the first year of life and in addition, lower scores on inhibitory control and attentional shifting in the second year of life, are hypothesised to be predictive of more ASD symptoms at the corrected age of 18 months.

METHODS

Participants

The study population included all the children born before 30 completed weeks of gestation in two hospitals in a geographically defined region in Belgium during a 13-month period (May 2012 - June 2013, N = 97). In Belgium, the development of these very preterm born children is systematically assessed by specialised clinical centres at fixed age points, starting from the corrected age of 4 months, approximately 4 months after discharge from the hospital. During that first visit, parents were invited to participate in the current study, which was presented as an additional follow-up of the social-communicative and behavioural development of their children, next to the standardised follow-up of medical and neuro-motor development. Families who did not show up at the 4-month follow-up were not invited to take part in the current study (n = 6). Families were excluded from the study when the responsible paediatrician judged that the parents would not be able to participate in the study due to limited cognitive abilities (n = 2), when not mastering the Dutch language (n = 13) or when the children were under supervision of the juvenile court (n = 2). As such, the parents of 74 children were invited to participate in the current study. Seven families did not wish to participate, resulting in a participation rate of 91% (n = 67).

Through leaflets distributed in well-baby clinics, 38 full term children and their parents were recruited.

Due to several reasons (e.g., illness), not all participating children were assessed at the different research contacts. In addition, not all the parents completed the extensive set of questionnaires at each research contact. Furthermore, six preterm born children only started participation at the second research contact and the same applies for two full term children. Table 2 describes the characteristics of the preterm and full term

groups of children with valid data at the first two research contacts (5 and 10 months of (corrected) age).

Preterm born children were older than full term children at both the first and the second research contact. Since multiple pregnancy is a clear risk factor for prematurity, the preterm sample also included a significantly higher number of twins. In addition, more children in the preterm group were first born. Families of preterm born children also had a lower SES than families of full term born children.

Only those preterm children with valid data at the three research contacts were included in analyses in which the three assessment moments were considered (n = 48) Characteristics of these preterm born children are also displayed in Table 2.

This study was approved by the local ethical committee. Parents gave written informed consents.

Procedure

The reported data were collected during the first three of five research contacts of a prospective follow-up study conducted in the first years of life. Preterm children were assessed at the corrected ages of 5, 10 and 18 months. Families were invited to the University lab but if necessary, observations were conducted at home. This was the case for 33, 33 and 11 children at the three different assessment moments, respectively. Full term infants and their parents are also assessed five times in the University lab. However, full term infants were not assessed at the age of 18 months, due to protocol differences, so in this paper, data of the two first research moments will be presented (5 and 10 months). Questionnaires were provided to the parents after each research contact, to be completed at home. An overview of the study protocol is provided in Table 3.

Table 2

Sample characteristics of the preterm and full term participants included in the group comparisons at the (corrected) ages of 5 and 10 months and of the preterm participants included in the stepwise regression analyses

	5 months			10 months			Regression analyses
	Preterm (n = 54)	Full term (n = 25)		Preterm (n = 50)	Full term (n = 33)		Preterm (n = 48)
	n =	n =	$\chi^2(1)$ =	n =	n =	$\chi^2(1)$ =	n =
Gender ratio M/F	28/26	13/12	0.00	27/23	18/15	0.00	27/21
Number of twins	28	0	20.08***	27	0	26.41***	24
First born/later born	37/17	0/25	32.22***	35/15	0/33	32.90***	34/14
	M(*SD*)	M(*SD*)	t =	M(*SD*)	M(*SD*)	t =	M(*SD*)
SES	42.04(*13.28*)	49.78(*9.62*)	-2.86**	44.27(*12.57*)	50.23(*8.83*)	-2.50*	44.00(*12.36*)
Birth weight (g)	1027.94(*267.80*)	3629.09(*561.84*)	-15.01***	1030.64(*249.56*)	3590.71(*504.72*)	-18.36***	1029.56(*250.55*)
GA (weeks)	27.22(*1.49*)	39.58(*1.10*)	-40.88***	27.30(*1.47*)	39.62(*1.12*)	-41.93***	27.25(*1.48*)
(Corrected) age (months)	6.06(*0.49*)	5.58(*0.70*)	3.37***	11.18(0.78)	10.31(*0.46*)	5.78***	
Apgar score 1 min	6.07(*2.39*)			6.24(*2.33*)			6.17(*2.34*)
Apgar score 5 min	7.81(*1.57*)			8.00(*1.43*)			7.94(*1.42*)
Hospitalization days	77.57(*21.11*)			78.13(*21.39*)			78.07(*20.69*)
Age mother at birth	30.34(*4.37*)	31.63(*2.61*)	-1.32	30.79(*4.34*)	31.56(*2.58*)	-1.00	30.68(*4.40*)
Age father at birth	31.41(*4.79*)	34.25(*3.90*)	-2.42*	31.77(*4.91*)	33.86(*4.08*)	-1.93	31.59(*4.92*)
	n =			n =			n =
CLD	13			11			11
RDS	18			14			14
IVH grade III/IV	5			5			5

Note. * p < .05 ** p < .01 ***p < .001 ; *GA* gestational age; *SES* socio-economic status (Hollingshead, 1975); *CLD* Chronic Lung Disease; *RDS* Respiratory Distress Syndrome; *IVH* Intraventricular Haemorrhage

Table 3

Study protocol

	5 months	10 months	18 months
Preterm sample	Temperament: IBQ-R Cognitive development: BSID-II	Temperament: IBQ-R Cognitive development: BSID-II	Temperament: ECBQ Cognitive development: BSID-II ASD symptomatology: Q-CHAT and ADOS-T
Full term sample	Temperament: IBQ-R	Temperament: IBQ-R	

Note. *IBQ-R* Infant Behavior Questionnaire - Revised (Gartstein & Rothbart, 2003); *ECBQ* Early Childhood Behavior Questionnaire (Putnam et al., 2006); *BSID-II* Bayley Scales of Infant Development - II (van der Meulen, Ruiter, Spelberg, & Smrkovsky, 2002); *ASD* autism spectrum disorder; *Q-CHAT* Quantitative Checklist for Autism in Toddlers (Allison et al., 2008); *ADOS-2* Autism Diagnostic Observation Schedule - 2 (Lord, Luyster, Gotham, & Guthrie, 2009)

Measures

Temperament. Temperament was assessed with Dutch versions of two well-validated temperament questionnaires, the Infant Behavior Questionnaire - Revised (IBQ-R; Gartstein & Rothbart, 2003; Dutch translation Roest-de Zeeuw & van Doesum, n.d.) and the Early Child Behavior Questionnaire – short form (ECBQ; Putnam, Gartstein, & Rothbart, 2006; Dutch translation De Kruif et al., n.d.). Both questionnaires were developed within the theoretical framework of Rothbart and colleagues (see for a review: Rothbart & Bates, 2006). The IBQ-R is a revision of the Infant Behavior Questionnaire (Rothbart, 1981), developed to assess temperament of infants between 3 and 12 months. The ECBQ short form assesses the behaviour of 18- to 36-months-old toddlers. Items of both questionnaires (191 and 107, respectively) are rated on a 7-point Likert-type scale. Scores on the items form 14 and 18 lower order scales, respectively, with three higher order constructs (see Table 1).

Internal consistency of the different lower order scales and higher order constructs was determined by means of Cronbach's alphas, with .60 as the minimum value

(Devellis, 2012). Both in the total group of assessed children as well as in the two subgroups (preterm and full term born infants), internal consistency for the lower order scales was mostly satisfactory, varying between .60 and .93. Only for full term approach behaviour 5 months (-.19), cuddliness 5 months (.51), duration of orienting 5 months (.59) and soothability 5 months (.15), and preterm high intensity pleasure 18 months (.56), sociability 18 months (.41), and attentional shifting 18 months (.47), internal consistency was not satisfactory.

Cronbach's alphas for the included higher order constructs varied between .61 and .77. Internal consistency of Surgency 18 months was not satisfactory in the preterm group (.35). Orienting 5 months was not internally consistent in the preterm (.33), the full term (.29) and the total sample (.31). Cronbach's alpha of full term Orienting 10 months was also not satisfactory (.40). Lower order scales and higher order constructs without satisfactory internal consistency were excluded from the analyses in question. An overview is provided in Table 1.

ASD symptomatology in preterm children at the corrected age of 18 months. A major revision of the Checklist for Autism in Toddlers (CHAT; Baron-Cohen et al., 1996; Baron-Cohen, Allen, & Gillberg, 1992), resulted in the Quantitative CHAT (Q-CHAT; Allison et al., 2008). This questionnaire contains 25 items, which need to be scored by parents on a 5-point scale. It takes about 5 to 10 minutes to complete.

The concern evaluation for ASD included the Toddler module (Luyster et al., 2011) of the Autism Diagnostic Observation Schedule - 2 (ADOS-2; Lord, Luyster, Gotham, & Guthrie, 2012). The ADOS-2 is a semi-structured assessment of communication, social interaction and play and consists of five modules, each of which is appropriate for children and adults of differing developmental and language levels. Scores were computed for the subscales Social Affect (SA) and Restricted Repetitive Behaviours (RRB) and a Total score was also computed. All assessments were performed by ADOS trained psychologists (LV and JV). Higher scores on both ASD instruments are indicative for more ASD symptomatology.

Developmental characteristics. The cognitive development of the preterm born children was assessed with the Bayley Scales of Infant Development – II (BSID-II; van der

Meulen, Ruiter, Spelberg, & Smrkovsky, 2002) at each research contact, providing us with a developmental index (DI; *M* = 100, *SD* = 15).

Neonatal and perinatal history. Information about neonatal and perinatal medical history of the preterm born children was collected from NICU reports.

Statistical analyses

Data were analysed using the Statistical Package for the Social Sciences software version 19 (SPSS Inc., Chicago, Il, USA). In the first part of the results section, temperament ratings of preterm and full term children at the ages of 5 and 10 months were compared by means of (Multivariate) ANOVA's.

Pearson correlation analyses and linear stepwise regression models, exploring the possible associations between temperamental characteristics and ASD symptomatology at the early age of 18 months, are presented. Spearman correlations and binary logistic regression models (stepwise likelihood ratio method) were used when applicable.

As mentioned above, due to various reasons, some data were missing. We expected that data were missing at random and this was confirmed by Little's Test of Missing Completely At Random (χ^2(342) = 252.20, *p* = 1.000; Little, 1988). Missing values were imputed for those children with one missing questionnaire (IBQ-R 5 months *n* = 9; IBQ-R 10 months *n* = 1; ECBQ 18 month *n* = 5). Given the exploratory nature of the study, we decided not to impute data for children with two missing questionnaires. For all analyses, the overall significance level was set at 0.05.

RESULTS

Descriptive comparison temperament between preterm and full term infants at the (corrected) ages of 5 months and 10 months

At the (corrected) age of 5 months, there were no significant group differences with respect to temperament between preterm and full term children. At the age of 10 months, there was a main effect of group in a MANOVA with the subscales of the

Negative Affect construct ($F(4,77) = 2.66$, $p = .039$). However, no significant differences were found for the separate subscales. There were no other significant differences. Table 4 gives an overview of the mean scores on the different subscales and constructs of the IBQ-R at the ages of 5 and 10 months in both groups of children.

Table 4

Comparison mean (SD) temperament scores as measured with the IBQ-R between the preterm sample and full term children at the (corrected) ages of 5 and 10 months

	5 months			10 months		
	Preterm (*n* = 54)	Full term (*n* = 25)	Cohen's *d*	Preterm (*n* = 50)	Full term (*n* = 33)	Cohen's *d*
Negative Affect	2.77(*0.68*)	3.06(*0.62*)	-0.45	2.98(*0.64*)	3.09(*0.67*)	-0.17
distress to limitations	2.89(*0.80*)	3.36(*0.83*)	-0.58	3.46(*0.79*)	3.63(*0.97*)	-0.19
fear	2.43(*1.09*)	2.35(*0.79*)	0.08	2.50(*0.92*)	2.84(*0.97*)	-0.36
falling reactivity	5.49(*0.96*)	5.10(*0.95*)	0.42	5.35(*0.92*)	5.60(*0.68*)	-0.31
sadness	3.23(*0.80*)	3.64(*0.68*)	-0.55	3.28(*0.80*)	3.48(*0.83*)	-0.25
Surgency/Extraversion	4.48(*0.48*)	4.48(*0.59*)	0.00	4.75(*0.52*)	4.78(*0.50*)	-0.06
activity level	3.82(*0.85*)	3.83(*0.82*)	0.00	4.02(*0.84*)	4.15(*0.98*)	-0.14
smiling and laughter	5.11(*0.78*)	4.97(*0.85*)	0.17	5.08(*0.81*)	4.88(*0.86*)	0.24
high intensity pleasure	5.51(*0.71*)	5.59(*0.63*)	-0.12	5.82(*0.59*)	5.85(0.53)	-0.04
perceptual sensitivity	3.68(*1.34*)	3.74(*1.08*)	-0.05	3.90(*1.16*)	3.67(*1.02*)	0.21
approach	4.60(*0.90*)			5.31(*0.69*)	5.55(*0.63*)	-0.36
vocal reactivity	4.18(*0.91*)	3.96(*0.95*)	0.24	4.41(*0.85*)	4.60(*0.86*)	-0.22
Orienting/Effortful Control				4.87(*0.58*)		
duration of orienting	3.83(*0.87*)			3.38(*0.97*)	3.01(*0.85*)	0.39
low intensity pleasure	5.46(*0.73*)	5.44(*0.54*)	0.03	5.21(*0.80*)	4.92(*0.70*)	0.41
soothability	5.25(*0.77*)			5.38(*0.76*)	5.31(*0.52*)	0.39
cuddliness	5.90(*0.62*)			5.55(*0.75*)	5.55(*0.52*)	0.11

Note. IBQ-R Infant Behavior Questionnaire - Revised (Gartstein & Rothbart, 2003); scales with unsatisfactory internal consistency are coloured in grey

Does temperament predict ASD symptomatology in a very preterm sample?

Significant correlations between temperamental characteristics at the corrected ages of 5, 10 and 18 months, and reported and observed ASD symptomatology (see Table 5) at the corrected age of 18 months were found.

Table 6 provides an overview of the significant correlations. Different stepwise regression models with the measures of ASD features as the dependent variables and the correlated temperament scales as possible predictors, were analysed. The developmental index (DI) of the BSID-II, measured at the corrected age of 18 months,

was also included as a possible predictor when it correlated with the measures of ASD features. Table 7 provides an overview of the different stepwise regression analyses.

Table 5

ASD symptomatology in the preterm sample at the corrected age of 18 months, as measured with the Q-CHAT and the ADOS-2

	Q-CHAT	ADOS-2 Total	ADOS-2 SA	ADOS-2 RRB
n =	42	44	44	44
M(*SD*)	33.10(*7.87*)	5.02(*3.10*)	3.95(*2.84*)	1.07(*1.02*)
Median	34	5	3.5	1
Range	18 - 53	0 - 12	0 – 12	0 - 4
Skewness	.25	.44	.73	.82
Kurtosis	-.03	.00	.33	.28
Kolmogorov-Smirnov test	.09	.12	.13	.23***

Note. ASD autism spectrum disorder; *Q-CHAT* Quantitative Checklist for Autism in Toddlers (Allison et al., 2008); *ADOS-2* Autism Diagnostic Observation Schedule – 2 (Lord et al., 2009); *SA* social affect; *RRB* restrictive and repetitive behaviours

Table 6

Significant correlations between temperamental characteristics at the corrected ages of 5, 10, and 18 months, developmental index at the corrected age of 18 months and ASD symptomatology at the corrected age of 18 months

	Q-CHAT	ADOS-2 Total	ADOS-2 SA	ADOS-2 RRB binary [a]
Negative Affect 5m		-.38**	-.32*	-.33*
Negative Affect 10m		-.30*		
Negative Affect 18m	.32*			.36*
fear 5m		-.32*		
sadness 5m		-.35*	-.31*	
frustration 18m	.29*			.33*
perceptual sensitivity 18m				.35*
perceptual sensitivity 5m				-.30*
high intensity pleasure 10m		.30*	.30*	
activity level 18m				.31*
cuddliness 10m	-.34*			
attentional focusing 18m				-.30*
developmental index 18m	-.57***	-.29*		

p < .05 **p* < .01 ***p* < .001; *ASD* autism spectrum disorder; *SA* social affect; *RRB* restrictive and repetitive behaviours; [a] Spearman correlations

Does temperament predict Q-CHAT scores at the corrected age of 18 months? DI at the age of 18 months correlated significantly with Q-CHAT scores. There were no significant associations between temperament measured at the age of 5 months and Q-CHAT scores. Cuddliness measured at 10 months (negative) and frustration and Negative Affect measured at 18 months (positive) did correlate significantly.

In the regression analysis, Q-CHAT score at 18 months was entered as the dependent variable and DI 18 months (step 1) and the different correlated temperament measures (step 2) were entered as predictors. In a first model, DI 18 months was a significant predictor (β = -0.57, t = -4.03, p < .001). In the second model, cuddliness 10 months was a second significant predictor (β = -0.39, t = -3.23, p = .003) on top of DI (β = -0.56, t = 4.73, p < .001). The first model predicted 31% (adjusted R^2 = .31 , $F(1,38)$ = 18.50, p < .001) and the second model 45% (adjusted R^2 = .45 , $F(2,37)$ = 16.77, p < .001) of the variance in Q-CHAT scores (see Table 7).

Does temperament predict ADOS-T total scores at the corrected age of 18 months? The total ADOS-T score correlated significantly with the DI as measured with the BSID-II at 18 months. ADOS-T total scores also correlated significantly with fear and sadness 5 months and with the higher order construct Negative Affect 5 months (negative). High intensity pleasure 10 months (positive) and the higher order construct Negative Affect 10 months (negative) also correlated with ADOS-T total scores.

Since the subscales fear and sadness correlated strongly with the higher order construct Negative Affect, two different stepwise regression models were analysed. In one regression analysis, DI was entered as a predictor for ADOS-T total scores in the first step, and Negative Affect 5 months, high intensity pleasure 10 months, and Negative Affect 10 months were entered as possible predictors in step 2. Only Negative Affect 5 months (β = -0.33, t = -2.21, p = .033) was a significant predictor. The temperament scale predicted 9% of the variance in ADOS-T total scores (R^2 = .09, $F(1,40)$ = 4.90, p = .033).

When only the subscales fear and sadness 5 months, along with high intensity pleasure 10 months, and Negative Affect 10 months were entered in step 2 of a stepwise regression model, next to DI in step 1, fear measured at the age of 5 months (β = -0.31, t = -2.09, p = .043) was a significant predictor for the total ADOS-T scores,

predicting 7% of the variance in ADOS-T total scores (R^2 = .07, $F(1,40)$ = 4.38, p = .043; see Table 7).

Does temperament predict ADOS-T Social Affect scores at the corrected age of 18 months? ADOS-T Social Affect scores also correlated negatively with sadness 5 months and with the higher order construct Negative Affect 5 months. High intensity pleasure 10 months correlated positively with ADOS-T Social Affect scores.

When entered in a stepwise regression model, high intensity pleasure 10 months (β = .30, t = 2.07, p = .045) was a significant predictor for the Social Affect score (R^2 = .07, $F(1,42)$ = 4.28, p = .045; see Table 7).

Does temperament predict ADOS-T Restrictive and Repetitive Behaviour scores at the corrected age of 18 months? Given the non-normal distribution of RRB scores, a binary variable was computed, differentiating children without any observed RRB symptomatology (score 0, n = 15, 34%) versus children with observed RRB symptomatology (scores 1 – 4; n = 29, 66%). There were a number of significant Spearman correlations between temperament and ADOS-T RRB binary scores. Perceptual sensitivity 5 months correlated negatively as did the higher order construct Negative Affect 5 months. Frustration 18 months correlated positively with the RRB scores, as did the higher order construct Negative Affect 18 months. Perceptual sensitivity 18 months and activity level 18 months correlated positively and attentional focusing 18 months correlated negatively.

Since the subscales perceptual sensitivity and frustration 18 months correlated strongly with Negative Affect 18 months, two different stepwise logistic regression models were analysed. The first logistic regression analysis included perceptual sensitivity 5 months, Negative Affect 5 months, Negative Affect 18 months, activity level 18 months and attentional focusing 18 months, as possible predictors. In the first model ($\chi^2(1)$ = 9.63, p = .002), Negative Affect 18 months was a significant predictor for RRB binary scores (R^2 = .20 (Cox & Snell), .27 (Nagelkerke)). In the second model ($\chi^2(1)$ = 17.34, p < .001), Negative Affect 5 months was also significantly predictive for RRB binary scores, next to Negative Affect 18 months (R^2 = .33 (Cox & Snell), .45

(Nagelkerke); see Table 7). The models respectively predicted 75% and 80% of the responses correctly.

Table 7

Stepwise multiple linear and logistic regression models with temperamental characteristics at the corrected ages of 5, 10, and 18 months and developmental index 18 months as possible predictors of ASD symptomatology at the corrected age of 18 months

Linear regression models	Adjusted R^2	B	SE B	β
Parent-reported ASD symptoms				
Model 1				
developmental index 18 months	.31	-0.23	0.05	-0.57***
Model 2				
developmental index 18 months	.45	-0.23	0.05	-0.56***
cuddliness 10 months		-4.28	1.33	-0.39**
Observed ASD symptoms Total Score				
Model 1				
Negative Affect 5 months	.09	-1.45	0.66	-0.33*
Observed ASD symptoms Total Score				
Model 1				
fear 5 months	.08	-0.87	0.41	-0.31*
Observed ASD symptoms Social Affect score				
Model 1				
high intensity pleasure 10 months	.07	1.43	0.69	0.30*

Logistic regression models	B(SE B)	95% CI for Odds Ratio		
Observed ASD symptoms Restrictive and Repetitive Behaviours binary		Lower	Odds Ratio	Upper
Model 1				
Negative Affect 18 months	2.17**(0.82)	1.76	8.73	43.28
Model 2				
Negative Affect 5 months	-1.74*(0.75)	0.04	0.18	0.77
Negative Affect 18 months	3.07**(1.06)	2.71	21.60	172.18
Observed ASD symptoms Restrictive and Repetitive Behaviours binary				
Model 1				
perceptual sensitivity 18 months	1.13**(0.44)	1.30	3.09	7.32
Model 2				
Negative Affect 5 months	-1.40*(0.64)	0.70	0.25	0.86
perceptual sensitivity 18 months	1.42**(0.52)	1.48	4.12	11.47

Note. $^†p < .10$ $^*p < .05$ $^{**}p < .01$ $^{***}p < .001$; *ASD* autism spectrum disorder

In a second logistic regression analysis, the following predictors were entered: perceptual sensitivity 5 months, Negative Affect 5 months, frustration 18 months, perceptual sensitivity 18 months, activity level 18 months and attentional focusing 18 months. Results are presented in Table 7. In model 1 ($\chi^2(1)$ = 8.43, p = .004), perceptual sensitivity 18 months significantly predicted RRB binary scores (R^2 = .17 (Cox & Snell), .24 (Nagelkerke)). In model 2 ($\chi^2(2)$ = 14.76, p = .001), Negative Affect 5 months was also significantly predictive, next to perceptual sensitivity 18 months (R^2 = .29 (Cox & Snell), .39 (Nagelkerke)). The models respectively predicted 64% and 77% of the responses correctly.

DISCUSSION

The objective of this study was to explore if there is an association between early preterm temperament and later ASD symptomatology. Given the evidence of temperament studies in high-risk groups for ASD (Bryson et al., 2007; Clifford et al., 2013; Garon et al., 2008; Zwaigenbaum et al., 2005), we expected to find some peculiarities in preterm temperament, related to ASD symptomatology. Taking into account the specific environmental characteristics which are related to preterm birth, such as intensive care and prolonged hospitalisation stays, which can influence the neurological and behavioural development of preterm born children, predictions about the link between temperament and ASD symptomatology had to be put forward with caution. Some first insights are provided.

The first finding concerns cuddliness as measured at the corrected age of 10 months, being predictive for *parent-reported* rates of ASD symptomatology, as measured with a screening questionnaire. On top of the explained variance by developmental index, cuddliness at the age of 10 months significantly increased the percentage of explained variance in Q-CHAT scores. Cuddliness is described as the baby's enjoyment in and molding of the body to being held by a caregiver (Gartstein & Rothbart, 2003; Putnam et al., 2006). Clifford and colleagues (2013) found that at-risk siblings who were later diagnosed with ASD showed less cuddliness at the age of 14 months, in comparison with

typically developing siblings and controls. In our sample of preterm born children, the association between cuddliness and ASD symptomatology was already evident by the end of the first year of life. Clifford and colleagues (2013) mentioned in their paper that lower rates of the according higher order construct Effortful Control were found in samples of older children with ASD, but then mainly caused by difficulties in attentional focusing or inhibitory control (Konstantareas & Stewart, 2006). At earlier ages, more immature measurements of the regulatory function, involving external involvement of the caregiver, seem to be more important (Gartstein & Rothbart, 2003). Rates of cuddliness could be an important early sign in the early assessment of ASD symptoms in preterm born children, being a domain of functioning that parents can easily interpret and report about. However, no significant differences between preterm and full term cuddliness during the first year of life could be found.

We also found that less Negative Affect at 5 months corrected age, and more specifically less fear, were indicative for more *observed* ASD symptomatology at the age of 18 months, as measured with the ADOS-T total score. This finding was unexpected, given the results of earlier temperament studies in high-risk siblings of children with ASD, indicating that siblings at-risk who later were diagnosed with ASD, were rated with more Negative Affect by the end of the first year of life than typically developing siblings and controls (Zwaigenbaum et al., 2005). A possible explanation for the observed link, could be that preterm born children who later develop more ASD symptoms express less emotional signs or show more neutral affect during the first year of life.

ADOS-T Social Affect scores were significantly predicted by high intensity pleasure, measured at the age of 10 months. Although there was a significant association, the percentage of explained variance was rather limited (7%). The lower order scale high intensity pleasure measures the pleasure or enjoyment related to situations involving high stimulus intensity, rate, complexity, novelty and incongruity (Gartstein & Rothbart, 2003). The more reported high intensity pleasure, the higher the scores on the ADOS-T SA domain. In a recent study by Cosentino-Rocha and colleagues (2014) preterm born children between the ages of 18 and 36 months were rated with higher levels of high intensity pleasure, in comparison with their full term born counterparts. In our study, this finding was not replicated in the first year of life. However, higher rates of high

intensity pleasure seem to play a role in the development of SA related symptoms of ASD. The finding is somehow counterintuitive, as for many items of the subscale, lower rates of high intensity pleasure could be expected in children with ASD.

The most robust results were found for the binary scores for restrictive and repetitive behaviours score on the ADOS-T. Almost 80% of the variance in RRB scores was predicted by temperament related measures. Firstly, perceptual sensitivity (detection of slight, low intensity stimuli from the external environment; Gartstein & Rothbart, 2003) at 18 months significantly predicted RRB scores. At 18 months of age, higher rates of this lower order scale were related to more RRB ASD symptomatology. The importance of perceptual sensitivity for ASD was already demonstrated in a study of high-risk siblings (Clifford et al., 2013). In this study, the temperamental profile of the siblings who went on to be diagnosed with ASD was already marked by increased perceptual sensitivity at the age of 7 months and this finding maintained during the second year of life. As was reported by Clifford and colleagues (2013), children with ASD are known to be more sensitive to certain sensory sensations. In addition, in previous comparison studies in which temperament of preterm born children was compared to the temperament of full term born children, preterm born children (GA < 37 weeks) were rated with more perceptual sensitivity than full term born children between the ages of 18 and 36 months (Cosentino-Rocha et al., 2014). Unfortunately, due to the study design, we could not compare temperament ratings of preterm and full term born children at this age.

We also found that less Negative Affect at 5 months of age was indicative for more RRB symptomatology at the age of 18 months, as was the case for the total ADOS-T score, as mentioned above. On the contrary, more Negative affect at the age of 18 months was indicative for more RRB symptomatology at this age. These results are more in line with what we expected and with the results of studies in infant siblings of children with ASD, in which higher rates of Negative Affect were consistently found to be related with ASD (Clifford et al., 2013; Garon et al., 2008).

Given the high rate of explained variance in RRB symptomatology, we conducted a stepwise regression analysis with the subscale restricted, repetitive and stereotyped behaviour of the Q-CHAT (as applied in Wong et al., 2014), including the different items

of the Q-CHAT that measure RRB by parent report. Again a very substantial part of the variance (57%) in RRB scores was explained by temperament, confirming that this domain of symptoms of ASD in preterm born children seems to be highly associated with early temperament development.

Summarising the abovementioned results, the reactive components of temperament, namely Negative Affect and Surgency were found to be associated with observed rates of ASD symptomatology, while Effortful Control, the regulatory component of temperament, and more specifically cuddliness, was associated with parent-reported rates of ASD symptoms.

Study limitations and future research

Some limitations of the study need to be acknowledged, along with some additional suggestions for future research. Firstly, temperamental assessment in our study was solely based on parental ratings, which could be subject to reporting bias. To compensate for this flaw in data collection, adding observational measures of temperament to the study design, would have enabled us to compare parent rated with directly observed measures of temperament. However, the use of parental reports has the advantage that the total functioning over a certain period of time can be assessed, in contrast with in time limited observations in the lab.

Another limitation of the study is the rather small sample size which reduces the power of the study. In addition, significant group differences with regard to twin status and birth order between the preterm and full term samples, limit the robustness of the findings of the comparison analyses. Controlling for these differences had no significant influence on the results of the group comparison analyses. Moreover, given the recommendations provided by Miller and Chapman (2001), including a factor that is inherent to the specific characteristics of a group as covariate is not recommended.

No exclusion criteria based on the functioning of the preterm children were applied, the group of preterm children thus included those children with major sensory, motor, and neurological impairment. The influence of these impairments on the temperament of preterm children was demonstrated in several studies (Gorman, Lourie, & Choudhury,

2001; Larroque, H'Guyen The Tich, Guédeney, Marchand, & Burguet, 2005; Ross, 1987; Sajaniemi, Salokorpi, & von Wendt, 1998), but the purpose of our study was to provide a picture of a heterogeneous group of preterm born children, with some of the children unfortunately prone to major impairment in their functioning. Excluding the children with major sensory impairments, did not significantly influence the results. Replication of the findings in the light of other impairments needs to be considered, to disentangle the differing influence of prematurity and the associated impairments on the relation between temperament and ASD. Certainly, the influence of neurological sequelae and motor deficits must be investigated.

Furthermore, the large number of statistical analyses could have raised the possibility of type I-errors.

We also need to mention the early age of ASD symptomatology assessment, which may have influenced the rate of reported and observed ASD symptomatology. Further follow-up of the groups of children until the ages of 2 and 3 years is planned and diagnostic ASD groups will be formed, based on ASD assessment at the two later research contacts.

Conclusions

This is to our knowledge the first study to assess preterm temperament at consecutive time points in the first years of life, in the light of later ASD symptomatology. Regression analyses indicated that temperament measured early in life explains a definite amount of variance in ASD symptomatology, both as reported by parents as observed by a trained clinician. Although some of the findings were unexpected and contradicted findings of studies with high-risk siblings, temperament should be considered as a possible early marker of ASD in preterm born children. Given the exploratory nature of the study, replication of the findings is necessary. Follow-up into later childhood is also needed, to investigate the association with ASD symptomatology at a later age. Before possible clinical implications can be expressed, more robust results are required.

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CHAPTER **6**

In this doctoral research we aimed to provide additional information about the relationship between preterm birth and autism spectrum disorder (ASD). The first aim was to further investigate whether there is an increased prevalence of symptoms and diagnoses of ASD in extremely and very preterm born children. The dissertation expanded on previous research by adding ASD-specific diagnostic measurements of ASD symptomatology on top of parent-reported screening measures. Moreover, prevalence was investigated in two different age groups. Secondly, we aimed to get an insight into the developmental pathways through which preterm born children develop symptoms of ASD. In a prospective follow-up study, characteristics of early mother-child interaction and early temperamental development were investigated in the light of later ASD symptomatology. In this final chapter, the most important findings are discussed and possible clinical implications are formulated. An overview of the most important strengths and limitations of the different studies and suggestions for future research are also provided.

RECAPITULATION OF THE RESEARCH GOALS

The main goals of this dissertation were: (1) to evaluate the prevalence of ASD symptoms and diagnoses in extremely and very preterm born children in Flanders (Chapters 2 and 3) and (2) to prospectively study developmental characteristics of preterm born children in the light of later ASD symptomatology (Chapters 4 and 5).

The prevalence of ASD in extremely and very preterm born children in Flanders

Previous studies about the link between prematurity and ASD symptoms and diagnoses are very disparate and results are inconsistent, dependent on the degree of prematurity and impairment of the children, the measures used and the age of assessment. However, several screening studies conducted in early childhood, around the (corrected) age of 24 months (Dudova, Kasparova, et al., 2014; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Kuban et al., 2009; Limperopoulos et al., 2008; Moore, Johnson, Hennessy, & Marlow, 2012; Stephens et al., 2012; Wong, Huertas-Ceballos, Cowan, & Modi, 2014) and a few screening studies conducted in late childhood and adolescence (Hack et al., 2002; Indredavik et al., 2010; Williamson & Jakobson, 2014) all indicated that ASD symptoms are significantly more prevalent in preterm children than in children in the general population.

Additional diagnostic evaluations were included in only a number of studies in early childhood (Dudova, Kasparova, et al., 2014; Gray et al., 2015), late childhood (Johnson et al., 2010), late adolescence (Pinto-Martin et al., 2011) and adulthood (Moster, Lie, & Markestad, 2008). They all confirmed the elevated prevalence of ASD in the preterm population and more specifically in extremely and very preterm born individuals.

In Chapter 2, we aimed to provide a more comprehensive picture of the prevalence of symptoms of ASD in a geographic cohort of extremely preterm born adolescents (gestational age (GA) < 27 weeks) by using ASD-specific established diagnostic instruments in addition to screening instruments. 53 participants passed a screening procedure with two screening instruments and a diagnostic evaluation with a semi-structured assessment and a parent interview.

Information about the prevalence of symptoms of ASD at the early corrected age of 18 months in a geographic cohort of very preterm born infants (GA < 30 weeks) was provided in Chapter 3. In this cohort, ASD symptomatology was also assessed by using an established diagnostic instrument in addition to parental screening instruments.

Developmental pathways through which very preterm born children develop ASD

Early developmental pathways to the emergence of ASD symptoms in the group of preterm born children are so far not well characterised. Drawing on the model of prospective studies of infant siblings of children with ASD, longitudinal investigations of children born prematurely, employing multiple measures and methods at multiple time-points, are needed to identify early markers and early developmental trajectories and to make comparisons between high- and low-risk groups.

In Chapter 4, results of the prospective assessment of early characteristics of mother-child interaction (MCI) of very preterm born children in the first year of life (corrected ages of 5 and 10 months), in the light of later ASD symptomatology, were presented.

In Chapter 5, early temperamental profiles of very preterm born children at consecutive time points in the first years of life were assessed (corrected ages of 5, 10 and 18 months) as possible predictors of later ASD symptomatology.

INTEGRATION OF THE MAIN FINDINGS

The main findings of this doctoral dissertation are threefold. Firstly, the higher prevalence of symptoms of ASD was confirmed in an extremely and very preterm population, very early in life and later, in early adolescence. In adolescence, prevalence numbers were remarkably higher than very early in life.

Secondly, currently available screening instruments should be used with caution in the preterm population. Moreover, there is no sufficient information to decide about the usability of ASD specific diagnostic instruments in preterm samples.

Lastly, specific characteristics of development of very preterm born children and their context in the first years of life are predictive for later presence of ASD symptomatology.

Prevalence of ASD symptomatology in two Flemish cohorts

Almost a decade ago, our research lab published a paper on the social-communicative development of Flemish preterm born children (De Groote, Roeyers, & Warreyn, 2006). High-risk preterm born children were assessed at the age of 2 with the Autism Diagnostic Observation Schedule (ADOS-G; Lord, Rutter, Dilavore, & Risi, 2008). Two children (8% of the assessed sample) who reached the defined cut-off values for autism on both the social-interactive and communicative domain of the ADOS-G were excluded from the analyses of the manuscript, because of the possible too strong influence of their scores on the results. The rationale was that the authors did not have a clear indication for a relationship between preterm birth and autism.

Ten years later, several studies that were discussed in detail in the different chapters of this dissertation, clearly demonstrated the association between preterm birth and ASD. The results of Chapters 2 and 3 confirm this association in two Flemish samples of preterm born children. In the EPIBEL-cohort of adolescents born before 27 weeks of gestation, a significant rate of elevated scores on both screening instruments was found. In the total sample, 62% of the children screened positive on the Social Responsiveness Scale (SRS; Constantino & Gruber, 2005; Roeyers, Thys, Druart, De Schryver, & Schittekatte, 2011) and 33% screened positive on the Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003). The prevalence of clinical and/or research diagnoses of ASD was found to be 40%. When only taking into account community based clinical diagnoses made before our evaluation, which were confirmed with a clinical score on the ADOS and/or the Autism Diagnostic Interview-Revised (ADI-R; Rutter, Le Couteur, & Lord, 2003), and thus applying a stricter rule to estimate the prevalence rate, the percentage of ASD diagnoses was still 26%. If we would assume that none of the drop-outs has a clinical diagnosis of ASD, which is very unlikely, the prevalence rate in the total Flemish EPIBEL-group would still be 16%.

A slightly different picture emerged from the study that we conducted early in life, in a sample of very preterm born children. When simply considering the results of the

individual screening instruments, positive screening rates were found to be 9% and 5% of the very preterm born children scoring above the cut-off for ASD at the corrected age of 18 months on the Quantitative Checklist for Autism in Toddlers (Q-CHAT; Allison et al., 2008) and the Early Screening of Autistic Traits Questionnaire (ESAT; Dietz, Swinkels, van Daalen, van Engeland, & Buitelaar, 2006; Swinkels et al., 2006), respectively. In addition to the use of two screening instruments, we also observed the social and communicative development of the children by means of the toddler module of the ADOS (ADOS-T; Luyster et al., 2009). Of the infants, 11% were assigned a concern-score on the ADOS-T, with 2% of the children having a score that represents 'moderate-to-severe-concern'. Implementing the cut-off score for research purposes resulted in a percentage of 6% of the children scoring above the cut-off for ASD.

The EPIBEL positive screening percentages, independent from diagnostic prevalence rates (i.e., 62% SRS and 33% SCQ), clearly exceed positive screening rates from prior studies in childhood and adolescence. In the British EPICure-cohort (GA < 26 weeks), there were 16% positive screens with the SCQ in 11-year-old extremely preterm born children (GA < 26 weeks). Of adolescents with a birth weight < 2000 g, 18.8% screened positive on the SCQ, the Autism Spectrum Screening Questionnaire (ASSQ; Ehlers, Gillberg, & Wing, 1999) or based on parent information about the diagnostic status of the child. Important for the SCQ and ASSQ scoring percentages in this latter study is that the cut-offs were lower than the cut-off points that are usually applied (Pinto-Martin et al., 2011).

The diagnostic prevalence rate of 40% in the EPIBEL-study is remarkable and it obviously exceeds prevalence rates in the general population (Elsabbagh et al., 2012) and in other studies that did not use ASD specific instruments to assess ASD symptomatology in preterm born children in childhood and adolescence. As was mentioned in Chapter 2, the prevalence rate is considerably higher than the rate reported in the EPICure-study, which found a prevalence rate of 8%, based on assessment with a general diagnostic parent interview (Diagnostic and Well-being Assessment, DAWBA (Goodman, Ford, Richards, Gatward, & Meltzer, 2000)) (Johnson et al., 2010). When psychiatric diagnoses were assessed with the DAWBA in 7-year old very preterm born children (GA < 30 weeks), an ASD prevalence rate of only 4.5% was found, likely reflecting the higher gestational ages in this cohort and possibly also the younger age of assessment (Treyvaud et al.,

2013). The estimated diagnostic prevalence rate of 5% in a population-representative cohort of adolescents (21-year-olds) with a birth weight of < 2000 g, was also clearly exceeded. The latter prevalence rate is the only available prevalence rate which is also based on assessments with both the ADOS and the ADI-R and best-estimate diagnosis was obtained (Pinto-Martin et al., 2011). Adolescents in this study were much older and they had higher birth weights than the adolescents in our EPIBEL-study.

With respect to the findings of the assessment at the early age of 18 months, positive screening percentages were overall lower than previously reported screening percentages. Positive screening rates based on assessments with the Modified-Checklist for Autism in Toddlers (M-CHAT; Robins, Fein, Barton, & Green, 2001) varied between 18 and 41% (Dudova, Markova, et al., 2014; Kuban et al., 2009; Limperopoulos, 2009; Moore et al., 2012). In the only study which also made use of the Q-CHAT to assess ASD symptomatology in slightly older preterm born infants (24-month-olds), the screening percentage based on the same cut-off as we applied (a score higher than 2 SD above the general population mean on the Q-CHAT) was 16%, almost twice as high as the positive screening percentage in our very preterm sample. Positive screening rates which are comparable with the rates that we obtained were based on assessment of an extremely preterm born sample (GA < 27 weeks) at the corrected age of 18-22 months, with the Pervasive Developmental Disorders Screening Test, second edition (Siegel, 2004) and two tasks of the ADOS, response to joint attention and response to name (10%, 6% and 9%, respectively; Stephens et al., 2012). A positive screening percentage that was however lower than the screening percentages that we reported, was based on assessment of 2-year-old preterm born children (GA < 30 weeks) with the M-CHAT and the necessary follow-up interview (Kleinman et al., 2008). Only 3% of the preterm infants remained positive after applying the interview (Gray et al., 2015).

Only two studies applied a diagnostic evaluation to confirm ASD diagnoses early in life (Dudova, Markova, et al., 2014; Gray et al., 2015). In a study with toddlers with a birth weight < 1500 g at the age of 2, best estimate clinical diagnosis by consensus of two experienced specialists was used, in addition to testing with the ADOS. The calculated ASD prevalence was as high as 9.7% of the sample (Dudova, Markova, et al., 2014). In the second study, clinical judgement by a paediatrician was also applied to assess the

functioning of preterm born children (GA < 30 weeks) who screened positive on the M-CHAT and remained positive after the follow-up interview. Only one child (1%) was diagnosed with ASD (Gray et al., 2015). As was mentioned in Chapter 3, the samples of our study and the latter discussed studies varied with respect to the inclusion of children with major impairments and with respect to age of assessment, the children in our sample were younger. Moreover, our prevalence rates were solely based on assessments with the ADOS-T, not on independent clinical judgement.

Age-related increase in ASD symptomatology?

The two different ages of assessment clearly resulted in differing prevalence rates. Positive screening rates as well as diagnostic rates were significantly lower in early childhood than in early adolescence.

Obviously, sample characteristics of the two groups of children are different with respect to some important markers. Mainly, children in the study in early childhood were born before 30 weeks of gestation, compared with the less than 27 weeks in the adolescence study. Given evidence of studies which assessed the total range of gestational ages, demonstrating an increased risk of ASD with shorter gestation, this clearly needs to be acknowledged (Kuzniewicz et al., 2014; Leavey, Zwaigenbaum, Heavner, & Burstyn, 2013).

Another issue is the time of birth, which differs between both groups of children. Children in the prospective follow-up study were born in the years 2012-2013, while the assessed adolescents were born more than 10 years earlier, in the years 1999-2000. Advances in neonatal care during the past decade may have enhanced developmental outcomes of preterm born children.

Assessing ASD at the very early age of 18 months can also be questioned. The ADOS-T was originally designed to offer a standardised way to reach an ASD diagnostic classification for very young children under the age of 30 months (Luyster et al., 2009). Yet, together with the promising results of the ADOS-T, the authors warned for possible elevated scores if certain developmental milestones were not attained. Moreover, the behaviour of very young children can be influenced by for example shyness (Luyster et al.,

2009) or the new testing environment (Guthrie, Swineford, Nottke, & Wetherby, 2013). The predictive value of very early diagnosis was a topic of interest of many studies in the past years (Luyster et al., 2009). High rates of stability of ASD have been demonstrated in children first diagnosed after age three (Woolfenden, Sarkozy, Ridley, & Williams, 2012). Support was also provided for stability of diagnosis and syndrome expression when children were referred for a differential diagnosis before the age of 2 (Chawarska, Klin, Paul, & Volkmar, 2007). With regard to the ADOS-T, excellent sensitivity and acceptable specificity for concurrent diagnosis and good predictive value for short-term follow-up diagnosis were demonstrated in full term children around the ages of 19 and 37 months (Guthrie et al., 2013). To our knowledge, the long-term stability of ADOS-T diagnoses into later childhood was not yet investigated and there is certainly no information available about stability of ASD diagnosis in preterm born children. However, this would imply that the prevalence rate based on the assessment with the ADOS-T is even an overestimation of the prevalence of ASD in this very preterm born cohort at the age of 18 months.

When taking a closer look into the gender distribution in both samples of children, in adolescence, 2.8 boys were diagnosed with ASD for every girl. In the prospective study, twice more girls than boys had a concern-score on the ADOS-T. This finding also needs further investigation.

A final caveat was formulated by Mazurek and colleagues (2014). They stated that early in life other psychiatric disorders or developmental disabilities problems may overshadow symptoms of ASD. In our very preterm sample, assessed at the early age of 18 months, parents' perception of the functioning of their child may have been affected by their preoccupation with the (fear for) other developmental disabilities. Obviously this caveat does not apply to ADOS-T assessments.

Despite the many possible influencing factors, our results seem to suggest an age-related increase in prevalence rates, which could be explained by several models of ASD symptom development. Firstly, late recognition of symptoms or late-onset diagnoses are a possibility. Perhaps there are no or only very subtle social-communicative symptoms during the first years of life, which only start to emerge or to have an impact on the functioning of the preterm born children later in life, when social demands exceed the capabilities of the child. Before the start of our study, clinicians who are involved in the

clinical follow-up of the very preterm born infants in the hospitals were we recruited the children who participated in the prospective study, stated that their experience taught them that many of the preterm born children seem to develop adequately during the first years of life on the social and communicative domain of functioning. On the other hand, they do sometimes show some restrictive or repetitive interests or behaviours already early in life. However, many of these children are later in life re-referred for diagnostic evaluation.

Another, less plausible, possibility is regression. The literature concerning regression, defined as normal development for the first year(s) of life, followed by an abrupt or gradual loss of previously acquired skills (Lainhart et al., 2002), is extensive and clearly describes this specific developmental trajectory in a vast amount of full term children with ASD. 'Developmental stagnation' or 'developmental plateau', characterised by a developmental pattern with intact early behaviours that fade away because they are not reinforced, might also apply to the development of symptoms of ASD in preterm born children (Ozonoff et al., 2010).

The idea that ASD should be conceptualised in terms of a combination of impairments has been put forward repeatedly, resulting in cascading effects models towards ASD which imply interactions between different developmental factors, while the brain is still highly plastic (Bedford et al., 2014). The models start from genetic vulnerabilities, which result in early low-level attention deficits for social stimuli. These social attention deficits lead to impaired or restricted early interactions, which in turn lead to an abnormal development of the neurocircuitry responsible for social cognition, resulting in adverse effects on later behavioural and functional development (Eapen, Crnčec, & Walter, 2013). The possibility of a cascading influence as development unfolds of early atypical development in four key domains of functioning (early attentional control, emotion regulation, social orienting/approach and communicative development) which has the potential to disrupt early interactions with the world, was also demonstrated (Brian, Bryson, & Zwaigenbaum, 2015). Gliga, Jones, Bedford, Charman, and Johnson (2014) also summarised that symptom presentation by the age of ASD diagnosis will not only be the result of early neurodevelopmental atypicalities, but also of behavioural adaptations that result from a child developing atypically within the social and physical environment for

several years. Given the recent advances in early identification of the abovementioned difficulties, researchers are now trying to evaluate the impact of tailored approaches before the developmental cascade that leads to ASD is fully manifested (Brian et al., 2015). However, the interactions between the different systems can make it difficult to disentangle primary and secondary causes (Gliga et al., 2014).

As was demonstrated in several studies, ASD in preterm born children is thought to be associated with altered brain development (Buchmayer et al., 2009; Johnson et al., 2010; Lampi et al., 2012; Limperopoulos et al., 2007), but other authors argued that prematurity as a risk factor for ASD could also play a secondary role in shaping clinical expression of a genetic vulnerability (Guinchat et al., 2012). Genetic vulnerability or altered brain development could be the starting point of the cascade model towards preterm ASD, resulting in difficulties in the abovementioned domains of functioning, such as attention development, which in turn could lead to problems in social interaction and the full-blown manifestation of ASD. A cascade effect of the preterm early atypical development towards ASD seems very plausible.

To provide answers about the patterns of symptom emergence and about the comparability of the patterns in preterm born children and full term born children, additional longitudinal research is necessary. We will come back to this in the final paragraph of this chapter.

Our results thus contradict the claim that studies with school-age children who were born preterm revealed a remarkable lower prevalence of ASD than could have been expected from the high positive screening rates in early childhood (Dudova, Markova, et al., 2014; Johnson & Marlow, 2014). It was put forward that this change in expected prevalence may suggest that the preterm population has the potential to "recover from autism" (Dudova, Markova, et al., 2014). In contrast, Johnson and colleagues (2011) stated, based on the results of the EPICure-study, that many extremely preterm children may present with emerging social and behavioural difficulties during childhood increasing the need for ASD screening and assessment at this later age. The results of the EPIBEL-study confirm this conclusion. Further follow-up of our very preterm sample at the ages of 2 and 3 years will provide additional information about the possible age-related

increase in prevalence rates and the model of symptom development that best fits the patterns in preterm born children.

Predictive value of screeners

Another main finding of both Chapters 2 and 3 concerns the limited predictive value of the results of screening questionnaires for ASD used in the extremely and very preterm born populations. In Chapter 2, the EPIBEL-study, there were 23% 'false-positive' screens, children with a positive screen on one or both screeners who had no community based clinical diagnosis of ASD nor a research diagnosis. In addition, the children in the clinical ASD-group all screened positive on at least one of both screeners but in the research ASD-group, the results were less clear. Four of the six children screened positive on the SRS, but only two children had a positive screen on the SCQ. Two of the children did not screen positive on either of both questionnaires. In the infant cohort, all children who screened positive on the screeners, were not assigned a concern-score on the ADOS-T, and vice-versa.

A consistent finding concerning the association between preterm birth and ASD, was that co-occurring developmental difficulties may account for the high rates of positive screens. Kuban and colleagues (2009) demonstrated that major cognitive, visual and hearing impairments accounted for more than half of the positive screens in a sample of 2-year-olds born before 28 weeks of gestation (Kuban et al., 2009). Positive screening percentages for ASD in extremely preterm born 2-year old infants (GA < 26 weeks) were 16.5% when only children without disability were included and 57% when only children with disabilities were included (Moore et al., 2012). These results clearly indicated that the impairments which characterise the functioning of very preterm born children may account for a substantial part of the ASD screening percentages. In other words, their visual, hearing and motor impairments could account for deficits commonly seen in ASD, such as visual avoidance, inconsistent response to voice, and failure to point or play (Kuban et al., 2009).

Other studies that deliberately excluded infants with major impairments, to correct for the possible confounding (Dudova, Markova, et al., 2014; Stephens et al., 2012; Wong et al., 2014) still resulted in positive screening percentages which clearly exceeded

population screening percentages, indicating that the higher screening percentages in preterm born children cannot solely be attributed to other impairments.

An important limitation of most of the abovementioned studies is that they did not include a diagnostic evaluation to check whether the assumptions about the confounding influence of major impairments, was really true. In our studies, as was mentioned above, we did include a diagnostic evaluation, so we can provide information about the characteristics of children with 'false-positive' classifications on the screeners.

In the EPIBEL-study, parents rated clinically significant social-communicative difficulties in 23% of the children without a community based or clinical diagnosis of ASD, 10 children without a diagnosis of ASD screened positive on the SRS (21% of the total assessed sample) and 5 on the SCQ (11% of the total assessed sample). The SRS had .62 specificity and the SCQ .80 for identifying ASD. The positive predictive values (PPV) were 65% and 67%, respectively. The values for the SRS unfortunately cannot be compared to previous studies. Only the EPICure-study also provided information about the utility of the SCQ in an extremely preterm born sample in late childhood. The SCQ had 88% specificity and a PPV of only 31%, indicating numerous over-referrals, but he authors nevertheless concluded that the SCQ has good diagnostic utility for ASD in extremely preterm born children (Johnson et al., 2011).

When comparing the functioning of the 'false positive' EPIBEL-children with the functioning of children without a positive screen or a diagnosis of ASD, we found that cognitive development was not significantly different between children with a 'false-positive' screen and children without a positive screen or diagnosis of ASD but the functioning of these 'false-positive' children was characterised by significantly lower language development scores. The motor development of the children in the EPIBEL-study was also rated on a parent questionnaire, mainly assessing risk for developmental coordination disorder (DCD). Of the 'false-positive' children, 42% were rated as at-risk for DCD, compared to 31% of the children without a positive screen or diagnosis. Moreover, neither major neuromotor, visual or auditory impairments were characteristic for children with a 'false-positive' screen. Furthermore, internalising and externalizing problems (based on parent-report) and more symptoms of hyperactivity/impulsivity, characterised the functioning of the 'false-positive' children. More specifically, children with a 'false-

positive' screen were rated by their parents as more anxious/depressed (p = .008), less social (p = .013) and as having more thought problems (p = .003), compared to children without a positive screen for or a diagnosis of ASD.

In the prospective study (Chapter 3), specificity of the Q-CHAT was .90 and of the ESAT, it was .94. However, PPV were twice 0% since all the children with a positive screen were not assigned a concern-score on the ADOS-T. When taking a closer look into the functioning of the very preterm born children with a 'false-positive' classification, by comparing their functioning with the functioning of the children without a positive screen or a diagnosis of ASD, some findings that were not described in chapter 3, deserve our attention. Children with a positive screen had a significantly lower gestational age (t(33) = 2.68, p = .011) and a marginally significantly lower birth weight (t(33) = 1.91, p = .066) than children without a positive ASD screen or a concern-score. Their functioning was also characterised by a lower developmental index at the corrected age of 18 months (t(33) = 2.58, p = .015) but there were no differences with regard to language or motor development at the ages of 5, 10 and 18 months. Two of the children with a 'false-positive' screen had severe visual impairments. Lastly, children with a 'false-positive' screen were also rated by their parents as having more anxiety problems (t(31) = -2.96, p = .006)

In conclusion, our results confirm a significant amount of 'false-positive' classifications on parent screeners. However, the results are not that clear with regard to the influence of major impairments on the positive screening rate in these 'false-positive' children. In preterm adolescents cognitive development did not have an influence, while it did in the very preterm infants. The opposite finding was found for language and motor development. Higher scores for anxiety problems were found in both 'false-positive' samples. Clearly, the results need to be interpreted with caution, given the small sample sizes.

Another scope to approach the high rate of 'false-positive' rates based on assessment with screening questionnaires, was first formulated following the results of the EPICure-study (Johnson et al., 2011). The authors suggested that diagnosed ASD appears to be the extreme end of a distribution of symptoms that are generally increased in extremely preterm children. They concluded that a significant number of extremely preterm born

children showed clinically important social and communication difficulties that fall below the diagnostic threshold of ASD. We will come back to this specific topic further on.

Although the high rate of 'false-positive' classifications for ASD, based on screening with parent-rated questionnaires, is a well-discussed subject in the literature concerning the prevalence of ASD in preterm born children, not many studies reported information about 'false-negative' classifications. However, this information is to our opinion at least as important as the information regarding 'false-positive' classifications. Sensitivity of the SCQ in the extremely preterm born sample of the British EPICure-study was .82, a rate which according to the authors exceeded standards required for screening tests. Accordingly, the NPV were high (Johnson et al., 2011). In another study with low birth weight adolescents, only 2.5% of the children with ASD were not picked up on screening (Pinto-Martin et al., 2011). Other studies that included a diagnostic procedure to confirm positive screens in younger children only assessed those infants with a positive screen (Dudova et al., 2014; Gray et al., 2015), which implies that children who were not detected with the screener were not assessed with a diagnostic procedure, providing no information about possible 'false-negative' classifications.

In our EPIBEL-study, four children with a diagnosis of ASD screened negative on the SRS (9% of the total assessed sample) and 10 children on the SCQ (22%), resulting in sensitivities of .83 and .50. The negative predictive values (NPV) of both screening instruments were 89% and 67%.

None of the very preterm born infants of our prospective study with a concern-score on the ADOS-T was also assigned a positive screen on one or both parent-reported screeners. The sensitivity of both screeners was thus 0. NPV were 88% for the Q-CHAT and 89% for the ESAT. These results tell us that some of the preterm born children who were not detected by their parents as showing clinically significant social-communicative impairments, did show some impairing difficulties in this domain of functioning, along with peculiarities in the domain of restrictive and repetitive patterns of behaviours, interests or activities.

In the abovementioned study with low birth weight adolescents, the authors mentioned that the 2.5% children who were not picked up on screening, were mainly

high-functioning boys (Pinto-Martin et al., 2011). Although results were not significant, EPIBEL-children with a clinical or research diagnosis who did not screen positive on the SCQ had higher intelligence and language scores than children who did screen positive. Major motor, visual or auditory impairments were not less prevalent in this group of children. The functioning of the two children with an ASD diagnosis who were not picked up with the SRS, was not different from the functioning of the children who screened positive on the SRS. Since none of the children of the prospective study who were assigned a concern-score on the ADOS-T, also screened positive, this comparison could not be performed.

The abovementioned findings clearly imply that the cut-off scores which are generally applied to assess risk status for ASD, should be used with caution and definitely not as an indication for the presence of ASD diagnosis and that screening for ASD in the preterm population thus cannot be performed reliably with existing screening instruments. However, the presence of clinically impairing social-communicative difficulties urges the need for sensitive and specific screening. Moreover, the results in childhood and adolescence clearly indicate that, despite the possible high rates of confound early in life, social-communicative symptoms appear to persist into later life, so this again emphasises the importance of valid early screening.

A better understanding of both child and background factors that may affect caretaker-completed screening instruments is needed as well as the best items to be included, so that we can be certain that their application to the preterm population would be appropriate. As was put forward by Johnson and colleagues (2011), parents who lack a conceptual understanding of the nature and aetiology of ASD may be unable to discriminate between ASD related symptoms and behaviours associated with other neurodevelopmental sequelae. Individual items of the M-CHAT associated with motor, cognitive, vision and hearing limitations were already examined in extremely preterm born children assessed at the age of 24 months and four of the six critical items on the M-CHAT were commonly affected by severe impairments in other domains of functioning (Luyster et al., 2011). Unfortunately, both our samples were too small to perform comparison analyses on an item level, to disentangle the influence of major impairments.

Other studies made an attempt to overcome the high rate of 'false-positive' screens by including multiple screening instruments. Dudova, Markova, and colleagues (2014) included three different instruments to screen for ASD symptomatology, as did Stephens and colleagues (2012). The former study concluded that simultaneous use of more than one screening instrument resulted in a higher number of positive screens. Combined use of the three instruments, however, decreased sensitivity, but clearly increased specificity, thus decreased the number of 'false-positive' screens. In the latter study, no information about true diagnostic ASD rates was provided, so no information about the sensitivity nor specificity was available.

In the EPIBEL-study, the combined use of both the SCQ and the SRS resulted in an increase in specificity and a decrease in sensitivity. Individual use of the SCQ resulted in values for sensitivity and specificity of respectively .50 and .80, and for the SRS individually, the following values were obtained: .83 and .58. The combined used of both instruments demonstrated a sensitivity of .50 and a specificity of .88. In the prospective study, the use of two screening measures had no added value, since all the children who screened positive on the ESAT also screened positive on the Q-CHAT. Again, these results need to be interpreted with caution, given the small sample sizes.

Standardised observational screening measures, such as the Systematic Observation of Red Flags (Wetherby et al., 2004) and the Screening Tool for Autism in Toddlers and Young Children (STAT; (Stone, Coonrod, & Ousley, 2000; Stone, Coonrod, Turner, & Pozdol, 2004) could provide good alternatives for screening for ASD in preterm born populations, since these instruments can be applied in the standardised clinical follow-up of preterm born children and the issues that come with the parental report of symptoms are this way overcome.

Value of diagnostic measures

Aylward (2009) stated with regard to general developmental screening and assessment that clinicians should not unquestioningly accept a test as being the gold standard. In the reported studies, we evaluated the predictive value of parental screening questionnaires for ASD in the preterm population, relying on the ADOS (-2) and the ADI-R as being the gold standard for diagnostic evaluation of ASD. In full term born individuals,

the ADOS(-2), together with the ADI-R, are known to be the instruments with the highest specificity and sensitivity in the diagnostic assessment of ASD (Falkmer, Anderson, Falkmer, & Horlin, 2013) and are as such considered to be the gold standards.

In the EPIBEL-study, all children with a clinical diagnosis who were assessed with the ADOS, scored in the clinical range. However, two of the children with a clinical diagnosis did not reach the ADI-R cut-off for communication deficits while they scored clinically on the other parts. ASD in preterm populations thus cannot be assessed completely reliable with these instruments and further validation for use in preterm populations, with their specific characteristics, is necessary. So together with the development of reliable screening instruments, screening for ASD must be followed by timely access to appropriate diagnostic assessment (Brian et al., 2008).

Developmental pathways

A fast growing field of research enabled several researchers in the past decades to identify early markers of a later diagnosis of ASD. Results clearly indicated that full term ASD symptoms emerge in the first two years of life, with behavioural symptoms being overt by the end of the first year (Elsabbagh & Johnson, 2009). Given the increased risk for ASD in preterm born children, the importance of finding early indicators of later ASD symptomatology is incontestable. Studying development of very preterm born children early in life offers the potential for earlier detection of possible emerging symptoms of ASD in these children and may provide us with more insights into the developmental pathways through which preterm born children develop ASD.

Next to the concurrent relationships between slower language and cognitive development, higher rates of behavioural difficulties and more ASD symptomatology, evidence was also found for the predictive value of both characteristics of early mother-child interaction and temperamental development.

Characteristics of early mother-child interaction. Differences were found between behaviour of preterm and full term infants and their mothers and between quality of interaction of preterm and full term dyads at the (corrected) age of 10 months, but not at the (corrected) age of 5 months. Maternal Sensitivity was rated lower in mothers of

preterm born children at the (corrected) age of 10 months, but we did not find a difference for overall maternal Intrusiveness. However, mothers of preterm infants in our sample did show more signs on the subscales Hostility, Anxiety and Negative affect than mothers of full term born infants.

Preterm born infants were less involved in the mother-child interaction than full term born infants but there was no evidence for more Negative emotionality. Preterm mother-infant dyads at the corrected age of 10 months were less reciprocal and more constricted than full term dyads.

We clearly expected that mothers of preterm children with higher rates of ASD symptoms would score higher on the composite of Intrusiveness. Mothers of children with ASD namely used more physical contact and more structuring and prompting behaviours when compared to mothers of typically developing children (Doussard-Roosevelt, Joe, Bazhenova, & Porges, 2003; Kasari, Sigman, Mundy, & Yirmiya, 1988; Lemanek, Stone, & Fishel, 1993). The first prospective evidence for interactive differences in mothers of infant siblings at-risk for ASD, was provided in a study which assessed quality of MCI at the ages of 6 and 12 months. Parent sensitivity and directiveness differed between mothers of younger siblings of children with and without ASD, but did not predict 3-year ASD outcome (Wan et al., 2012; 2013). In these studies with full term born children, higher rates of Intrusiveness thus were related with less optimal outcomes, with more ASD symptomatology.

However, higher rates of *parent-reported* ASD symptomatology in the preterm sample, as measured with the Q-CHAT at the corrected age of 18 months, were significantly predicted by less maternal Intrusiveness measured at the corrected age of 10 months, on top of prediction by developmental index at the age of 18 months. When taking a closer look into the subscales of maternal Intrusiveness, we found that the scales Forcing ($r = -.46$, $p = .002$) and Criticising ($r = -.37$, $p = .014$) were correlated significantly with later ASD symptomatology. The more frequently the parent physically manipulated the child in order to change activity and criticised the child when he or she failed in achieving a goal, the less ASD symptoms were reported at the age of 18 months.

Furthermore, our results suggest that mainly infant Involvement is predictive for later *observed* ASD symptoms. Both total scores and Social Affect (SA) scores on the ADOS-T at the age of 18 moths were predicted by less infant Involvement at the corrected age of 5 months, and in addition, SA scores were also predicted by less infant Involvement at the corrected age of 10 months. These findings clearly are in agreement with studies that demonstrated that children with autism were found to be less compliant and more avoidant than typically developing children and children with other disabilities (Lemanek et al., 1993), that children who later were diagnosed with ASD showed a lack of interactive initiative and responsiveness (Saint-Georges et al., 2011) and that high-risk infant siblings were also rated as less lively and less attentive, when compared to typically developing infants at the ages of 6-10 months and 12 months, respectively (Wan et al., 2013). Moreover, our results, as mentioned above, also indicated that preterm born infants were less involved in the interaction than full term born infants at the corrected age of 10 months.

The abovementioned findings clearly disentangle the influences of both social partners: the child and his or her mother. However, the development of a child is known to be a product of the continuous dynamic interactions of the child and the experiences provided by his or her family and context (Sameroff, 2009) and the primary relationship between a mother and her child plays a primordial role in early development (Bozzette, 2007). We thus clearly need to integrate the findings regarding maternal Intrusiveness and infant Involvement.

In typical development, parental Intrusiveness is in general linked with less optimal developmental outcomes, through insecure attachment (Hall et al., 2015). For example, maternal intrusiveness at the age of 15 months was related to increases in negativity directed toward mothers, decreases in engagement with them and a trend towards decreases in dyadic mutuality at the age of 25 months (Ispa et al., 2004). In dyads of mothers and their child with intellectual disability, evidence was also found for increased Intrusiveness, when compared to control dyads. However, developmental outcomes in children with cognitive impairments sometimes seemed to be enhanced by more intrusive behaviour of the mother (Doussard-Roosevelt et al., 2003).

In preterm samples, the association between maternal Intrusiveness and developmental outcome in other domains of functioning was also investigated. Could maternal Intrusiveness in preterm born children possibly be an adaptive parenting style and could mothers be compensating for the vulnerability of their preterm born child (De Schuymer, Beyers, De Groote, & Roeyers, 2010)? Wijnroks (1998), for example, found that there was no indication that high rates of maternal stimulation had a negative impact on later cognitive development and attention in preterm infants (GA < 37 weeks). In contrast, Forcada-Guex and colleagues (2006) reported that more controlling maternal behaviour in the first year of life related to a less favourable outcome of the preterm infant at 18 months. Higher rates of maternal directiveness were clearly associated with less initiation in preterm children. The authors suggested that when mothers provided more directions, children were less stimulated to become an active interaction partner (Landry, Smith, Miller-Loncar, & Swank, 1998). Studies in infant siblings at-risk for ASD also suggested that intrusive parents may be compensating for the lack of social interactions of their child and thus for their child's disability (El-Ghoroury & Romanczyk, 1999; Saint-Georges et al., 2011; Spiker, Boyce, & Boyce, 2002). These findings would suggest that more Intrusiveness would be related to more symptoms of ASD.

However, children who showed difficulties in taking active roles, may also have influenced their mother in using more intrusive strategies (Landry, Smith, Miller-Loncar, & Swank, 1998). Following the latter suggestion, our results regarding the association between higher rates of maternal Intrusiveness and lower rates of ASD symptomatology, could also be explained in a similar way. At the age of 5 months, there were no significant differences between preterm and full term characteristics of MCI. Moreover, only infant Involvement seemed to play a predictive role towards ASD symptomatology. The less Involvement, the more ASD symptoms at the age of 18 months. At the age of 10 months, preterm children showed less involvement than their full term peers. When comparing preterm Involvement at the ages of 5 months and 10 months, results indicated a significant decrease in Involvement ($t(45) = 2.09$, $p = .043$). Also infant Involvement at the age of 10 months was predictive for observed ASD symptomatology. Moreover, at the age of 10 months, Intrusiveness was found to be predictive for parent-reported rates of ASD symptomatology. The more Intrusiveness, the less ASD symptoms. Following these

results, we could assume that parents who experience less Involvement of the child in the interaction, become more Intrusive, to compensate for the lack of involvement of their child. However, this would then imply that the Intrusive behaviour of the mother at the age of 10 months enhances social-communicative development at the age of 18 months, resulting in less ASD symptoms at the age of 18 months. This is possible, but further research is necessary to investigate this. It should be noted that we found no significant correlations between maternal Intrusiveness measured at the corrected age of 10 months and infant Involvement at 5 months (r = -.07, p = .623) or infant Involvement at 10 months (r = -.18, p = .180).

A related explanation was first provided based on the results of two subsequent studies in a cohort of at-risk siblings. The authors suggested that the higher levels of parental directiveness may reflect higher parental stress levels (Wan et al., 2012; 2013). This seems plausible since higher parental stress levels in parents of preterm born children were indeed demonstrated during NICU admission (Carter, Mulder, Bartram, & Darlow, 2005; Dudek-shriber, 2004), at hospital discharge (Holditch-Davis, Bartlett, Blickman, & Miles, 2003) and during the subsequent period at home (for a review, see Treyvaud, 2014). Moreover, associations between parental stress levels and parenting behaviour in parents of preterm born children were demonstrated. For example, mothers who experienced posttraumatic stress in the perinatal period, were less sensitive and more controlling at 6 months (Muller-Nix et al., 2004). Parents are the first to experience the devastating effects of the child's social impairment (Doussard-Roosevelt et al., 2003) so mothers of children in our sample who were anxious or worried about the social-communicative development of their child, may likewise have stimulated their child more intensively. We however found no significant correlations between maternal levels of anxiety or posttraumatic stress and Intrusiveness. Again, this would then imply that the Intrusive behaviour of the mother at the age of 10 months enhances social-communicative development at the age of 18 months, resulting in less ASD symptoms at the age of 18 months.

Clearly, the different explanations do not provide a comprehensive explanation for the observed link between higher rates of Intrusiveness and less ASD symptoms. Before making any further conclusions about this relationship, follow-up of the children into later

childhood is necessary. Furthermore, since studies with older children with ASD clearly demonstrated a reversed relationship, it is possible that the relationship between Intrusiveness and ASD symptomatology changes over time, so follow-up is also necessary to answer questions about the stability of this association. In addition, more research into the underlying transactional mechanisms is certainly necessary.

An important note with regard to the abovementioned results considering the relationship between maternal behaviour and outcome, was summarised by Wan and colleagues (2013). The findings do not indicate that parents in any way 'cause' the disorder. Rather, following the assumptions of the transactional model, any interactive difficulties – whether originating in the infant or in the mother – may become increasingly clear with time, impacting on later social communicative functioning. Both interactional partners adapt their behaviour in response to the other partner's characteristics (Doussard-Roosevelt et al., 2003).

Regardless of the interaction between infant Involvement and maternal Intrusiveness, we also investigated the correlations between infant Involvement and maternal Sensitivity. These results indicate significant correlations between Involvement 5m and Sensitivity 5m (r = .45, p = .001) and between Involvement 10 months and Sensitivity 10 months (r = .63, p < .001). There were no significant correlations across ages. Given the importance of infant Involvement and the correlation with maternal Sensitivity, this aspect of maternal behaviour also warrants our attention in intervention. Of course, the correlational findings need to be completed with more longitudinal results to investigate possible causal links.

A final remark considering the associations between characteristics of MCI and ASD symptomatology, is that the restrictive and repetitive ASD symptoms were not predicted by quality of mother-child interaction. This implies that mainly the social and communicative symptoms of ASD seem to be related with early MCI.

Temperamental development. During the past years, several studies compared temperamental profiles between children with and without ASD and clearly demonstrated temperamental specificities in children with ASD (e.g., Adamek, Nichols, Tetenbaum, Ponzio, & Carr, 2011; Bailey, Hatton, Mesibov, Ament, & Skinner, 2000; De

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Pauw, Mervielde, Van Leeuwen, & De Clercq, 2011; Kasari & Sigman, 1997; Konstantareas & Stewart, 2006)**.** Temperament as a possible predictor for ASD symptomatology was for the first time introduced in a study that investigated developmental pathways in infant-siblings at-risk for ASD. The authors stated that, although there is a conceptual overlap between dimensions of temperament and behaviours considered to be part of the autistic phenotype (e.g., poor adaptation to novelty or change), temperament may be a useful construct in understanding early differences in development between children who are and who are not at-risk for ASD (Zwaigenbaum et al., 2005). Indeed, some clear associations between temperament and ASD symptoms were found in our preterm sample and regression analyses indicated that temperament measured early in life with the Infant Behaviour Questionnaire - Revised (Gartstein & Rothbart, 2003) or the Early Child Behaviour Questionnaire (Putnam, Gartstein, & Rothbart, 2006) significantly increased the explained variance in ASD symptomatology, beyond the explained variance accounted for by developmental index.

The first finding concerns cuddliness as measured at the corrected age of 10 months, being predictive for parent-reported rates of ASD symptomatology, as measured with a screening questionnaire. On top of the explained variance by developmental index, cuddliness at the age of 10 months significantly increased the percentage of explained variance in Q-CHAT scores. We found that the less the preterm infant enjoyed being held by a caregiver at the age of 10 months (Gartstein & Rothbart, 2003; Putnam et al., 2006), the more ASD symptomatology was reported at 18 months of age.

Clifford and colleagues (2013) also found that at-risk siblings who were later diagnosed with ASD showed less cuddliness at the ages of 14 and 24 months, in comparison with typically developing siblings and controls. In our sample of preterm born children, the association between cuddliness and ASD symptomatology was already evident by the end of the first year of life. Clifford and colleagues (2013) mentioned in their paper that lower rates of the linked higher order construct Effortful Control were found in samples of older children with ASD, but then mainly caused by difficulties in attentional focusing or inhibitory control (Konstantareas & Stewart, 2006). At earlier ages, more immature measurements of the regulatory function, involving external involvement of the caregiver, seem to be more important (Gartstein & Rothbart, 2003). Rates of cuddliness could be an

important early sign in the early assessment of ASD symptoms in preterm born children, being a domain of functioning that parents can easily interpret and report about. However, no significant differences between preterm and full term cuddliness during the first year of life could be found. This finding is in contrast with results in older preterm born children between the ages of 18 and 36 months, who were found to show lower rates of cuddliness when compared to full term born children (Cosentino-Rocha, Klein, & Linhares, 2014).

We also found that *less* Negative Affect at 5 months corrected age, and more specifically less fear, were indicative for more observed ASD symptomatology at the age of 18 months, as measured with the ADOS-T total score. This finding was unexpected, given the results of earlier temperament studies in high-risk siblings of children with ASD, indicating that siblings at-risk who later were diagnosed with ASD, were rated with more Negative Affect by the end of the first year of life than typically developing siblings and controls (Zwaigenbaum et al., 2005). Also at later ages (i.e., 14 and 24 months), more Negative affect in high-risk siblings who are later diagnosed with ASD, was reported, when compared to controls (Clifford, Hudry, Elsabbagh, Charman, & Johnson, 2013).

A possible explanation for the observed link in our study, could be that preterm born children who later develop more ASD symptoms express less emotional signs or show more neutral affect during the first year of life. Also a higher tolerance rate for Negative Affect by mothers of preterm born children with more difficult developmental trajectories, is likely.

ADOS-T SA scores were significantly predicted by high intensity pleasure, measured at the age of 10 months. The lower order scale high intensity pleasure of the reactive temperament-component Surgency/Extraversion, measures the pleasure or enjoyment related to situations involving high stimulus intensity, rate, complexity, novelty and incongruity (Gartstein & Rothbart, 2003). Behaviours which are assessed in this temperament scale express positive emotionality in infancy (Putnam et al., 2006; Zentner & Bates, 2008), a greater predisposition to express positive feelings and experiences (Cosentino-Rocha et al., 2014).

Preterm born children between the ages of 18 and 36 months were rated with higher levels of high intensity pleasure, in comparison with their full term born counterparts (Cosentino-Rocha et al., 2014). In our study, this finding was not replicated in the first year of life and unfortunately, high intensity pleasure could not be compared at the age of 18 months.

The more parents of our preterm born sample reported high intensity pleasure at the age of 10 months, the higher the scores on the ADOS-T SA domain. This finding considering higher rates of high intensity pleasure related to ASD, was already demonstrated in children with ASD, aged $2-8$ years. Parents rated their children as having a greater preference for both high intensity and low intensity pleasure activities than controls (Adamek et al., 2011). In contrast, in a group of high-risk siblings, lower rates of high intensity pleasure were measured, when compared to controls, at the early age of 7 months. However, there was no significant relationship with later ASD outcome (Clifford et al., 2013).

The finding in our study is somehow counterintuitive, as for many items of the subscale, lower rates of high intensity pleasure could be expected in children with ASD. A possible explanation for the finding in our preterm sample is that preterm born children with later higher rates of ASD symptomatology are only clearly expressing enjoyment when involved in high intensity interactions.

High intensity pleasure is also linked to the subscale approach. The first study which assessed temperament trajectories across different ages in the first years of life among infant siblings, provided evidence for a clear decrease in approach behaviours. In the first year of life, parents of siblings who went on to be diagnosed with ASD, rated their children as more inclined to approach than typically developing siblings. However, at the later ages of 24 and 36 months, the relationship was reversed (Del Rosario, Gillespie-Lynch, Johnson, Sigman, & Hutman, 2014). Follow-up of temperament until later ages is necessary to unravel the patterns of the association between high intensity pleasure and ASD symptomatology.

Although MCI characteristics were not predictive for the restrictive and repetitive behaviours (RRB) score of the ADOS-T, the most robust results with regard to

temperament were found for this subdomain since almost 80% of the variance in RRB scores was predicted by temperament related measures. Firstly, perceptual sensitivity (detection of slight, low intensity stimuli from the external environment; Gartstein & Rothbart, 2003) at 18 months significantly predicted RRB scores. At 18 months of age, higher rates of this lower order scale were related to more RRB ASD symptomatology. The importance of perceptual sensitivity for ASD was already demonstrated in high-risk siblings (Clifford et al., 2013). The temperamental profile of the siblings who went on to be diagnosed with ASD was already marked by increased perceptual sensitivity at the age of 7 months and this finding maintained during the second year of life. As was reported by Clifford and colleagues (2013), children with ASD are known to be more sensitive to certain sensory sensations. In addition, when temperament of preterm born children was compared to the temperament of full term born children, preterm born children (GA < 37 weeks) were rated with more perceptual sensitivity than full term born children between the ages of 18 and 36 months (Cosentino-Rocha et al., 2014). Unfortunately, due to the study design, we could not compare temperament ratings of preterm and full term born children at this age.

We also found that less Negative Affect at 5 months of age was indicative for more RRB symptomatology at the age of 18 months, as was the case for the total ADOS-T score, as mentioned above. In contrast, more Negative affect at the age of 18 months was indicative for more RRB symptomatology at this age. These results are more in line with what we expected and with the results in infant siblings of children with ASD, in which higher rates of Negative Affect were consistently found to be related with ASD (Clifford et al., 2013; Garon et al., 2008).

Summarising the abovementioned results, the reactive components of temperament, namely Negative Affect and Surgency were found to be associated with observed rates of ASD symptomatology, while Effortful Control, the regulatory component of temperament, and more specifically cuddliness, was associated with parent-reported rates of ASD symptoms.

Predicting preterm ASD symptomatology. Both characteristics of mother-child interaction and temperamental development were so far considered separately, in the light of later ASD symptomatology. However, recent research clearly demonstrated an

interaction between both domains of functioning in preterm development. Following suggestions of the differential susceptibility model (Belsky, 1997), Poehlmann and colleagues (2012), for example, investigated the association between proneness to distress, sometimes referred to as negative emotionality, parenting and behavioural and cognitive outcomes. For temperamentally prone-to-distress preterm infants, more optimal parenting predicted higher cognitive skills and less behavioural problems. This indicates the importance of considering temperament and interactive behaviours in one model for predicting later ASD in future research.

When summarising the abovementioned results with regard to both characteristics of MCI and temperament, we can conclude that although we assumed that symptoms of ASD only start to emerge at a later age in preterm born children, some clear indicators of later ASD were found in the first years of life. Preterm born children with later higher rates of ASD symptomatology, seem to express less emotions at the corrected age of 5 months: they were rated by their parents as expressing less Negative affect. Later, at the corrected age of 10 months, the lower rates of expression of emotions seem to persist, since children were rated as showing more high intensity pleasure, which could be explained by lower rates of expressing enjoyment during daily lower intensity activities. Also the expression of enjoyment of cuddliness seems to be impaired. The results with regard to infant Involvement are in line with these findings, since two of the subscales of the construct are Positive affect and Expression of affection to the parent. Finally, at the corrected age of 18 months, higher rates of Negative Affect were found to be predictive for more ASD symptomatology and more specifically, for restrictive and repetitive behaviours. The results suggest that difficulties in emotion expression and regulation seem to play a significant role in the developmental pathways towards preterm ASD.

Moreover, a clear overlap between the mother-child interaction characteristic Involvement and the temperament factor Cuddliness, can be noticed. Both constructs describe behaviours that reduce the child's opportunities to learn from social experiences (Zwaigenbaum et al., 2005). These results are supportive for the above suggested cascade model of development of ASD symptomatology in preterm born children.

As was demonstrated, a clear distinction needs to be made between predicting parent-reported symptoms of ASD and observer-based ratings. In both domains of

functioning, different predictors were found for parent versus observer ratings. These results again underscore the abovementioned discrepancy between parent-reported and observer-based ratings of ASD symptomatology in the preterm population. Since previous studies in full term groups of children with or at-risk for ASD, mainly worked with diagnostic status as the outcome measure, comparison with results of these studies concerning this specific topic is not possible.

In addition, results clearly demonstrated that the different diagnostic domains of ASD need to be considered separately. Characteristics of MCI were found to only be predictive for the social and communicative symptoms of ASD, whereas temperamental characteristics were found to be mainly predictive for the restrictive and repetitive behaviours.

Furthermore, when comparing the results of our predictive studies with the results of studies in children with or at-risk for ASD, we clearly see some similarities but we also found some clear differences, some unexpected findings. This information, together with results from future studies, can tell us something about the phenotypic expression of ASD in preterm born children.

However, as was mentioned in both chapters, given the exploratory nature of the study, replication of the findings is necessary. Follow-up into later childhood is also needed, to investigate the association with ASD symptomatology at a later age. ADOS-T evaluations namely need to be considered as a concern evaluation for the presence of ASD, not as a definite diagnostic evaluation. Further follow-up of the groups of children until the ages of 2 and 3 years is planned and diagnostic ASD groups will be formed, based on ASD assessment at the two later research contacts.

Specific relational problems, milder forms of ASD or the preterm phenotype?

Studies demonstrating that preterm born children show impairments in the social and communicative domain of functioning date back to the past century (e.g., Garner, Landry, & Richardson, 1991; Ross, Lipper, & Auld, 1990) but also more recent studies provided evidence for problems with regard to social competencies in preterm born children with differing gestational ages throughout childhood (e.g., Farooqi, Hägglöf, Sedin, Gothefors,

& Serenius, 2007). In one of the first studies to actually assess ASD symptomatology, the authors mentioned that the mean ASSQ score in the VLBW sample was far below the cut-off for an ASD, and should not be overstated as autistic symptoms, but rather understood as specific relational problems (Indredavik et al., 2010). The abovementioned paper which was published by our lab (De Groote et al., 2006) also clearly demonstrated less optimally developed social, communicative and joint attention abilities in high-risk preterm born children. Although the authors made use of the ADOS to assess the abilities, it was not their intention to assess prevalence of ASD. As was mentioned above, they even excluded the children who scored above the cut-off for autism.

Some authors also described the deficits in social and communicative functioning that are seen in the preterm population as autistic-like traits (Williamson & Jakobson, 2014). The authors also demonstrated significantly more symptoms in preterm children than in full term controls, but the mean score of the preterm group was much lower than the mean score for children with ASD and only a subgroup of the preterm children scored above the cut-off score for ASD. Indredavik, Vik, Skranes, and Brubakk (2008) speculated that very low birth weight adolescents may exhibit a milder form of ASD, with struggles in encoding social cues. The authors found that many very-low-birth-weight adolescents showed relational problems and deficits in social skills, with only some of them having ASD symptoms (Indredavik et al., 2004). However, a recent study which compared ASD symptomatology in children with ASD, both with and without low birth weight, found that autism severity was not different in these two groups, suggesting no specific effect of VLBW on core autism symptoms (Ben Itzchak, Lahat, & Zachor, 2011).

Johnson and colleagues (2010) were the first to suggest that diagnosed ASD appears to be the extreme end of a distribution of symptoms that are generally increased in preterm born children. Results of a later study with the Q-CHAT were also indicative for this right-shift in frequency distribution of ASD symptoms, when compared to the distribution in the general population (Wong et al., 2014). Our results also confirm this shift to the right in the distribution of the scores. Mean scores on for example the Q-CHAT, were significantly higher than the general population mean but were also significantly lower than the ASD population mean. The results of our studies thus confirm the findings considering a subgroup of preterm born children with subclinical social-communicative

problems and an important group of children, certainly in early adolescence, who were diagnosed with ASD.

An additional way of thinking which was repeatedly described in the literature concerning preterm development and preterm ASD, concerns the preterm behavioural phenotype (Johnson & Marlow, 2011) which resulted from a consistency in the behavioural deficits that were found in different studies. It is associated with a specific risk for a triad of disorders, namely ASD, ADHD and emotional disorders (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Indredavik, Vik, Heyerdahl, Kulseng, & Brubakk, 2005; Johnson & Wolke, 2013; Treyvaud et al., 2013).

Both in the EPIBEL-study and the prospective study, parents completed the Child Behaviour Checklist (Achenbach, 1991), which can give us an indication about the association between ASD symptoms and parent-reported symptomatology on the domains of attention and emotional disorders. Additional analyses with the EPIBEL-data demonstrated clear associations between anxiety symptoms ($r = .37$, $p = .005$) and attention problems ($r = .74$, $p < .001$) with scores on the SRS. Withdrawn behaviours ($r = .31$, $p = .046$) and attention problems ($r = .55$, $p < .001$) were clearly associated with scores on the SCQ. Both withdrawn behaviours ($r = .39$, $p = .022$) and attention problems ($r = .40$, $p = .016$) were also significantly correlated with the restrictive and repetitive behaviours score of the ADOS. In the prospective study, there were no associations between ASD symptomatology and the subscales attention, emotional reactivity or anxiety of the CBCL 1.5-5. A possible explanation for this finding could be the early age of assessment of the behavioural difficulties (18 months corrected age). So at the early age of 18 months, our results do not underscore the idea of preterm ASD being part of a preterm phenotype, but in early adolescence they seem to suggest that it does.

Next to the suggestion of a preterm phenotype, some other phenotypic atypicalities were encountered, when preterm ASD and full term ASD were compared. Only recently, a first paper describing phenotypic differences in individuals with ASD born preterm and born at term was published. Of the children born preterm, more males had co-morbid sleep apnea, seizure disorders and attention-deficit/hyperactivity disorder. Female preterm born children with ASD were more often nonverbal (Bowers, Wink, Pottenger, McDougle, & Erickson, 2014). When children with ASD with and without low birth weight

were compared, the ASD group with low birth weight showed more deficits in various other developmental areas, such as daily living skills, socialisation and motor skills (Ben Itzchak et al., 2011).

Moreover, other studies clearly suggested that other core deficits underlie preterm ASD: internalising behavioural problems such as excessive shyness or withdrawal (Nadeau, Boivin, Tessier, Lefebvre, & Robaey, 2001) or externalising problems such as inattentiveness and impulsivity (Elgen, Sommerfelt, & Markestad, 2002), were found to underlie many of the problems that preterm children have on the social-communicative domain. Others have suggested that impaired social perception plays an important role (Indredavik et al., 2008; Williamson & Jakobson, 2014).

Idiopathic versus syndromic

Following a screening study in extremely low GA two-year-olds, authors suggested that ASD in preterm born children resembles more the pattern seen in children with syndromic ASD. Findings that led to this conclusion were the gender ratio between 1:1 and 2:1, the increased rate of microcephaly and the very high rates of cognitive impairment among the children who screened positive for ASD (Kuban et al., 2009).

The results of the EPIBEL-study are in line with these findings. Extremely preterm born boys were more likely to be diagnosed with ASD than girls. However, the gender ratio in the ASD groups was only 2.79:1, which is higher than the abovementioned 1:1 – 2:1, but still lower than the ratio in idiopathic ASD, which is more likely 4:1. Moreover, no gender differences were found for screening results. Children with ASD were also characterised by a lower IQ. Not only were their IQ scores significantly below the mean intelligence score of the children without any suspicion of ASD, almost half of the children with a diagnosis of ASD had intellectually disability.

In the prospective study, no relationship between gender and ASD symptomatology was demonstrated and children with more ASD symptoms showed slower cognitive development at the age of 18 months, but not during the first year of life.

What other factors contribute to the higher prevalence of ASD symptoms in preterm born children?

Although investigating possible causes for the higher prevalence of ASD symptoms in the preterm population was not the scope of this study, some important findings of previous studies need to be underscored. Johnson and colleagues (2010) suggested that ASD in preterm born children is associated with altered brain development. Lampi and colleagues (2012), for example, suggested that NICU infants may experience intraventricular haemorrhages and white matter injuries, which may mediate the relationship between prematurity and ASD. The association between cerebellar haemorrhagic injury and positive ASD screening rates was demonstrated in a study of Limperopoulos and colleagues (2007). Buchmayer and colleagues (2009) showed that the association between ASD and preterm birth is mediated by neonatal complications, such as intracranial bleeding, cerebral oedema, or seizures in the neonatal period. Intracranial haemorrhage was also associated with ASD in infants born before 34 weeks of gestation. Movsas and colleagues (2013) found in a prospective study into early adulthood that the risk of being diagnosed with ASD depended on type of white matter injury. With ventricular enlargement in the newborn period, the risk of ASD diagnosis was almost seven-fold that of no cranial ultrasound abnormality but no elevated risk was found for parenchymal lesion without ventricular enlargement. IVH also did not increase the risk for either ASD screening positivity or ASD diagnosis. These results clearly indicate that preterm ASD seems to have a different pathogenic pathway than full term ASD involving global impairment in brain development (Johnson et al., 2010). In the EPIBEL-sample, 40% of the children with ASD experienced intracranial haemorrhage grade III/IV, compared to 20% in the children with a 'false-positive' screen and only 5% in the group of children without a positive screen for or a diagnosis of ASD. With respect to leukomalacia, we found that 17% of the children with an ASD diagnosis experienced cystic periventricular leukomalacia or cystic subcortical/mixed leukomalacia, compared to 0% in both samples with a 'false-positive' screen and without a positive screen for or a diagnosis of ASD.

As was mentioned above, genetic vulnerability or altered brain development could be the starting points of the cascade model towards preterm ASD, resulting in difficulties in the abovementioned domains of functioning, such as temperamental development,

which in turn could lead to problems in social interaction and the full-blown manifestation of ASD.

Preterm ASD versus full term ASD

The abovementioned findings, together with results of previous studies, clearly indicate that there is an increased prevalence of symptoms of ASD and diagnoses of ASD in the preterm population. However, characteristics of ASD in the preterm population, suggest that preterm ASD seems to be the extreme end of a distribution of general increased social-communicative symptoms (Johnson et al., 2010; Wong et al., 2014), with an assumed age-related increase in symptoms. Moreover, preterm ASD seems to be part of a preterm phenotype (Wong et al., 2014) and resembles more the pattern seen in children with syndromic ASD (Kuban et al., 2009) and it seems to have a different pathogenic pathway involving global impairment in brain development (Johnson et al., 2010). Moreover, the results considering early developmental pathways towards ASD also clearly demonstrated that results were not always in line with findings from studies with full term children at-risk for or with ASD, although some similarities were found. Our results also suggest that emotion expression and certainly emotion regulation seem to be important in defining preterm ASD. Lastly, taking a closer look into the different subdomains of ASD symptomatology seems to be recommended, since results suggest differences between preterm and full term ASD. In conclusion, we cannot presume that the ASD seen in the preterm born children is the "same" as the ASD seen in full term born children.

CLINICAL IMPLICATIONS

Our studies, together with previously published studies, described the higher prevalence of ASD symptomatology in preterm born children. However, describing the increased prevalence is one thing, but this information raises also a lot of additional questions. The first main issue concerns the necessity of good screening and diagnostic

instruments. The second issue concerns the importance of early follow-up of development of the child and the context, in the light of later ASD symptomatology.

Firstly, clinicians who are involved in the clinical follow-up of preterm born children need to be alarmed about the higher prevalence of ASD in young and older preterm born children. Obviously, clinicians are well aware of the unusual social and behavioural profile observed in preterm born children (Limperopoulos et al., 2008), but given the very high rates of ASD later in life, the importance of continued awareness for signs of ASD from early childhood until adolescence, is obvious.

Secondly, given the abovementioned importance of clinical awareness for the presence of ASD and the recommendation considering universal screening for ASD with an ASD-specific screening instrument at the ages of 18 and 24 months by the American Academy of Pediatrics (although this recommendation is not followed in Flanders), information about the usability of existing screening and diagnostic instruments, also needs to be translated to the clinical practice.

The most important caveat with regard to the use of the existing instruments, is the high rate of confound, leading to false-positive classifications. However, since current follow-up in this high-risk population mainly focuses on neuromotor and cognitive modalities (Limperopoulos et al., 2008), clinicians will probably be attentive for the influence of impairments in other domains of functioning, that could increase screening rates. Specific information about which items of currently available instruments are mainly influenced by impairments (Luyster et al., 2011), should be provided, based on results of future large-scale studies.

Furthermore, as was demonstrated by Gray and colleagus (2015), a follow-up interview to validate positive screening on the parent-completed questionnaire, may result in reduction of false-positive screening rates. The use of the M-CHAT and the accompanying follow-up interview first needs to be evaluated in research in Flemish preterm populations and can then possibly be implemented in the clinical practice.

Next to the importance of early screening for ASD, the importance of consequent diagnostic testing and close follow-up of children with positive screening tests, needs to be stressed. Along with the suggestions for the individual uses of both screening and

diagnostic measures, one important general remark has to be emphasised. None of the instruments we used should be the sole element of a diagnostic evaluation for ASD in preterm born children. As was mentioned by Luyster and colleagues (2009) about the use of the ADOS-T, this is particularly important for very young children.

An important issue, which was not really addressed in previous studies concerns the false-negative classifications on screening questionnaires. In our prospective study, none of the children with a concern-score on the ADOS-T, was assigned a positive screening score based on parent-report. This finding stresses the importance of clinical knowledge of the early signs of later ASD symptomatology and the importance of increased awareness for these signs and demonstrates again that risk-assessment for ASD cannot solely be based on parental questionnaires.

Our results considering the possible age-related increase of ASD symptomatology further stress the importance of early screening and more importantly, of consequent early intervention. Overall, the demonstrated shift to the right in distribution of ASD symptomatology stresses the importance of social-communicative intervention for the majority of preterm born children. The available interventions which are used with full term born children at-risk for or with ASD, need to be evaluated in preterm populations. Given the specificities of preterm ASD, adaptations will probably be necessary. Also existing, more general interventions which are already applied in the preterm population, need to be considered in the light of ASD.

Before possible clinical implications can be expressed with regard to the predictive value of characteristics of mother-child interaction and temperamental development for later ASD symptoms, more robust results are required. However, as both MCI and temperament were already found to be important predictors of other domains of functioning, both areas of development should be subject of investment during early follow-up. Moreover, as was suggested repeatedly before, early intervention should include mothers and other caregivers. Konstanteras and Stewart (2006) concluded, based on the individual differences they found with regard to temperament, that including a temperament measure into ASD assessment batteries may be helpful in alerting us to the children's status regarding reactivity to stimulation and self-regulation. Our results also support this conclusion.

During the announcement of our prospective study at the corrected age of 4 months, we experienced that parents' concerns were mainly focused on the medical and neurological development of their child. When parents were told about the possible developmental problems in the domains of social and communicative functioning, we often had the impression that these domains of development were not their priority at that moment, which is of course understandable. However, given the importance of early detection of social-communicative problems, parents of preterm born children should also be educated about the possible problems in these domains of functioning.

One final issue with regard to the implementation of our findings in clinical practice, concerns the important difference between group-level results and individual variability with regard to ASD symptomatology. The translation of our group-level results to the individual functioning of each preterm child, with his or her particular strengths and weaknesses, forms an additional challenge for the clinical examiner.

STRENGTHS AND LIMITATIONS

Strengths

The most important strength of the studies that were discussed in this dissertation, was the inclusion of well-validated ASD specific diagnostic instruments on top of parent-reported screening instruments, to investigate the prevalence of ASD symptomatology. Investigating all the children with the diagnostic instruments and not only those children with a positive screen, also provided important additional information. Furthermore, the use of multi-informant data, as applied in the EPIBEL-study is generally advocated for mental health assessment (Johnson & Marlow, 2014). Although the self-report of behavioural functioning in the EPIBEL-sample was rather limited, the clearly differing outcomes when compared to parent-report stress the importance of self-report in late childhood and adolescence (Johnson & Wolke, 2013).

Another important strength was the assessment of two different age groups, which provided an insight in the possible emergence patterns of ASD symptomatology in the preterm population. The prospective design which was applied in both studies also has

numerous advantages. Given the longitudinal design of both studies we discussed, our results provide some information about the stability of the delays in development preterm born children show (van de Weijer-Bergsma, Wijnroks, & Jongmans, 2008).

Since we decided not to exclude those children with severe impairments, the heterogeneity of the population of very preterm born children was also reflected in our study samples. Although we assessed the preterm sample as one group, we were well aware of the heterogeneity of functioning of the children which is reflected in the analyses investigating the correlations between developmental characteristics and outcomes.

Moreover, using gestational age as the inclusion criterion is preferred to using birth weight. Results of studies with birth weight as inclusion-criterion may be confounded by the inclusion of babies born small-for-gestational age, who are known to develop in a particular way (Johnson & Wolke, 2013; O'Shea et al., 2009).

Limitations

In each research chapter, specific limitations were discussed. In this section, some general limitations of the research project are discussed.

Although we succeeded in reaching 58% of the children of a complete birth cohort (67% of the children who qualified for participation) in the cross-sectional study and although 91% of the parents of the children who were eligible for participation in the prospective study agreed to participate, sample sizes in both the EPIBEL-study and the prospective study were modest.

In addition to the initial small sample size of the prospective study, due to several reasons (e.g., illness, fatigue), not all participating children were assessed at the different contacts and not all the parents completed the extensive set of questionnaires. Furthermore, six preterm born children only started participation at the second research contact and the same applies for two full term children. These limitations are inherent to the prospective study design and are quasi inevitable. Although extensive efforts were made to collect data as complete as possible, quite a number of missing values were encountered. Both the initial small sample sizes and the missing values limit the robustness and the generalizability of the findings.

Data for the different research contacts could be missing completely at random, but the drop-out of missing values could also be related to characteristics of the participants. The latter can lead to misinterpretation of the results. In chapter four, we tested if the temperament data were missing completely at random and this was confirmed.

Moreover, although we did an extra effort to include all families eligible for participation, we unfortunately had to exclude the non-Dutch speaking families from participation. The measures that we used in both studies required that the parents of the children mastered the Dutch language. This limitation, which re-occurs in many studies, needs to be addressed, to be able to make predictions about the functioning of children of non-Dutch speaking mothers, who are at increased risk for preterm birth.

Another related aspect is the high number of twins in both studies. The inclusion of both members of preterm twins is a statistical issue, since data of twins cannot be seen an independent measures. Controlling for the twin/singleton status of the participating children, in order to control for the not independent observations, would have been preferable in case we had larger samples. However, we decided to include all the children in the study, in order to provide a complete picture of the cohort of extremely and very preterm born children. In addition, excluding all the twins or one of both twins randomly would have diminished the sample sizes even more. Moreover, multiple pregnancy is a clear risk factor for prematurity, so the high rate of twins in the sample is inherent to the preterm born statuses of the assessed samples.

Finally, the significant differences between the preterm and the control sample in the prospective study with regard to twin status and birth order also need to be taken into account.

The fact that we recruited children in only two hospitals (although in both cases the largest hospitals in the province, responsible for the caretaking of very preterm born children) in the prospective follow-up study resulted in a study that was more practical to manage, but groups of babies born in individual hospitals may not be representative of the wider population (Johnson & Marlow, 2014).

In addition, inclusion of a control sample in the EPIBEL-study would have increased the ecological validity of the results, although we worked with well-validated normed

instruments. The absence of a full term control group allowed comparison only with general population estimates of ASD prevalence.

Results of the comparison analyses in Chapters 4 and 5, comparing the development of preterm and full term children, indicating that preterm born children, as a group, develop less optimal than full term children, also do not provide sufficient information about the within-group variance in the preterm sample (van de Weijer-Bergsma et al., 2008).

Some limitations with regard to measures that were used also need to be acknowledged. Apgar score was in this study used as an indication of immediate postnatal health, although this scale was found to have limited use in preterm born children. Other measures, that take into account several more important markers of preterm postnatal health could be of better use in future research. Unfortunately, we lacked important clinical information to make use of these more comprehensive measures of preterm neonatal and perinatal health.

Inherent to the prospective study design of chapters 3, 4 and 5, is the small sample size of the diagnostic ASD group, in which we expected only a small percentage of the children to show symptoms of ASD. Unfortunately, this impeded comparison analyses in which the functioning of children with and without ASD could have been compared. The analyses we could perform were restricted to correlational and regression analyses.

A final issue concerns the blindness of the researcher for the diagnostic status of the children in the EPIBEL-study, which was not guaranteed. The knowledge of the researcher about the ASD clinical diagnostic status of the child may have influenced the results of the observer-ratings. We do need to acknowledge the possible influence of this clinician knowledge. However, to control for this knowledge, several administrations of the ADOS and ADI-R were double scored by other researchers who are trained to research reliability for ADOS and ADI-R and who were blind for the diagnostic status of the children.

DIRECTIONS FOR FUTURE RESEARCH

Prevalence studies

Although we aimed to provide a more comprehensive picture of the prevalence of ASD symptoms with our studies, also our studies had some flaws that need to be addressed in future research. Studies with larger sample sizes, assessing social-communicative functioning and restrictive and repetitive behaviours, both with parent-reported screening questionnaires and observer-based diagnostic instruments, are needed.

A second important direction concerns the inclusion of children born after gestational ages varying between 23/24 and 42 weeks. Previous studies, as did our studies, mainly focused on the functioning of extremely and very preterm born children. An increased risk of ASD with shorter gestation was demonstrated by Leavey and colleagues (2013) and the authors warned against the use of pre-specified gestational age cut-offs. Moreover, a recent paper which assessed the prevalence of positive ASD screens in infants at the age of 2 who were born late and moderately preterm, indicated that also infants born between 32 and 36 weeks of gestation are at increased risk for a positive ASD screen (Guy et al., 2015).

Given the limited predictive value of existing parental screening questionnaires, a conclusion which was drawn in several studies, including ours, usability of other standardised observational screening measures, such as the Systematic Observation of Red Flags and the Screening Tool for Autism in Two-year-olds, need to be assessed in future research.

Also prospective research, starting early in life and continuing into later childhood and even adolescence, would provide us with very useful information about the ASD symptom trajectories in preterm born children.

Developmental characteristics

In this doctoral dissertation, we made a first attempt in providing information about possible early indicators of ASD symptomatology in preterm born children during the first year of life. Our findings indicated a clear distinction between predictors of the different

domains of ASD symptomatology, which suggests that future studies should provide more information considering the subdomains of ASD symptomatology in preterm born children.

Future studies should also investigate several other developmental domains, in the light of later ASD symptoms.

A first domain of functioning, which needs to be considered, is attention. A review on attention development in preterm born children during the first 4 years of life indicated that attention development in preterm born children is less optimal and differences with full term attention development even increase when infants grow into toddlers (van de Weijer-Bergsma et al., 2008).

Other more general domains of functioning, which can be assessed or both sleep problems and feeding problems (e.g., Pridham, Steward, Thoyre, Brown, & Brown, 2007). Together with the assessment of possible feeding problems, motor anticipation failure during spoon feeding, can also be assessed (Brisson, Warreyn, Serres, Foussier, & Adrien-Louis, 2012).

Although in Chapter 3, some results considering early joint attention development were presented, which indicated no relationship between joint attention and later ASD symptomatology, further research into this domain of functioning seems recommended.

Given the known association between language difficulties and ASD and the evidence which was demonstrated in our study considering the association between lower word comprehension scores and ASD scores, further research into language difficulties as predictors of ASD symptomatology is appropriate.

Given the evidence for the relationship between negative affectivity and ASD symptomatology which was demonstrated in Chapter 5, and the known link between self-regulating behaviour and later positive emotional development (Nigg, 2006), self-regulating behaviours in early life may also be predictive for later ASD. Moreover, as was suggested above, studies into the link between emotion expression and regulation, and ASD symptomatology, certainly seem recommended.

To enhance early identification of ASD in preterm born children during standard follow-up, research into easily assessable early signs of ASD, is necessary. One clear

example concerns the withdrawn behaviour scale of the Achenbach questionnaires, which was demonstrated to be related to ASD symptomatology (Johnson et al., 2010). The repeatedly demonstrated relationship between ASD symptoms and developmental index also indicates that the predictive value of general development needs to be further assessed. In a Japanese sample of very low birth weight children a significantly lower developmental quotient in children later diagnosed with ASD, was presented (Kihara & Nakamura, 2015).

Finally, studies focusing on possible resilience factors, such as the specific characteristics of mother-child interaction, are also wanted.

Phenotypic differences

As was concluded above, we cannot presume that the ASD seen in preterm born children is the "same" as the ASD seen in full term born children. Therefore, future studies could focus on comparing both early development and phenotypical expression of ASD in preterm born children, children born at term and other at-risk populations, such as younger siblings of children with ASD (e.g., Ozonoff et al., 2011).

Intervention studies

A recent longitudinal follow-up of secondary outcomes of a randomised controlled trial that evaluated the Family Nurture Intervention (FNI), a nurture-based NICU intervention, clearly demonstrated that the FNI had a positive impact on social-relatedness. Children in the FNI group had significantly lower scores on the M-CHAT when compared to children in the standard care group (Welch et al., 2015). An intervention implemented during the neonatal period, with an emphasis on optimal transactional exchange, influenced certain aspects of social-communicative development in preterm infants at the age of 1 (Olafsen et al., 2006).

These promising results indicate that future research also has to focus on good intervention research. Next to general NICU interventions, more specialised interventions, focused on social and communicative development in the first year of life, should be undertaken.

Given the findings concerning the associations between characteristics of MCI and ASD symptomatology, a focus on this aspect of early development, or certainly inclusion of the child's context, seems recommended.

CONCLUSION

Our results, together with the existing literature, clearly demonstrated the increased prevalence of ASD symptomatology in preterm populations. However, we cannot presume that the ASD seen in the preterm born children is the "same" as the ASD seen in full term born children. We certainly hope that future research will investigate the underlying mechanisms which lead to this increased prevalence rate and that developmental pathways will be examined thoroughly, to provide the necessary information about early signs of later ASD symptomatology in the preterm population.

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PREMATURITEIT

Prematuriteit of vroeggeboorte wordt gedefinieerd als een geboorte voor de 37[ste] zwangerschapsweek, meer dan drie weken voor de verwachte geboortedatum. Vroeggeboortes worden gecategoriseerd aan de hand van het aantal zwangerschapsweken of het geboortegewicht. Men spreekt van een extreme vroeggeboorte bij een geboorte voor de 28[ste] zwangerschapsweek, van een zeer vroege geboorte wanneer het kind ter wereld komt tussen de 28ste en de 32ste zwangerschapsweek en van matige tot late vroeggeboorte na een zwangerschapsduur van 32 tot 36 weken 6 dagen (March of Dimes, PMNCH, Save the Children, & World Health Organization, 2012). Op basis van geboortegewicht worden de volgende categorieën onderscheiden: < 1000 g extreem laag, 1000 - 1500 g zeer laag en 1500 - 2500 g laag geboortegewicht (World Health Organization, 2011).

Vroeggeboorte vormt wereldwijd een belangrijk gezondheidsprobleem (Beck et al., 2010). Zo werden in het jaar 2010 wereldwijd naar schatting 14,9 miljoen kinderen te vroeg geboren (Blencowe et al., 2012). In Vlaanderen is er in 7,4% van de geboortes sprake van prematuriteit, waarvan er in 0,4% van de gevallen sprake is van een extreme vroeggeboorte en in 0,7% van een zeer vroege geboorte (Devlieger, Martens, Martens, Van Mol, & Cammu, 2015).

Hoewel er de voorbije decennia een duidelijke stijging werd vastgesteld in de overlevingskansen van prematuur geboren kinderen (Lemola, 2015), is het helaas ook zo dat prematuur geboren kinderen, in vergelijking met op tijd geboren kinderen, een hoger risico hebben op moeilijkheden in verschillende domeinen van hun functioneren. Naast acute en chronische medische, sensorische, (neuro-)motorische en cognitieve moeilijkheden (Committee on Understanding Premature Birth and Assuring Healthy Outcomes, 2007), is er ook evidentie voor meer subtiele ontwikkelingsmoeilijkheden, zoals taal-, aandachts-, gedrags- en sociaal-emotionele problemen en voor een groter

risico op psychiatrische symptomen en diagnoses (Johnson & Marlow, 2014; Treyvaud et al., 2013). Tijdens de voorbije jaren was autismespectrumstoornis (ASS) één van de ontwikkelingsstoornissen die steeds meer onder de loep werd genomen als een mogelijk gevolg van vroeggeboorte.

AUTISMESPECTRUMSTOORNIS

Autismespectrumstoornis (ASS) in een neurobiologische ontwikkelingsstoornis die wordt gekenmerkt door moeilijkheden op het vlak van sociale communicatie en sociale interactie en door repetitieve gedragingen, interesses en activiteiten (American Psychiatric Association, 2013). De prevalentie van ASS wordt doorgaans geschat op 60-70 per 10.000 kinderen, wat betekent dat ASS één van de meest voorkomende ontwikkelingsstoornissen is. Jongens hebben een hoger risico op het ontwikkelen van de stoornis (Elsabbagh et al., 2013) en slechts in een klein aantal van de gevallen kan ASS worden gelinkt aan een medische conditie of een syndroom (Chakrabarti & Fombonne, 2005). Een recente review vatte de mogelijke oorzaken van ASS samen in vier gedachtelijnen: ASS als een stoornis van het sociale brein, als het resultaat van algemene neuro-cognitieve factoren, als een gevolg van een combinatie van beide eerste mogelijkheden, of als het resultaat van algemene neurologische moeilijkheden (Gliga, Jones, Bedford, Charman, & Johnson, 2014).

PREMATURITEIT EN ASS

Al sinds halfweg de voorbije eeuw werd een laag geboortegewicht gezien als een risicofactor voor ASS (Pasamanick, Rogers, & Lilienfeld, 1956). Deze studie werd gevolgd door een groot aantal epidemiologische, populatie-gebaseerde, cross-sectionele en case-control studies die aantoonden dat prematuriteit, een laag geboortegewicht en een korte zwangerschapsduur, een rol spelen in de etiologie van ASS (Nelson, 1991). Recente studies

toonden zelfs aan dat het risico op ASS stijgt met kortere zwangerschapsduur (Kuzniewicz et al., 2014; Leavey, Zwaigenbaum, Heavner, & Burstyn, 2013; Movsas & Paneth, 2012).

Naast de onderzoekslijn die nagaat of prematuriteit een risicofactor is voor ASS, gingen meer recente studies na wat de prevalentie van ASS symptomen is in de premature populatie. Verschillende screeningsstudies werden uitgevoerd rond de leeftijd van 2 jaar; ze toonden aan dat symptomen van ASS disproportioneel meer aanwezig zijn in de premature populatie dan in de algemene populatie (Dudova et al., 2014; Gray, Edwards, O'Callaghan, & Gibbons, 2015; Kuban et al., 2009; Limperopoulos et al., 2008; Moore, Johnson, Hennessy, & Marlow, 2012; Stephens et al., 2012; Wong, Huertas-Ceballos, Cowan, & Modi, 2014). Ook screeningsstudies in de kindertijd en de adolescentie bevestigden dit (Hack et al., 2009; Indredavik, Vik, Skranes, & Brubakk, 2008; Williamson & Jakobson, 2014).

Aangezien verschillende resultaten aantoonden dat de neurologische, cognitieve, motorische en sensorische moeilijkheden die het functioneren van prematuur geboren kinderen kenmerken, mogelijks kunnen leiden tot vals-positieve screeningsresultaten voor ASS (Johnson & Marlow, 2009; Kuban et al., 2009; Moore et al., 2012; Stephens et al., 2012), leken studies die een diagnostische evaluatie hanteerden voor het onderzoeken van de werkelijke diagnostische prevalenties, aangewezen. Twee studies voegden een diagnostische evaluatie toe op de leeftijd van 2 jaar (Dudova et al., 2014; Gray et al., 2015) en twee studies in de late kindertijd en de vroege adolescentie (Johnson et al., 2010; Pinto-Martin et al., 2011). Ook deze studies bevestigden de verhoogde prevalentie van symptomen van ASS in de premature populatie.

DOELSTELLING DOCTORAATSONDERZOEK

Hoewel bovenvermelde studies duidelijk aantoonden dat er in de premature populatie duidelijk sprake is van een verhoogde prevalentie van symptomen van ASS, waren de resultaten erg onduidelijk en inconsistent, afhankelijk van de bijkomende moeilijkheden van de kinderen, de instrumenten die werden gebruikt en de leeftijd waarop kinderen werden onderzocht.

Daarnaast zijn de ontwikkelingspaden naar deze symptomen bij prematuur geboren kinderen nog niet goed in kaart gebracht. Naar analogie met de prospectieve studies die de ontwikkeling van jongere broers en zussen (*siblings*) van kinderen met ASS nagaan, leken longitudinale studies met meerdere meetmomenten die verschillende ontwikkelingsdomeinen onder de loep nemen, aangewezen om vroege signalen van ASS in de premature populatie in kaart te brengen en de ontwikkelingspaden te beschrijven.

De belangrijkste doelstellingen van dit doctoraatsonderzoek waren daarom: 1) de prevalentie van symptomen van ASS in extreem en zeer prematuur geboren kinderen in Vlaanderen in kaart brengen (hoofdstukken 2 en 3) en 2) het prospectief onderzoeken van kenmerken van de ontwikkeling van zeer prematuur geboren kinderen in het licht van latere symptomen van ASS (hoofdstukken 4 en 5).

In hoofdstuk 2 was het onze doelstelling een grondige weergave te geven van de prevalentie van ASS symptomen in een geografische cohorte van extreem prematuur geboren adolescenten, op basis van twee screeningsinstrumenten en een diagnostische evaluatie met een gevalideerde spelobservatie en een ouderinterview.

Ook in hoofdstuk 3 werden twee screeningslijsten door de ouders ingevuld en het sociaal-communicatief functioneren van de kinderen werd ook geobserveerd met de gestandaardiseerde spelobservatie. De kinderen in dit hoofdstuk waren zeer prematuur geboren en 18 maanden oud (gecorrigeerde leeftijd) op het moment van de assessment van de ASS symptomen. Mogelijke associaties met de vroege motorische, cognitieve en taalontwikkeling, en met adaptieve vaardigheden, joint attention en gedragsproblemen op 5, 10 en 18 maanden gecorrigeerde leeftijd werden ook onderzocht.

Nadat de prevalentie van ASS symptomen op 18 maanden in kaart werd gebracht, werden in hoofdstuk 4 kenmerken van de vroege moeder-kind interactie onderzocht. Kenmerken van interacties tussen moeders en hun prematuur geboren kinderen werden vergeleken met kenmerken van interacties tussen moeders met hun typisch ontwikkelende, op tijd geboren kinderen en dit op de leeftijden van 5 en 10 maanden. In de prematuur geboren groep werd verder onderzocht of er een verband kon worden gevonden tussen deze karakteristieken en ASS-symptomen op 18 maanden.

In hoofdstuk 5, ten slotte, werden temperamentskenmerken, gemeten op de leeftijden van 5 en 10 maanden, vergeleken tussen prematuur geboren kinderen en op tijd geboren kinderen. Daarna werd dit aspect van de vroege ontwikkeling, meer bepaald temperament gemeten op de leeftijden van 5, 10 en ook 18 maanden binnen de premature groep gelinkt aan latere symptomen van ASS.

OVERZICHT VAN DE BELANGRIJKSTE BEVINDINGEN

De belangrijkste bevindingen van dit doctoraatsonderzoek zijn drievoudig. Ten eerste werd de verhoogde prevalentie van ASS symptomen bevestigd in zowel een extreem premature als een zeer premature groep kinderen, in de vroege adolescentie en in de vroege kindertijd. Verder werd gevonden dat ASS symptomen meer werden gerapporteerd en geobserveerd in de adolescentie dan in de vroege kindertijd.

Ten tweede bevestigden onze resultaten dat de voorhanden zijnde screeningsinstrumenten voor ASS met de nodige voorzichtigheid moeten worden gebruikt in de premature populatie. Bovendien hebben we onvoldoende evidentie voor de bruikbaarheid van gevalideerde diagnostische instrumenten voor ASS in deze populatie.

Ten slotte vonden we dat specifieke kenmerken van de vroege ontwikkeling van prematuur geboren kinderen en hun context voorspellend zijn voor de latere aanwezigheid van symptomen van ASS.

Prevalentie van symptomen van ASS in twee Vlaamse cohorten

Zoals hierboven aangehaald, bevestigen de resultaten van hoofdstukken 2 en 3 de verhoogde prevalentie van symptomen van ASS in de premature populatie. In de groep extreem prematuur geboren adolescenten werd gevonden dat 63% van de kinderen positief screenden op de Social Responsiveness Scale (SRS; Constantino & Gruber, 2005; Roeyers, Thys, Druart, De Schryver, & Schittekatte, 2011) en 33% op de Social Communication Questionnaire (SCQ; Rutter, Bailey, & Lord, 2003). De prevalentie van klinische en onderzoeksdiagnoses van ASS was 40%. Wanneer enkel die klinische diagnoses in rekening worden gebracht die werden gesteld voor ons onderzoek en die

bovendien werden bevestigd met een klinische score op de gestandaardiseerde spelobservatie (Autism Diagnostic Observation Schedule; ADOS; Lord, Rutter, Dilavore, & Risi, 2008) of op het klinisch ouderinterview (Autism Diagnostic Interview-Revised; ADI-R; Rutter, Le Couteur, & Lord, 2003), werd nog steeds een prevalentie van 26% gevonden.

De resultaten van het onderzoek op de vroege leeftijd van 18 maanden waren duidelijk verschillend. Wanneer enkel de resultaten van de twee gebruikte screeningsinstrumenten in rekening worden gebracht, kunnen screeningspercentages van 9% en 5% worden gevonden, voor de Quantitative Checklist for Autism in Toddlers (Q-CHAT; Allison et al., 2008) en de Early Screening of Autistic Traits Questionnaire (ESAT; Dietz, Swinkels, van Daalen, van Engeland, & Buitelaar, 2006; Swinkels et al., 2006), respectievelijk. Daarnaast werd het sociaal-communicatief functioneren van de kinderen ook geobserveerd aan de hand van de peutermodule van de hierboven vernoemde diagnostische spelobservatie (ADOS-T; Luyster et al., 2009). Een bezorgdheidscore voor ASS werd toegekend aan 11% van de kinderen, waarbij 2% van de kinderen scoorden in de categorie 'matige-tot-ernstige-bezorgdheid'.

Wanneer we de prevalenties van onze studie in de vroege adolescentie vergelijken met eerdere studies die prematuur geboren kinderen onderzochten in deze leeftijdscategorie, is het direct duidelijk dat zowel onze screening percentages als de diagnostische prevalentiewaarden eerder gerapporteerde cijfers substantieel overschrijden.

Wat betreft de data van de prospectieve studie zien we duidelijk dat onze screeningsresultaten lager zijn dan de meeste eerder gerapporteerde bevindingen. Ouders rapporteerden klinisch significante ASS symptomen bij minder kinderen. Er zijn echter ook twee studies die een lager screeningspercentage rapporteerden. Deze studies betroffen enerzijds een studie die ook kinderen onderzocht vanaf de leeftijd van 18 maanden (tot 22 maanden; Stephens et al., 2012) en anderzijds een studie die gebruik maakte van een screeningsvragenlijst en het bijhorende follow-up interview, waardoor de antwoorden van ouders steeds werden gecontroleerd (Gray et al., 2015).

Slechts twee eerdere studies onderzochten diagnostische prevalenties van ASS in jonge prematuur geboren kinderen (Dudova et al., 2014; Gray et al., 2015). De prevalentie

van geobserveerde ASS symptomen die in onze prospectieve studie op de jonge leeftijd van 18 maanden werd gevonden, is lager dan de berekende prevalentie van 9.7% in een studie die zich baseerde op de *best estimate clinical diagnosis* en duidelijk hoger dan de 1% die werd gevonden in de hierboven genoemde studie met zeer vroeg geboren kinderen die gescreend werden op basis van een screeningsvragenlijst en het bijhorende follow-up interview (Gray et al., 2015). Het meest belangrijk verschil tussen deze eerder gerapporteerde studies en onze studie betreft de leeftijd waarop de kinderen werden onderzocht: onze kinderen waren substantieel jonger. Bovendien baseerden beide studies zich op de *best estimate clinical diagnosis*, terwijl wij ons enkel baseerden op de resultaten van de ADOS-T.

Doordat onze studies de prevalentie van ASS symptomen onderzochten op twee verschillende leeftijden, konden wij aantonen dat er sprake lijkt te zijn van een stijging van symptomen van ASS met de leeftijd. Natuurlijk zijn er verklaringen voor deze stijging, gerelateerd aan de kenmerken van de onderzochte groepen, zoals de gestationele leeftijden en de geboortejaren, maar ook andere verklaringen zijn mogelijk. Zo zou er sprake kunnen zijn van een te vroege assessment van symptomen op de leeftijd van 18 maanden, van geen of subtiele symptomen van ASS op de leeftijd van 18 maanden, van regressie na de leeftijd van 18 maanden of van een cascade model waarbij een combinatie van vroege factoren in de ontwikkeling leiden tot de symptomen van ASS op latere leeftijd.

Bruikbaarheid van bestaande instrumenten in de screening naar en de diagnostiek van ASS

Een tweede belangrijke bevinding van zowel hoofdstuk 2 als 3 betreft de beperkte voorspellende waarde van de resultaten bekomen op basis van de screeningsinstrumenten. In het onderzoek met de adolescenten waren er 23% van de kinderen met een vals-positieve score op één of beide screeningsinstrumenten. Deze groep kinderen had dus geen klinische of onderzoeksdiagnose van ASS maar hun ouders oordeelden wel dat hun kinderen klinisch significante moeilijkheden vertoonden op sociaal-communicatief vlak. In de prospectieve studie hadden alle kinderen met een positieve screen geen bezorgdheidsscore op de ADOS-T, en omgekeerd.

Auteurs van eerdere studies naar het verband tussen prematuriteit en ASS gaven als mogelijke verklaring voor deze hoge mate van vals-positieve classificaties aan dat andere moeilijkheden die het functioneren van de prematuur geboren kinderen kenmerken, hiervoor verantwoordelijk zouden zijn. Aangezien veel van deze studies echter geen diagnostische instrumenten gebruikten, konden hierover geen definitieve uitspraken worden gedaan.

De resultaten van onze studies tonen aan dat er inderdaad sprake is van een hoge mate van vals-positieve classificaties, maar de resultaten met betrekking tot de mogelijke invloed van co-morbide moeilijkheden waren minder eenduidig. Een belangrijke opmerking met betrekking tot het gebruik van de term 'vals-positieve' classificaties is dat deze misleidend kan zijn. Verschillende auteurs stelden namelijk dat ASS misschien moet gezien worden als het eindpunt van een spectrum van symptomen die algemeen meer voorkomen bij prematuur geboren kinderen (Johnson et al., 2011).

Wat in veel van de eerdere studies met betrekking tot het verband tussen prematuriteit en ASS niet werd vermeld, was de mate van vals-negatieve classificaties op basis van screeningsinstrumenten. De meeste studies konden hierover namelijk niet rapporteren omdat ze enkel die kinderen verder onderzochten die positief screenen. In de EPIBEL-studie screende 9% van de kinderen met een diagnose van ASS negatief op de SRS en 22% negatief op de SCQ. Daarnaast was er in de prospectieve studies geen enkel kind met een bezorgdheidsscore op de ADOS-T dat ook een positieve screen had voor ASS op basis van ouderrapportage.

De bovengenoemde resultaten tonen duidelijk aan de screeningsinstrumenten die vandaag worden gebruikt in de diagnostische procedure naar ASS met de nodige voorzichtigheid moeten worden gehanteerd in de premature populatie. Verder moet ook worden geopperd dat er op dit ogenblik onvoldoende evidentie is voor het betrouwbaar gebruiken van de gerapporteerde diagnostische instrumenten.

Ontwikkelingspaden naar ASS

Onafhankelijk van de hierboven vermelde bevindingen met betrekking tot de bruikbaarheid van screenings- en diagnostische instrumenten voor ASS in de premature

populatie, tonen de resultaten duidelijk aan dat er sprake is van een verhoogde prevalentie van ASS symptomatologie. Daarom was het belangrijk dat er gestart werd met het onderzoeken van de ontwikkelingspaden waarlangs prematuur geboren kinderen deze symptomen ontwikkelen.

Naast de duidelijke relaties met een lagere cognitieve en taalontwikkeling en het meer voorkomen van gedragsmoeilijkheden, vonden wij ook evidentie voor de voorspellende waarde van kenmerken van de vroege moeder-kind interactie en van temperament.

Zo vonden we dat ouder-gerapporteerde symptomen van ASS op de gecorrigeerde leeftijd van 18 maanden, zoals gemeten met de Q-CHAT, significant werden voorspeld door intrusiviteit van de moeder op de gecorrigeerde leeftijd van 10 maanden. Meer intrusiviteit, dat geoperationaliseerd werd als het veelvuldig onderbreken van de bezigheden van het kind, het proberen te verplaatsen van de aandachtsfocus van het kind en het negeren van de signalen van het kind, kon worden gelinkt aan minder symptomen van ASS. Studies met op tijd geboren kinderen met (een verhoogd risico voor) ASS toonden aan dat er sprake was van meer controlestrategieën bij de moeders van kinderen met ASS, dan bij moeders van typisch ontwikkelende kinderen. Wij verwachtten dus dat moeders van prematuur geboren kinderen met meer ASS symptomen ook als meer intrusief zouden worden beoordeeld, maar we vonden het tegenovergestelde resultaat.

Wat betreft de geobserveerde symptomen van ASS, tonen onze resultaten aan dat voornamelijk de betrokkenheid van het kind in de moeder-kind interactie, voorspellend is voor latere symptomen van ASS. Zowel de totale score als de score voor sociaal affect, werden significant voorspeld door betrokkenheid van het kind op 5 maanden en daarnaast werden de sociaal affect-scores ook voorspeld door de betrokkenheid van het kind op de leeftijd van 10 maanden. Deze resultaten zijn vergelijkbaar met resultaten van studies die aantoonden dat kinderen met (een verhoogd risico op) ASS minder meegaand zijn en meer vermijdend gedrag stellen (Lemanek et al., 1993), dat ze minder interactief gedrag tonen (Saint-Georges et al., 2011) en dat ze minder aandacht hebben voor de ouder (Wan et al., 2013) dan typisch ontwikkelende kinderen en kinderen met andere moeilijkheden. Deze overeenkomsten tussen onze resultaten en resultaten van studies met kinderen met ASS en ook de observatie dat betrokkenheid van het kind verschilde tussen prematuur geboren kinderen en op tijd geboren kinderen, tonen aan dat dit

construct een belangrijke variabele kan zijn in de assessment van prematuur geboren kinderen, in het licht van latere symptomen van ASS.

Een laatste belangrijke bevinding was dat er geen verband werd gevonden tussen kenmerken van de vroege moeder-kind interactie en de scores voor beperkt en repetitief gedrag.

Ook aspecten van temperament gemeten aan de hand van de Infant Behaviour Questionnaire - Revised (Gartstein & Rothbart, 2003) of de Early Child Behaviour Questionnaire (Putnam, Gartstein, & Rothbart, 2006) gemeten op de gecorrigeerde leeftijden van 5, 10 en 18 maanden waren significant voorspellend voor ASS symptomen op de gecorrigeerde leeftijd van 18 maanden. Er werden geen verschillen gevonden tussen temperament van prematuur geboren kinderen en op tijd geboren kinderen op de leeftijden van 5 en 10 maanden.

Aaibaarheid, of de mate waarin een kind geniet van het te worden vastgehouden door zijn of haar verzorger, gemeten op de leeftijd van 10 maanden, was significant voorspellend voor ouder-gerapporteerde symptomen van ASS, zoals gemeten met de Q-CHAT. Clifford, Hudry, Elsabbagh, Charman, en Johnson (2013) toonden aan dat *siblings* van kinderen met ASS die later ook gediagnosticeerd werden met ASS minder aaibaarheid toonden op de leeftijd van 14 maanden, wanneer ze werden vergeleken met typisch ontwikkelende *siblings* en controlekinderen. In onze groep prematuur geboren kinderen was de relatie tussen aaibaarheid en latere symptomen van ASS al duidelijk tijdens het eerste levensjaar. Deze temperamentsfactor zou een belangrijk vroeg signaal kunnen zijn in de assessment naar ASS symptomen bij prematuur geboren kinderen, aangezien de aaibaarheid een domein van functioneren vormt dat door ouders goed kan worden beoordeeld.

We vonden verder ook dat minder geuit negatief affect op de leeftijd van 5 maanden, en meer bepaald minder angst, voorspellend was voor meer geobserveerde symptomen. Dit resultaat was onverwacht, aangezien studies met hoog-risico *siblings* aantoonden dat *siblings* die later gediagnosticeerd werden met ASS, juist meer negatief affect vertoonden tijdens het eerste levensjaar (Zwaigenbaum et al., 2005). Een mogelijke verklaring voor de gevonden associatie zou kunnen zijn dat prematuur geboren kinderen die later meer

symptomen van ASS ontwikkeling, algemeen minder emoties uiten of een meer neutraal affect tonen.

Scores voor sociaal affect werden voorspeld door *high intensity pleasure*. Deze temperamentschaal meet de mate waarin kinderen genieten van activiteiten met een hoge stimulerende waarde, omwille van de complexiteit, de frequentie, de nieuwheid of de incongruentie van de stimuli (Gartstein & Rothbart, 2003). Hoe meer *high intensity pleasure*, hoe hoger de scores op het sociaal affect domein van de ADOS-T. Deze bevinding is contra-intuïtief, aangezien voor vele items die deze subschaal vormen, lagere scores kunnen worden verwacht bij kinderen met meer ASS symptomen.

De meest robuuste resultaten werden gevonden voor de scores voor beperkt en repetitief gedrag. Bijna 80% van de variantie in deze scores kon worden voorspeld door temperamentskenmerken. Meer perceptuele gevoeligheid, gemeten op de leeftijd van 18 maanden was gelinkt aan meer beperkt en repetitief gedrag. Deze temperamentschaal meet de mate waarin kinderen subtiele stimuli in de omgeving opmerken. Het belang van perceptuele gevoeligheid voor ASS werd al aangetoond in een studie met hoog-risico *siblings* (Clifford et al., 2013). In deze studie werd het temperamentsprofiel van *siblings* die later werden gediagnosticeerd met ASS al op de leeftijd van 7 maanden gekenmerkt door verhoogde perceptuele gevoeligheid.

Daarnaast was meer negatief affect op de leeftijd van 18 maanden ook gelinkt aan meer beperkt en repetitief gedrag in onze prematuur geboren groep. Deze resultaten zijn meer vergelijkbaar met eerder gerapporteerde resultaten van studies met hoog-risico *siblings* (Clifford et al., 2013; Garon et al., 2008). Daarentegen vonden we ook opnieuw dat minder negatief affect op 5 maand was gelinkt aan meer beperkt en repetitief gedrag.

Samengevat leren de resultaten van hoofdstukken 4 en 5 ons enkele belangrijke zaken over mogelijke vroege signalen van ASS in de premature populatie. Zoals aangetoond moet er ten eerste een duidelijk onderscheid worden gemaakt tussen ouder-gerapporteerde en door een clinicus geobserveerde symptomen van ASS. Aangezien voorgaande studies met op tijd geboren kinderen voornamelijk werkten met diagnostische status als uitkomstmaat, is het moeilijk om onze specifieke resultaten te vergelijken met eerdere resultaten. Daarnaast tonen de resultaten ook aan de

verschillende domeinen binnen een ASS diagnose, sociale interactie en communicatie versus repetitieve gedragingen, interesses of activiteiten, afzonderlijk moeten worden onderzocht. Ook is het zo dat onze resultaten gedeeltelijk vergelijkbaar zijn met de resultaten van studies met op tijd geboren kinderen met ASS of van studies met jongere broers en zussen van kinderen met ASS, maar daarnaast zijn er ook duidelijke onverwachte bevindingen. Deze resultaten kunnen ons iets vertellen over het fenotype van ASS in de premature populatie.

Een belangrijke opmerking met betrekking tot bovenstaande resultaten is dat, gegeven het exploratieve karakter van de studies, replicatie zeker noodzakelijk is. Daarnaast is verdere opvolging van de kinderen tot in de latere kindertijd ook nodig, om ook het verband met symptomen van ASS op een latere leeftijd na te gaan.

ASS in de premature populatie

Op basis van de resultaten van ons proefschrift kunnen we besluiten dat er inderdaad sprake lijkt te zijn van een verhoogde prevalentie van symptomen van ASS in de premature populatie, maar we kunnen niet besluiten dat het autisme dat we zien in de premature populatie hetzelfde is als het autisme in de populatie op tijd geboren kinderen met ASS. Onze resultaten, samen met resultaten van eerdere studies, tonen namelijk aan dat ASS bij prematuur geboren kinderen het eindpunt vormt van sociaal-communicatieve moeilijkheden die algemeen meer voorkomen bij prematuur geboren kinderen (Johnson et al., 2010; Wong et al., 2014), waarbij er duidelijk sprake is van een leeftijdsgerelateerde stijging in de prevalentie van symptomen. Daarnaast lijken symptomen van ASS deel uit te maken van wat men noemt het premature fenotype (Wong et al., 2014) en het patroon van symptomen lijkt meer aan te sluiten bij het symptomen patroon bij kinderen met ASS met een gekende oorzaak (Kuban et al., 2009). Bovendien lijkt ASS in de premature populatie een andere pathogenese te kennen waarbij moeilijkheden in de hersenontwikkeling een rol spelen (Johnson et al., 2010). Ook de resultaten met betrekking tot de ontwikkelingspaden tonen aan dat sommige bevindingen lijken aan te sluiten bij bevinden van onderzoek naar ASS bij op tijd geboren kinderen, maar we vonden evenzeer enkele onverwachte resultaten. Verder tonen onze resultaten ook aan dat emotie-regulatie een belangrijke rol lijkt te spelen in de vroege ontwikkeling van ASS

symptomen. Ten slotte werden ook een aantal opmerkelijk verschilpunten gevonden met betrekking tot de verschillende domeinen van symptomen van ASS.

KLINISCHE IMPLICATIES

Hoewel onze resultaten, samen met resultaten van andere studies duidelijk aantonen dat er sprake is van een verhoogde prevalentie van ASS symptomen in de premature populatie, roepen onze resultaten ook opnieuw enkele vragen op. Een eerste belangrijk vraagstuk betreft de noodzaak aan valide screeningsinstrumenten en diagnostische instrumenten. Een tweede belangrijke klinische implicatie betreft het belang van de vroege opvolging van het prematuur geboren kind en zijn context, in het licht van latere symptomen van ASS.

Hoewel de meeste clinici uiteraard op de hoogte zijn van de verhoogde prevalentie van sociaal-communicatieve moeilijkheden bij prematuur geboren kinderen moet het belang van een verhoogde alertheid voor symptomen van ASS, gedurende de volledige kindertijd, worden benadrukt.

Ten tweede moet de informatie over de bruikbaarheid van bestaande screeningsinstrumenten en diagnostische instrumenten ook worden vertaald naar de klinische praktijk. De meest belangrijke waarschuwing met betrekking tot het gebruik van de bestaande screeningsinstrumenten betreft de hoge mate van vals-positieve classificaties, die gedeeltelijk lijken te wijten zijn aan andere problematieken die het functioneren van prematuur geboren kinderen kenmerken. Aangezien de bestaande klinische follow-up van prematuur geboren kinderen zich voornamelijk focust op de neuromotore en cognitieve ontwikkeling, wordt er verwacht dat clinici zich steeds bewust zijn van de mogelijke invloed van eventuele andere problematieken op de resultaten van screening naar ASS.

Tijdens de aankondiging van onze prospectieve studie op de gecorrigeerde leeftijd van 4 maanden, ondervonden wij als onderzoeker heel sterk dat ouders voornamelijk gericht waren op de medische en neurologische ontwikkeling van hun kind. Wanneer we ouders aanspraken over eventuele moeilijkheden op het vlak van de sociaal-communicatieve

ontwikkeling, hadden wij heel vaak de indruk dat dit domein van functioneren voor de ouders weinig belangrijk leek.

Verder lijkt een goede kennis van vroege kenmerken van ASS en een verhoogde waakzaamheid voor deze signalen in de premature populatie steeds aangewezen, ook wanneer kinderen niet positief screenen op een oudervragenlijst. Onze resultaten toonden namelijk aan dat er naast een hoge mate van vals-positieve resultaten ook duidelijk sprake is van een grote hoeveelheid vals-negatieve classificaties.

Onze resultaten met betrekking tot de met leeftijd gerelateerde stijging van ASS symptomen, benadrukken nog eens het belang van vroege screening, en belangrijker nog, van vroege interventie. De aangetoonde scheefheid in de verdeling van ASS symptomen binnen de premature populatie benadrukt ook het belang van het stimuleren van de sociaal-communicatieve vaardigheden van de meerderheid van de prematuur geboren kinderen.

Voor er klinische implicaties kunnen worden geformuleerd met betrekking tot de voorspellende waarde van kenmerken van de vroege moeder-kind interactie en temperament, zijn er zoals gezegd meer robuuste resultaten nodig. Maar aangezien voor beide domeinen van functioneren ook al werd aangetoond dat deze voorspellend zijn voor andere uitkomsten, lijkt het aangewezen beide ontwikkelingsdomeinen steeds onder de loep te nemen tijdens de vroege follow-up. En zoals eerder reeds herhaaldelijk werd benadrukt, is het betrekken van zorgverleners bij de vroege interventie onmisbaar.

Een laatste opmerking met betrekking tot de implementatie van onze resultaten in de klinische praktijk, betreft het belang van het verschil tussen onze groepsresultaten en de individuele variabiliteit wat betreft ASS symptomatologie. De vertaling van onze groep gebaseerde resultaten naar het individueel functioneren van elk kind, met zijn of haar eigen moeilijkheden en sterktes, vormt een extra uitdaging voor de clinicus.

CONCLUSIE

Hoewel onze resultaten, samen met de bestaande literatuur, duidelijk aantonen dat er sprake is van een verhoogde prevalentie van symptomen van ASS in de premature populatie, doet ons doctoraatsonderzoek ook vragen rijzen over het verband tussen prematuriteit en ASS. Wij hopen dat toekomstig onderzoek de onderliggende mechanismen van dit verband zal kunnen uitpluizen en dat de vroege ontwikkelingspaden naar de symptomen van ASS verder in kaart zullen worden gebracht, om meer informatie te verstrekken over vroege indicatoren van ASS in de premature populatie. In welke mate ASS in de premature populatie kan worden vergeleken met ASS in de op tijd geboren populatie, zal ook verder moeten worden uitgezocht.

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DANKWOORD

'Een doctoraat is een beetje zoals een steile berg beklimmen.' Dat zijn de woorden die op het kaartje stonden dat ik kreeg van Leen wanneer ze het project waarop ik de voorbije vier jaar werkte, aan mij en Julie overliet. Een steile berg, dat was het zeker, en heel vaak heb ik met het idee gespeeld om gewoon terug af te dalen en het bergbeklimmen aan anderen over te laten. Maar nu is het boekje er dan toch, de top werd gehaald. Maar dit zou niet gelukt zijn zonder heel wat supporters en medebergbeklimmers.

Herbert, op 7 oktober 2011 ontving ik van u een e-mail met daarin volgende zin 'Zelf heb ik voor begin 2012 een aanbod voor onderzoek bij jonge kinderen. Mocht je interesse hebben, dan zou het goed zijn als je eens tot hier kon komen.' Nu zijn we ruim vier jaar later en blijkbaar ben ik toen bij u langs geweest en heb ik ja gezegd op het zeer interessante onderzoeksaanbod. Bedankt voor deze unieke kans. En ook bedankt voor wat u me de voorbije 4 jaar heeft bijgeleerd, op veel verschillende vlakken. Het is duidelijk dat u gedreven bent in wat u doet op wetenschappelijk gebied en ik hoop toch iets van die gedrevenheid mee te nemen in mijn verdere loopbaan.

Ook de leden van mijn begeleidingscommissie, prof. dr. Piet Vanhaesebrouck, dr. Isabel De Groote, dr. Leen De Schuymer en dr. Mieke Dereu wil ik zeker bedanken voor hun waardevolle bijdrage aan dit proefschrift. Prof. Vanhaesebrouck en Isabel, bedankt dat ik mocht verder werken op de grote inspanningen die jullie de voorbije jaren reeds leverden voor de EPIBEL-studie. Leen, zonder jou was er van het project geen sprake geweest. Bovendien waren de eerste maanden van mijn doctoraat vast veel moeilijker verlopen als jij er niet was geweest. Dankzij jou werd het project goed opgestart en kreeg ik steeds grondige feedback over hoe het project er zou gaan uitzien. Ook zorgde je voor de nodige aanmoedigingen! Mie, ik denk stiekem dat ik zonder jou nooit op de universiteit zou zijn beland. Bedankt voor alles wat je vanaf mijn 1ste master tot nu allemaal hebt bijgedragen.

Verder gaat mijn dank ook uit naar de voorzitters van onze vakgroep Experimenteel-Klinische en Gezondheidspsychologie, prof. dr. Geert Crombez en prof. dr. Rudi De Raedt, voor het mogelijk maken van dit proefschrift.

Sylvie, Annick, Wouter en Willem, bedankt voor jullie hulp bij de soms moeilijke vragen die ik jullie stelde, de vele administratie, de scanner, de centjes op donderdag, maar ook voor de fijne babbels.

Lieve collega's van het team OSS, jullie waren één voor één 'prahtuhu collegats'. Dank je wel voor de heerlijke lachsalvo's, de lekkernijen, het geroddel en de zaaguurtjes. Jullie zal ik missen!

Ellen, Nele en Julie, bedankt om zoveel meer dan collega's te zijn. Ik kan me niet voorstellen hoe ik de voorbije vier jaar zou zijn doorgesparteld zonder jullie dagelijkse aanwezigheid. Uren hebben we gespendeerd aan discussiëren, beredeneren, dramatiseren en relativeren, maar ook aan lachen, huilen, roddelen, plagen, eten tot we er bij neer vielen,… Ik kan alleen maar hopen dat deze momenten in de toekomst zullen worden verdergezet. Tot gauw, op onze volgende date.

Julie, voor jou toch ook nog even een speciaal woordje van dank. Uiteindelijk is dit doctoraat niet helemaal alleen van mij, maar evenzeer ook van jou. Want uiteindelijk hebben we dit alles samen gerealiseerd. Samen hebben we de dokters gecontacteerd, samen hebben we de ouders overtuigd om aan het onderzoek deel te nemen en samen hebben we de kinderen opgevolgd. Ook bij het uitschrijven van dit alles, hoefde ik maar over mijn schouder te kijken om iets met jou te bespreken. Ik kan me niemand anders voorstellen met wie dit beter zou zijn gelukt dan met jou. Ik ben dan ook super blij dat jij het onderzoek de komende jaren nog verder zal zetten.

Ook de kinderen die deelnamen aan beide onderzoeken alsook hun ouders, wil ik van harte bedanken. Zonder hun bereidheid tot deelname, was dit doctoraat nooit geweest wat het nu geworden is. De vele onderzoeksmomenten met de fantastische kinderen en hun trotse ouders, herinnerden me er steeds weer aan waarom ik nu weer precies vier jaar aan een onderzoek werkte.

Lieve vriendjes, bedankt dat jullie de voorbije vier jaar bleven vragen hoe het met me ging, hoewel ik steeds op dezelfde manier antwoordde en bedankt dat jullie tot het

einde samen mee aftelden. Dank je voor alle fijne dingen die we de voorbije vier jaar samen deden en in de toekomst nog zullen blijven doen. Ik beloof dat ik de komende jaren alleen maar enthousiast zal zijn.

Zus, zonder veel woorden heb ook jij veel voor mij betekend de voorbije jaren. Van rebelse, kleine zus tot trotse mama van die fantastische Juliette, ik heb altijd op jou kunnen rekenen.

Mama en papa, jullie zijn zo een sterke, harde werkers en mijn bewondering voor jullie is dan ook grenzeloos. Dank jullie wel om ondanks jullie lange werkdagen toch ook steeds aan mij te vragen hoe het met mijn doctoraat ging en vol trots en spanning af te wachten tot jullie kunnen verkondigen dat jullie dochter doctor in de psychologie is.

Lieve Anne, dank je wel om zo onvoorwaardelijk in mij te geloven en mijn grootste fan te zijn. Elke kleine overwinning was voor jou een reden tot feesten en vol trots verkondigde je overal dat ik een mondelinge presentatie mocht geven of dat ik een publicatie had. Dank je om mijn dagelijkse frustraties te aanhoren, mij op te peppen voor een nieuwe werkdag, maar ook voor het delen in de mooie momenten. En wat kijk ik er naar uit om samen met jou een nieuwe uitdaging aan te gaan. Kleine 'Mireille', we kunnen niet wachten tot je er bent.

<div align="right">

Liedewij,

januari 2016

</div>

Data storage fact sheet chapter 2 (17/12/15)

```
% Data Storage Fact Sheet (versie 17/12/2015)
% Data Storage Fact Sheet < Liedewij Verhaeghe, Chapter 2, High
prevalence of ASD in extremely preterm children >
% Author: Liedewij Verhaeghe
% Date: 17/12/2015
```

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2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:
    - Verhaeghe, L., Dereu, M., Warreyn, P., De Groote, I.,
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    children at very high risk for developing autism spectrum
    disorder. *Child Psychiatry & Human Development*, online first,
    pp.1 -11. doi: 10.1007/s10578-015-0606-3
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Data storage fact sheet chapter 3 (17/12/15)

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% Data Storage Fact Sheet < Liedewij Verhaeghe, Chapter 3, The
prevalence of autism spectrum disorder symptoms in very preterm infants
at 18 months of corrected age>
% Author: Liedewij Verhaeghe
% Date: 17/12/2015
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    0606-3
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% Data Storage Fact Sheet < Liedewij Verhaeghe, Chapter 4, Quality of interaction between preterm infants and their mother in the first year of life is associated with ASD symptomatology at 18 months >
% Author: Liedewij Verhaeghe
% Date: 17/12/2015

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    - Verhaeghe, L., Vermeirsch, J., Demurie, E., & Roeyers, H. (2015). Quality of interaction between preterm infants and their mother in the first year of life is associated with ASD symptomatology at 18 months. *Infant Behavior and Development*, online first, pp.1 -11. doi: 10.1007/s10578-015-0606-3
    - Chapter 4 Quality of interaction between preterm infants and their mother in the first year of life is associated with ASD symptomatology at 18 months.

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   * On which platform are these other files stored?
   - [ ] individual PC
   - [x] research group file server
   - [ ] other: responsible ZAP PC

   * Who has direct access to these other files (i.e., without
intervention of another person)?
   - [ ] main researcher
   - [ ] responsible ZAP
   - [ ] all members of the research group
   - [ ] all members of UGent
   - [x] other (specify): members of the research group who are
involved in infant studies

   4. Reproduction
   ==
   * Have the results been reproduced?: [ ] YES / [x] NO
   * If yes, by whom (add if multiple):
   – name
   – address
   – affiliation
   – e-mail

Data storage fact sheet chapter 5 (17/12/15)

```
% Data Storage Fact Sheet (versie 17/12/2015)
% Data Storage Fact Sheet < Liedewij Verhaeghe, Chapter 5, Early
temperament development and signs of autism spectrum disorder in very
preterm born infants >
% Author: Liedewij Verhaeghe
% Date: 17/12/2015
```

1. Contact

1a. Main researcher

– name: Liedewij Verhaeghe
– address: Henri Dunantlaan 2, 9000 Gent
– e-mail: <u>liedewij.verhaeghe@Ugent.be</u>

1b. Responsible ZAP (if different from the main researcher)
– name: Herbert Roeyers
– address: Henri Dunantlaan 2, 9000 Gent
– e-mail: herbert.roeyers@ugent.be

If a response is not received when using the above contact details,
please send an email to data-ppw@ugent.be or contact Data Management,
Faculty of Psychology and Educational Sciences, Henri Dunantlaan 2,
9000 Ghent, Belgium.

2. Information about the datasets to which this sheet applies

* Reference of the publication in which the datasets are reported:
    - Verhaeghe, L., Vermeirsch, J., Warreyn, P., & Roeyers, H.
    (2015). Early temperament development and signs of autism
    spectrum disorder in very preterm born infants. *Infant Behavior
    and Development*, online first, pp.1 -11. doi: 10.1007/s10578-
    015-0606-3
    - Chapter 5 Early temperament development and signs of autism
    spectrum disorder in very preterm born infants.

* Which datasets in that publication does this sheet apply to?:
   All datasets reported in this publication and the chapter of the
doctoral dissertation

3. Information about the files that have been stored

3a. Raw data

* Have the raw data been stored by the main researcher? [X] YES /
[ ] NO
   If NO, please justify:

* On which platform are the raw data stored?
   [] researcher PC
   [x] research group file server
   [ ] research group file server via DICT
   [ ] responsible ZAP PC

* Who has direct access to the raw data (i.e., without intervention
of another person)?
   [] main researcher
   [] responsible ZAP
   [] all members of the research group
   [ ] all members of UGent

[x] other (specify): members of the research group who are involved
in infant studies

    3b. Other files
    _____

    * Which other files have been stored?
    - [x] file(s) describing the transition from raw data to reported
results.   Specify:
         Several sps-files, containing the syntax for computing the
         different scales
    - [x] file(s) containing processed data. Specify:
    - Datafile Chapter 5 with imputed values for children with only
         one missing questionnaire
    - [x] file(s) containing analyses. Specify:
         Several sps-files, containing the syntax of the different
         reported analyses
    - [ ] files(s) containing information about informed consent.
Specify:
    - [ ] a file specifying legal and ethical provisions. Specify: ...
    - [] file(s) that describe the content of the stored files and how
this content should be interpreted. Specify:
    - [ ] other files. Specify:
         Several spv-files, containing the output of the different
         reported analyses

    * On which platform are these other files stored?
    - [ ] individual PC
    - [x] research group file server
    - [ ] other: responsible ZAP PC

    * Who has direct access to these other files (i.e., without
intervention of another person)?
    - [ ] main researcher
    - [ ] responsible ZAP
    - [ ] all members of the research group
    - [ ] all members of UGent
    - [x] other (specify): members of the research group who are
involved in infant studies

    4. Reproduction
    ===
    * Have the results been reproduced?: [ ] YES / [x] NO
    * If yes, by whom (add if multiple):
    - name
    - address
    - affiliation
    - e-mail

    _____

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