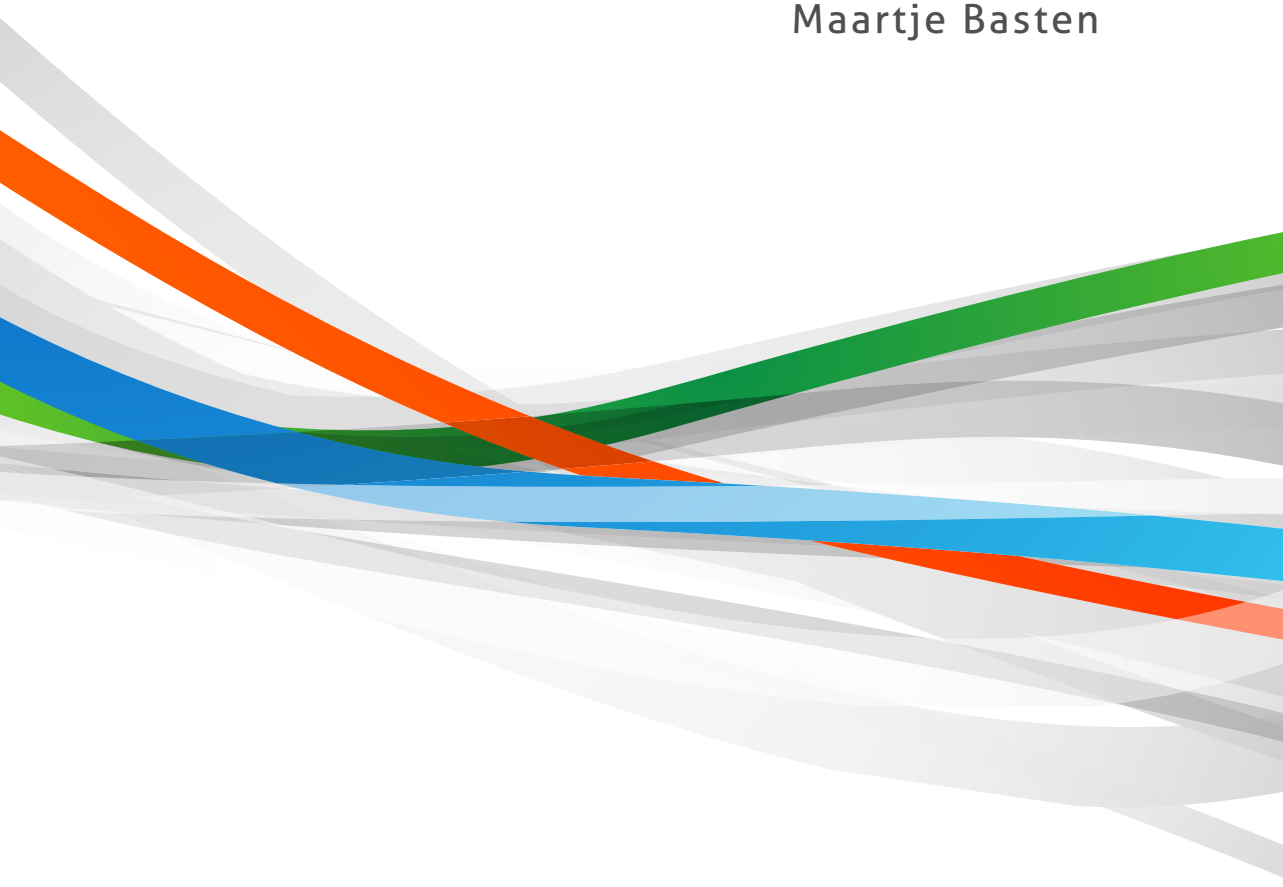
Poor Self-Regulation *in* Young Children

Maartje Basten



Poor **Self-Regulation** *in* Young Children

Maartje Basten

ISBN: 978-94-6169-567-3

Cover design: Optima Grafische Communicatie, Rotterdam, The Netherlands
Layout and printed by: Optima Grafische Communicatie, Rotterdam, The Netherlands

POOR SELF-REGULATION IN YOUNG CHILDREN

ERNSTIGE PROBLEMEN IN DE ZELFREGULATIE BIJ JONGE KINDEREN

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de
rector magnificus
prof.dr. H.A.P. Pols

en volgens besluit van het College voor Promoties.
De openbare verdediging zal plaatsvinden op
donderdag 6 november 2014 om 13.30 uur

door

Maria Geertruida Johanna Basten
geboren te Vierlingsbeek

PROMOTIECOMMISSIE

Promotoren: Prof.dr. F.C. Verhulst
Prof. J.J. Hudziak
Prof.dr. H. Tiemeier

Overige leden: Prof.dr. V.W.V. Jaddoe
Prof.dr. L.R. Arends
Prof.dr. J. Mesman

Paranimfen: Anneke van Wieringen - Basten
Femke Bastiaanssen

CONTENTS

Chapter 1

Introduction

Child psychiatry continues to struggle how best to characterize children with severe psychopathology. It has long been recognized that a certain group of children has problems in multiple domains. These children show emotional problems, such as anxiety or depression, and behavioral problems, including hyperactivity, oppositional behavior or aggression. The Diagnostic and Statistical Manual of mental disorder (DSM) does not provide a diagnostic category that describes the wide range of problems from which these children suffer. Instead, these children are likely to meet criteria from multiple diagnoses. An adequate characterization of these severely disturbed children is needed to study the determinants and consequences of these problems. Several attempts have been performed to describe these children.

Comorbidity

Severely disturbed children are likely to be given two or more DSM diagnoses. The recognition that comorbidity in children is not just a matter of chance and that children with problems in multiple domains should be studied as a separate group has led to several studies on comorbidity (Angold et al., 1999; Caron & Rutter, 1991). Common forms of comorbid behavioral and emotional disorders are conduct disorder with depression and attention deficit hyperactivity disorder with anxiety disorder (Costello et al., 2006). Comorbidity of DSM diagnoses in all its varieties, receives increasing attention in psychiatric research. However, comorbidity suggests that a child has two or more different disorders while this range of symptoms may reflect one underlying syndrome. Therefore, researchers have been searching for one diagnosis that describes the problems in these children.

Juvenile bipolar disorder

Over the last 20 years, a tendency has arisen in the United States to give children with severe emotional and behavioral problems the diagnosis juvenile bipolar disorder. Bipolar disorder is considered as one of the most severe psychiatric disorders in adulthood. It is characterized by depressive episodes and manic episodes which are marked by abnormally elevated, expansive or irritable mood. In the United States 0.42% of the children that visited a physician for a mental disorder received the diagnosis of juvenile bipolar disorder in 1994-1995. In 2002-2003, this number was increased to 6.67% (Moreno et al., 2007).

Disruptive mood dysregulation disorder

Closer examination of these children with juvenile bipolar disorder showed that this diagnosis was often unjustified because only few who received a diagnosis of juvenile bipolar disorder showed episodic manic symptoms. In fact, most children showed chronic irritable behavior. Therefore, Leibenluft et al. (2003) proposed a new diagnosis to study these children with chronic irritability and labelled this diagnosis severe mood dysregulation. Studies comparing children with severe mood dysregulation and children with bipolar disorder with episodic manic symptoms found evidence that these disorders could be differentiated by psychiatric outcomes later

in life, family characteristics, and biological correlates (Leibenluft, 2011). The criteria of severe mood dysregulation were further refined and the diagnosis has now been introduced in the DSM-5 as disruptive mood dysregulation disorder. Disruptive mood dysregulation disorder, abbreviated as DMDD, is defined by frequent severe temper outbursts combined with persistently negative and irritable mood between outbursts. Even though already included in the DSM-5, studies on the validity of this diagnosis are only now starting to emerge (e.g. Axelson et al., 2012; Copeland et al., 2013; Dougherty et al., 2014; Regier et al., 2013)

CBCL dysregulation profile

A related research line examined children with juvenile bipolar disorder using the Child Behavior Checklist (CBCL), a validated parent report questionnaire on emotional and behavioral problems in children (Achenbach & Rescorla, 2001). Biederman et al. (1995) showed that children with juvenile bipolar disorder are characterized by high levels on three specific scales of the CBCL, namely Anxious/Depressed, Attention Problems, and Aggressive Behavior. Others found very similar results (e.g. Carlson & Kelly, 1998; Geller et al., 1998; Hazell et al., 1999). Based on a review of these studies, Mick et al. (2003) proposed to combine these three scales into a CBCL juvenile bipolar profile that could be used as screening instrument for juvenile bipolar disorder. To examine the utility of this CBCL juvenile bipolar profile for screening, subsequent studies examined whether children scoring high on this profile met criteria for bipolar disorder. It turned out that children with this profile had severe problems, but most of them did not meet criteria for manic episodes (Holtmann et al., 2008; Volk & Todd, 2007; Youngstrom et al., 2006). These findings showed that the label 'bipolar disorder' was not justified for this profile. Ayer et al. (2009) further examined this profile and proposed to rename the profile into 'dysregulation' since the high scores on these three scales reflect poor regulation of emotions (Anxious/Depressed scale), poor regulation of attention (Attention Problems scale), and poor regulation of behavior (Aggressive Behavior scale).

Another important step in the validation of the CBCL dysregulation profile (CBCL-DP) was to find empirical evidence for this profile in the general population. Therefore Althoff and colleagues examined this profile using latent class analysis. Latent class analysis is a statistical person centered method to empirically derive groups of children with similar patterns of problems on a set of variables. Althoff and colleagues performed latent class analysis on the items from the CBCL Anxious/Depressed, Attention Problems and Aggressive Behavior scales. Evidence for the profile was found: a pattern characterized by high levels of anxiety and depressive symptoms, attention problems, and aggressive behavior problems was identified in three different population-based samples and across different informants (Althoff et al., 2010a; Althoff et al., 2010b; Althoff et al., 2006).

Additionally, determinants and consequences of the CBCL-DP have been studied. Cross-sectional studies on correlates of this profile showed that children with the CBCL-DP are at increased risk for suicidal thoughts and behavior and decreased functioning in school and social settings (Althoff et al., 2006; Ayer et al., 2009). These children were found to be more likely to be raised in families characterized by parental psychopathology, maladaptive parenting styles, and poor family functioning than children without problems (Jucksch et al., 2011; Kim et al., 2012). Studies in a large twin sample suggested that the profile is to a large extent heritable (Althoff et al., 2006; Boomsma et al., 2006; Hudziak et al., 2005). In addition, longitudinal studies showed that the CBCL-DP is a risk factor for severe psychopathology in adulthood, including depression and substance use disorder (Althoff et al., 2010b; Holtmann et al., 2011; Meyer et al., 2009).

Aims

In this thesis, research on the CBCL-DP is extended to young children aged 5 to 7 years. Very little is known about this profile in this age group. It is well recognised that psychopathology emerges at a young age. Consequently, research on the development of emotional and behavioral problems must be initiated when children are young. Importantly, emotional and behavioral problems present differently in young children than in school-age children. To take into account these differences, a preschool version of the CBCL has been developed for children aged 1.5 to 5 years (Achenbach & Rescorla, 2000). It is unknown if the CBCL-DP, which is derived using data from school-age children and adolescents, can also be found in young children. The aims of this thesis were 1) to explore whether a CBCL-DP could be identified in 5- to 7-year-old children; 2) to examine the correspondence between the CBCL-DP and other diagnostic approaches and informants of child emotional and behavioral problems; 3) to examine cognitive correlates of the CBCL-DP; 4) to study socioeconomic and familial determinants of the CBCL-DP; and 5) to study the development of dysregulated behavior across the preschool years. A central research aim behind these aims was to study whether children with the CBCL-DP differ from children with other profiles of emotional or behavioral problems with respect to risk factors and preschool development.

Setting

This thesis is embedded in Generation R, a population-based prospective cohort study from fetal live onwards, in Rotterdam, the Netherlands (Jaddoe et al., 2012; Tiemeier et al., 2012). The Generation R Study was designed to identify early determinants of children's growth, development, and health. All pregnant women living in Rotterdam with an expected delivery date between April 2002 and January 2006 were invited to participate. In total, 9778 pregnant women participated in the study. At enrolment, maternal, paternal and familial characteristics were collected. Across the preschool period, parents reported on the development of their child via questionnaires. When children reached the age of 5 to 7 years, more detailed assessments were

performed. At this stage 8,305 children were participating. Apart from parental questionnaires, children and their mothers were invited to the research centre for cognitive and behavioral assessments, teachers were asked to report on children's emotional and behavioral problems, and home visits were conducted for in-depth assessment of child psychopathology.

Outline

Chapter 2 describes the identification of a CBCL-DP in 5- to 7-year-old children. In this chapter, we empirically identified profiles of emotional and behavioral problems on the CBCL and examined socio-economic and parental risk factors of the CBCL-DP. Chapter 3 describes the overlap between the CBCL-DP and psychiatric classification according to the DSM-IV. In this chapter we also examined associations between CBCL profiles and child and teacher reports of emotional and behavioral problems. In chapter 4 we examined nonverbal intelligence levels of children with the CBCL-DP. Chapter 5 describes a study on the bidirectional relationships between children's dysregulated behavior, parental psychiatric symptoms, and family functioning. In chapter 6 we focus on the development of dysregulated behavior across the preschool period. This chapter describes the stability of empirically derived profiles of emotional and behavioral problems from 1.5 and 3 years of age to 5-to-7 years of age. In chapter 7 I discuss the main findings of these studies, methodological considerations, and implications for clinical practice and future research.

REFERENCES

Achenbach, T.M., & Rescorla, L.A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Achenbach, T.M., & Rescorla, L.A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families.

Althoff, R.R., Rettew, D.C., Ayer, L.A., & Hudziak, J.J. (2010a). Cross-informant agreement of the Dysregulation Profile of the Child Behavior Checklist. *Psychiatry Research, 178*(3), 550-555. doi: 10.1016/j.psychres.2010.05.002

Althoff, R.R., Verhulst, F.C., Rettew, D.C., Hudziak, J.J., & van der Ende, J. (2010b). Adult outcomes of childhood dysregulation: a 14-year follow-up study. Journal of the American Academy of Child and Adolescent Psychiatry, 49(11), 1105-1116. doi: 10.1016/j.jaac.2010.08.006

Althoff, R.R., Rettew, D.C., Faraone, S.V., Boomsma, D.I., & Hudziak, J.J. (2006). Latent class analysis shows strong heritability of the child behavior checklist-juvenile bipolar phenotype. *Biological Psychiatry, 60*(9), 903-911. doi: 10.1016/j.biopsych.2006.02.025

Angold, A., Costello, E.J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*(1), 57-87.

Axelson, D., Findling, R.L., Fristad, M.A., Kowatch, R.A., Youngstrom, E.A., Horwitz, S.M., et al. (2012). Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. *Journal of Clinical Psychiatry, 73*(10), 1342-1350. doi: 10.4088/JCP.12m07674

Ayer, L., Althoff, R., Ivanova, M., Rettew, D., Waxler, E., Sulman, J., & Hudziak, J. (2009). Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. *Journal of Child Psychology and Psychiatry, 50*(10), 1291-1300. doi: 10.1111/j.1469-7610.2009.02089.x

Biederman, J., Wozniak, J., Kiely, K., Ablon, S., Faraone, S., Mick, E., et al. (1995). CBCL clinical scales discriminate prepubertal children with structured interview-derived diagnosis of mania from those with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*(4), 464-471.

Boomsma, D.I., Rebollo, I., Derks, E.M., van Beijsterveldt, T.C., Althoff, R.R., Rettew, D.C., & Hudziak, J.J. (2006). Longitudinal stability of the CBCL-juvenile bipolar disorder phenotype: A study in Dutch twins. *Biological Psychiatry, 60*(9), 912-920. doi: 10.1016/j.biopsych.2006.02.028

Carlson, G.A., & Kelly, K.L. (1998). Manic symptoms in psychiatrically hospitalized children—what do they mean? *Journal of Affective Disorders, 51*(2), 123-135.

Caron, C., & Rutter, M. (1991). Comorbidity in child psychopathology: concepts, issues and research strategies. *Journal of Child Psychology and Psychiatry, 32*(7), 1063-1080.

Copeland, W.E., Angold, A., Costello, E.J., & Egger, H. (2013). Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *American Journal of Psychiatry, 170*(2), 173-179. doi: 10.1176/appi.ajp.2012.12010132

Costello, E.J., Foley, D.L., & Angold, A. (2006). 10-year research update review: The epidemiology of child and adolescent psychiatric disorders: II. Developmental epidemiology. *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(1), 8-25. doi: 10.1097/01.chi.0000184929.41423.cO

Dougherty, L.R., Smith, V.C., Bufferd, S.J., Carlson, G.A., Stringaris, A., Leibenluft, E., & Klein, D.N. (2014). DSM-5 disruptive mood dysregulation disorder: correlates and predictors in young children. *Psychological Medicine*, 1-12. doi: 10.1017/S0033291713003115

Geller, B., Warner, K., Williams, M., & Zimerman, B. (1998). Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL and TRF. *Journal of Affective Disorders, 51*(2), 93-100.

Hazell, P.L., Lewin, T.J., & Carr, V.J. (1999). Confirmation that Child Behavior Checklist clinical scales discriminate juvenile mania from attention deficit hyperactivity disorder. *Journal of Paediatrics and Child Health, 35*(2), 199-203.

Holtmann, M., Buchmann, A.F., Esser, G., Schmidt, M.H., Banaschewski, T., & Laucht, M. (2011). The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis. *Journal of Child Psychology and Psychiatry, 52*(2), 139-147. doi: 10.1111/j.1469-7610.2010.02309.x

Holtmann, M., Goth, K., Wockel, L., Poustka, F., & Bolte, S. (2008). CBCL-pediatric bipolar disorder phenotype: severe ADHD or bipolar disorder? *Journal of neural transmission, 115*(2), 155-161. doi: 10.1007/s00702-007-0823-4

Hudziak, J.J., Althoff, R.R., Derks, E.M., Faraone, S.V., & Boomsma, D.I. (2005). Prevalence and genetic architecture of Child Behavior Checklist-juvenile bipolar disorder. *Biological Psychiatry, 58*(7), 562-568. doi: 10.1016/j.biopsych.2005.03.024

Jaddoe, V.W., van Duijn, C.M., Franco, O.H., van der Heijden, A.J., van Iizendoorn, M.H., de Jongste, J.C., et al. (2012). The Generation R Study: design and cohort update 2012. *European Journal of Epidemiology, 27*(9), 739-756. doi: 10.1007/s10654-012-9735-1

Jucksch, V., Salbach-Andrae, H., Lenz, K., Goth, K., Dopfner, M., Poustka, F., et al. (2011). Severe affective and behavioural dysregulation is associated with significant psychosocial adversity and impairment. *Journal of Child Psychology and Psychiatry, 52*(6), 686-695. doi: 10.1111/j.1469-7610.2010.02322.x

Kim, J., Carlson, G.A., Meyer, S.E., Bufferd, S.J., Dougherty, L.R., Dyson, M.W., et al. (2012). Correlates of the CBCL-dysregulation profile in preschool-aged children. *Journal of Child Psychology and Psychiatry, 53*(9), 918-926. doi: 10.1111/j.1469-7610.2012.02546.x

Leibenluft, E. (2011). Severe mood dysregulation, irritability, and the diagnostic boundaries of bipolar disorder in youths. *American Journal of Psychiatry, 168*(2), 129-142. doi: 10.1176/appi.ajp.2010.10050766

Leibenluft, E., Charney, D.S., Towbin, K.E., Bhangoo, R.K., & Pine, D.S. (2003). Defining clinical phenotypes of juvenile mania. *American Journal of Psychiatry, 160*(3), 430-437.

Meyer, S.E., Carlson, G.A., Youngstrom, E., Ronsaville, D.S., Martinez, P.E., Gold, P.W., et al. (2009). Long-term outcomes of youth who manifested the CBCL-Pediatric Bipolar Disorder phenotype during childhood and/or adolescence. *Journal of Affective Disorders, 113*(3), 227-235. doi: 10.1016/j.jad.2008.05.024

Mick, E., Biederman, J., Pandina, G., & Faraone, S.V. (2003). A preliminary meta-analysis of the child behavior checklist in pediatric bipolar disorder. *Biological Psychiatry, 53*(11), 1021-1027.

Moreno, C., Laje, G., Blanco, C., Jiang, H., Schmidt, A.B., & Olfson, M. (2007). National trends in the outpatient diagnosis and treatment of bipolar disorder in youth. *Archives of General Psychiatry, 64*(9), 1032-1039. doi: 10.1001/archpsyc.64.9.1032

Regier, D.A., Narrow, W.E., Clarke, D.E., Kraemer, H.C., Kuramoto, S.J., Kuhl, E.A., & Kupfer, D.J. (2013). DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *American Journal of Psychiatry, 170*(1), 59-70. doi: 10.1176/appi.ajp.2012.12070999

Tiemeier, H., Velders, F.P., Szekely, E., Roza, S.J., Dieleman, G., Jaddoe, V.W., et al. (2012). The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(11), 1119-1135.e1117. doi: 10.1016/j.jaac.2012.08.021

Volk, H.E., & Todd, R.D. (2007). Does the Child Behavior Checklist juvenile bipolar disorder phenotype identify bipolar disorder? *Biological Psychiatry, 62*(2), 115-120. doi: 10.1016/j.biopsych.2006.05.036

Youngstrom, E., Meyers, O., Youngstrom, J.K., Calabrese, J.R., & Findling, R.L. (2006). Comparing the effects of sampling designs on the diagnostic accuracy of eight promising screening algorithms for pediatric bipolar disorder. *Biological Psychiatry, 60*(9), 1013-1019. doi: 10.1016/j.biopsych.2006.06.023

Chapter 2

The dysregulation profile in young children: empirically defined classes in the Generation R Study

Basten, M. M., Althoff, R. R., Tiemeier, H., Jaddoe, V. W., Hofman, A., Hudziak, J. J., Verhulst, F. C., & van der Ende, J. (2013)

Journal of the American Academy of Child and Adolescent Psychiatry, 52(8), 841-850 e842. Doi:10.1016/j.jaac.2013.05.007

ABSTRACT

Objective: Children with co-occurring internalizing and externalizing problems have higher levels of impairment and worse outcomes later in life, but it is unclear whether these children can be distinguished validly from children who have problems in a single domain. We used a person-centered statistical approach to examine whether a group of children with co-occurring internalizing and externalizing problems can be identified in a general-population sample of young children.

Method: This study included a population-based sample of 6,131 children, aged 5-to-7 years. Mothers (92.6%) reported emotional and behavioral problems using the Child Behavior Checklist/1.5-5 (CBCL). A latent profile analysis was performed on the CBCL syndrome scales. Identified classes were compared on early socioeconomic and parental risk factors using multinomial logistic regression.

Results: We identified four classes: 1) a class scoring high on all internalizing and externalizing scales (1.8%), 2) a class with internalizing problems (5.3%), 3) a class with externalizing problems and emotional reactivity (7.3%), and 4) a class without problems (85.6%). The first class, with co-occurring problems, was associated with higher levels of maternal and paternal affective symptoms and hostility than the other three classes.

Conclusions: The class with co-occurring internalizing and externalizing problems appears to be highly similar to the CBCL Dysregulation Profile described in older children. This empirically-based dysregulation profile offers a promise to the study of the development of poor self-regulation.

INTRODUCTION

Internalizing and externalizing problems co-occur at rates that are much higher than expected by chance. Co-occurrence of internalizing and externalizing problems has been associated with higher levels of impairment and higher risk for adult psychiatric disorders, criminal offences and suicide (Angold et al., 1999; Fombonne et al., 2001; Sourander et al., 2007). Studying co-occurrence may increase our understanding of the etiology, course, and treatment of psychiatric disorders (Angold et al., 1999). So far, most research on the co-occurrence of internalizing and externalizing problems has been done in school-age children and adolescents. However, since psychiatric symptoms begin in the preschool period, research on co-occurrence should also start at an early age (Egger & Angold, 2006).

One of the methodological challenges to investigating children with co-occurring internalizing and externalizing problems is validly distinguishing them from children who have problems in a single domain. Co-occurring problems are often defined using cut-points on internalizing and externalizing dimensions (Briggs-Gowan et al., 2006; Sourander et al., 2007; Youngstrom et al., 2003). However, the use of cut-points on continuous variables results in loss of information. Additionally, it is debatable as to which cut-points should be used. Lastly, it is unclear how many groups are needed to adequately describe these co-occurring problems in children. Person-centered methods, such as latent class analysis (LCA) or latent profile analysis (LPA) help to identify homogeneous groups of individuals with similar patterns of psychopathology.

Person-centered methods have previously been used to examine children with co-occurring internalizing and externalizing problems. To our knowledge, these studies focused only on high-risk samples, and not on the general population. Connell et al. (2008) performed LCA on the preschool Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2000) in a sample of preschool children with behavioral problems, family problems and/or low socioeconomic status. They identified four classes: a) comorbid internalizing and externalizing, b) externalizing only, c) internalizing only, and d) normative. Interestingly, children with comorbid internalizing and externalizing problems appeared to benefit more from a family-centered intervention than children with problems in a single domain (Connell et al., 2008). Tolan and Henry (1996) found four very similar patterns of psychopathology using LCA in urban poor school-age children. The class of children with high scores on internalizing and externalizing scales was most strongly associated with poor psychosocial functioning two years later. These studies showed the importance of identifying children with co-occurring internalizing and externalizing problems for examining intervention effects and prognosis. However, the selection of children who are at high risk might have resulted in biased prevalence and patterns of co-occurring problems (Angold et al., 1999).

In school-age children LCA has also been used to identify the CBCL Dysregulation Profile, a phenotype that is characterized by co-occurring internalizing and externalizing problems (Ayer et al., 2009). The CBCL Dysregulation Profile latent class captures children with high scores on the items of Anxiety/Depression, Attention Problems, and Aggressive Behavior scales (Althoff et al., 2010a; Althoff et al., 2006; Althoff et al., 2010b). This class was associated with suicidal behavior and predicted increased rates of anxiety, mood and disruptive behavior disorders in adulthood (Althoff et al., 2006; Althoff et al., 2010b).

The co-occurrence of internalizing and externalizing problems presented in the CBCL Dysregulation Profile is thought to stem from an underlying syndrome of poor self-regulation (Ayer et al., 2009). A common factor underlying internalizing and externalizing problems has been studied by others using related concepts such as irritability (Stringaris, 2011) and mood lability (Stringaris & Goodman, 2009). In preschool children, self-regulation is often studied from a temperamental perspective (Eisenberg et al., 2010). At this young age, poor self-regulation has also been shown to be a key feature of emerging and persisting internalizing and externalizing problems (Briggs-Gowan et al., 2006; Eisenberg et al., 2010). The identification of the CBCL Dysregulation Profile in young children would allow continued study of poor self-regulation from preschool to adolescence using an empirically-based measure.

In person-centered methods it is important to study risk factors or other correlates of classes. External validity can be demonstrated if class membership can be predicted from variables other than the ones used to create the classes (Lenzenweger, 2004). Studying risk factors can also aid to understand differential etiology of classes. Many family and environmental factors, such as parental psychopathology, poverty, and stressful life events, are related to both internalizing and externalizing problems (Oland & Shaw, 2005). Co-occurring internalizing and externalizing problems have, in comparison with problems on a single domain, been associated with higher levels of risk factors (Oland & Shaw, 2005).

In the present study, we used a person-centered method to examine whether a group of children with co-occurring internalizing and externalizing problems can be distinguished in a general population sample of young children. We performed LPA on the syndrome scales of the preschool CBCL in a large sample of 5-to-7 year-old children. A wide range of continuously measured psychological problems was used to overcome the limitations of previous studies that used LCA based on dichotomized scale scores (Connell et al., 2008; Tolan & Henry, 1996), or that investigated only a subset of problems (Althoff et al., 2010a; Althoff et al., 2006; Althoff et al., 2010b). We hypothesized to find a highly problematic group of children scoring high on internalizing and externalizing scales. We were interested in whether this group would have elevated scores on all scales or only on the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales contributing to the CBCL Dysregulation Profile. We also hypothesized to observe a group of

children with mainly internalizing problems and a group of children with mainly externalizing problems. We expected the majority of the children to be in a class characterized by no psychopathology. To examine external validity and differential etiology, the classes were examined in relation to known risk factors of psychopathology, i.e. gender, ethnicity, maternal education, family income and parental psychological problems. We expected the highly problematic class to be most strongly associated with these socioeconomic and parental risk factors.

METHODS

Setting and population

This study was embedded in the Generation R Study, a multi-ethnic population-based cohort from fetal life onwards. The Generation R Study has been described in detail previously (Jaddoe et al., 2012; Tiemeier et al., 2012). Briefly, all pregnant women living in Rotterdam, the

Table 1 Sample characteristics.

	N=6,131
Child age in years, mean (sd)	6.0 (0.4)
Child gender %	
Girls	49.7
Boys	50.3
Child ethnicity %	
Dutch	62.5
Other Western	9.2
Non-Western	28.4
Maternal education %	
High	50.2
Medium	29.2
Low	20.6
Family income %	
> €2,000	66.0
€1,200 - €2,000	17.4
< €1,200	16.6
Maternal psychiatric symptoms	
Affective symptoms, mean (sd)	0.18 (0.33)
Hostility, mean (sd)	0.19 (0.29)
Paternal psychiatric symptoms	
Affective symptoms, mean (sd)	0.14 (0.25)
Hostility, mean (sd)	0.18 (0.28)

Note: Missing values: child ethnicity 4.7%, maternal education 6.6%, family income 21.1%, maternal psychiatric symptoms 31.5%, paternal psychiatric symptoms 43.3%.

Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants. At birth, 9,749 children participated in the study (participation rate 61%). When the children reached the age of 5 years, 8,305 parents gave consent for further participation. At this time point, 6,210 primary caregivers completed the CBCL. We excluded 79 children who were 8 years or older, which resulted in a study sample of 6,131 children (63% of the original sample). Table 1 presents sample characteristics.

Child Behavior Checklist/1.5-5

We assessed emotional and behavioral problems using the 100-item Child Behavior Checklist for ages 1.5 to 5 (CBCL; Achenbach & Rescorla, 2000). The CBCL/1.5-5 was chosen because we expected most children to be younger than 6 years at assessment. At the end of the assessment, while most children were 5 years old (58%), some were 6 (38%) or 7 (4%) years old. The CBCL was completed by the primary caregiver (92.6% mothers). Based on the behavior of the child in the preceding two months, each item was rated as 0 for not true, 1 for somewhat or sometimes true, and 2 for very true or often true. We used syndrome scales that are part of the Internalizing and Externalizing broad-band scales. The Internalizing scale consists of four scales: Emotionally Reactive (e.g. 'rapid shifts between sadness and excitement', 'disturbed by any change in routine'), Anxious/Depressed (e.g. 'Looks unhappy without good reason', 'nervous, highstrung or tense'), Somatic Complaints (e.g. 'headaches', 'nausea, feels sick') and Withdrawn (e.g. 'refuses to play active games', 'seems unresponsive to affection'). The Externalizing scale contains two scales: Attention Problems (e.g. 'can't concentrate', 'wanders away') and Aggressive Behavior (e.g. 'angry moods', 'defiant'). Good reliability and validity have been reported for the CBCL/1.5-5 (Achenbach & Rescorla, 2000), and the syndrome scales were found to be generalizable across 23 societies (Ivanova et al., 2010). In our sample, for all scales Cronbach's alphas were the same in 5 year-old children and in children older than 5, indicating that problems were also reliably measured in children older than 5.

Early risk factors

Information on risk factors was obtained by questionnaires. Ethnicity of the child was defined by the country of birth of the parents (Statistics Netherlands, 2004). Children were classified as non-Dutch if one of the parents was born abroad. Three categories were defined: Dutch, other Western, and non-Western. Maternal education level was examined at time of enrollment. It was defined as highest education finished and was classified into three categories (Statistics Netherlands, 2003) : low (primary school or lower vocational education), medium (intermediate vocational education), and high (higher vocational education or university). Family income was also examined at enrollment. It was defined by the total net month income of the household and categorized as '< €1,200' (below social security level), '€1,200-2,000',

and '> €2,000' (more than modal income). When the child was 3 years old (mean=3.1±0.1), psychological problems of both parents were measured using the Brief Symptom Inventory (BSI), a validated self-report questionnaire (De Beurs, 2004). The BSI consists of 53 items that have to be answered on a 5-point scale and can be classified in eight subscales; Depression, Hostility, Anxiety, Phobic Anxiety, Paranoid Ideation, Psychoticism, Interpersonal Sensitivity, and Obsessive-Compulsive. We aimed to focus on internalizing and externalizing symptoms. Therefore, we calculated a mean affective symptom score, which included the items from the Depression and Anxiety scales, and the mean symptom score on the Hostility scale.

Data analysis

We conducted latent profile analysis (LPA) using Mplus version 6. LPA is a person-centered method using continuous variables as indicators. LPA identifies classes of individuals with similar scoring patterns. T-scores on the syndrome scales, which have the same norms for boys and girls on the CBCL/1.5-5, were used as indicators. To reduce the influence of skewed variables, a maximum likelihood estimator with robust standard errors was used. We started with a one-class model and increased the number of classes until a stable, best fitting model was achieved. The best fitting model was determined by looking at the Bayesian information criterion (BIC) and the Bootstrapped Likelihood-Ratio Test (BLRT) as these fit indices appeared to perform best in a simulation study by Nylund et al. (2007). For the BIC, a lower value represents a better fitting model, taking parsimony into account. The BLRT tests if the addition of a class leads to a significant improvement in model fit. In determining the number of classes we also considered the rule of parsimony and the substantive relevance of a class. Entropy, a measure of how well the children were classified, was also taken into account. We tested whether age entered as a covariate would improve model fit. Once the best fitting model was determined, we assigned each individual to the class for which the individual had the highest probability of membership. To examine the relationship between risk factors and the latent classes, we performed multinomial logistic regression in SPSS. First, we made pairwise comparisons between classes on each risk factor. Second, to examine which factors were most strongly associated, we made pairwise comparisons between classes on each risk factor while adjusting for other factors. Maternal education and family income were not adjusted for each other because they are highly related. For similar reasons parental affective and hostility symptoms were not adjusted for each other. All analyses were also adjusted for age child. Scores on the BSI were transformed to z scores to facilitate the interpretation of the findings. Percentages of missing data on early risk factors were 4.7% for child ethnicity, 6.6% for maternal education, 21.1% for family income, 31.5% for maternal psychiatric symptoms, and 43.3% for paternal psychiatric symptoms. To avoid selection bias due to missing data, we used multiple imputations. It has been shown that missing values up to 60% can be adequately dealt with using multiple imputations (Barzi & Woodward, 2004; Janssen et al., 2010). We imputed missing values using a fully conditional specification method in SPSS. Because a large fraction of the data was imputed, we generated

20 imputed data sets (Sterne et al., 2009). Imputations were based on class membership and all risk factors in the model. We added prenatal parental BSI as additional indicators to improve the imputation model. We imputed parental psychiatric symptoms regardless of whether the parent was present in the home, to account for a possible genetic effect of parental psychiatric symptoms. To examine if the multiple imputations were not fatal, analyses were repeated in a sample with complete paternal psychiatric symptoms data (n=3,475).

Non-response analysis

We compared child and maternal characteristics of the children included in the analysis (n=6,131) with those excluded because of missing data on CBCL (n=3,618). Children of responding mothers were more likely to be Dutch (60.6% vs. 30.8%, χ^2=1,062, df=3, p<0.001). Responding mothers were more likely to be highly educated (48.7% vs. 18.9%, χ^2=1,250, df=3, p<0.001) and to have a high family income (55.2% vs. 20.3%, χ^2=1,328, df=3, p<0.001).

RESULTS

Table 2 presents the model fit indices for one-to-five class solutions of the LPA. According to the BIC and the BLRT, more classes resulted in better model fit. The four-class solution resulted in clearly distinct classes. A comparison of the four-class and five-class solutions showed that the five-class solution included an additional class with a profile that was not clearly different from that of the lowest scoring class. Furthermore the probability of membership in the highest scoring class decreased to include only 0.9% of the sample. Because of minimal differentiation from four to five classes we chose the four-class solution. The entropy was 0.98. Adding age as a covariate did not improve model fit.

Table 2 Fit statistics for latent profile models.

Number of classes	BIC	BLRT	Entropy
1 class	217,304	-	-
2 class	204,285	<0.001	0.98
3 class	199,746	<0.001	0.97
4 class	196,759	<0.001	0.98
5 class	194,392	<0.001	0.99

Note: BIC = Bayesian information criterion, BLRT = Bootstrapped likelihood-ratio test.

Figure 1 and Table 3 show the mean T-scores for the classes. Table 3 also provides standard deviations of the T-scores. The first class, containing 1.8% of the sample, showed the highest scores on all scales ranging from 62 on Somatic Complaints to 73 on Emotionally Reactive. We labeled this class "highly problematic". As shown in Figure 1, there were two intermediate classes

with elevations around 60, which corresponds to 1 SD above the mean. Class 2, including 5.3% of the sample, showed T-scores around 60 on the internalizing scales Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn, and was labeled "internalizing". Class 3 showed elevations around 60 on Emotionally Reactive and Aggressive Behavior, moderate elevations on Somatic Complaints, Withdrawn, and Attention Problems (range:57-58), but no elevation on Anxious/Depressed. Because of the elevation on the Emotionally Reactive scale, the relatively higher scores on Attention Problems and Aggressive Behavior in comparison with the internalizing class, and the absence of problems on Anxious/Depressed, we labeled this class "externalizing/emotionally-reactive". This class contained 7.3% of the children. Class 4, including 85.6% of the children, scored low on all scales (range: 50-52) and was labeled "no problems".

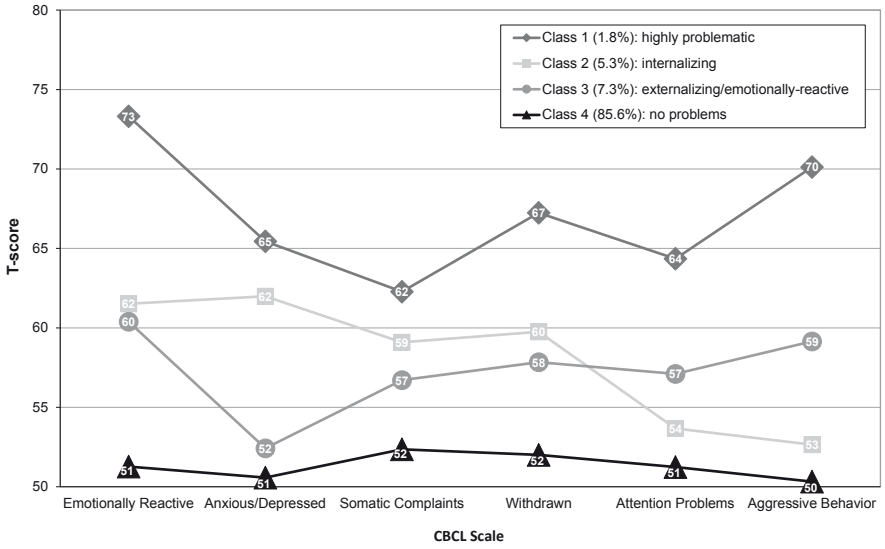


Figure 1 Mean T-scores from the latent profile model with four classes.
Note: CBCL = Child Behavior Checklist/1.5–5.

Table 3 Mean T-scores from the latent profile model with four classes.

	Highly problematic n=110	Internalizing n=326	Externalizing/ emotionally-reactive n=443	No problems n=5,252
CBCL scale	mean (sd)	mean (sd)	mean (sd)	mean (sd)
Emotionally Reactive	73.4 (9.0)	61.5 (6.1)	60.4 (5.9)	51.3 (2.9)
Anxious/Depressed	65.4 (8.1)	62.0 (4.8)	52.4 (2.7)	50.6 (1.4)
Somatic Complaints	62.2 (9.2)	59.1 (8.0)	56.7 (7.4)	52.4 (4.5)
Withdrawn	67.2 (8.5)	59.7 (7.3)	57.9 (6.7)	52.0 (3.3)
Attention Problems	64.3 (8.1)	53.7 (5.1)	57.1 (6.8)	51.2 (2.8)
Aggressive Behavior	70.2 (7.9)	52.7 (3.1)	59.2 (3.7)	50.3 (1.0)

Note: CBCL = Child Behavior Checklist/1.5–5.

We examined the relationship between risk factors and class membership using multinomial logistic regression. In the unadjusted analyses, all risk factors predicted membership to the three problem classes (Supplementary Table S1). To investigate which risk factors were most strongly associated with the classes, we controlled effects for other factors. Table 4 reports the results for each problem class relative to the no problems class. The highly problematic class included more boys (OR=2.10, p<0.01) and more mothers with a low education level (OR=1.97, p<0.05) than the no problems class. Both mothers and fathers of the highly problematic class reported higher levels of affective symptoms (mother OR=1.54, p<0.001; father OR=1.40, p<0.001) and hostility (mother OR=1.60, p<0.001; father OR=1.47, p<0.001) than the

Table 4 Adjusted associations between risk factors and class membership: the highly problematic, internalizing and externalizing/emotionally-reactive classes compared with the no problems class.

	No problems (reference)	Highly problematic		Internalizing		Externalizing/ emotionally-reactive	
	OR	OR	95% CI	OR	95% CI	OR	95% CI
Child gender							
Girls (reference)							
Boys	1.00	2.10**	1.37-3.23	1.00	0.80-1.26	1.92***	1.56-2.36
Child ethnicity							
Dutch (reference)							
Other Western	1.00	1.00	0.46-2.14	0.97	0.61-1.56	0.88	0.53-1.48
Non-Western	1.00	0.92	0.53-1.61	1.53**	1.13-2.07	1.07	0.81-1.41
Maternal education							
High (reference)							
Medium	1.00	1.45	0.87-2.40	1.16	0.86-1.56	1.14	0.90-1.46
Low	1.00	1.97*	1.15-3.36	1.76***	1.29-2.41	1.31	0.94-1.83
Family income							
> €2,000 (reference)							
€1,200 - €2,000	1.00	1.52	0.84-2.76	1.50*	1.06-2.11	1.16	0.83-1.62
< €1,200	1.00	2.29	0.91-5.78	1.63*	1.13-2.36	1.40	0.92-2.12
Maternal psychiatric symptoms							
Affective symptoms	1.00	1.54***	1.37-1.73	1.32***	1.19-1.46	1.29***	1.16-1.43
Hostility	1.00	1.60***	1.40-1.83	1.30***	1.14-1.48	1.43***	1.30-1.56
Paternal psychiatric symptoms							
Affective symptoms	1.00	1.40***	1.22-1.61	1.13*	1.00-1.28	1.07	0.93-1.22
Hostility	1.00	1.47***	1.26-1.72	1.08	0.95-1.24	1.11	0.98-1.26

Note: The model was based on multinomial logistic regression analysis. The no problems class is the reference group against which the odds ratios are calculated. OR = odds ratio; CI = confidence interval

* p<0.05, ** p<0.01, *** p<0.001

no problems class. The internalizing class was associated with non-Western ethnicity (OR=1.53, p<0.01), low maternal education (OR=1.76, p<0.001) and low family income (OR=1.63, p<0.05) in comparison with the no problems class. The internalizing class was also related to higher levels of maternal affective symptoms (OR=1.32, p<0.001), maternal hostility (OR=1.30, p<0.001) and paternal affective symptoms (OR=1.13, p<0.05). The externalizing/emotionally-reactive class included more boys (OR=1.92, p<0.001) and was associated with higher levels of

Table 5 Adjusted associations between risk factors and class membership: the highly problematic class compared with the internalizing and externalizing/emotionally-reactive classes.

	Highly problematic versus Internalizing			Highly problematic versus Externalizing/emotionally-reactive		
	Internalizing (reference)	Highly problematic		Externalizing/ emotionally-reactive (reference)	Highly problematic	
	OR	OR	95% CI	OR	OR	95% CI
Child gender						
Girls (reference)						
Boys	1.00	2.10**	1.31-3.36	1.00	1.09	0.69-1.74
Child ethnicity						
Dutch (reference)						
Other Western	1.00	1.02	0.42-2.49	1.00	1.13	0.45-2.84
Non-Western	1.00	0.60	0.33-1.12	1.00	0.86	0.48-1.55
Maternal education						
High (reference)						
Medium	1.00	1.25	0.70-2.24	1.00	1.26	0.73-2.19
Low	1.00	1.12	0.61-2.04	1.00	1.50	0.82-2.75
Family income						
> €2,000 (reference)						
€1,200 - €2,000	1.00	1.02	0.53-1.95	1.00	1.32	0.69-2.51
< €1,200	1.00	1.40	0.54-3.63	1.00	1.64	0.62-4.33
Maternal psychiatric symptoms						
Affective symptoms	1.00	1.17*	1.02-1.34	1.00	1.19*	1.04-1.38
Hostility	1.00	1.24*	1.03-1.48	1.00	1.12	0.97-1.30
Paternal psychiatric symptoms						
Affective symptoms	1.00	1.24**	1.07-1.44	1.00	1.32**	1.10-1.57
Hostility	1.00	1.36**	1.14-1.62	1.00	1.33**	1.10-1.60

Note: The model was based on multinomial logistic regression analysis. The internalizing class and externalizing/emotionally-reactive class are the reference groups against which the odds ratios are calculated. OR = odds ratio; CI = confidence interval
* p<0.05, ** p<0.01, *** p<0.001

maternal affective symptoms (OR=1.29, p<0.001) and maternal hostility (OR=1.43, p<0.001) than the no problems class. Next, we made pairwise comparisons between the highly problematic class and the internalizing and externalizing/emotionally-reactive classes. Results are shown in Table 5. Mothers and fathers of the highly problematic class reported higher levels of affective symptoms (mother OR=1.17, p<0.05; father OR=1.24, p<0.01) and hostility (mother OR=1.24, p<0.05; father OR=1.36, p<0.01) than the internalizing class. Mothers and fathers of the highly problematic class reported also more psychiatric symptoms than the externalizing/emotionally-reactive class (maternal affective symptoms OR=1.19, p<0.05; paternal affective symptoms OR=1.32, p<0.01; paternal hostility OR=1.33, p<0.01). All significant associations between parental psychiatric symptoms and class membership were also found in the sample with complete data on paternal psychiatric symptoms (Supplementary Tables S2-S4).

DISCUSSION

In this study, we aimed to identify a pattern of co-occurring internalizing and externalizing problems in a large population-based sample of 5-to-7 year-old children. Using latent profile analysis on the CBCL/1.5-5 syndrome scales, we identified four classes: 1) a class scoring high on all internalizing and externalizing scales, 2) an intermediate class with internalizing problems, 3) an intermediate class with predominantly externalizing problems and emotionally reactive behavior, and 4) a class without problems. The highly problematic class was associated with high levels of maternal and paternal psychiatric symptoms.

This study was performed in a population-based sample of young children. In general, the selection of the sample may affect the structure and the prevalence of the latent classes (Lenzenweger, 2004). Interestingly, the identified patterns of emotional and behavioral problems in our study are largely in line with the four identified classes in high risk samples (Connell et al., 2008; Tolan & Henry, 1996). Additionally, we found that internalizing and externalizing problems were always accompanied by emotional reactivity, which was less clear in the study of Connell et al. (2008). The agreement across studies suggests that the structure of the classes is less dependent on the socioeconomic background of the sample. In our study we found a lower prevalence rate for the highly problematic class than other studies in high risk samples (Connell et al., 2008; Tolan & Henry, 1996). The internalizing and externalizing/emotionally-reactive classes were also smaller in our study than in the study by Connell et al. (2008). The prevalences of the three problem classes in our study may be somewhat lower than in our target population because of a higher non-response among non-western and low socioeconomic families.

The CBCL Dysregulation Profile captures children with elevations on the Anxious/Depressed, Attention Problems and Aggressive Behavior scales (Althoff et al., 2010a; Althoff et al., 2006; Althoff et al., 2010b). The highly problematic class in our study also showed elevations on the Emotionally Reactive, Somatic Complaints, and Withdrawn scales. The question arises whether the highly problematic class identifies the same children as the CBCL Dysregulation Profile. There could be several explanations why we did not find a Dysregulation Profile. First, Althoff and colleagues identified a dysregulation class by performing latent class analyses based on the items from the Anxious/Depressed, Attention Problems and Aggressive Behavior scales (Althoff et al., 2010a; Althoff et al., 2006; Althoff et al., 2010b). We based our analyses on a broader spectrum of emotional and behavioral problems using all internalizing and externalizing scales. Second, the content of the CBCL/1.5-5 differs from the school-age CBCL/6-18. Five of the six scales used in our study have comparable counterparts on the CBCL/6-18 (Achenbach & Rescorla, 2000). The scale Emotionally Reactive is only present in the CBCL/1.5-5, but includes items from the Anxious/Depressed and Aggressive Behavior scales of the CBCL/6-18. This makes it likely that the Dysregulation Profile in preschool children would also include elevations on the Emotionally Reactive scale. Third, the Dysregulation Profile might emerge only at an age later than 5-to-7 years. However, confirmatory factor analyses on symptoms from DSM disorders in 2-to-5 year-old children have shown that differentiation of syndromes is visible at this young age (Sterba et al., 2007), suggesting that the Dysregulation Profile may also appear at a young age. Fourth, LPA might have been unable to detect different patterns within the 1.8% of children with co-occurring internalizing and externalizing problems. This is possible if one assumes a Dysregulation Profile prevalence of 0.7-1.0%, which was reported in studies that based the Dysregulation Profile on cut-points on the scales (Holtmann et al., 2007; Hudziak et al., 2005). However, according to the LCA studies the prevalence of the Dysregulation Profile is 4-8% (Althoff et al., 2010a; Althoff et al., 2006; Althoff et al., 2010b). This makes it less likely that the LPA in our study could not identify a Dysregulation Profile. At the same time, there is little evidence that children who fulfill the Dysregulation Profile only have elevations on Anxious/Depressed, Attention Problems and Aggressive Behavior. Several studies found that children with dysregulation also have high scores on other scales, including Somatic Complaints and Withdrawn/Depressed (Biederman et al., 2012; Holtmann et al., 2007; Holtmann et al., 2008). Based on these findings, the current study, and the studies of Connell et al. (2008) and Tolan and Henry (1996), we propose that, even though the profiles differ, children in the highly problematic class are similar to children with the CBCL Dysregulation Profile. At least for very young children, dysregulation should not be restricted to elevations on the Anxious/Depressed, Attention Problems and Aggressive Behavior scales. Children with dysregulation show high levels of problems across the range of both internalizing and externalizing problems.

All three of the problem classes were related to several socioeconomic and parental risk factors. Pairwise comparisons between the classes showed that the highly problematic or 'dysregulation' class was most strongly associated with parental psychiatric symptoms. Maternal and paternal psychiatric symptoms independently contributed to the risk of dysregulation. These results are in-line with evidence that parents of children with co-occurring internalizing and externalizing disorders are more likely to show psychiatric symptoms than parents of children with a single disorder (Oland & Shaw, 2005). Because of the high correlation between affective symptoms and hostility in this study, the specificity of these symptoms remains unclear. The results suggest that psychiatric symptoms of both parents play a role in the development of dysregulation. More research is needed to understand the genetic and environmental mechanisms that operate in the transmission of psychiatric symptoms to children with dysregulation.

Gender was also related to class membership. Dysregulation was more prominent in boys. This has also been reported in another sample (Althoff et al., 2010a), though others did not find a predominance of boys (Holtmann et al., 2007; Hudziak et al., 2005). These mixed results might be related to age or could be explained by the use of cut-points to define dysregulation (Holtmann et al., 2007; Hudziak et al., 2005). The externalizing/emotionally-reactive class was also associated with male gender and gender was equally distributed in the internalizing class. This is consistent with male preponderance of externalizing disorders at early age while gender differences in internalizing disorders arise only in adolescence (Rutter et al., 2003).

This study has limitations. First, we relied only on parental report. However, we included both maternal and paternal psychiatric symptoms and variables were measured at different time points. Second, data on parental psychiatric symptoms were missing in 32-43% of the cases. We used multiple imputations to account for the missing data. To examine possible biases of the multiple imputations, we repeated the analyses in a sample with complete paternal data. Similar results were found regarding the association between parental psychiatric symptoms and dysregulation. The most important reasons for missing data on parental psychiatric symptoms were that part of the Generation R sample was not reached at 3 years (Jaddoe et al., 2012) or that parents refused to fill out the questionnaire. However, it was also possible that the parent was not involved in raising the child which might in itself be a risk for the development of dysregulation. Third, we measured parental psychiatric symptoms only when the child was 3 years old. Thus, we were unable to study the effects of the development of parental psychiatric symptoms over time on dysregulation. Fourth, our non-response analysis demonstrated that our study included relatively more families with a Dutch background and higher socioeconomic status. Because ethnicity and socioeconomic status were associated with class membership, the non-response might have led to an underestimation of the associations between sociodemographic risks and class membership.

In conclusion, we identified a pattern of co-occurring internalizing and externalizing problems in a general-population sample of 5-to-7 year-old children. This class seems to be highly overlapping with the CBCL Dysregulation Profile. The profile provides an empirically-based measure to study poor self-regulation at an early age. It allows characterizing poor self-regulation in relation to typically developing children of the same age and gender. A new diagnosis that covers both internalizing and externalizing symptoms is proposed for the DSM-5, namely Disruptive Mood Dysregulation Disorder. Future studies should examine to what extent this new diagnosis identifies these children with poor self-regulation.

Previous research on the CBCL Dysregulation Profile has shown a heterotypic development from self-regulatory problems in childhood to different forms of adult psychiatric disorders (Althoff et al., 2010b). Continued empirically-based investigation of self-regulation is necessary to determine how and why children with dysregulation will proceed down a particular course towards psychiatric illness and may provide insights into prevention. Our results suggest that parental psychiatric symptoms play a role in the etiology of dysregulated behavior. Although more research is needed to understand which mechanisms are involved, it suggests that intervention strategies for dysregulated behavior should focus on psychiatric symptoms of both parents to prevent these children from developing severe psychopathology later in life.

REFERENCES

Achenbach, T.M., & Rescorla, L.A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Althoff, R.R., Rettew, D.C., Ayer, L.A., & Hudziak, J.J. (2010a). Cross-informant agreement of the Dysregulation Profile of the Child Behavior Checklist. *Psychiatry Research, 178*(3), 550-555. doi: 10.1016/j.psychres.2010.05.002

Althoff, R.R., Rettew, D.C., Faraone, S.V., Boomsma, D.I., & Hudziak, J.J. (2006). Latent class analysis shows strong heritability of the child behavior checklist-juvenile bipolar phenotype. *Biological Psychiatry, 60*(9), 903-911. doi: 10.1016/j.biopsych.2006.02.025

Althoff, R.R., Verhulst, F.C., Rettew, D.C., Hudziak, J.J., & van der Ende, J. (2010b). Adult outcomes of childhood dysregulation: a 14-year follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(11), 1105-1116. doi: 10.1016/j.jaac.2010.08.006

Angold, A., Costello, E.J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*(1), 57-87.

Ayer, L., Althoff, R., Ivanova, M., Rettew, D., Waxler, E., Sulman, J., & Hudziak, J. (2009). Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. *Journal of Child Psychology and Psychiatry, 50*(10), 1291-1300. doi: 10.1111/j.1469-7610.2009.02089.x

Barzi, F., & Woodward, M. (2004). Imputations of missing values in practice: results from imputations of serum cholesterol in 28 cohort studies. *American journal of epidemiology, 160*(1), 34-45. doi: 10.1093/aje/kwh175

Biederman, J., Petty, C.R., Day, H., Goldin, R.L., Spencer, T., Faraone, S.V., et al. (2012). Severity of the aggression/anxiety-depression/attention child behavior checklist profile discriminates between different levels of deficits in emotional regulation in youth with attention-deficit hyperactivity disorder. *Journal of developmental and behavioral pediatrics, 33*(3), 236-243. doi: 10.1097/DBP.0b013e3182475267

Briggs-Gowan, M.J., Carter, A.S., Bosson-Heenan, J., Guyer, A.E., & Horwitz, S.M. (2006). Are infant-toddler social-emotional and behavioral problems transient? *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(7), 849-858. doi: 10.1097/01.chi.0000220849.48650.59

Connell, A., Bullock, B.M., Dishion, T.J., Shaw, D., Wilson, M., & Gardner, F. (2008). Family intervention effects on co-occurring early childhood behavioral and emotional problems: a latent transition analysis approach. *Journal of Abnormal Child Psychology, 36*(8), 1211-1225. doi: 10.1007/s10802-008-9244-6

De Beurs, E. (2004). *Brief symptom inventory, handleiding*. Leiden, The Netherlands

Egger, H.L., & Angold, A. (2006). Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. *Journal of Child Psychology and Psychiatry, 47*(3-4), 313-337. doi: 10.1111/j.1469-7610.2006.01618.x

Eisenberg, N., Spinrad, T.L., & Eggum, N.D. (2010). Emotion-related self-regulation and its relation to children's maladjustment. *Annual Review of Clinical Psychology, 6*, 495-525. doi: 10.1146/annurev.clinpsy.121208.131208

Fombonne, E., Wostear, G., Cooper, V., Harrington, R., & Rutter, M. (2001). The Maudsley long-term follow-up of child and adolescent depression. 2. Suicidality, criminality and social dysfunction in adulthood. *British Journal of Psychiatry, 179*, 218-223.

Holtmann, M., Bolte, S., Goth, K., Dopfner, M., Pluck, J., Huss, M., et al. (2007). Prevalence of the Child Behavior Checklist-pediatric bipolar disorder phenotype in a German general population sample. *Bipolar disorders, 9*(8), 895-900. doi: 10.1111/j.1399-5618.2007.00463.x

Holtmann, M., Goth, K., Wockel, L., Poustka, F., & Bolte, S. (2008). CBCL-pediatric bipolar disorder phenotype: severe ADHD or bipolar disorder? *Journal of neural transmission, 115*(2), 155-161. doi: 10.1007/s00702-007-0823-4

Hudziak, J.J., Althoff, R.R., Derks, E.M., Faraone, S.V., & Boomsma, D.I. (2005). Prevalence and genetic architecture of Child Behavior Checklist-juvenile bipolar disorder. *Biological Psychiatry, 58*(7), 562-568. doi: 10.1016/j.biopsych.2005.03.024

Ivanova, M.Y., Achenbach, T.M., Rescorla, L.A., Harder, V.S., Ang, R.P., Bilenberg, N., et al. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1215-1224. doi: 10.1016/j.jaac.2010.08.019

Jaddoe, V.W., van Duijn, C.M., Franco, O.H., van der Heijden, A.J., van Iizendoorn, M.H., de Jongste, et al. (2012). The Generation R Study: design and cohort update 2012. *European Journal of Epidemiology, 27*(9), 739-756. doi: 10.1007/s10654-012-9735-1

Janssen, K.J., Donders, A.R., Harrell, F.E., Jr., Vergouwe, Y., Chen, Q., Grobbee, D.E., & Moons, K.G. (2010). Missing covariate data in medical research: to impute is better than to ignore. *Journal of clinical epidemiology, 63*(7), 721-727. doi: 10.1016/j.jclinepi.2009.12.008

Lenzenweger, M.F. (2004). Consideration of the challenges, complications, and pitfalls of taxometric analysis. *Journal of Abnormal Psychology, 113*(1), 10-23. doi: 10.1037/0021-843X.113.1.10

Nylund, K.L., Asparouhov, T., & Muthén, B.O. (2007). Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study. *Structural Equation Modeling, 14*(4), 535-569.

Oland, A.A., & Shaw, D.S. (2005). Pure versus co-occurring externalizing and internalizing symptoms in children: the potential role of socio-developmental milestones. *Clinical Child and Family Psychology Review, 8*(4), 247-270. doi: 10.1007/s10567-005-8808-z

Rutter, M., Caspi, A., & Moffitt, T.E. (2003). Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. *Journal of Child Psychology and Psychiatry, 44*(8), 1092-1115.

Sourander, A., Jensen, P., Davies, M., Niemela, S., Elonheimo, H., Ristkari, T., et al. (2007). Who is at greatest risk of adverse long-term outcomes? The Finnish From a Boy to a Man study. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(9), 1148-1161. doi: 10.1097/chi.0b013e3180986 1e9

Statistics Netherlands. Migrants in the Netherlands 2004 (Allochtonen in Nederland 2004). (Voorburg/Heerlen 2004). Retrieved June 4, 2012 http://www.cbs.nl

Statistics Netherlands. Standard classification of education 2003 (Standaard Onderwijsindeling 2003).Voorburg/Heerlen 2004. Retrieved June 4, 2012 http://www.cbs.nl

Sterba, S., Egger, H.L., & Angold, A. (2007). Diagnostic specificity and nonspecificity in the dimensions of preschool psychopathology. *Journal of Child Psychology and Psychiatry, 48*(10), 1005-1013. doi: 10.1111/j.1469-7610.2007.01770.x

Sterne, J.A., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., et al. (2009). Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ, 338*, b2393. doi: 10.1136/bmj.b2393

Stringaris, A. (2011). Irritability in children and adolescents: a challenge for DSM-5. *European Child & Adolescent Psychiatry, 20*(2), 61-66. doi: 10.1007/s00787-010-0150-4

Stringaris, A., & Goodman, R. (2009). Mood lability and psychopathology in youth. *Psychological Medicine, 39*(8), 1237-1245. doi: 10.1017/S0033291708004662

Tiemeier, H., Velders, F.P., Szekely, E., Roza, S.J., Dieleman, G., Jaddoe, V.W., et al. (2012). The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(11), 1119-1135.e1117. doi: 10.1016/j.jaac.2012.08.021

Tolan, P.H., & Henry, D. (1996). Patterns of psychopathology among urban poor children: comorbidity and aggression effects. *Journal of Consulting and Clinical Psychology, 64*(5), 1094-1099.

Youngstrom, E.A., Findling, R.L., & Calabrese, J.R. (2003). Who are the comorbid adolescents? Agreement between psychiatric diagnosis, youth, parent, and teacher report. *Journal of Abnormal Child Psychology, 31*(3), 231-245.

Supplementary Table S1 Risk factor characteristics per class and unadjusted effects of risk factors on class membership.

	Highly problematic n=110	Internalizing n=326	Externalizing/ emotionally-reactive n=443	No problems n=5,252
	M or %	M or %	M or %	M or %
Child gender %				
Girls (reference)	33.6	51.2	35.7	51.1
Boys	66.4[a,c]	48.8	64.3[a,c]	48.9
Child ethnicity %				
Dutch (reference)	48.0	46.9	58.7	64.0
Other Western	9.1	7.6	8.4	9.3
Non-Western	42.9[b,c]	45.6[b,c]	32.9[c]	26.6
Maternal Education %				
High (reference)	32.6	36.8	45.6	51.8
Medium	32.1[c]	29.0[c]	30.3	29.1
Low	35.4[b,c]	34.2[b,c]	24.1[c]	19.2
Family income %				
> €2,000 (reference)	40.1	48.1	59.1	68.3
€1,200 - €2,000	21.0[c]	23.3[c]	18.9	16.8
< €1,200	38.9[b,c]	28.6[b,c]	21.9[c]	15.0
Maternal psychiatric symptoms*				
Affective symptoms, mean	0.60[a,b,c]	0.32[c]	0.26[c]	0.15
Hostility, mean	0.52[a,b,c]	0.28[c]	0.31[c]	0.17
Paternal psychiatric symptoms*				
Affective symptoms, mean	0.43[a,b,c]	0.21[c]	0.17[c]	0.13
Hostility, mean	0.51[a,b,c]	0.23[c]	0.23[c]	0.17

Note: The model was based on multinomial logistic regression analysis.

* Presented scores are mean raw scores. Z-standardized scores were used in the multinomial logistic regression analysis.

[a] higher than internalizing class ($p < 0.05$)

[b] higher than externalizing/emotionally-reactive class ($p < 0.05$)

[c] higher than no problems class ($p < 0.05$)

Supplementary Table S2 Parental psychological symptom scores per class and unadjusted effects of parental psychiatric symptoms on class membership in subsample with complete paternal data (n=3,475).

	Highly problematic n=39	Internalizing n=145	Externalizing/ emotionally-reactive n=222	No problems n=3,069
	M or %	M or %	M or %	M or %
Maternal psychiatric symptoms*				
Affective symptoms, mean	0.54[a,b,c]	0.24[c]	0.20[c]	0.12
Hostility, mean	0.53[a,b,c]	0.25[c]	0.27[c]	0.16
Paternal psychiatric symptoms*				
Affective symptoms, mean	0.37[a,b,c]	0.18[c]	0.15[c]	0.11
Hostility, mean	0.47[a,b,c]	0.20[c]	0.22[c]	0.15

Note: The model was based on multinomial logistic regression analysis.
* Presented scores are mean raw scores. Z-standardized scores were used in the multinomial logistic regression analysis.
[a] higher than internalizing class (p <0.05)
[b] higher than externalizing/emotionally-reactive class (p <0.05)
[c] higher than no problems class (p <0.05)

Supplementary Table S3 Adjusted associations between parental psychiatric symptoms and class membership: the highly problematic, internalizing and externalizing/emotionally-reactive classes compared with the no problems class in subsample with complete paternal data (n=3,475).

	No problems (reference)	Highly problematic		Internalizing		Externalizing/ emotionally-reactive	
	OR	OR	95% CI	OR	95% CI	OR	95% CI
Maternal psychiatric symptoms							
Affective symptoms	1.00	1.69***	1.44-1.98	1.31***	1.15-1.48	1.29***	1.15-1.45
Hostility	1.00	1.75***	1.46-2.10	1.32***	1.15-1.52	1.41***	1.26-1.58
Paternal psychiatric symptoms							
Affective symptoms	1.00	1.46***	1.23-1.75	1.16*	1.01-1.32	1.08	0.95-1.23
Hostility	1.00	1.52***	1.25-1.85	1.10	0.94-1.28	1.14*	1.01-1.29

Note: The model was based on multinomial logistic regression analysis. The no problems class is the reference group against which the odds ratios are calculated. Analyses were adjusted for child gender, child ethnicity, maternal education level, and family income. OR = odds ratio; CI = confidence interval
* p<0.05, ** p<0.01, *** p<0.001

Supplementary Table S4 Adjusted associations between parental psychiatric symptoms and class membership: the highly problematic class compared with the internalizing and externalizing/emotionally-reactive classes in subsample with complete paternal data (n=3,475).

	Highly problematic versus Internalizing			Highly problematic versus Externalizing/emotionally-reactive		
	Internalizing (reference)	Highly problematic		Externalizing/ emotionally-reactive (reference)	Highly problematic	
	OR	OR	95% CI	OR	OR	95% CI
Maternal psychiatric symptoms						
Affective symptoms	1.00	1.29**	1.07-1.55	1.00	1.31**	1.10-1.57
Hostility	1.00	1.33*	1.07-1.64	1.00	1.24*	1.03-1.51
Paternal psychiatric symptoms						
Affective symptoms	1.00	1.26*	1.03-1.55	1.00	1.36**	1.11-1.66
Hostility	1.00	1.39**	1.10-1.76	1.00	1.33**	1.07-1.65

Note: The model was based on multinomial logistic regression analysis. The internalizing class and externalizing/emotionally-reactive class are the reference groups against which the odds ratios are calculated. Analyses were adjusted for child gender, child ethnicity, maternal education level, and family income. OR = odds ratio; CI = confidence interval

* p<0.05, ** p<0.01, *** p<0.001

Chapter 3

Empirically derived CBCL profiles and DISC DSM-IV diagnoses in young children: overlap and cross-informant validity

Basten, M., Althoff, R.R., Tiemeier, H., Rijlaarsdam, J., Ringoot, A.P., Jaddoe, V.W.V., Hofman, A., Hudziak, J.J., Verhulst, F.C., & van der Ende, J.

Manuscript in preparation for submission

ABSTRACT

Objective: As an alternative to classification using DSM diagnoses, children can be classified using empirical profiles on symptom checklists. We examined the overlap and cross-informant validity across these approaches.

Method: Parents of 6,131 children from a population-based cohort, aged 5 through 7 years, reported problem behavior on the Child Behavior Checklist 1.5-5 (CBCL). Latent profile analysis (LPA) was performed on the CBCL syndrome scales and four previously described latent profiles were distinguished: 1) a dysregulation profile (1.8%; CBCL-DP) with high levels of problems across the internalizing and externalizing scales, 2) an internalizing profile (5.3%; CBCL-INT), 3) a profile with externalizing and emotionally reactive behavior (7.3%; CBCL-EXT/ER), and 4) a profile without problems (85.6%). The Diagnostic Interview Schedule (DISC) was administered to parents of 1,152 children. This subsample was enriched for psychopathology by oversampling children with high scores on the CBCL. Children's problem behavior was also assessed by the teacher (Teacher's Report Form; TRF) and child self-report (Berkeley Puppet Interview; BPI).

Results: Weighted analyses showed moderate overlap across classification approaches. Of children with the CBCL-DP, 68% met criteria for at least one DSM-IV diagnosis, including externalizing disorders (36%) or comorbid internalizing and externalizing disorders (28%). In children with CBCL-EXT/ER, 46% met criteria for a DSM-IV externalizing disorder. Children with CBCL-INT met criteria for a DSM-IV internalizing disorder in only 26% of the cases. The empirical CBCL profiles were associated with higher TRF and BPI scores of internalizing and externalizing problems. DSM-IV externalizing disorders were associated with higher scores of TRF and BPI externalizing problems. In contrast, DSM-IV internalizing disorders were not associated with TRF or BPI internalizing problems.

Conclusions: This study presents the agreement between different approaches and different informants of child psychopathology and demonstrates that empirically derived profiles of parent checklist reports are an informative complement to standard psychiatric classification.

INTRODUCTION

The choice of categories or dimensions for the assessment of psychopathology remains an important debate in child psychiatry (Coghill & Sonuga-Barke, 2012). The best known categorical system is the Diagnostic and Statistical Manual of Mental Disorder (DSM). The development of DSM diagnoses is based on consensus among panels of experts of the field. Categorical systems such as the DSM reflect a medical model according to which clinicians have to decide whether a child needs treatment or not. A critique to the DSM categories has been, however, that categories are not exclusive groupings of symptoms and as a result comorbidity of disorders is very common. There is also heterogeneity within categories and many children with serious impairment may fall just short to meet all criteria for a diagnosis (Coghill & Sonuga-Barke, 2012; Krueger & Bezdjian, 2009).

Dimensional assessment of psychopathology typically includes rating scales that have been empirically derived using statistical methods. For example, factor-analytical models have been used to extract groups of symptoms that tend to co-occur and measure the same underlying dimension of psychopathology. Dimensional scores provide the degree to which problems are present and are therefore suitable to examine treatment effects and to make comparisons across ages and informants (Hudziak et al., 2007). However, these rating scales do not typically provide categorical distinctions between normal versus "problematic" levels of behaviors which are needed for clinical decision making, although cut-points based on frequency distributions of problem scores may provide such a distinction (Achenbach & Rescorla, 2001).

A more comprehensive basis for classification and decision making than individual dimensions are empirically based profiles. An approach by which profiles can be derived on a set of dimensional measures is latent profile analysis (LPA). LPA is a person-centered method to identify homogeneous groups of individuals with similar patterns on a set of dimensions. LPA groupings are empirically based and not based on cut-points that may be rather arbitrary. In addition, co-occurrence of different types of problems is taken into account in these profiles. LPA has been used to categorize children on a variety of dimensions (e.g. De Caluwe et al., 2013; Rettew et al., 2008). Studying the relations between empirically derived profiles and categorical DSM diagnoses will facilitate the translation of information across approaches and will indicate to what extent they can complement each other.

So far, the overlap between empirically derived profiles and the DSM diagnostic system has received little attention. Instead, there have been several studies on the associations between DSM diagnoses and dimensional scales in school-age children and adolescents (Edelbrock & Costello, 1988; Gould et al., 1993; Hudziak et al., 2004; Kasius et al., 1997) and more recently also in younger children (Luby et al., 2002; Sveen et al., 2013). These studies examined both

clinical and population-based samples and used different psychiatric interviews to assess DSM diagnoses as well as different questionnaires to assess dimensions of problem behavior. Most studies found moderate convergence between DSM diagnoses and dimensions. DSM internalizing disorders, including anxiety and mood disorders, were found to be associated with internalizing scales, while DSM externalizing disorders, including attention deficit hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD), were associated with externalizing scales. However, cross-domain findings were also found. For example, Kasius et al. (1997) observed that the CBCL Anxious/depressed scale was related with the majority of DSM-III-R anxiety and mood disorders, but also with DSM externalizing disorders. Similarly, the CBCL Delinquent Behavior scale predicted ODD and CD, but also DSM mood disorders. Kasius et al. (1997) concluded that these cross-domain findings reflect high rates of co-occurrence of different types of problems that are intrinsic to child and adolescent psychiatry. Empirically derived profiles take into account the co-occurrence of different type of problems. Therefore, examining the overlap between empirically derived profiles and DSM diagnoses may improve our understanding of these cross-domain findings.

To understand how empirically derived profiles and DSM diagnoses can complement each other, not only the overlap should be considered but also how both approaches relate to independent external validators (Dirks & Boyle, 2010; Ferdinand et al., 2004; Gould et al., 1993; Jensen et al., 1996). The use of information from other informants, who have a different perspective or experience the child in a different setting, is very suitable for comparing the validity of both classifications. Jensen et al. (1996), for example, examined how parent reported problems on CBCL scales and DSM-III-R diagnoses assessed with the Diagnostic Interview Schedule for Children (DISC) were associated with child self-reported levels of depression and anxiety. The authors found that in school-age children and adolescents, both approaches were comparable in their prediction of problems reported by the child.

The aim of the current study is to present the correspondence between empirically derived profiles on a symptom checklist and DSM diagnostic groupings in the service of how best to classify children with developmental psychopathology. Previously, we identified profiles of emotional and behavioral problems in 5- to 7-year-old children from the general population (Basten et al., 2013). These profiles were derived by performing LPA on the syndrome scales of the Child Behavior Checklist/1.5-5 (Achenbach & Rescorla, 2000). Four profiles were identified: 1) a profile with no problems, 2) a profile with moderate internalizing problems, 3) a profile with moderate externalizing problems and emotional reactivity, and 4) a combined profile with high levels of problems on the internalizing and externalizing syndrome scales, which we labeled dysregulation similar to the CBCL dysregulation profile (CBCL-DP) identified in school-age children and adolescents (Althoff et al., 2010; Ayer et al., 2009).

The first aim is to examine to what extent these empirically derived profiles of the CBCL syndrome scales overlap with DSM-IV diagnostic groupings of internalizing disorders, externalizing disorders, and co-occurring internalizing and externalizing disorders in 5- to 7-year-old children. We assessed DSM-IV diagnoses using the DISC young child version. The second aim is to examine the external validity of the empirically derived CBCL profiles and DSM-IV DISC diagnoses. Therefore we examined how both classifications are associated with internalizing and externalizing problems reported by the teacher and the children themselves.

METHODS

Study population

This research was embedded in the Generation R Study, a population-based cohort from fetal life onwards. The Generation R Study has been described in detail previously (Jaddoe et al., 2012; Tiemeier et al., 2012). Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants. At birth, 9,749 children and their parents participated in the study. When the children reached the age of 5 years, 8,305 parents gave consent for further participation. At this time point, parents of 6,210 children completed the CBCL. We excluded 79 children who were 8 years or older, which resulted in a study sample of 6,131 children. Sample characteristics are presented in Table 1.

A subsample was recruited for in-depth psychiatric interview. This sample was enriched for psychopathology by including all children within the top 15 percent of the CBCL total problems score or in the top 2 percent on one of the CBCL syndrome scales (n=1,080). Also a random sample of children with scores below these cut points was recruited (n=327). Interview data were obtained for 1,164 participants. Twelve children were 9 years or older at the time of interview and were excluded. This left 1,152 children with interview data (participation rate 82%): 876 children with high scores on the CBCL and 276 children with low scores. Responders were representative of the full sample in terms of gender (47.9% vs 49.7% girl), child ethnicity (64.5% vs. 61.7% Dutch), maternal education (59.6% vs. 56.7% high education), marital status (13.4% vs. 13.4% single), and total net month family income (55.2% vs. 48.0% >3,200 euro).

The collection of teacher report on child emotional and behavioral problems was restricted to elementary schools in Rotterdam city and suburbs. In our sample of 6,131 children, teachers of 5,269 children were invited. For 3,418 children (58% of the total sample) we received a completed questionnaire from the teacher. Child self-report of emotional and behavioral problems

was obtained during a visit to the research center at the ages of 5 to 7 years. A total of 5,401 children (88%) were interviewed on their emotional and behavioral problems.

Table 1 Sample characteristics

	N=6,131
Gender, girls %	49.7
Child ethnicity %	
Dutch	61.7
Other Western	9.0
Non-Western	29.2
Missing	0.1
Maternal education %	
High	56.7
Medium	29.9
Low	12.1
Missing	1.3
Family income (net per month) %	
> €3,200	48.0
€1,600 - €3,200	30.8
< €1,600	14.6
Missing	6.6
Marital status %	
Married/living together	85.5
Single	13.4
Missing	1.1

Child Behavior Checklist profiles

Emotional and behavioral problems were assessed using the Child Behavior Checklist for ages 1.5 to 5 (CBCL; Achenbach & Rescorla, 2000). The CBCL for ages 1.5 to 5 was chosen because we expected the majority of the children to be younger than 6 years at assessment. At the end of the assessment, while the majority of the sample was 5 years old (58%), some children were 6 (38%) or 7 (4%) years old (mean age 6.0, SD=0.4). The CBCL for ages 1.5 to 5 consists of 100 items. The primary caregiver (92.6% mothers) rated each item as 0 for not true, 1 for somewhat or sometimes true, and 2 for very true or often true, based on the behavior of the child in the preceding two months. Good reliability and validity have been reported for the CBCL (Achenbach & Rescorla, 2000) and the scales were found to be generalizable across 23 societies (Ivanova et al., 2010). In our sample, for all scales Cronbach's alphas were the same in 5-year-old children and in children older than 5, indicating that problems were also reliably measured in children older than 5.

Empirical profiles of emotional and behavioral problems were derived using latent profile analysis, which has been described previously (Basten et al., 2013). In short, latent profile analysis was performed on six syndrome scales of the CBCL: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn, which are part of the internalizing domain, and Attention Problems and Aggressive Behavior, which are part of the externalizing domain. Four profiles were identified: 1) a no problems profile, including 85.6% of the children (CBCL-NP); 2) an internalizing profile (5.3%; CBCL-INT) with moderate levels of problems on the four internalizing syndrome scales; 3) an externalizing/emotionally-reactive profile (7.3%; CBCL-EXT/ER) with moderate problems on the Attention Problems, Aggressive Behavior and Emotionally Reactive scales; and 4) a dysregulation profile characterized by high levels of problems across the range of both internalizing and externalizing problems (1.8%; CBCL-DP). For analysis we used a profile membership variable that was based on the most likely latent profile membership for each child. This was justified because entropy was high at 0.98 (Clark & Muthen, 2009).

Psychiatric DSM-IV diagnoses

Psychiatric diagnoses were assessed using the Diagnostic Interview Schedule for Children (DISC) young child version (Fisher & Lucas, 2006). The DISC young child version is an adaptation of the DISC for school-age children and adolescents and is suitable for children aged 3 to 8 years. This version includes a 3 month timeframe. The DISC was administered to the primary caregiver during a home visit at the ages of 5 to 8 years (mean age 6.7 years, SD=0.6). We assessed the internalizing disorders: social phobia, separation anxiety, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, major depressive episode, and dysthymia; and the externalizing disorders: ADHD, ODD, and CD. The test-retest reliability for the symptom scales is acceptable to high (Lavigne et al., 2009). The DISC is designed to be administered by lay interviewers, who do not need formal clinical training. Bilingual interviewers (Dutch and Turkish, Dutch and Arabic or Dutch and Berber) were trained to interview parents with difficulty in Dutch language. Interviewers were blind to the CBCL scores. We used the computer-assisted DISC, which is programmed to derive DSM-IV diagnoses by applying the algorithms provided by the developers.

Teacher and child report of emotional and behavioral problems

Teachers reported emotional and behavioral problems on the Teacher's Report Form for ages 6-18 (TRF; Achenbach & Rescorla, 2001). The TRF was completed when children were between 4 and 10 years old (mean age 6.7 years, SD=1.3). Since the majority of the children were 6 years or older (62%) by the time the TRF was presented to the teachers, we used the 6-18 version for all children. Good reliability and validity have been reported for the TRF (Achenbach & Rescorla, 2001). The TRF includes 120 items that were rated as 0 for not true, 1 for somewhat or sometimes true, and 2 for very true or often true. We summed all items into a total problems

score. The internalizing problems scale, including the syndrome scales Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints, and the Externalizing scale, including the Rule Breaking Behavior and Aggressive Behavior syndrome scales, were also calculated. The average time difference between TRF and CBCL assessments was 1.1 years (SD=1.0) and between TRF and DISC assessments was 1.0 years (SD=0.8).

The Berkeley Puppet Interview (BPI; Ablow et al., 2003) was used to obtain children's self-reports of emotional and behavioral problems (mean age 6.1 years, SD=0.4). The BPI is a validated semi structured interactive interview technique for children 4-to-8 years old (Ablow et al., 1999; Ringoot et al., 2013). In the Generation R Study we administered three internalizing scales, i.e. Depression, Separation Anxiety, and Overanxious, three externalizing scales, i.e. Oppositional Defiant, Overt Hostility, and Conduct Problems, and 2 peer relations scales, i.e. Bullied by Peers and Peer Acceptance/Rejection. Interviews were video-taped for scoring by coders. Items were scored on a 7-point scale with higher scores indicating more problems. The inter-rater reliability for each scale was high (range .96-.98; Ringoot et al., 2013). Total problems, internalizing problems, and externalizing problems scores were calculated. The average time difference between BPI and CBCL assessments was 0.1 years (SD=0.2) and between the BPI and DISC assessments was 0.7 years (SD=0.5).

Data analysis

Statistical analyses were performed using the computer package SPSS version 21. We used Complex Sample Statistics, a procedure that takes account of the complex survey design and applies weights to adjust for unequal sampling probabilities to represent rates of disorder in the full sample. First, we examined the overlap between the CBCL profiles and DISC DSM-IV diagnoses. For each CBCL group we calculated weighted prevalence for DSM-IV diagnoses. We examined the prevalence of any DSM-IV disorder, comorbid internalizing and externalizing disorder, internalizing disorder only, externalizing disorder only, and the prevalence of each diagnosis separately.

Next, we examined to what extent the CBCL profiles and DISC DSM-IV diagnoses were associated with total problems, internalizing problems, and externalizing problems reported by the teacher on the TRF and by the child on the BPI. To allow comparisons across analyses, for both the CBCL profiles and DISC DSM-IV diagnoses weighted univariate linear regression analyses were performed on the subsample of children with a DISC available. For the CBCL profiles the CBCL-NP was the reference category. DSM-IV diagnoses were categorized into comorbid internalizing and externalizing disorder, internalizing disorder only, and externalizing disorder only. No DSM-IV diagnosis was the reference category. Teacher and child reported problems were dependent variables. A square root transformation and z-standardization was applied

to teacher and child reported problem scores to improve normality and to allow comparison across informants.

Secondary analyses were conducted to further examine the consistency of associations. To examine the influence of time between assessments on CBCL profiles and DISC DSM-IV diagnoses associations with teacher and child reported problems, we repeated analyses in children with above average time difference between assessments and in children with below average time difference between assessments. To examine possible bias of the weighting procedure on the association between CBCL profiles and teacher and child reported problems, these analyses were repeated using unweighted linear regression in the total sample.

Non-response analysis

We compared prenatal child and maternal characteristics of the children included in the analysis (n=6,131) with those excluded because of missing data on CBCL (n=3,618). Children of responding mothers were more likely to be Dutch (60.6% vs. 30.8%, χ^2=1,062, df=3, p<0.001). Responding mothers were more likely to be highly educated (48.7% vs. 18.9%, χ^2=1,250, df=3, p<0.001) and to have a high family income (55.2% vs. 20.3%, χ^2=1,328, df=3, p<0.001).

RESULTS

Table 2 provides the prevalence of DISC DSM-IV diagnoses per CBCL profile. The prevalence, based on a selected group of 1,152 interviewed children, was weighted to represent rates in the full sample (N=6,131). In the CBCL-DP, which included 1.8% of the total sample, 67.9% met criteria for at least one diagnosis. The most common diagnostic groups were comorbid internalizing and externalizing disorder (28.2%) and externalizing disorder only (35.9%). In the CBCL-INT (5.3%), 35.1% met criteria for at least one diagnosis: 12.5% met criteria for an internalizing disorder, 9.5% met criteria for an externalizing disorder, and 13.2% met criteria for comorbid internalizing and externalizing disorder. In the CBCL-EXT/ER (7.3%), 51.4% of the children met criteria for at least one diagnosis. Children with this profile met criteria for an externalizing disorder in 46.3%, in 11.4% this was comorbid with an internalizing disorder. Children with the CBCL-NP (85.6%) met criteria for a disorder in 22.6% of the time, with relatively equivalent percentages of externalizing and internalizing disorders and low comorbidity. The prevalence of specific DISC DSM-IV diagnoses per CBCL profile is provided in Supplementary Table S1.

Table 3 shows results for the associations of CBCL profiles and DISC DSM-IV diagnostic groupings with teacher reported problems on the TRF. The CBCL-DP, CBCL-INT, and CBCL-EXT/ER were all associated with higher levels of problems on each scale, with one exception:

Table 2 Prevalence of DSM-IV diagnoses per CBCL profile

	DISC DSM-IV diagnoses									
	Any disorder[a]		Comorbid int-ext		Internalizing disorder only		Externalizing disorder only		No Disorder	
CBCL Profiles	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
CBCL-DP (1.8%)	67.9	(56.8;77.3)	28.2	(19.3;39.2)	3.8	(1.2;11.3)	35.9	(26.1;47.1)	32.1	(22.7;43.2)
CBCL-INT (5.3%)	35.1	(25.7;45.9)	13.2	(5.6;27.8)	12.5	(8.5;18.0)	9.5	(6.1;14.4)	64.9	(54.1;74.3)
CBCL-EXT/ER (7.3%)	51.4	(44.6;58.1)	11.4	(8.3;15.6)	5.1	(3.1;8.2)	34.8	(27.8;42.7)	48.6	(41.9;55.4)
CBCL-NP (85.6%)	22.6	(18.4;27.5)	2.0	(0.9;4.2)	9.8	(7.0;13.6)	10.9	(7.9;14.7)	77.4	(72.5;81.6)

Note: Prevalences represent weighted prevalence estimates based on parental Diagnostic Interview Schedule for Children (DISC) interviews in 1,152 children from a population-based study of 6,131 children.

[a] Any disorder includes the internalizing disorders: social phobia, separation anxiety, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, major depressive episode, and dysthymia; the externalizing disorders: attention deficit hyperactivity disorder, oppositional defiant disorder, and conduct disorder;

Comorbid int-ext= comorbid internalizing and externalizing disorder; CBCL= Child Behavior Checklist/1.5-5; CBCL-DP=CBCL dysregulation profile; CBCL-INT=CBCL internalizing profile; CBCL-EXT/ER=CBCL externalizing/emotionaly-reactive profile; CBCL-NP=CBCL no problems profile.

the CBCL-INT was associated with higher levels of teacher reported total problems (B=0.24, p<0.05), and internalizing problems (B=0.59, p<0.001), but not with externalizing problems. For the DISC DSM-IV diagnostic groupings, we found that the group with comorbid internalizing and externalizing disorders was associated with higher levels of total problems (B=0.71, p<0.01), but not specifically with higher levels of teacher reported internalizing or externalizing problems. Children with an internalizing disorder were not considered to have problems by their teacher, while children with an externalizing disorder showed increased levels of teacher reported total problems (B=0.83, p<0.01) and externalizing problems (B=0.96, p<0.01).

Associations of CBCL profiles and DISC DSM-IV diagnostic groupings with child self-reported problems on the BPI (Table 4), were weaker, but showed a very similar pattern. Children with the CBCL-DP, CBCL-INT, and CBCL-EXT/ER showed higher levels of child reported problems on each scale with, again, one exception: children with the CBCL-INT did not report more externalizing problems. Children with DISC comorbid internalizing and externalizing disorders did not report more problems, contrary to the findings with teacher report. Children with an internalizing disorder did not report more problems in any of the domains, while children with an externalizing disorder reported more total problems (B=0.40; p<0.05) and externalizing problems (B=0.54; p<0.01).

Secondary analyses showed that associations of CBCL profiles and DISC DSM-IV diagnostic groupings with TRF and BPI were comparable for children with above average and below average time between assessments. When the associations between CBCL profiles and teacher and child reported problems were studied using unweighted regressions in the total sample (N=6,131), the same associations were found.

Table 3 Empirical CBCL profiles and DISC DSM-IV diagnoses: associations with teacher report of problem behavior

		Teacher report[a]								
		Total problems			Internalizing problems			Externalizing problems		
	n[b]	B	(95%CI)	R^2	B	(95%CI)	R^2	B	(95%CI)	R^2
CBCL profiles				0.05			0.03			0.05
CBCL-DP	32	1.05***	(0.67;1.43)		.51*	(0.08;0.95)		1.07***	(0.64;1.50)	
CBCL-INT	123	0.24*	(0.02;0.46)		.59***	(0.36;0.81)		.06	(-0.16;0.27)	
CBCL-EXT/ER	159	0.80***	(0.51;1.09)		.43*	(0.06;0.80)		.82***	(0.50;1.14)	
CBCL-NP (reference)	342	-	-		-	-		-	-	
DISC diagnoses (exclusive groups)				0.09			0.02			0.10
Comorbid int-ext	53	0.71**	(0.18;1.23)		0.48	(-0.23;1.19)		0.31	(-0.18;0.80)	
Internalizing disorder only	56	0.16	(-0.34;0.65)		0.12	(-0.30;0.53)		0.21	(-0.36;0.78)	
Externalizing disorder only	124	0.83***	(0.46;1.19)		0.24	(-0.10;0.58)		0.96***	(0.55;1.37)	
No disorder (reference)	423	-	-		-	-		-	-	

Note: [a] Scores of teacher reported problems are square root transformed and z-standardized

[b] Group sizes are number of children for whom a Diagnostic Interview Schedule for Children (DISC) and teacher report is available, effect estimates are based on weighted analyses

***p<0.001; ** p<0.01; * p<0.05

CBCL= Child Behavior Checklist/1.5-5; CBCL-DP=CBCL dysregulation profile; CBCL-INT=CBCL internalizing profile; CBCL-EXT/ER=CBCL externalizing/emotionaly-reactive profile; CBCL-NP=CBCL no problems profile; DISC= Diagnostic Interview Schedule for Children, young child version; Comorbid int-ext= comorbid internalizing and externalizing disorder

Table 4 Empirical CBCL profiles and DISC DSM-IV diagnoses: associations with child self-report of problem behavior

		Child self-report[a]								
		Total problems			Internalizing problems			Externalizing problems		
	n[b]	B	(95%CI)	R^2	B	(95%CI)	R^2	B	(95%CI)	R^2
CBCL profiles				0.03			0.02			0.02
CBCL-DP	70	0.72***	(0.43;1.01)		0.48**	(0.21;0.76)		.59***	(0.30;0.88)	
CBCL-INT	199	0.29**	(0.10;0.48)		0.33***	(0.16;0.50)		.13	(-0.04;0.31)	
CBCL-EXT/ER	277	0.56***	(0.33;0.78)		0.35**	(0.10;0.61)		.49***	(0.30;0.68)	
CBCL-NP (reference)	540	-	-		-	-		-	-	
DISC diagnoses (exclusive groups)				0.02			0.00			0.04
Comorbid int-ext	93	0.27	(-0.12;0.65)		0.11	(-0.25;0.48)		0.24	(-0.06;0.54)	
Internalizing disorder only	100	0.13	(-0.19;0.45)		0.08	(-0.25;0.41)		0.11	(-0.15;0.37)	
Externalizing disorder only	229	0.40*	(0.08;0.73)		0.16	(-0.14;0.45)		0.54**	(0.22;0.87)	
No disorder (reference)	726	-	-		-	-		-	-	

Note: [a] Scores of child reported problems are square root transformed and z-standardized

[b] Group sizes are number of children for whom a Diagnostic Interview Schedule for Children (DISC) and child self-report is available, effect estimates are based on weighted analyses

***p<0.001; ** p<0.01; * p<0.05

CBCL= Child Behavior Checklist/1.5-5; CBCL-DP=CBCL dysregulation profile; CBCL-INT=CBCL internalizing profile; CBCL-EXT/ER=CBCL externalizing/emotionaly-reactive profile; CBCL-NP=CBCL no problems profile; DISC= Diagnostic Interview Schedule for Children, young child version; Comorbid int-ext= comorbid internalizing and externalizing disorder

DISCUSSION

In this study we examined how empirically derived profiles of emotional and behavioral problems on the CBCL overlap with DSM-IV diagnoses assessed with the DISC in a general population sample of 5- to 7-year-old children. We found that children with the CBCL-DP and CBCL-EXT/ER profiles showed high prevalences of DSM-IV externalizing disorders on the DISC, which supports convergence across classifications. The CBCL-DP and CBCL-INT showed, although to a lesser extent, overlap with DSM-IV internalizing disorders. Further, we examined the associations of both approaches to two other informants, the teacher and the child. The CBCL profiles corresponded with internalizing and externalizing problems reported by the teacher and the child, while the DISC DSM-IV diagnoses corresponded with child and teacher reports on externalizing problems only.

Previous studies found moderate correspondence across DSM diagnoses and dimensional approaches. One of the important findings in these studies was the association between diagnoses and dimensions across domains: DSM internalizing disorders were associated with externalizing dimensions and DSM externalizing disorders were associated with internalizing dimensions (Edelbrock & Costello, 1988; Gould et al., 1993; Kasius et al., 1997). These findings are best explained by a high level of co-occurrence intrinsic to child psychiatry. In the present study we took co-occurrence of problems into account. We found that children with the CBCL-DP, which was characterized by high levels of internalizing and externalizing problems, were more likely to meet criteria for both DISC internalizing and externalizing disorders. However, we also found cross-domain overlap: for the CBCL-INT, 25% of children met criteria for a DISC DSM-IV externalizing disorder. In addition, there was also a large group of children who were classified as problematic by only one of the approaches. A large proportion of children with CBCL-DP, CBCL-INT, and CBCL-EXT/ER did not meet a DISC DSM-IV disorder. Furthermore, 23% of the children with the CBCL-NP met criteria for a DISC DSM-IV disorder. The lack of overlap in these cases might in part be explained by the 6 months interval between assessments. A more important explanation is that both approaches assess different problems. Children who are considered to have no problems according to the CBCL profiles might meet criteria for a DSM diagnosis because they show problems in only a specific domain. Also, children with one of the three CBCL problem profiles might have problems that are not severe enough to meet criteria for a full DSM diagnosis. The lack of overlap suggests that both approaches are needed for a thorough assessment of children's psychopathology.

The associations with teacher and child reported problems showed how the CBCL profiles and DSM diagnoses can complement each other. In general, associations across informants were small, but in line with previous findings on cross-informant agreement (De Los Reyes & Kazdin, 2005). The CBCL profiles were associated in the expected directions with teacher report

and child report. These findings support the validity of the CBCL profiles across settings and informants. The similar associations between parent and teacher report compared to parent and child report also support the validity of child reported emotional and behavioral problems with the BPI in 5- to 7-year-old children.

DISC DSM-IV externalizing disorders corresponded well with teacher and child reported externalizing problems. In contrast, children with a DISC DSM-IV internalizing disorder did not have internalizing problems according to the teacher and the child. Carter et al. (2010) suggested that in 6-year-old children DSM internalizing disorders are not well recognized by the environment. In their study, parents of children with an internalizing disorder, which was based on parent interview, reported that their children had adequate adaptive and social skills. Also, teachers did not consider these children problematic on a measure of social competence. If children, as Carter et al. (2010) states, 'suffer in silence' we would have expected to find an association between DSM internalizing disorders and child self-report on internalizing problems, which was not the case. Similar to our findings, other studies in young children also found that the associations between internalizing dimensions and DSM disorders were less strong than associations between externalizing dimensions and DSM disorders (Luby et al., 2002; Sveen et al., 2013). In the study of Sveen et al. (2013) a different psychiatric interview was used, suggesting that findings are not only dependent on the DISC. This suggests that the external validity of DSM internalizing disorders in 5- to 7-year-old children deserves further attention. In addition an empirical assessment of internalizing problems may be a particularly important complement to the DSM classification system to adequately assess children's internalizing problems.

The CBCL-DP is used to describe children with most severe problems in regulating their emotions, attention, and behavior (Ayer et al., 2009). These children are at high risk for poor outcomes later in life (Althoff et al., 2010; Holtmann et al., 2011; Meyer et al., 2009). Our findings demonstrate that in the general population children with this profile are likely to meet criteria for internalizing and externalizing disorders. Results of previous studies suggested that the CBCL-DP was only related to externalizing disorders, which is likely explained by the selected samples in these studies (Holtmann et al., 2008; Volk & Todd, 2007). Only in offspring of mothers with a mood disorder, Meyer et al. (2009) previously found children with CBCL-DP to be more likely to meet criteria for anxiety disorders. This study also showed that children with the CBCL-DP are considered problematic in other settings and based on other informants. These results confirm previous studies showing that the CBCL-DP captures children with severe problems in regulating emotions and behavior.

Important strengths of the study are the population-based design, the large number of participants and the inclusion of multiple informants. This study has also limitations. First, a two-stage

sampling design was used for estimating prevalence of psychiatric disorders in the total population in an efficient way. However, by using this design and calculating weighted prevalences, statistical precision was reduced (Dunn et al., 1999). Second, the CBCL, DISC, TRF, and BPI were all measured at different time points with varying time between assessments. In the large study sample of Generation R it was not feasible to assess four different measures of emotional and behavioral problems from three different informants all at the same time point. The time between assessments might have lowered the correspondence among the different measures. However, we found no stronger associations for children with below average time between assessments than in children with above average time between assessments. Third, the CBCL and TRF are very similar questionnaires, which may partly explain why the CBCL profiles corresponded better with the teacher reported problems than the DSM disorders did. Even though this might have played a role, similar results were found for child reported problems assessed with the BPI, which is a very different instrument. Another limitation is that the non-response analyses indicated that higher educated mothers and Dutch children were more likely to be included in the study, which resulted in an under-representation of more disadvantaged families and may have impacted on the prevalence of psychopathology. However, prevalence of DSM diagnoses was very similar to a previously performed population-based study in 6-year-old children (Carter et al., 2010).

Our findings are important for clinical settings, where the lack of time to do standardized assessments often leads to clinical classification of a child as either having an internalizing or externalizing disorder. The use of a simple checklist provides important additional information. Empirically derived profiles on checklist dimensions may give a more comprehensive basis for decision making than individual checklist scales. This study showed that empirically derived CBCL profiles show moderate overlap with DSM-IV diagnoses in a population-based sample of 5- to 7-year-old children. The convergence across approaches, especially on the externalizing domain, supports the validity of both approaches. Our results indicated that empirically derived CBCL profiles are an informative complement to DSM-IV diagnoses in young children, especially in the assessment of internalizing problems. In addition, the CBCL dysregulation profile identifies children with severe emotional and behavioral problems who are at high risk for poor outcomes later in life.

REFERENCES

Ablow, J.C., Measelle, J.R., & Assessment, the MacArthur Working Group on Outcome Assessment (2003). *Manual for the Berkeley Puppet Interview: Symptomatology, social, and academic modules (BPI 1.0)*. Pittsburgh, PA: University of Pittsburgh.

Ablow, J.C., Measelle, J.R., Kraemer, H.C., Harrington, R., Luby, J., Smider, N., et al. (1999). The MacArthur Three-City Outcome Study: evaluating multi-informant measures of young children's symptomatology. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(12), 1580-1590. doi: 10.1097/00004583-199912000-00020

Achenbach, T.M., & Rescorla, L.A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Achenbach, T.M., & Rescorla, L.A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families.

Althoff, R.R., Verhulst, F.C., Rettew, D.C., Hudziak, J.J., & van der Ende, J. (2010). Adult outcomes of childhood dysregulation: a 14-year follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(11), 1105-1116. doi: 10.1016/j.jaac.2010.08.006

Ayer, L., Althoff, R., Ivanova, M., Rettew, D., Waxler, E., Sulman, J., & Hudziak, J. (2009). Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. *Journal of Child Psychology and Psychiatry, 50*(10), 1291-1300. doi: 10.1111/j.1469-7610.2009.02089.x

Basten, M.M., Althoff, R.R., Tiemeier, H., Jaddoe, V.W., Hofman, A., Hudziak, J.J., et al. (2013). The dysregulation profile in young children: empirically defined classes in the generation R study. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(8), 841-850 e842. doi: 10.1016/j.jaac.2013.05.007

Carter, A.S., Wagmiller, R.J., Gray, S.A., McCarthy, K.J., Horwitz, S.M., & Briggs-Gowan, M.J. (2010). Prevalence of DSM-IV disorder in a representative, healthy birth cohort at school entry: sociodemographic risks and social adaptation. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(7), 686-698. doi: 10.1016/j.jaac.2010.03.018

Clark, S., & Muthen, B. (2009). Relating Latent Class Analysis Results to Variables not Included in the Analysis. http://www.statmodel.com/download/relatinglca.pdf

Coghill, D., & Sonuga-Barke, E.J. (2012). Annual research review: categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders—implications of recent empirical study. *Journal of Child Psychology and Psychiatry, 53*(5), 469-489.

De Caluwe, E., Decuyper, M., & De Clercq, B. (2013). The child behavior checklist dysregulation profile predicts adolescent DSM-5 pathological personality traits 4 years later. *European Child & Adolescent Psychiatry, 22*(7), 401-411. doi: 10.1007/s00787-013-0379-9

De Los Reyes, A., & Kazdin, A.E. (2005). Informant discrepancies in the assessment of childhood psychopathology: A critical review, theoretical framework, and recommendations for further study. *Psychological Bulletin, 131*(4), 483-509. doi: 10.1037/0033-2909.131.4.483

Dirks, M.A., & Boyle, M.H. (2010). The comparability of mother-report structured interviews and checklists for the quantification of youth externalizing symptoms. *Journal of Child Psychology and Psychiatry, 51*(9), 1040-1049. doi: 10.1111/j.1469-7610.2010.02244.x

Dunn, G., Pickles, A., Tansella, M., & Vazquez-Barquero, J.L. (1999). Two-phase epidemiological surveys in psychiatric research. *British Journal of Psychiatry, 174*, 95-100. doi: 10.1192/Bjp.174.2.95

Edelbrock, C., & Costello, A.J. (1988). Convergence between Statistically Derived Behavior Problem Syndromes and Child Psychiatric Diagnoses. *Journal of Abnormal Child Psychology, 16*(2), 219-231. doi: 10.1007/Bf00913597

Ferdinand, R.F., Visser, J.H., Hoogerheide, K.N., van der Ende, J., Kasius, M.C., Koot, H.M., & Verhulst, F.C. (2004). Improving estimation of the prognosis of childhood psychopathology; combination of DSM-

III-R/DISC diagnoses and CBCL scores. *Journal of Child Psychology and Psychiatry, 45*(3), 599-608. doi: 10.1111/j.1469-7610.2004.00249.x

Fisher, P., & Lucas, C. (2006). *Diagnostic Interview Schedule for Children (DISC-IV) - Young Child*. New York, NY: Columbia University.

Gould, M.S., Bird, H., & Jaramillo, B.S. (1993). Correspondence between Statistically Derived Behavior Problem Syndromes and Child Psychiatric Diagnoses in a Community Sample. *Journal of Abnormal Child Psychology, 21*(3), 287-313. doi: 10.1007/Bf00917536

Holtmann, M., Buchmann, A.F., Esser, G., Schmidt, M.H., Banaschewski, T., & Laucht, M. (2011). The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis. *Journal of Child Psychology and Psychiatry, 52*(2), 139-147. doi: 10.1111/j.1469-7610.2010.02309.x

Holtmann, M., Goth, K., Wockel, L., Poustka, F., & Bolte, S. (2008). CBCL-pediatric bipolar disorder phenotype: severe ADHD or bipolar disorder? *Journal of neural transmission, 115*(2), 155-161. doi: 10.1007/s00702-007-0823-4

Hudziak, J.J., Achenbach, T.M., Althoff, R.R., & Pine, D.S. (2007). A dimensional approach to developmental psychopathology. *International Journal of Methods in Psychiatric Research, 16 Suppl 1*, S16-23. doi: 10.1002/mpr.217

Hudziak, J.J., Copeland, W., Stanger, C., & Wadsworth, M. (2004). Screening for DSM-IV externalizing disorders with the Child Behavior Checklist: a receiver-operating characteristic analysis. *Journal of Child Psychology and Psychiatry, 45*(7), 1299-1307. doi: 10.1111/j.1469-7610.2004.00314.x

Ivanova, M.Y., Achenbach, T.M., Rescorla, L.A., Harder, V.S., Ang, R.P., Bilenberg, N., et al. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1215-1224. doi: 10.1016/j.jaac.2010.08.019

Jaddoe, V.W., van Duijn, C.M., Franco, O.H., van der Heijden, A.J., van Iizendoorn, M.H., de Jongste, et al. (2012). The Generation R Study: design and cohort update 2012. *European Journal of Epidemiology, 27*(9), 739-756. doi: 10.1007/s10654-012-9735-1

Jensen, P.S., Watanabe, H.K., Richters, J.E., Roper, M., Hibbs, E.D., Salzberg, A.D., & Liu, S. (1996). Scales, diagnoses, and child psychopathology: II. Comparing the CBCL and the DISC against external validators. *Journal of Abnormal Child Psychology, 24*(2), 151-168. doi: 10.1007/Bf01441482

Kasius, M.C., Ferdinand, R.F., van den Berg, H., & Verhulst, F.C. (1997). Associations between different diagnostic approaches for child and adolescent psychopathology. *Journal of Child Psychology and Psychiatry, 38*(6), 625-632. doi: 10.1111/j.1469-7610.1997.tb01689.x

Krueger, R.F., & Bezdjian, S. (2009). Enhancing research and treatment of mental disorders with dimensional concepts: toward DSM-V and ICD-11. *World Psychiatry, 8*(1), 3-6.

Lavigne, J.V., Lebailly, S.A., Hopkins, J., Gouze, K.R., & Binns, H.J. (2009). The prevalence of ADHD, ODD, depression, and anxiety in a community sample of 4-year-olds. *Journal of Clinical Child and Adolescent Psychology, 38*(3), 315-328. doi: 10.1080/15374410902851382

Luby, J.L., Heffelfinger, A., Measelle, J.R., Ablow, J.C., Essex, M.J., Dierker, L., et al. (2002). Differential performance of the macarthur HBQ and DISC-IV in identifying DSM-IV internalizing psychopathology in young children. *Journal of the American Academy of Child and Adolescent Psychiatry, 41*(4), 458-466. doi: 10.1097/00004583-200204000-00019

Meyer, S.E., Carlson, G.A., Youngstrom, E., Ronsaville, D.S., Martinez, P.E., Gold, P.W., et al. (2009). Long-term outcomes of youth who manifested the CBCL-Pediatric Bipolar Disorder phenotype during childhood and/or adolescence. *Journal of Affective Disorders, 113*(3), 227-235. doi: 10.1016/j.jad.2008.05.024

Rettew, D.C., Althoff, R.R., Dumenci, L., Ayer, L., & Hudziak, J.J. (2008). Latent profiles of temperament and their relations to psychopathology and wellness. *Journal of the American Academy of Child and Adolescent Psychiatry, 47*(3), 273-281. doi: 10.1097/CHI.0b013e318160b403

Ringoot, A.P., Jansen, P.W., Steenweg-de Graaff, J., Measelle, J.R., van der Ende, J., Raat, H., et al. (2013). Young children's self-reported emotional, behavioral, and peer problems: the Berkeley Puppet Interview. *Psychological Assessment, 25*(4), 1273-1285. doi: 10.1037/a0033976

Sveen, T.H., Berg-Nielsen, T.S., Lydersen, S., & Wichstrom, L. (2013). Detecting Psychiatric Disorders in Preschoolers: Screening With the Strengths and Difficulties Questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(7), 728-736. doi: 10.1016/j.jaac.2013.04.010

Tiemeier, H., Velders, F.P., Szekely, E., Roza, S.J., Dieleman, G., Jaddoe, V.W., et al. (2012). The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(11), 1119-1135.e1117. doi: 10.1016/j.jaac.2012.08.021

Volk, H.E., & Todd, R.D. (2007). Does the Child Behavior Checklist juvenile bipolar disorder phenotype identify bipolar disorder? *Biological Psychiatry, 62*(2), 115-120. doi: 10.1016/j.biopsych.2006.05.036

Supplementary Table S1 Prevalence of individual internalizing and externalizing DISC DSM-IV diagnoses per CBCL-profile

	DISC DSM-IV externalizing disorders											
	Any ADHD		ADHD inattentive		ADHD hyperactive		ADHD combined		Oppositional defiant disorder		Conduct disorder	
CBCL profile	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
CBCL-DP (1.8%)	43.6	(33.0;54.7)	3.9	(1.3;11.4)	19.2	(11.9;29.5)	20.5	(13.0;30.9)	48.1	(37.2;59.1)	8.5	(3.6;18.8)
CBCL-INT (5.3%)	14.5	(6.7;28.5)	11.9	(4.7;27.3)	1.7	(0.6;4.6)	0.9	(0.2;3.4)	9.9	(6.5;15.0)	-	
CBCL-EXT/ER (7.3%)	26.4	(21.4;32.0)	6.4	(4.1;9.8)	8.6	(5.9;12.4)	11.5	(8.3;15.7)	31.8	(24.7;39.8)	2.3	(1.0;5.1)
CBCL-NP (85.6%)	6.3	(4.2;9.4)	2.5	(1.3;4.8)	2.1	(1.0;4.3)	1.7	(0.8;3.7)	8.2	(5.7;11.8)	0.1	(0.0;0.2)
	DISC DSM-IV internalizing disorders											
	Social phobia		Separation anxiety		Specific phobia		Generalized anxiety disorder		Major depressive episode		Dysthymia	
CBCL profile	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)	%	(95% CI)
CBCL-DP (1.8%)	10.3	(5.2;19.2)	5.1	(1.9;12.9)	18.4	(11.2;28.8)	7.7	(3.5;16.1)	2.6	(0.6;9.8)	6.6	(2.8;14.9)
CBCL-INT (5.3%)	4.7	(2.6;8.5)	8.9	(2.5;27.0)	20.0	(11.4;32.7)	3.4	(1.7;6.9)	-		-	
CBCL-EXT/ER (7.3%)	3.2	(1.7;5.8)	1.3	(0.5;3.4)	12.5	(9.2;16.9)	1.9	(0.9;4.2)	0.3	(0.0;2.2)	0.6	(0.2;2.5)
CBCL-NP (85.6%)	0.5	(0.1;1.9)	0.8	(0.2;2.6)	9.9	(7.0;13.8)	0.0	(0.0;0.2)	0.3	(0.0;2.4)	0.4	(0.1;2.2)

Note: Prevalences represent weighted prevalence estimates based on parental Diagnostic Interview Schedule for Children (DISC) interviews in 1,152 children from a population-based study of 6,131 children.

DISC= Diagnostic Interview Schedule for Children, young child version; ADHD=attention deficit hyperactivity disorder; CBCL=Child Behavior Checklist/1.5-5; CBCL-DP=CBCL dysregulation profile; CBCL-INT=CBCL internalizing profile; CBCL-EXT/ER=CBCL externalizing/emotionaly-reactive profile; CBCL-NP=CBCL no problems profile.

Chapter 4

Nonverbal intelligence in young children with dysregulation: the Generation R Study

Basten, M., van der Ende, J., Tiemeier, H., Althoff, R. R., Rijlaarsdam, J., Jaddoe, V. W., Hofman, A., Hudziak, J.J., Verhulst, F.C., White, T. (*2014*)

European Child & Adolescent Psychiatry. Doi: 10.1007/s00787-014-0551-x

ABSTRACT

Children with the CBCL Dysregulation Profile (CBCL-DP) suffer from high levels of co-occurring internalizing and externalizing problems. Little is known about the cognitive abilities of these children with CBCL-DP. We examined the relationship between CBCL-DP and nonverbal intelligence. Parents of 6,131 children from a population-based birth cohort, aged 5 through 7 years, reported problem behavior on the CBCL/1.5-5. The CBCL-DP was derived using latent profile analysis on the CBCL/1.5-5 syndrome scales. Nonverbal intelligence was assessed using the Snijders Oomen Nonverbal Intelligence Test 2.5-7-Revised. We examined the relationship between CBCL-DP and nonverbal intelligence using linear regression. Analyses were adjusted for parental intelligence, parental psychological symptoms, socio-economic status, and perinatal factors. In a subsample with diagnostic interview data we tested if the results were independent of the presence of attention deficit hyperactivity disorder (ADHD) or autism spectrum disorders (ASD). The results showed that children with the CBCL-DP (n=110, 1.8%) had a 11.0 point lower nonverbal intelligence level than children without problems and 7.2-7.3 points lower nonverbal intelligence level than children with other profiles of problem behavior (all p-values <0.001). After adjustment for covariates, children with CBCL-DP scored 8.3 points lower than children without problems (p<0.001). The presence of ADHD or ASD did not account for the lower nonverbal intelligence in children with CBCL-DP. In conclusion, we found that children with CBCL-DP have a considerable lower nonverbal intelligence score. The CBCL-DP and nonverbal intelligence may share a common neurodevelopmental etiology.

INTRODUCTION

Children with co-occurring internalizing and externalizing problems have high levels of impairment and are at high risk for psychiatric disorders in adulthood (Althoff et al., 2010b; Angold et al., 1999; Sourander et al., 2007). An empirically derived profile that describes children with co-occurring internalizing and externalizing problems is the Child Behavior Checklist dysregulation profile (CBCL-DP; Althoff et al., 2010a; Althoff et al., 2006; Althoff et al., 2010b; Ayer et al., 2009). The CBCL-DP in school-age children and adolescents is operationalized by high scores on the anxious/depressed, attention problems, and aggressive behavior scales of the CBCL (Achenbach & Rescorla, 2001). It was first thought that high levels on these three scales were specific for juvenile bipolar disorder (Biederman et al., 1995), but later studies have shown that this profile identifies children with poor regulation of emotion, attention, and behavior (Ayer et al., 2009). Recently, we empirically identified a CBCL-DP on the preschool CBCL (Achenbach & Rescorla, 2000; Basten et al., 2013). In young children, this profile was characterized by a wider range of problems across the internalizing and externalizing domains. The CBCL-DP has been found to be highly heritable and stable over time and is related to social problems, school problems, and suicidality (Althoff et al., 2006; Ayer et al., 2009; Jucksch et al., 2011). Studies in clinical or at risk samples have shown that the CBCL-DP is related to the presence of several psychiatric diagnoses, including attention deficit hyperactivity disorder (ADHD) or hyperkinetic disorder (Holtmann et al., 2008; Meyer et al., 2009; Volk & Todd, 2007), anxiety disorder (Meyer et al., 2009), conduct disorder (Holtmann et al., 2008; Volk & Todd, 2007) and oppositional defiant disorder (Volk & Todd, 2007). The poor outcomes of the CBCL-DP argue for further study of the mechanisms underlying this phenotype. So far, little is known as to what extent children with CBCL-DP experience cognitive impairment.

Impairment in cognitive functioning is a key characteristic of neurodevelopmental disorders. Neurodevelopmental disorders are a heterogeneous constellation of disorders that are marked by impairment in the growth and development of the brain, such as autism spectrum disorders (ASD) and ADHD. Impairment in cognitive functioning can involve specific deficits or more general impairment, which is often assessed using intelligence tests. For example, children with ADHD score on average 9 points lower on intelligence tests than healthy controls (Frazier et al., 2004). Many children with ASD have an intelligence level <70 (Chakrabarti & Fombonne, 2001; Coolican et al., 2008). However, cognitive impairment is not limited to neurodevelopmental disorders. Population-based studies have shown that general measures of psychopathology, such as the CBCL total problems score, correlate mildly with lower intelligence level (Goodman et al., 1995; Jacobs et al., 2002). Externalizing problems, including antisocial behavior and aggression, are also negatively related to intelligence level (Cook et al., 1994; Goodman et al., 1995; Koenen et al., 2006; Lynam et al., 1993). For internalizing problems, such as anxiety and depressive symptoms, mixed results have been found (Davis et al., 2008; Goodman et al.,

1995; Sorensen et al., 2011). Co-occurring internalizing and externalizing problems tend to be more strongly related to a lower intelligence level than only internalizing or only externalizing problems, however results have not been fully consistent (Brunnekreef et al., 2007; Goodman, 1995; Yoo et al., 2009). The association between cognitive impairment and psychopathology has also been found in studies on children with intellectual disability. Children with an intelligence level between 30 and 60, as well as children with an intelligence level between 60 and 80, are more likely to experience emotional and behavioral problems than typically developing children (Dekker et al., 2002).

A few studies have investigated the relation between CBCL-DP and cognitive impairment. Biederman et al. (2013) found that children with bipolar disorder and CBCL-DP had a lower intelligence level than children with only bipolar disorder and healthy controls. Peyre et al. (2012) compared children with ADHD and CBCL-DP to children with only ADHD on four cognitive subdomains: planning, flexibility, interference control, and sustained attention. No group differences were found. These studies were performed in clinical samples, which may have resulted in a selection towards more severely affected children. Additionally, these studies did not control for any potential confounding variables.

The goal of this study was to examine the relationship between CBCL-DP and intelligence in 5- to 7-year-old children from the general population. This study was conducted within Generation R, a multi-ethnic population-based cohort (Jaddoe et al., 2012). Because of differences in exposure to the Dutch language in young children from different ethnic minorities, we examined nonverbal intelligence. We investigated if children with CBCL-DP have a lower nonverbal intelligence level than children without problem behavior or children with predominantly internalizing or predominantly externalizing problems. We examined if an association between CBCL-DP and a lower nonverbal intelligence level is independent of the intelligence level of the parents. If children with CBCL-DP have a lower nonverbal intelligence level than what would be expected based on the intelligence level of their parents, this may point toward altered trajectories of typical brain development. As measures of parental intelligence we examined maternal nonverbal intelligence and paternal education level. We also tested if a relationship between CBCL-DP and nonverbal intelligence is independent of parental psychopathology and perinatal factors that are related to intelligence, such as maternal alcohol use during pregnancy, child's birth weight, and gestational age at birth (Neisser et al., 1996). We hypothesized that children with CBCL-DP have a lower nonverbal intelligence than children without problem behavior or children with predominantly internalizing or externalizing problems. Additionally, we expected that the nonverbal intelligence level in children with CBCL-DP is lower than what would be expected by parental intelligence. To examine the specificity of the association between CBCL-DP and nonverbal intelligence, we investigated if a lower nonverbal intelligence level in children with CBCL-DP is independent of a) the presence

of severe intellectual disabilities defined as a nonverbal intelligence level <70; b) the presence of ADHD or ASD, two neurodevelopmental disorders that are known to be related to a lower intelligence level; and c) the overall level of emotional and behavioral problems, measured with the CBCL total problems score.

METHOD

Setting and population

This study was embedded in the Generation R study, a population-based cohort from fetal life onwards in Rotterdam, the Netherlands. The Generation R Study has been described previously (Jaddoe et al., 2012; Tiemeier et al., 2012). Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was conducted in accordance with the guidelines proposed in the World Medical Association Declaration of Helsinki and was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants. At birth, 9,749 children participated in the study. When the children in the Generation R study reached the age of 5-to-7 years, their primary caregivers received the Child Behavior Checklist for ages 1.5 to 5 (CBCL/1.5-5) and all children were invited to visit the research center where nonverbal intelligence was measured. We included all children for whom the CBCL/1.5-5 was completed and that were younger than 8 years, n=6,131. Of this sample, nonverbal intelligence was measured in 5,083 (83%) children. Table 1 presents sample characteristics.

A subsample was recruited for a psychiatric interview and a screening procedure for ASD. This sample was enriched for psychopathology by including all children within the top 15 percent of the CBCL/1.5-5 total problems score or in the top 2 percent on one of the CBCL/1.5-5 syndrome scales (n=1,080). Also a random sample of children with scores below these cut points was recruited (n=327). Interview and screening data were obtained for 786 children with high scores on the CBCL/1.5-5 and for 257 children with low scores (participation rate 74%). Children participating in the psychiatric interview (n=1,043) were more likely to be Dutch (55.8% vs. 42.3%, χ^2=28, df=2, p<0.001), to have a higher nonverbal intelligence level (100.7 vs. 95.9, p<0.001), and to have a lower CBCL total problems score (37.5 vs. 41.3, p=0.002) than non-participating children (n=364).

CBCL Dysregulation Profile

Emotional and behavioral problems were assessed using the Child Behavior Checklist for ages 1.5 to 5 (CBCL/1.5-5; Achenbach & Rescorla, 2000). The CBCL/1.5-5 was chosen because we expected the majority of the children to be younger than 6 years at assessment. At the end of

Table 1 Sample Characteristics

	N=6,131
Age in years, mean (SD)	6.1 (0.4)
Gender %	
Girls	49.7
Boys	50.3
Birth weight in grams, mean (SD)	3,425 (575)
Apgar score at 5 minutes after birth, mean (SD)	9.6 (0.8)
Gestational age at birth in weeks, mean (SD)	39.8 (1.9)
Ethnicity %	
Dutch	61.7
Other Western	9.0
Non-Western	29.3
Maternal smoking during pregnancy	
Never smoked	77.7
Quit when pregnancy was known	7.8
Continued during pregnancy	14.5
Maternal drinking during pregnancy	
No drinking	41.5
Until pregnancy was known	13.7
Continued during pregnancy	44.8
Maternal age at birth in years, mean (SD)	31.1 (4.8)
Maternal APM score mean, SD	9.1 (2.3)
Paternal education level %	
High	55.3
Medium	26.9
Low	17.8
Maternal psychological symptoms, mean (SD)	0.22 (0.27)
Paternal psychological symptoms, mean (SD)	0.15 (0.21)
Family income %	
< €1,600	15.9
€1,600-3,200	33.4
> €3,200	50.7

the assessment, while the majority of the sample was 5 years old (58%), some children were 6 (38%) or 7 (4%) years old. The CBCL/1.5-5 consists of 100 items. Based on the behavior of the child in the preceding two months, the primary caregiver (92.6% mothers) rated each item as 0 for not true, 1 for somewhat or sometimes true, and 2 for very true or often true. Good reliability and validity have been reported for the CBCL/1.5-5 (Achenbach & Rescorla, 2000) and the scales were found to be generalizable across 23 societies (Ivanova et al., 2010). In our

sample, for all scales Cronbach's alphas were the same in 5 year-old children and in children older than 5, indicating that problems were also reliably measured in children older than 5. The CBCL-DP was derived using latent profile analysis, which has been described previously (Basten et al., 2013). In short, latent profile analysis was performed on six syndrome scales of the CBCL/1.5-5: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn, which are part of the internalizing domain, and Attention Problems and Aggressive Behavior, which are part of the externalizing domain. Four profiles were identified. The CBCL-DP was characterized by high levels of problems across the range of both internalizing and externalizing problems and included 1.8% of the sample. Additionally, we identified an internalizing profile (5.3%) with moderate levels of problems on the four internalizing syndrome scales, an externalizing/emotionally-reactive profile (7.3%) with moderate problems on the Attention Problems, Aggressive Behavior and Emotionally Reactive scales, and a no problems profile (85.6%). For analysis we used a group membership variable that was based on the most likely latent profile membership for each child. This was justified because entropy was high at 0.98 (Clark & Muthen, 2009).

Nonverbal intelligence

A nonverbal intelligence test was chosen to minimize bias by possible differences in Dutch language abilities in non-Dutch children. We used the Snijders-Oomen Nonverbal Intelligence Test 2.5-7-Revised (SON-R 2.5-7; Tellegen et al., 2005), a reliable and valid measure (Jenkinson et al., 1996; Moore et al., 1998; Tellegen et al., 2005). Spoken or written language are not required for this test and instructions can also be given non-verbally. The total score of the SON-R 2.5-7 and the performance IQ score of the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R) have been found to correlate .60 to .83 (Jenkinson et al., 1996; Moore et al., 1998; Tellegen et al., 2005). The SON-R 2.5-7 covers two domains: performance and reasoning. Due to time constraints, one performance subtest, i.e. Mosaics, and one reasoning subtest, i.e. Categories, were selected. These two subtests cover spatial insight (Mosaics) and abstract reasoning abilities (Categories). Among 4.5- to 7-year-old children in the norm sample (n=626, mean age=6.0 years, SD=0.85) the two subtests showed a correlation of 0.36 (Tellegen et al., 2005). Correlations between each subtest and the sum of the other subtests were 0.63 for Mosaics and 0.47 for Categories and the correlation of the sum of these two subtests with the total SON-R 2.5-7 score was 0.86 (P. Tellegen, personal communication, March 7, 2011). The test was administered by trained research assistants. Raw subtest scores were transformed according to population- and age-specific norms with a mean value of 100 and an SD of 15. We found a correlation of 0.31 between the subtests. In line with the guidelines of the manual only the total SON-R 2.5-7 score was used. During the assessment, research assistants also observed concentration, motivation, collaboration, and understanding of the test. Based on these observations a compliance variable was defined with two categories 'good test compliance' and 'variable to bad test compliance'.

Covariates

Several child, parental, and perinatal characteristics were considered as possible explanatory variables. Birth weight and Apgar score at 5 minutes after birth were derived from medical records. Gestational age at birth was established using ultrasound measures during pregnancy. Child's ethnicity, maternal age, and maternal prenatal smoking and drinking were obtained by questionnaires during pregnancy. Ethnicity was based on country of birth of the parents and was defined into Dutch, other Western, or non-Western. Maternal alcohol use was categorized into 'never drank in pregnancy', 'drank until pregnancy was known', and 'continued to drink during pregnancy'. Maternal smoking was categorized into 'never smoked during pregnancy', 'smoked until pregnancy was known', and 'continued smoking during pregnancy'. Maternal and paternal psychological problems were assessed at 20 weeks of pregnancy and when the child was 3 years old using the Brief Symptom Inventory (BSI), a validated self-report questionnaire (De Beurs, 2004; Derogatis, 1993). At 20 weeks of pregnancy the complete 53 item questionnaire was assessed, while at 3 years a short form was used, including 21 items from the Depression, Hostility, Anxiety, and Interpersonal Sensitivity subscales. We computed the Global Severity Index (GSI; De Beurs, 2004), which we defined as the average item score across the two time points. Nonverbal intelligence of the mother was assessed during the visit to the research center at the age of 5-to-7 years using a computerized version of the Ravens Advanced Progressive Matrices Test, set I (Prieler, 2003). Set I consists of 12 items and has been shown to be a reliable and valid short form of the Raven's Progressive Matrices to asses nonverbal intelligence (Chiesi et al., 2012). Paternal education and family income were obtained by questionnaire when the child was 5-to-7 years old. Paternal education was categorized into low (primary school or lower vocational education), medium (intermediate vocational education), and high (higher vocational education or university). Family income was defined by the total net month income of the household and categorized as follows: < €1,600 (below low income threshold for a family with two children), €1,600-3,200, and > €3,200 (more than average family income).

ADHD and ASD

ADHD and ASD diagnoses were assessed to examine if the hypothesized relationship between CBCL-DP and nonverbal intelligence was independent of these diagnoses. ADHD diagnosis was assessed using the Diagnostic Interview Schedule for Children-young child version (DISC-YC; Fisher & Lucas, 2006), which was administered to the primary caregiver. The DISC-YC is an adaptation of the DISC parent version and is suitable for children aged 3-to-8 years. The test-retest reliability for ADHD scales is .67 (Lavigne et al., 2009). Children received an ADHD diagnosis if they fulfilled the criteria for the inattentive, hyperactive, or combined subtype, irrespective of impairment. The presence of ASD was assessed using the Social Communication Questionnaire (SCQ). The SCQ is a 40-item parent-reported screening measure that taps characteristic autistic behavior. The questionnaire is based on the ADI-R (Lord et al., 1994) and has established validity for screening of ASD (Berument et al., 1999). Children with SCQ scores

of 15 or above were considered as screen-positives (Chandler et al., 2007). Data on ADHD diagnosis and ASD screening was available in 70 children with CBCL-DP (64%), 179 children in the internalizing group (55%), 275 children in the externalizing/emotionally-reactive group (62%), and 519 children in the no problems group (10%).

Data analysis

To examine the relation between CBCL-DP and nonverbal intelligence, we performed linear regression with nonverbal intelligence of the child as the dependent variable and group membership as the independent variable. Group membership was dummy coded, with the no problems group as the reference category. To examine if the relationship between CBCL-DP and nonverbal intelligence was independent of parental and perinatal factors, we entered the covariates into the regression model.

Secondary analyses were conducted to further examine the association. To examine if the association was independent of the presence of severe intellectual disabilities, we repeated the analysis excluding children with a nonverbal intelligence score <70. To investigate if our results were independent of the presence of ADHD or ASD, we tested the relation between CBCL-DP and nonverbal intelligence among the subgroup of children who had received a psychiatric interview, excluding those children diagnosed with ADHD or screen-positive for ASD. Finally, to examine whether the association was independent of the overall level of emotional and behavioral problems, we compared the nonverbal intelligence level between children with CBCL-DP and a group of children with the same level of CBCL total problems. We conducted all data analyses using SPSS (IBM SPSS Statistics version 20.0).

In the total sample, percentages of missing data were up to 23% for covariates. To account for missing data on covariates and nonverbal intelligence, we imputed missing values using fully conditional specification method in SPSS and generated 20 imputed datasets. The imputation model included all variables that were used for further analyses. We added maternal education and a measure of child cognitive functioning at 3 years of age as additional indicators to improve the imputation model. To examine possible biases of the multiple imputations, analyses were repeated in the sample with complete nonverbal intelligence data (n=5,083).

Non-response analysis

We compared prenatal child and maternal characteristics of the children included in the analysis (n=6,131) with those excluded because of missing data on CBCL/1.5-5 (n=3,618). Children of responding mothers were more likely to be Dutch (60.6% vs. 30.8%, χ^2=1,062, df=3, p<0.001). Responding mothers were more likely to be highly educated (48.7% vs. 18.9%, χ^2=1,250, df=3, p<0.001) and to have a high family income (55.2% vs. 20.3%, χ^2=1,328, df=3, p<0.001).

RESULTS

The mean nonverbal intelligence level of the total sample was 102.0 (SD=14.9). The correlation between CBCL Total Problems and nonverbal intelligence was -0.16. Figure 1 presents nonverbal intelligence scores for the CBCL-DP group and the other groups. The CBCL-DP group scored 11.0 points lower than the no problems group (95% CI: -14.1; -7.9, p<0.001), 7.2 points lower than the internalizing group (95% CI: -10.6; -3.7, p<0.001), and 7.3 points lower than the externalizing/emotionally-reactive group (95% CI: -10.6; -4.0, p<0.001). Children in the internalizing and externalizing/emotionally-reactive groups scored respectively 3.8 points (95% CI: -5.6; -2.1, p<0.001) and 3.7 points (95% CI: -5.2; -2.1, p<0.001) lower than the no problems group.

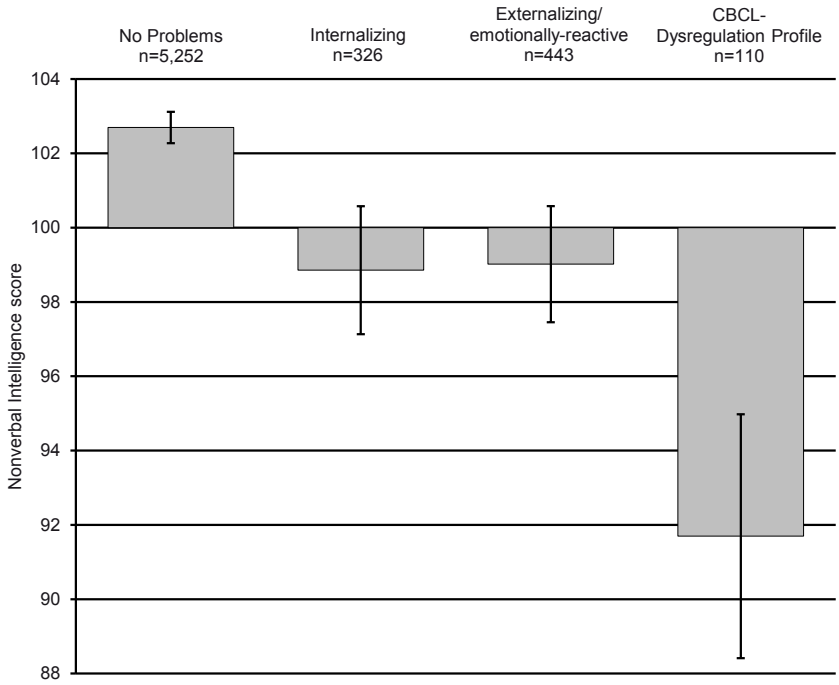


Figure 1 Unadjusted nonverbal intelligence levels per group.
Note: Error bars represent 95% confidence intervals. CBCL = Child Behavior Checklist/1.5–5.

Table 2 provides differences in nonverbal intelligence scores between the CBCL-DP, internalizing, and externalizing/emotionally-reactive groups and the no problems group after adjustment for child, parental, and perinatal factors. After adjusting for child age and gender, maternal cognitive ability, and paternal education level (model 2), the difference in nonverbal intelligence level between children with CBCL-DP and children with no problems was -8.6

points (95% CI: -11.6; -5.7, p<0.001). When all covariates were entered (model 5) nonverbal intelligence level of children with CBCL-DP was 8.3 points lower than children with no problems (95% CI: -11.4; -5.3, p<0.001). Further adjustment for test compliance resulted in a 1 point decrease to a -7.3 points difference (95% CI: -10.3; -4.2, p<0.001).

Table 2 Association between CBCL-Dysregulation Profile, Internalizing, and Externalizing/emotionally-reactive profiles and nonverbal intelligence.

	Internalizing n=326			Externalizing/Emotionally-reactive n=443			CBCL-Dysregulation Profile n=110		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Model 1	-3.7	-5.5; -2.0	<0.001	-3.8	-5.3; -2.3	<0.001	-10.9	-14.0; -7.8	<0.001
Model 2	-2.0	-3.6; -0.3	0.020	-2.8	-4.3; -1.4	<0.001	-8.6	-11.6; -5.7	<0.001
Model 3	-2.9	-4.7; -1.1	0.001	-3.3	-4.9; -1.8	<0.001	-8.9	-12.1; -5.7	<0.001
Model 4	-2.9	-4.6; -1.2	0.001	-3.1	-4.5; -1.6	<0.001	-9.9	-12.9; -6.9	<0.001
Model 5	-1.4	-3.0; 0.3	0.105	-2.5	-3.9; -1.0	0.001	-8.3	-11.4; -5.3	<0.001

Note: The no problems group (n=5,252) is the reference group.
Model 1: adjusted for age and gender
Model 2: adjusted for age, gender, maternal cognitive ability, and paternal education level
Model 3: adjusted for age, gender, maternal and paternal psychological symptoms
Model 4: adjusted for age, gender, maternal prenatal alcohol use and smoking, Apgar score, birth weight, and gestational age at birth
Model 5: adjusted for age, gender, maternal cognitive ability, paternal education level, maternal and paternal psychological symptoms, family income, maternal age, ethnicity child, maternal prenatal alcohol use and smoking, Apgar score, birth weight, and gestational age at birth.

When all covariates were entered, the nonverbal intelligence level of children with CBCL-DP also remained lower than the internalizing group (-7.0 points, 95% CI: -10.3; -3.7, p<0.001) and externalizing/emotionally-reactive group (-5.9 points, 95% CI: -9.1; -2.7, p<0.001). The internalizing group no longer had a lower nonverbal intelligence score than the no problems group, while the lower nonverbal intelligence level for the externalizing/emotionally-reactive group remained significant (-2.5 points, 95% CI: -3.9; -1.0, p<0.001).

Secondary analyses conducted revealed comparable results. After the exclusion of children with a nonverbal intelligence score <70 the CBCL-DP group scored 9.5 points lower than the no problems group (95% CI: -12.5; -6.4, p<0.001), 6.2 points lower than the internalizing group (95% CI: -9.7; -2.7, p<0.001), and 6.6 points lower than the externalizing/ emotionally-reactive group (95% CI: -10.0; -3.2, p<0.001).

We also examined if the lower nonverbal intelligence level in children with CBCL-DP was independent of an ADHD or ASD diagnosis. A psychiatric interview was available in 70 children with CBCL-DP. Children with CBCL-DP and an ADHD diagnosis or screen-positive for ASD

(n=39; mean nonverbal intelligence 91.0) did not significantly differ in nonverbal intelligence level from children with CBCL-DP only (n=31; mean nonverbal intelligence 94.4; B= -3.4, 95% CI: -11.8; 5.0, p=0.431). In the subsample of children with a psychiatric interview excluding children with ADHD or ASD, we found that the CBCL-DP group (n=31) scored 8.1 points (95% CI: -13.9; -2.2, p=0.007) lower than the no problems group (n=456). The CBCL-DP group scored also 5.3 points (95% CI: -11.5; 0.9, p=0.095) lower than the internalizing group (n=157), and 5.1 points (95% CI: -11.3; 1.0, p=0.099) lower than the externalizing/emotionally-reactive group (n=190), however these differences were not significant.

Finally, we examined whether children with CBCL-DP had a lower nonverbal intelligence level than children with the same level of CBCL total problems. The first 49 children with the highest CBCL total problems score were all in the CBCL-DP group. For 52 children with CBCL-DP a child from the Internalizing or Externalizing/Emotionally-reactive group was identified with the same score on the CBCL total problems scale (mean CBCL total problems score in both groups=66.4). The nonverbal intelligence level for the 52 children with CBCL-DP was 3.0 points (95% CI: -9.4; 3.4, p=0.363) lower than the group children without CBCL-DP. This difference was not significant.

All analyses were repeated in the subsample with complete data on nonverbal intelligence (n=5,083). Similar results were found.

DISCUSSION

This study examined the relationship between CBCL-DP and nonverbal intelligence in a large population-based study. Children with CBCL-DP had an 11 point lower nonverbal intelligence score than children without any emotional or behavioral problems and a 7 point lower score than children with moderate internalizing problems or moderate externalizing and emotionally reactive behavior. These differences remained after adjustment for parental cognitive and psychosocial functioning and perinatal factors. Interestingly, CBCL-DP remained related to a lower nonverbal intelligence after exclusion of children meeting criteria for ADHD or ASD.

To our knowledge, this is the first study that examined the relationship between CBCL-DP and cognitive abilities among children from the general population. Our results build on findings from a clinical study, which reported that children with both CBCL-DP and bipolar disorder had a lower nonverbal intelligence level than children with only bipolar disorder and controls (Biederman et al., 2013). The 11 points lower nonverbal intelligence level in children with CBCL-DP found in this study is comparable to the on average 9-10 points lower intelligence levels that have been reported for children with ADHD (Frazier et al., 2004; Kuntsi et al., 2004)

and for children with severe antisocial behavior (Koenen et al., 2006; Lynam et al., 1993; Nigg & Huang-Pollock, 2003).

One question arises as to whether the relationship between CBCL-DP and nonverbal intelligence is merely a global relationship with the total CBCL score. Indeed, children in the CBCL-DP group have the highest levels of problems across the internalizing and externalizing domain. Thus, it is difficult to examine to what extent the relation between the CBCL-DP and nonverbal intelligence is specific. We found a 3 points difference in nonverbal intelligence level between 52 children with CBCL-DP and 52 children without CBCL-DP but with the same score on the CBCL total problems scale. This difference was not significant, which may be explained by the small sample size. A difference of 3 points, which is equal to 0.2 standard deviation, suggests that a small difference remains.

A possible explanation for the relationship between CBCL-DP and nonverbal intelligence is that CBCL-DP and intelligence share a common neurodevelopmental etiology. Such a process has also been proposed in a model for the relationship between antisocial behavior and intelligence (Nigg & Huang-Pollock, 2003). The interplay between genetic and environmental factors may result in altered trajectories of typical brain development, affecting both intelligence and behavior. Population-based twin studies have shown that the association between various forms of psychopathology and intelligence is largely explained by genetic factors. In 5-year-old children, 86% of the relationship between ADHD and intelligence, and 100% of the relationship between antisocial behavior and intelligence have been shown to be accounted for by genetic influences (Koenen et al., 2006; Kuntsi et al., 2004). Similarly, genetic factors have been shown to account for 50 to 84% of the relationship between overall levels of psychopathology and intelligence in twin studies (Jacobs et al., 2002; Plomin et al., 2002). Environmental factors are likely to be highly important in moderating these genetic effects. Since we measured CBCL-DP and intelligence only at 5-to-7 years of age, we do not know when trajectories of children with CBCL-DP deviated from typical brain development.

Rutter and colleagues (Rutter et al., 2006) proposed that neurodevelopmental disorders have eight main features: 1) a deviance in maturationally-influenced psychological features; 2) cognitive impairment; 3) overlap with other neurodevelopmental disorders; 4) male preponderance; 5) strong genetic influences; 6) contributory environmental influences; 7) persistence into adulthood in combination with a decrease in impairment across age; and 8) no remissions and relapses. Our study and previous studies showed that CBCL-DP meets many of these characteristics. In this study, we found that CBCL-DP is related to a lower nonverbal intelligence level considerable overlap with ADHD and ASD was found: 55% of children met criteria for ADHD or were screen-positive for ASD. Also, 66% of children with CBCL-DP were boys (Basten et al., 2013) although mixed results regarding male preponderance have been found in other studies

(Althoff et al., 2010a; Hudziak et al., 2005). Additionally, several studies in a Dutch twin sample have shown that while the CBCL-DP is highly heritable, environmental factors also play a significant role (Althoff et al., 2006; Boomsma et al., 2006; Hudziak et al., 2005). We and others have also found that the CBCL-DP is stable over time (Althoff et al., 2010b; Boomsma et al., 2006) and children with the profile likely continue having dysregulatory problems reflected by psychiatric disorders in adulthood (Althoff et al., 2010b; Holtmann et al., 2011; Meyer et al., 2009). These findings suggest that the CBCL-DP fits the pattern of a neurodevelopmental disorder. However, future studies should examine to what extent impairment in children with CBCL-DP lessens with age and if relapses and remissions occur.

Problems in self-regulation could also have interfered with test performance and have resulted in a lower nonverbal intelligence score. Moreover, attention problems may have led to lower scores. Children with CBCL-DP have also been shown to be less persistent (Althoff et al., 2012). Additionally, decreased motivation, which is an important predictor for test performance (Duckworth et al., 2011), might have played a role in these children. In our analyses however, the adjustment for observed test compliance resulted in only one point difference in nonverbal intelligence. This is similar to a study on the relationship between ADHD and intelligence, where observed inattentive behavior explained only a two point difference in intelligence level (Kuntsi et al., 2004). Dysregulated behavior could also interfere with learning in school or everyday life, with a subsequent decrease in intelligence scores. Alternatively, a lower intelligence level may cause CBCL-DP. For example, children with a lower intelligence level may experience more frustration in their daily lives that in turn results in dysregulated behavior.

A lower nonverbal intelligence level was also found in children in the group with moderate externalizing and emotionally-reactive behavior, although the adjusted difference with children without problems was only -2.5 points. This is in line with population-based studies that found small correlations around -0.20 between externalizing behavior and intelligence (Goodman et al., 1995; Koenen et al., 2006). For the group of children with moderate internalizing problems the relationship with nonverbal intelligence no longer held after adjustment for covariates. Previous studies found mixed results regarding the relation between internalizing problems and intelligence (Davis et al., 2008; Goodman et al., 1995; Sorensen et al., 2011). Possibly, positive findings for a negative relationship between internalizing problems and intelligence in earlier studies were confounded by factors that accounted for the difference in intelligence level in our study.

The strengths of this study are the large number of participants and the population-based design. Other strengths are the empirically based method to define CBCL-DP and the many covariates that we controlled for, including parental cognitive functioning. Finally, the presence of psychiatric information in a subsample allowed us to study the relation between CBCL-DP

and nonverbal intelligence independent of the presence of ADHD and ASD. There are also limitations to the study. We did not measure verbal intelligence. A nonverbal intelligence test was chosen to minimize bias by possible language problems in non-Dutch children (38% of the sample). Due to time restrictions, we used an abbreviated version of the intelligence test. However, the two subtests used in this study were highly correlated with the total score on the nonverbal intelligence test. Another limitation is that the non-response analyses indicated that higher educated mothers and Dutch children were more likely to be included in the study, which resulted in an under-representation of more disadvantaged families.

In conclusion, this study showed that children with CBCL-DP have a considerable lower nonverbal intelligence level than children without problems or with other patterns of problem behavior. Impaired cognitive abilities place these children at risk for poor academic achievement. Understanding the underlying mechanisms will be important in designing interventions to help these children perform in academic environments. More in-depth neuropsychological testing is needed to understand if these children have a global impairment or impairments only within specific cognitive domains. Brain imaging studies can help to understand neurobiological underpinnings of CBCL-DP and differences in neurodevelopmental trajectories.

REFERENCES

Achenbach, T.M., & Rescorla, L.A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Achenbach, T.M., & Rescorla, L.A. (2001). *Manual for the ASEBA School-Age Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth & Families.

Althoff, R.R., Ayer, L.A., Crehan, E.T., Rettew, D.C., Baer, J.R., & Hudziak, J.J. (2012). Temperamental profiles of dysregulated children. *Child Psychiatry & Human Development, 43*(4), 511-522. doi: 10.1007/s10578-012-0280-7

Althoff, R.R., Rettew, D.C., Ayer, L.A., & Hudziak, J.J. (2010a). Cross-informant agreement of the Dysregulation Profile of the Child Behavior Checklist. *Psychiatry Research, 178*(3), 550-555. doi: 10.1016/j.psychres.2010.05.002

Althoff, R.R., Rettew, D.C., Faraone, S.V., Boomsma, D.I., & Hudziak, J.J. (2006). Latent class analysis shows strong heritability of the child behavior checklist-juvenile bipolar phenotype. *Biological Psychiatry, 60*(9), 903-911. doi: 10.1016/j.biopsych.2006.02.025

Althoff, R.R., Verhulst, F.C., Rettew, D.C., Hudziak, J.J., & van der Ende, J. (2010b). Adult outcomes of childhood dysregulation: a 14-year follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(11), 1105-1116. doi: 10.1016/j.jaac.2010.08.006

Angold, A., Costello, E.J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*(1), 57-87.

Ayer, L., Althoff, R., Ivanova, M., Rettew, D., Waxler, E., Sulman, J., & Hudziak, J. (2009). Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. *Journal of Child Psychology and Psychiatry, 50*(10), 1291-1300. doi: 10.1111/j.1469-7610.2009.02089.x

Basten, M.M., Althoff, R.R., Tiemeier, H., Jaddoe, V.W., Hofman, A., Hudziak, J.J., et al. (2013). The dysregulation profile in young children: empirically defined classes in the generation R study. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(8), 841-850 e842. doi: 10.1016/j.jaac.2013.05.007

Berument, S.K., Rutter, M., Lord, C., Pickles, A., & Bailey, A. (1999). Autism screening questionnaire: diagnostic validity. *The British Journal of Psychiatry, 175*, 444-451.

Biederman, J., Martelon, M., Faraone, S.V., Woodworth, K.Y., Spencer, T.J., & Wozniak, J.R. (2013). Personal and familial correlates of bipolar (BP)-I disorder in children with a diagnosis of BP-I disorder with a positive child behavior checklist (CBCL)-severe dysregulation profile: A controlled study. *Journal of Affective Disorders, 147*(1-3), 164-170. doi: 10.1016/j.jad.2012.10.028

Biederman, J., Wozniak, J., Kiely, K., Ablon, S., Faraone, S., Mick, E., et al. (1995). CBCL clinical scales discriminate prepubertal children with structured interview-derived diagnosis of mania from those with ADHD. *Journal of the American Academy of Child and Adolescent Psychiatry, 34*(4), 464-471.

Boomsma, D.I., Rebollo, I., Derks, E.M., van Beijsterveldt, T.C., Althoff, R.R., Rettew, D.C., & Hudziak, J.J. (2006). Longitudinal stability of the CBCL-juvenile bipolar disorder phenotype: A study in Dutch twins. *Biological Psychiatry, 60*(9), 912-920. doi: 10.1016/j.biopsych.2006.02.028

Brunnekreef, J.A., De Sonneville, L.M.J., Althaus, M., Minderaa, R.B., Oldehinkel, A.J., Verhulst, F.C., & Ormel, J. (2007). Information processing profiles of internalizing and externalizing behavior problems: evidence from a population-based sample of preadolescents. *Journal of Child Psychology and Psychiatry, 48*(2), 185-193. doi: 10.1111/j.1469-7610.2006.01695.x

Chakrabarti, S., & Fombonne, E. (2001). Pervasive developmental disorders in preschool children. *JAMA, 285*(24), 3093-3099.

Chandler, S., Charman, T., Baird, G., Simonoff, E., Loucas, T., Meldrum, D., et al. (2007). Validation of the social communication questionnaire in a population cohort of children with autism spectrum disorders. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(10), 1324-1332. doi: 10.1097/chi.0b013e31812f7d8d

Chiesi, F., Ciancaleoni, M., Galli, S., & Primi, C. (2012). Using the Advanced Progressive Matrices (Set I) to assess fluid ability in a short time frame: An item response theory-based analysis. *Psychological Assessment, 24*(4), 892-900. doi: 10.1037/a0027830

Clark, S., & Muthen, B. (2009). Relating Latent Class Analysis Results to Variables not Included in the Analysis. http://www.statmodel.com/download/relatinglca.pdf

Cook, E.T., Greenberg, M.T., & Kusche, C.A. (1994). The relations between emotional understanding, intellectual functioning, and disruptive behavior problems in elementary-school-aged children. *Journal of Abnormal Child Psychology, 22*(2), 205-219.

Coolican, J., Bryson, S.E., & Zwaigenbaum, L. (2008). Brief report: data on the Stanford-Binet Intelligence Scales (5th ed.) in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 38*(1), 190-197. doi: 10.1007/s10803-007-0368-2

Davis, T.E., III, Ollendick, T.H., & Nebel-Schwalm, M. (2008). Intellectual ability and achievement in anxiety-disordered children: A clarification and extension of the literature. *Journal of Psychopathology and Behavioral Assessment, 30*(1), 43-51. doi: 10.1007/s10862-007-9072-y

De Beurs, E. (2004). *Brief symptom inventory, handleiding*. Leiden, The Netherlands

Dekker, M.C., Koot, H.M., van der Ende, J., & Verhulst, F.C. (2002). Emotional and behavioral problems in children and adolescents with and without intellectual disability. *Journal of Child Psychology and Psychiatry, 43*(8), 1087-1098. doi: 10.1111/1469-7610.00235

Derogatis, L.R. (1993). *Brief symptom inventory (bsi): Administration, scoring and procedures manual* (3rd ed.). Minneapolis: National Computer Systems Inc.

Duckworth, A.L., Quinn, P.D., Lynam, D.R., Loeber, R., & Stouthamer-Loeber, M. (2011). Role of test motivation in intelligence testing. *Proceedings of the National Academy of Sciences of the United States of America, 108*(19), 7716-7720. doi: 10.1073/pnas.1018601108

Fisher, P., & Lucas, C. (2006). *Diagnostic Interview Schedule for Children (DISC-IV) - Young Child*. New York, NY: Columbia University.

Frazier, T.W., Demaree, H.A., & Youngstrom, E.A. (2004). Meta-analysis of intellectual and neuropsychological test performance in attention-deficit/hyperactivity disorder. *Neuropsychology, 18*(3), 543-555. doi: 10.1037/0894-4105.18.3.543

Goodman, R. (1995). The relationship between normal variation in IQ and common childhood psychopathology: a clinical study. *European Child & Adolescent Psychiatry, 4*(3), 187-196.

Goodman, R., Simonoff, E., & Stevenson, J. (1995). The impact of child IQ, parent IQ and sibling IQ on child behavioural deviance scores. *Journal of Child Psychology and Psychiatry, 36*(3), 409-425.

Holtmann, M., Buchmann, A.F., Esser, G., Schmidt, M.H., Banaschewski, T., & Laucht, M. (2011). The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis. *Journal of Child Psychology and Psychiatry, 52*(2), 139-147. doi: 10.1111/j.1469-7610.2010.02309.x

Holtmann, M., Goth, K., Wockel, L., Poustka, F., & Bolte, S. (2008). CBCL-pediatric bipolar disorder phenotype: severe ADHD or bipolar disorder? *Journal of neural transmission, 115*(2), 155-161. doi: 10.1007/s00702-007-0823-4

Hudziak, J.J., Althoff, R.R., Derks, E.M., Faraone, S.V., & Boomsma, D.I. (2005). Prevalence and genetic architecture of Child Behavior Checklist-juvenile bipolar disorder. *Biological Psychiatry, 58*(7), 562-568. doi: 10.1016/j.biopsych.2005.03.024

Ivanova, M.Y., Achenbach, T.M., Rescorla, L.A., Harder, V.S., Ang, R.P., Bilenberg, N., et al. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1215-1224. doi: 10.1016/j.jaac.2010.08.019

Jacobs, N., Rijsdijk, F., Derom, C., Danckaerts, M., Thiery, E., Derom, R., et al. (2002). Child psychopathology and lower cognitive ability: a general population twin study of the causes of association. *Molecular Psychiatry, 7*(4), 368-374. doi: 10.1038/sj.mp.4000971

Jaddoe, V.W., van Duijn, C.M., Franco, O.H., van der Heijden, A.J., van Iizendoorn, M.H., de Jongste, J.C., et al. (2012). The Generation R Study: design and cohort update 2012. *European Journal of Epidemiology, 27*(9), 739-756. doi: 10.1007/s10654-012-9735-1

Jenkinson, J., Roberts, S., Dennehy, S., & Tellegen, P. (1996). Validation of the Snijders-Oomen Nonverbal Intelligence Test-Revised 2 1/2-7 for Australian children with disabilities. *Journal of Psychoeducational Assessment, 14*(3), 276-286.

Jucksch, V., Salbach-Andrae, H., Lenz, K., Goth, K., Dopfner, M., Poustka, F., et al. (2011). Severe affective and behavioural dysregulation is associated with significant psychosocial adversity and impairment. *Journal of Child Psychology and Psychiatry, 52*(6), 686-695. doi: 10.1111/j.1469-7610.2010.02322.x

Koenen, K.C., Caspi, A., Moffitt, T.E., Rijsdijk, F., & Taylor, A. (2006). Genetic influences on the overlap between low IQ and antisocial behavior in young children. *Journal of Abnormal Psychology, 115*(4), 787-797. doi: 10.1037/0021-843X.115.4.787

Kuntsi, J., Eley, T.C., Taylor, A., Hughes, C., Asherson, P., Caspi, A., & Moffitt, T.E. (2004). Co-occurrence of ADHD and low IQ has genetic origins. *American journal of medical genetics. Part B, Neuropsychiatric genetics, 124B*(1), 41-47. doi: 10.1002/ajmg.b.20076

Lavigne, J.V., Lebailly, S.A., Hopkins, J., Gouze, K.R., & Binns, H.J. (2009). The prevalence of ADHD, ODD, depression, and anxiety in a community sample of 4-year-olds. *Journal of Clinical Child and Adolescent Psychology, 38*(3), 315-328. doi: 10.1080/15374410902851382

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: a revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders, 24*(5), 659-685.

Lynam, D., Moffitt, T., & Stouthamer-Loeber, M. (1993). Explaining the relation between IQ and delinquency: class, race, test motivation, school failure, or self-control? *Journal of Abnormal Psychology, 102*(2), 187-196.

Meyer, S.E., Carlson, G.A., Youngstrom, E., Ronsaville, D.S., Martinez, P.E., Gold, P.W., et al. (2009). Long-term outcomes of youth who manifested the CBCL-Pediatric Bipolar Disorder phenotype during childhood and/or adolescence. *Journal of Affective Disorders, 113*(3), 227-235. doi: 10.1016/j.jad.2008.05.024

Moore, C., O'Keefe, S.L., Lawhon, D., & Tellegen, P. (1998). Concurrent validity of the Snijders-Oomen Nonverbal Intelligence Test 2 1/2-7-Revised with the Wechsler Preschool and Primary Scale of Intelligence - Revised. *Psychol Rep, 82*(2), 619-625. doi: 10.2466/pr0.82.2.619-625

Neisser, U., Boodoo, G., Bouchard, T.J., Jr., Boykin, A.W., Brody, N., Ceci, S.J., et al. (1996). Intelligence: Knowns and Unknowns. *American Psychologist, 51*(2), 77-101.

Nigg, J.T., & Huang-Pollock, C.L. (2003). An early-onset model of the role of executive functions and intelligence in conduct disorder/delinquency. In B. B. Lahey, T. E. Moffitt & A. Caspi (Eds.), *Causes of conduct disorder and juvenile delinquency* (pp. 227-253). New York: The Guilford Press.

Peyre, H., Speranza, M., Cortese, S., Wohl, M., & Purper-Ouakil, D. (2012). Do ADHD Children With and Without Child Behavior Checklist-Dysregulation Profile Have Different Clinical Characteristics, Cognitive Features, and Treatment Outcomes? *Journal of Attention Disorders*. doi: 10.1177/1087054712452135

Plomin, R., Price, T.S., Eley, T.C., Dale, P.S., & Stevenson, J. (2002). Associations between behaviour problems and verbal and nonverbal cognitive abilities and disabilities in early childhood. *Journal of Child Psychology and Psychiatry, 43*(5), 619-633.

Prieler, J. (2003). *Raven's Advanced Progressive Matrices* (Vol. 24). Mödling, Austria: Schufried.

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry, 47*(3-4), 276-295. doi: 10.1111/j.1469-7610.2006.01614.x

Sorensen, L., Plessen, K.J., Nicholas, J., & Lundervold, A.J. (2011). Is behavioral regulation in children with ADHD aggravated by comorbid anxiety disorder? *Journal of Attention Disorders, 15*(1), 56-66. doi: 10.1177/1087054709356931

Sourander, A., Jensen, P., Davies, M., Niemela, S., Elonheimo, H., Ristkari, T., et al. (2007). Who is at greatest risk of adverse long-term outcomes? The Finnish From a Boy to a Man study. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(9), 1148-1161. doi: 10.1097/chi.0b013e3180981e9

Tellegen, P.J., Winkel, M., Wijnberg-Williams, B.J., & Laros, J.A. (2005). *Snijders-Oomen Niet-Verbale Intelligentietest SON-R 2 1/2 - 7: Handleiding en Verantwoording*. Amsterdam: Boom Testuitgevers.

Tiemeier, H., Velders, F.P., Szekely, E., Roza, S.J., Dieleman, G., Jaddoe, V.W., et al. (2012). The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(11), 1119-1135.e1117. doi: 10.1016/j.jaac.2012.08.021

Volk, H.E., & Todd, R.D. (2007). Does the Child Behavior Checklist juvenile bipolar disorder phenotype identify bipolar disorder? *Biological Psychiatry, 62*(2), 115-120. doi: 10.1016/j.biopsych.2006.05.036

Yoo, J.P., Brown, P.J., & Luthar, S.S. (2009). Children With Co-Occurring Anxiety and Externalizing Disorders: Family Risks and Implications for Competence. *American Journal of Orthopsychiatry, 79*(4), 532-540. doi: 10.1037/a0017848

Chapter 5

Young children's externalizing problems predict parental psychiatric symptoms and poor family functioning

Basten, M., van der Ende, J., Trajanoska, K., Mileva-Seitz, V.R., Althoff, R.R., Jaddoe, V.W.V., Hofman, A., Hudziak, J.J., Verhulst, F.C., & Tiemeier, H.

Manuscript submitted for publication

ABSTRACT

The current study examined whether child externalizing problems are prospectively associated with maternal and paternal psychiatric symptoms and poor family functioning. This study was performed in a population-based sample of 5,527 preschool children. After adjustment for parental psychiatric symptoms and family functioning prior to birth, child externalizing problems at age 1.5 years predicted psychiatric symptoms in the mother and the father at age 3 years. Externalizing problems at ages 1.5 and 3 years predicted poor family functioning at age 6 years. These effects were independent of informant and socio-economic factors. This study suggests that child externalizing problems have a negative influence not only on mothers' mental health, but also on fathers' mental health and on broader family functioning.

INTRODUCTION

The family environment is critical for the child's early development. Poor family functioning, parental psychopathology, and negative parenting styles place children at risk for problem behavior (Connell & Goodman, 2002; Gershoff, 2002; Rothbaum & Weisz, 1994; Sturge-Apple et al., 2010). However, the reverse is also true. Theoretical models postulate that the behavior of the child influences family dynamics (Pardini, 2008). Several longitudinal studies have examined the effect of child problem behavior on parenting behaviors and attitudes. Yet, few studies have investigated whether negative effects of the behavior of the child extend to other aspects of the family system, such as parental psychopathology and family functioning. Research on the influences of child problem behavior on parental psychopathology and family functioning will demonstrate to what extent problem behavior is a burden to the family environment. In addition, examining the bi-directionality of relations between the child and his or her environment is key for understanding the persistence of problem behavior.

In 1968, Bell first suggested that associations between parental factors and child behavior problems should not be interpreted as unidirectional from parent to child, but rather as potentially bidirectional. Several theoretical models have since then described the influence of the child on the parents and the family (e.g. Belsky, 1981; Cox & Paley, 1997, 2003; Minuchin, 1985; Pardini, 2008; Patterson et al., 1984). For example, according to Patterson's coercion theory (Patterson et al., 1984) child irritability and defiance elicit harsh discipline to control the child. Harsh discipline techniques in turn lead to increased externalizing behavior in the child, leading to a vicious cycle that perpetuates the child's behavioral problems. According to the family systems framework, not only the relationship between the child and the parent should be studied but the child should also be considered in relation with the family as a whole. In this framework, the family is thought of as an organized system with all family members considered to be interdependent. All members, including the child, actively contribute to the overall configuration of the family (Cox & Paley, 1997, 2003; Minuchin, 1985).

Several studies have incorporated longitudinal designs with repeated measures to unravel the effects of child problem behavior on parenting (e.g. Bradley & Corwyn, 2013; Burke et al., 2008; Combs-Ronto et al., 2009; Hawes et al., 2011; Hipwell et al., 2008; Hughes & Gullone, 2008; Kok et al., 2013; Larsson et al., 2008; Pardini et al., 2008; Yates et al., 2010). After controlling for baseline levels of parenting factors, these studies showed that child or adolescent problem behavior associates with lowered maternal sensitivity (Bradley & Corwyn, 2013; Kok et al., 2013) and parental involvement (Burke et al., 2008; Hawes et al., 2011), as well as greater parental harshness (Bradley & Corwyn, 2013; Hipwell et al., 2008) at a later time point.

Similarly, the bidirectional relation between child problem behavior and parental mental health has been studied with longitudinal models (Allen et al., 2010; Bagner et al., 2013; Fanti et al., 2013; Gross et al., 2008a; Harvey & Metcalfe, 2012; Jaffee & Poulton, 2006; Kouros & Garber, 2010; Nicholson et al., 2011). Yet most studies have focused solely on maternal depressive symptoms. Typically, a negative effect of child externalizing problems, including aggression, oppositional behavior, and hyperactivity, on maternal depressive symptoms was reported. For example, in low-income families boys' aggressive behavior at age 5 was associated with higher levels of maternal depressive symptoms at age 6, and self-reported antisocial behavior at age 11 was associated with maternal depressive symptoms one year later (Gross et al., 2008a).

Excluding fathers from these models is an important omission. Most children are raised in a family with a mother and a father and the relationship between the child and the father is important for our understanding of child development. Very few studies have examined the effect of child problem behavior on the father's mental health (Fanti et al., 2013; Gross et al., 2008b; Harvey & Metcalfe, 2012). Fanti et al. (2013) found that child externalizing problems at 11 years of age were found to predict paternal depressive symptoms one year later. Harvey and Metcalfe (2012) showed that symptoms of Oppositional Defiant Disorder at age 3 years predicted paternal depressive symptoms at 4 years. However, in these studies fathers reported on the behavior of the child and on their own problems and the findings might be biased by shared method variance. Finally, Gross et al. (2008b) studied the relation between observed child compliance at age 2 years and latent growth curves of depressive symptoms in fathers from 2 to 4 years. However an association between child compliance and change in paternal depressive symptoms was not confirmed.

A few studies have examined child effects on the family system beyond the parent-child relationship. Some have reported a negative influence of child problem behavior on the marital relationship (Cui et al., 2007; Schermerhorn et al., 2007; Vandervalk et al., 2007). However, despite the family systems theory emphasizing the influence of the child on the family as a unit, the possible negative effects of child problem behavior on broader family functioning have received little attention. Poor family functioning, characterized by low cohesion, low warmth, too rigid or too diffuse boundaries between family members, and lack of open communication, is known to be associated with child problem behavior (Johnson, 2003; Pagani et al., 2008; Schermerhorn et al., 2011; Sturge-Apple et al., 2010). These associations are often interpreted as poor family functioning influencing the child. From the viewpoint that the child is an active contributor to the family, his or her behavior problems may directly influence the family system. Alternatively, the child may affect family functioning via parental psychiatric symptoms. It is well-known that parental psychiatric symptoms, such as depressive symptoms and substance dependence, are associated with family dysfunction (Burstein et al., 2012; Hughes & Gullone, 2008; Katz & Woodin, 2002; Moss et al., 2002)

The purpose of this study was to investigate the influence of externalizing problems of the preschool child on mothers' and fathers' psychiatric symptoms and on family functioning. A unique feature of the current study is the measurement of parental psychopathology and family functioning before the birth of the child, when the behavior of the child could not have impacted parental symptoms or family functioning. This enabled us to examine child effects while adjusting for baseline levels of parental psychopathology and family functioning that are not influenced by the child. In the current study both mother and father reported on child problem behavior to minimize potential biases of shared method variance. Also, we carefully controlled for possible confounding effects of socio-economic and family characteristics which are likely to influence the child, the parent, and the family in concert.

This study was performed in Generation R, a large population-based birth cohort (Jaddoe et al., 2012). This study builds on a prior study within Generation R that examined the effects of prenatal and postnatal parental psychiatric symptoms and prenatal family functioning on child emotional and behavioral problems at 3 years of age (Velders et al., 2011). Velders et al. (2011) showed that high levels of prenatal parental psychiatric symptoms and poor family functioning were independently associated with an increased risk for child problem behavior.

Our first aim was to examine the relation between child externalizing problems at age 1.5 years and psychiatric symptoms of the mother and of the father at age 3 years. Second, we examined the relation between child externalizing problems at ages 1.5 and 3 years on family functioning at age 6 years. Finally, we examined to what extent the relation between child externalizing problems and family functioning was mediated by parental psychiatric symptoms. Based on family systems theory, we hypothesized that child externalizing problems predict higher levels of psychiatric symptoms in both parents and poorer family functioning. The influence of child externalizing problems on family functioning was hypothesized to be partly mediated by parental psychiatric symptoms.

METHODS

Setting and population

This study was embedded in the Generation R Study, a multi-ethnic population-based cohort from fetal life onwards in Rotterdam, the Netherlands. The Generation R Study has been described previously (Jaddoe et al., 2012; Tiemeier et al., 2012). Briefly, all pregnant women living in Rotterdam, the Netherlands, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants. After birth, parents of 7,893 gave consent for follow-up studies from 0 to 4 years. For the current study we included all children with at least one measurement of problem behavior at 1.5 years

reported by the mother or at 3 years reported by the father. In total, 5,527 children and their parents were included in the study (response rate 70%). Sample characteristics are presented in Table 1.

Table 1 Sample characteristics (N=5,527)

Characteristic	M or %
Gender, girl %	50.0
Age at each wave, years, mean (SD)	
Age 1.5	1.5 (0.1)
Age 3	3.1 (0.1)
Age 6	6.0 (0.3)
Ethnicity %	
Dutch	65.2
Other Western	9.5
Non-Western	25.3
Birth order, first child %	58.5
Maternal age at birth, years, mean (SD)	31.3 (4.7)
Maternal education %	
High	55.5
Medium	27.9
Low	16.6
Family income (net per month) %	
> €2,000	70.9
€1,200 - €2,000	16.3
< €1,200	12.7
Marital status, single %	8.7

Child externalizing problems

Child externalizing problems were assessed using the Child Behavior Checklist for ages 1.5 to 5 (CBCL/1.5-5; Achenbach & Rescorla, 2000). Mothers filled out this questionnaire when children were on average 1.5 years of age, 3 years of age, and 5-7 years of age. Fathers filled out the CBCL/1.5-5 when the children were 3 years of age. The preschool version of the CBCL was also chosen at age 5-7 years, because most children were expected to be 5 years old. At the end of the assessment, the majority of the sample was 5 years old (67%), some children were 6 (31%) or 7 (2%) years old. Because the mean age was 6.0 (SD=0.3) this wave was hereafter referred to as age 6 years. The CBCL/1.5-5 consists of 100 items. Based on the behavior of the child in the preceding two months, the parent rated each item as 0 for not true, 1 for somewhat or sometimes true, and 2 for very true or often true. Good reliability and validity have been reported for the CBCL/1.5-5 (Achenbach & Rescorla, 2000). The Externalizing scale consists of the items (n=24) from the Attention Problems and Aggressive Behavior syndrome scales.

Parental psychiatric symptoms

Mothers and fathers reported on their psychiatric symptoms at 20 weeks of pregnancy and when the child was 3 years old. The Brief Symptom Inventory (BSI) was used. The BSI is a validated self-report questionnaire with 53 items to be answered on a five-point scale, ranging from "0=not at all" to "4=extremely" (De Beurs, 2004; Derogatis, 1993). The BSI includes 8 subscales; Depression, Hostility, Anxiety, Phobic Anxiety, Paranoid Ideation, Psychoticism, Interpersonal Sensitivity, and Obsessive-Compulsive. At 20 weeks of pregnancy the complete 53 item questionnaire was employed, while at 3 years a short form was used including four subscales: Depression, Hostility, Anxiety, and Interpersonal Sensitivity. Correlations among subscales were high (mean correlation range = 0.58-0.67). Therefore, for each measurement we computed the Global Severity Index (GSI; De Beurs, 2004), which is the mean score of all items. The correlation between the GSI based on the full questionnaire and the GSI based on the short form was 0.96 in the prenatal maternal assessment.

Family functioning

Family functioning was assessed at 20 weeks of pregnancy, via mother and father report, and when the child was 6 years of age, via mother report. The subscale General Functioning of the McMaster Family Assessment Device was used (Epstein et al., 1983). The McMaster model of family functioning identifies six dimensions of family functioning: problem solving, communication, roles, affective responsiveness, affective involvement and behavior control. The General Functioning subscale is a reliable and valid measure of overall health/pathology of the family (Byles et al., 1988). It consists of 12 items (e.g. 'In times of crisis, we can turn to each other for support', 'There are a lot of unpleasant and painful feelings in our family'). Items were answered by selecting from four responses: strongly agree, agree, disagree, and strongly disagree. A mean item score was calculated, ranging from 1 to 4. A higher score indicates worse family functioning.

Covariates

The following variables were considered as potential confounders based on previous studies (Hawes et al., 2011; Hipwell et al., 2008; Pagani et al., 2008): gender and ethnicity of the child, family income, maternal education level, marital status, birth order, and maternal age. All variables were obtained by questionnaires during pregnancy. Ethnicity was based on country of birth of the parents and was defined into Dutch, other Western, or non-Western. Family income was defined by the total net month income of the household and categorized as '< €1,200' (below social security level), '€1,200-2,000', and '> €2,000' (more than modal income). Maternal education level was defined as highest education finished and was classified into three categories: low (primary school or lower vocational education), medium (intermediate vocational education), and high (higher vocational education or university). Marital status was dichotomized into 'married or living together' and 'no partner'. Birth order was dichotomized into 'first child' and 'not first child'.

Statistical analysis

Analyses were performed in Mplus version 7.11. To explore the associations between the various measures of child externalizing problems, parental psychiatric symptoms, and family functioning, we calculated Pearson correlation coefficients. Two approaches were used to examine the effects of child externalizing problems on parental psychiatric symptoms and family functioning. First, effects of child externalizing problems and the influence of possible confounders were examined using univariate linear regressions. We examined the effects of child externalizing problems at 1.5 years on maternal and paternal psychiatric symptoms at 3 years. In addition, we examined the effects of child externalizing problems at 1.5 and 3 years on family functioning at 6 years. All regression analyses were adjusted for prenatal levels of parental psychiatric symptoms and family functioning. Next, we added the covariates to each regression model to check if effect estimates were affected by confounding. All regression analyses were repeated in boys and girls separately.

In the second approach, we built a path model including all measures of child externalizing problems, family functioning, and parental psychiatric symptoms to examine the bidirectional relations between these variables. To examine effects across informants, we built separate models for maternal report and paternal report of child externalizing problems. Covariates were entered as predictors of all endogenous variables in the model. In addition, our model took into account possible covariance among variables which were measured at the same time point. We used a robust maximum likelihood estimator (MLR), which provides test statistics and standard errors robust to non-normality. Model fit was based on the Root Mean Square Error of Approximation (RMSEA), the Comparative Fit Index (CFI), and the Tucker-Lewis Index (TLI; Hu & Bentler, 1999). For the RMSEA, values of .05 or lower indicate close fit. For CFI and TLI, values greater than .90 indicate reasonably good fit.

Finally, we examined if the relation between child externalizing problems and family functioning was mediated by parental psychiatric symptoms. A path analysis was used to examine whether there were indirect effects of child externalizing problems at 1.5 years on family functioning at age 6 via maternal or paternal psychiatric symptoms at age 3. We used the model constraint option in Mplus to test the indirect effects.

Percentages of missing data for the various measures of child externalizing problems, parental psychiatric symptoms, and family functioning ranged from 10% for child externalizing problems at 1.5 years, to 35% for prenatal paternal psychiatric symptoms (mean percentage missing data = 22.5%). For covariates, percentages of missing data all were < 5% except for family income with 17.7% missing data. We imputed missing values using a fully conditional specification method in SPSS. We generated 20 imputed data sets. The imputation model included all variables that were used for further analyses. The imputed datasets were analyzed in Mplus and parameter

estimates were averaged over the set of analyses. To examine possible biases of multiple imputations, analyses were repeated in children with complete data on determinant and outcome.

Non-response analysis

We compared family characteristics of the children included in the analysis (n=5,527) with those excluded because of missing data on CBCL at 1.5 or 3 years (n=2,366). Children of responding families were more likely to be Dutch (64.6% vs. 27.3%, χ^2=1,429, df=3, p<0.001) and to be the first child (56.8% vs. 43.7%, χ^2=135, df=2, p<0.001). Responding mothers were older (mean age difference = 2.9 years, p<0.001) more likely to be highly educated (53.5% vs. 15.8%, χ^2=1,516, df=3, p<0.001) and less likely to be single (8.2% vs. 18.2%, χ^2=1,083, df=2, p<0.001). Responding families were more likely to have an income > €2,000 (59.8% vs. 17.4%, χ^2=1,420, df=3, p<0.001).

RESULTS

Table 2 presents the correlations between the various measures of child externalizing problems, parental psychiatric symptoms, and family functioning. Child externalizing problems were correlated with higher levels of maternal and paternal psychiatric symptoms and worse family functioning. Correlations ranged from 0.10, between prenatal family functioning reported by

Table 2 Unadjusted correlations between child, parent, and family variables (N=5,527)

Variables		1	2	3	4	5	6	7	8	9	10
Child externalizing problems											
1	Age 1.5, mother report	-									
2	Age 3, mother report	.58	-								
3	Age 3, father report	.35	.54	-							
4	Age 6, mother report	.45	.60	.41	-						
Maternal psychiatric symptoms											
5	Prenatal	.23	.22	.12	.17	-					
6	Age 3	.21	.30	.14	.23	.40	-				
Paternal psychiatric symptoms											
7	Prenatal	.15	.13	.16	.12	.26	.17	-			
8	Age 3	.15	.18	.26	.16	.17	.27	.39	-		
Family functioning											
9	Prenatal, mother report	.19	.19	.10	.18	.35	.25	.20	.17	-	
10	Prenatal, father report	.16	.13	.14	.13	.26	.15	.30	.18	.44	-
11	Age 6, mother report	.17	.21	.11	.23	.20	.24	.11	.17	.41	.29

Note: Pearson's correlation coefficients are presented. All correlations were significant at p<0.001

mother and child externalizing problems at 3 years reported by father, to 0.30, between child externalizing reported by mother at 3 years and maternal psychiatric symptoms at 3 years.

We examined the effects of child externalizing problems on parental psychiatric symptoms using linear regression (Table 3). Effect estimates were adjusted for prenatal levels of parental psychiatric symptoms and family functioning. Child externalizing problems at 1.5 years reported by the mother were related to maternal psychiatric symptoms (β=0.11, p<0.001). Importantly, a cross-informant effect was found for child externalizing problems on parental psychiatric symptoms: mother reported externalizing problems at 1.5 years were significantly related to a higher level of psychiatric symptoms of the father (β=0.07, p<0.001). The effects of child externalizing problems on family functioning are shown in Table 4. Child externalizing problems at 1.5 and 3 years were related to poor family functioning at 6 years (assessed by mother) and again these effects were also found independent of informant of child behavior (age 1.5 mother report: β=0.08, p<0.001; age 3 mother report: β=0.12, p<0.001; age 3 father report: β=0.06, p=0.001). Effects did not change materially after adjustment for covariates. We found similar results in analyses in boys and girls separately (data not shown). Analyses in children with complete data on determinant and outcome also yielded similar results (data not shown).

Table 3 Adjusted association between child externalizing problems at 1.5 years of age reported by the mother and parental psychiatric symptoms at 3 years (N=5,527)

	Parental psychiatric symptoms at 3 years			
	Mother		Father	
Child externalizing problems	β (se)	p	β (se)	p
Age 1.5, mother report				
Model 1	0.11 (0.02)	<0.001	0.07 (0.02)	<0.001
Model 2	0.11 (0.02)	<0.001	0.07 (0.02)	<0.001

Note: Model 1: adjusted for prenatal psychiatric symptoms of the parents and prenatal family functioning reported by the mother and the father
Model 2: as model 1 but additionally adjusted for child's gender, child's age, ethnicity of the child, birth order, maternal age, maternal education level, marital status, and family income.

Next, we built a path model including all measurements of child externalizing problems reported by the mother, parental psychiatric symptoms, and family functioning to examine bi-directional relations between these variables (Figure 1). Structural equation modeling showed a good fit to the data (RMSEA=0.043, CFI=0.99, TLI=0.86). To focus on effects across informants we only show the part of the model that comprises paternal psychiatric symptoms and family functioning reported by the father (for the complete model see Supplementary Figure S1). Standardized path coefficients are shown. Covariates, non-significant paths (p>0.05), covariances between variables measured at the same time, standard errors, and residual variances

are not presented in the figures to further enhance the readability. The model shows the effect of child externalizing problems at 1.5 years on paternal psychiatric symptoms, similar to what was found in the linear regression analysis. Additionally, prenatal paternal psychiatric symptoms (β=0.06, p=0.007), and prenatal family functioning as reported by the father (β=0.05, p=0.006) predicted child externalizing problems.

Table 4 Adjusted associations between child externalizing problems at ages 1.5 and 3 and family functioning reported by the mother at 6 years (N=5,527)

	Family functioning at age 6 mother report	
Child externalizing problems	β (se)	p
Age 1.5, mother report		
Model 1	0.08 (0.02)	<0.001
Model 2	0.09 (0.02)	<0.001
Age 3, mother report		
Model 1	0.12 (0.02)	<0.001
Model 2	0.12 (0.02)	<0.001
Age 3, father report		
Model 1	0.06 (0.02)	0.001
Model 2	0.06 (0.02)	<0.001

Note: Model 1: adjusted for prenatal psychiatric symptoms of the parents and prenatal family functioning reported by the mother and the father
Model 2: as model 1 but additionally adjusted for child's gender, child's age, ethnicity of the child, birth order, maternal age, maternal education level, marital status, and family income.

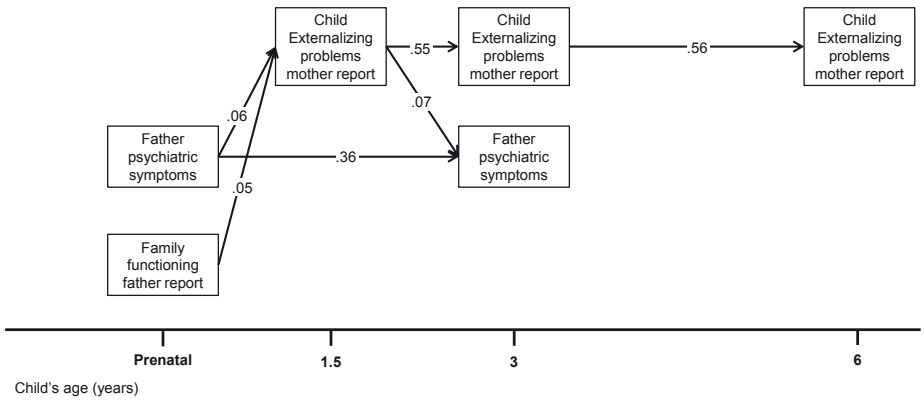


Figure 1 Associations between child externalizing problems reported by the mother, paternal psychiatric symptoms, and family functioning
Note: for the complete figure see Supplementary Figure 1

We also built a path model including father reported externalizing problems, which was only available at age 3. Fit indices indicated good model fit (RMSEA=0.027, CFI=0.99, TLI=0.92). Figure 2 shows the standardized path coefficients between child externalizing problems and maternal psychiatric symptoms and family functioning (the full model is depicted in Supplementary Figure S2). In this model the effect of child externalizing problems at 3 years on family functioning was adjusted for parental psychiatric symptoms at 3 years. Yet, the effect remained significant (β=0.04, p<0.001). Prenatal maternal psychiatric symptoms (β=0.06, p=0.009) predicted child externalizing problems reported by the father at 3 years.

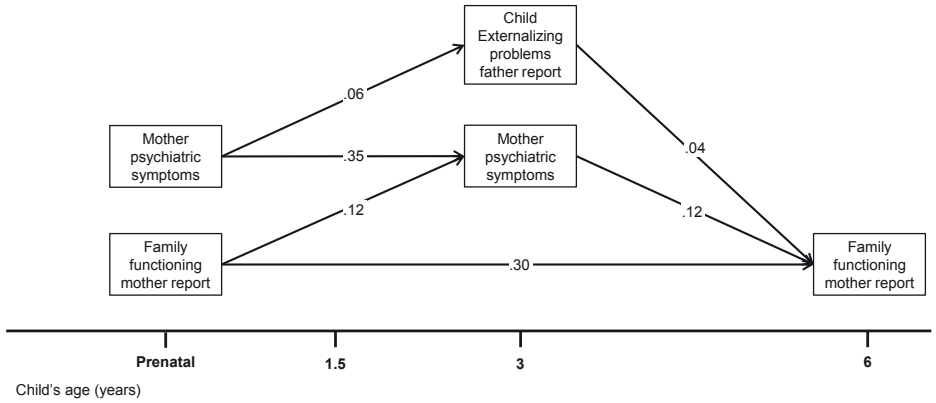


Figure 2 Associations between child externalizing problems reported by the father, maternal psychiatric symptoms, and family functioning
Note: for the complete figure see supplementary Figure 2

Finally, we tested whether externalizing problems at 1.5 years had a direct effect on family functioning at 6 years and indirect effects via maternal and paternal psychiatric symptoms at 3 years (model is shown in Supplementary Figure S3). The adjusted direct effect was β=0.07 (p<0.001). Moreover, we also observed indirect effects: β=0.004 (p=0.012) for an effect via paternal psychiatric symptoms and β=0.012 (p<0.001) for an effect via maternal psychiatric symptoms.

DISCUSSION

The purpose of the study was to investigate the prospective association of externalizing problems in preschoolers with maternal and paternal psychiatric symptoms and family functioning. We showed that young children's externalizing problems have a negative influence on maternal psychiatric symptoms, paternal psychiatric symptoms, and on family functioning assessed 1.5

to 3 years later. These findings were independent of the informant. Also, findings were not explained by pre-existing parental psychiatric symptoms or family functioning, and socio-economic and family characteristics.

The current study adds valuable information to existing literature on the role of the father in the development of the child. Connell and Goodman (2002) showed in their meta-analysis that not only maternal psychiatric symptoms but also paternal psychiatric symptoms predict problem behavior in the child. Previous studies have shown that the relation between maternal psychiatric symptoms and child externalizing problems is bidirectional (e.g. Allen et al., 2010; Gross et al., 2008a; Jaffee & Poulton, 2006). We showed that the relation between paternal psychiatric symptoms and child externalizing problems is also bi-directional: prenatal psychiatric symptoms of the father predicted child externalizing problems at 1.5 years, and child externalizing problems at 1.5 years predicted psychiatric symptoms in the father at 3 years. The current study also adds to previous studies on the bi-directional relation between child problem behavior and maternal mental health by showing that the negative influence of child externalizing problems on the parents can already be demonstrated early in life at 1.5 years of age. The mechanisms through which child problem behavior influences parental mental health remain largely unknown. Child-related stress has been found to play a mediating role in the relation between child psychopathology and maternal depression (Raposa et al., 2011). Other mediating factors that have been hypothesized are decreased parenting self-efficacy and feelings of social isolation (Donenberg & Baker, 1993).

To our knowledge, no previous studies have demonstrated the effects of child externalizing problems on overall levels of family functioning using a longitudinal design. While numerous studies have shown that physical health problems in the child are a risk factor for poor family functioning, mental health problems have mostly been regarded as an outcome of poor family functioning (Pagani et al., 2008; Schermerhorn et al., 2011; Sturge-Apple et al., 2010). We showed that the presence of problem behavior can also be a burden for the family. Moreover, the results suggest that having a young child with externalizing problems makes it difficult for family members to interact in an open and harmonious manner with each other. We found that the relation between child externalizing problems and family functioning was partially mediated by maternal and paternal psychiatric symptoms. However, these indirect effects appeared very small. This suggests that the child influences overall family functioning not only via the mental health of his or her parents. This is in line with family systems theory which describes each family member, including the child, as an active contributor to the broader family system (Cox & Paley, 1997; Minuchin, 1985).

Externalizing problems at a young age are, to a certain degree, part of normal development. In most children externalizing problems decrease over time, but in some children externalizing

problems become persistent. The reciprocal pattern between the child's behavior and parenting styles influences the persistence of externalizing problems from a young age onwards (Bradley & Corwyn, 2013; Burke et al., 2008; Hawes et al., 2011; Hipwell et al., 2008; Larsson et al., 2008). The bidirectional findings from this study suggest that parental mental health and family functioning also play an important role in this negative cyclical pattern. Therefore, we suggest that intervention programs should not only target parenting behaviors, but should also consider to what extent maternal and paternal mental health and overall family functioning influence and are influenced by the externalizing problems of the child.

Both boys' and girls' externalizing problems predicted parental psychiatric symptoms and poor family functioning. The absence of sex differences is in agreement with studies in preschool children that examined child effects on parental depression or parenting style (Combs-Ronto et al., 2009; Harvey & Metcalfe, 2012; Larsson et al., 2008). These findings suggest that having a young child with externalizing problems impacts parents' mental health, independent of the sex of the child. In older children some studies found stronger effects for girls' externalizing problems on mothers' depressive symptoms than for boys' externalizing problems (Fanti et al., 2013; Jaffee & Poulton, 2006) while other studies reported no sex differences (Bagner et al., 2013).

The present study has several strengths. The study included a large number of participants from a multi-ethnic population-based birth cohort and used a longitudinal design. Another strength is that child externalizing problems, parental psychiatric symptoms, and family functioning were reported by both parents. Also, parental psychiatric symptoms and family functioning were measured before the birth of the child and are therefore independent of child influences. There were also limitations. First, we focused only on overall levels of psychiatric symptoms of the parents. In a population-based sample the subscales of the BSI are highly correlated, thus we were unable to test for specificity of associations between child externalizing problems and different psychiatric symptoms in the parents. Second, we measured the overall attitude of the parents towards functioning of the family. To obtain a more comprehensive measurement of family functioning, complex assessment procedures are needed, including observational measures and the examination of patterns of family processes using pattern-based approaches (Sturge-Apple et al., 2010). Unfortunately, observational measurements in our large cohort were not feasible. However, we used the general functioning subscale of the McMaster Family Assessment Device, which is a measure with good validity and reliability (Byles et al., 1988). Third, the non-respondents at baseline more often had a lower socioeconomic status and a non-western ethnicity. This may affect the generalizability of the findings. To reduce selection-bias through missing data on outcome measures, we performed multiple imputations. This is a valid method assuming missing data at random.

Previous research has stressed the negative influences of parental psychopathology and poor family functioning for the development of the child, but the results of the current study suggest that the reverse is also true: child externalizing problems at early age can be a burden for the family. An accurate understanding how the child, the parents, and the family influence and are influenced by each other is key for future intervention.

REFERENCES

Achenbach, T.M., & Rescorla, L.A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Allen, J.P., Manning, N., & Meyer, J. (2010). Tightly Linked Systems: Reciprocal Relations Between Maternal Depressive Symptoms and Maternal Reports of Adolescent Externalizing Behavior. *Journal of Abnormal Psychology, 119*(4), 825-835. doi: 10.1037/a0021081

Bagner, D.M., Pettit, J.W., Lewinsohn, P.M., Seeley, J.R., & Jaccard, J. (2013). Disentangling the Temporal Relationship Between Parental Depressive Symptoms and Early Child Behavior Problems: A Transactional Framework. *Journal of Clinical Child and Adolescent Psychology, 42*(1), 78-90. doi: 10.1080/15374416.2012.715368

Bell, R.Q. (1968). A reinterpretation of the direction of effects in studies of socialization. *Psychological Review, 75*(2), 81-95.

Belsky, J. (1981). Early Human-Experience - a Family Perspective. *Developmental Psychology, 17*(1), 3-23. doi: 10.1037/0012-1649.17.1.3

Bradley, R.H., & Corwyn, R. (2013). From parent to child to parent…: paths in and out of problem behavior. *Journal of Abnormal Child Psychology, 41*(4), 515-529. doi: 10.1007/s10802-012-9692-x

Burke, J.D., Pardini, D.A., & Loeber, R. (2008). Reciprocal relationships between parenting behavior and disruptive psychopathology from childhood through adolescence. *Journal of Abnormal Child Psychology, 36*(5), 679-692. doi: 10.1007/s10802-008-9219-7

Burstein, M., Stanger, C., & Dumenci, L. (2012). Relations Between Parent Psychopathology, Family Functioning, and Adolescent Problems In Substance-Abusing Families: Disaggregating the Effects of Parent Gender. *Child Psychiatry & Human Development, 43*(4), 631-647. doi: 10.1007/s10578-012-0288-z

Byles, J., Byrne, C., Boyle, M.H., & Offord, D.R. (1988). Ontario Child Health Study: reliability and validity of the general functioning subscale of the McMaster Family Assessment Device. *Family Process, 27*(1), 97-104.

Combs-Ronto, L.A., Olson, S.L., Lunkenheimer, E.S., & Sameroff, A.J. (2009). Interactions Between Maternal Parenting and Children's Early Disruptive Behavior: Bidirectional Associations across the Transition from Preschool to School Entry. *Journal of Abnormal Child Psychology, 37*(8), 1151-1163. doi: 10.1007/s10802-009-9332-2

Connell, A.M., & Goodman, S.H. (2002). The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychological Bulletin, 128*(5), 746-773.

Cox, M.J., & Paley, B. (1997). Families as systems. *Annual Review of Psychology, 48*, 243-267. doi: 10.1146/annurev.psych.48.1.243

Cox, M.J., & Paley, B. (2003). Understanding families as systems. *Current Directions in Psychological Science, 12*(5), 193-196. doi: 10.1111/1467-8721.01259

Cui, M., Donnellan, M.B., & Conger, R.D. (2007). Reciprocal influences between parents' marital problems and adolescent internalizing and externalizing behavior. *Developmental Psychology, 43*(6), 1544-1552. doi: 10.1037/0012-1649.43.6.1544

De Beurs, E. (2004). *Brief symptom inventory, handleiding*. Leiden, The Netherlands

Derogatis, L.R. (1993). *Brief symptom inventory (bsi): Administration, scoring and procedures manual* (3rd ed.). Minneapolis: National Computer Systems Inc.

Donenberg, G., & Baker, B.L. (1993). The Impact of Young-Children with Externalizing Behaviors on Their Families. *Journal of Abnormal Child Psychology, 21*(2), 179-198. doi: 10.1007/Bf00911315

Epstein, N.B., Baldwin, L.M., & Bishop, D.S. (1983). The Mcmaster Family Assessment Device. *Journal of Marital and Family Therapy, 9*(2), 171-180. doi: 10.1111/j.1752-0606.1983.tb01497.x

Fanti, K.A., Panayiotou, G., & Fanti, S. (2013). Associating Parental to Child Psychological Symptoms: Investigating a Transactional Model of Development. *Journal of Emotional and Behavioral Disorders, 21*(3), 193-210. doi: 10.1177/1063426611432171

Gershoff, E.T. (2002). Corporal punishment by parents and associated child behaviors and experiences: a meta-analytic and theoretical review. *Psychological Bulletin, 128*(4), 539-579.

Gross, H.E., Shaw, D.S., & Moilanen, K.L. (2008a). Reciprocal associations between boys' externalizing problems and mothers' depressive symptoms. *Journal of Abnormal Child Psychology, 36*(5), 693-709. doi: 10.1007/s10802-008-9224-x

Gross, H.E., Shaw, D.S., Moilanen, K.L., Dishion, T.J., & Wilson, M.N. (2008b). Reciprocal models of child behavior and depressive symptoms in mothers and fathers in a sample of children at risk for early conduct problems. *Journal of Family Psychology, 22*(5), 742-751. doi: 10.1037/a0013514

Harvey, E.A., & Metcalfe, L.A. (2012). The Interplay Among Preschool Child and Family Factors and the Development of ODD Symptoms. *Journal of Clinical Child and Adolescent Psychology, 41*(4), 458-470. doi: 10.1080/15374416.2012.673161

Hawes, D.J., Dadds, M.R., Frost, A.D.J., & Hasking, P.A. (2011). Do Childhood Callous-Unemotional Traits Drive Change in Parenting Practices? *Journal of Clinical Child and Adolescent Psychology, 40*(4), 507-518. doi: 10.1080/15374416.2011.581624

Hipwell, A., Keenan, K., Kasza, K., Loeber, R., Stouthamer-Loeber, M., & Bean, T. (2008). Reciprocal influences between girls' conduct problems and depression, and parental punishment and warmth: a six year prospective analysis. *Journal of Abnormal Child Psychology, 36*(5), 663-677. doi: 10.1007/s10802-007-9206-4

Hu, L.T., & Bentler, P.M. (1999). Cutoff Criteria for Fit Indexes in Covariance Structure Analysis: Conventional Criteria Versus New Alternatives. *Structural Equation Modeling-a Multidisciplinary Journal, 6*(1), 1-55. doi: 10.1080/10705519909540118

Hughes, E.K., & Gullone, E. (2008). Internalizing symptoms and disorders in families of adolescents: A review of family systems literature. *Clinical Psychology Review, 28*(1), 92-117. doi: 10.1016/j.cpr.2007.04.002

Jaddoe, V.W., van Duijn, C.M., Franco, O.H., van der Heijden, A.J., van Iizendoorn, M.H., de Jongste, J.C., et al. (2012). The Generation R Study: design and cohort update 2012. *European Journal of Epidemiology, 27*(9), 739-756. doi: 10.1007/s10654-012-9735-1

Jaffee, S.R., & Poulton, R. (2006). Reciprocal effects of mothers' depression and children's problem behaviors from middle childhood to early adolescence. In A. C. Huston & M. N. Ripke (Eds.), *Developmental Contexts in Middle Childhood: Bridges to Adolescence and Adulthood* (pp. 107-129): Cambridge University Press.

Johnson, V.K. (2003). Linking changes in whole family functioning and children's externalizing behavior across the elementary school years. *Journal of Family Psychology, 17*(4), 499-509. doi: 10.1037/0893-3200.17.4.499

Katz, L.F., & Woodin, E.M. (2002). Hostility, hostile detachment, and conflict engagement in marriages: Effects on child and family functioning. *Child Development, 73*(2), 636-651. doi: 10.1111/1467-8624.00428

Kok, R., Linting, M., Bakermans-Kranenburg, M.J., van Ijzendoorn, M.H., Jaddoe, V.W., Hofman, A., et al. (2013). Maternal sensitivity and internalizing problems: evidence from two longitudinal studies in early childhood. *Child Psychiatry & Human Development, 44*(6), 751-765. doi: 10.1007/s10578-013-0369-7

Kouros, C.D., & Garber, J. (2010). Dynamic Associations between Maternal Depressive Symptoms and Adolescents' Depressive and Externalizing Symptoms. *Journal of Abnormal Child Psychology, 38*(8), 1069-1081. doi: 10.1007/s10802-010-9433-y

Larsson, H., Viding, E., Rijsdijk, F.V., & Plomin, R. (2008). Relationships between parental negativity and childhood antisocial behavior over time: a bidirectional effects model in a longitudinal genetically informative design. *Journal of Abnormal Child Psychology, 36*(5), 633-645. doi: 10.1007/s10802-007-9151-2

Minuchin, P. (1985). Families and Individual Development - Provocations from the Field of Family-Therapy. *Child Development, 56*(2), 289-302. doi: 10.1111/j.1467-8624.1985.tb00106.x

Moss, H.B., Lynch, K.G., Hardie, T.L., & Baron, D.A. (2002). Family functioning and peer affiliation in children of fathers with antisocial personality disorder and substance dependence: Associations with problem behaviors. *American Journal of Psychiatry, 159*(4), 607-614. doi: 10.1176/appi.ajp.159.4.607

Nicholson, J.S., Deboeck, P.R., Farris, J.R., Boker, S.M., & Borkowski, J.G. (2011). Maternal Depressive Symptomatology and Child Behavior: Transactional Relationship With Simultaneous Bidirectional Coupling. *Developmental Psychology, 47*(5), 1312-1323. doi: 10.1037/a0023912

Pagani, L.S., Japel, C., Vaillancourt, T., Cote, S., & Tremblay, R.E. (2008). Links between life course trajectories of family dysfunction and anxiety during middle childhood. *Journal of Abnormal Child Psychology, 36*(1), 41-53. doi: 10.1007/s10802-007-9158-8

Pardini, D.A. (2008). Novel insights into longstanding theories of bidirectional parent-child influences: introduction to the special section. *Journal of Abnormal Child Psychology, 36*(5), 627-631. doi: 10.1007/s10802-008-9231-y

Pardini, D.A., Fite, P.J., & Burke, J.D. (2008). Bidirectional associations between parenting practices and conduct problems in boys from childhood to adolescence: the moderating effect of age and African-American ethnicity. *Journal of Abnormal Child Psychology, 36*(5), 647-662. doi: 10.1007/s10802-007-9162-z

Patterson, G.R., Dishion, T.J., & Bank, L. (1984). Family-Interaction - a Process Model of Deviancy Training. *Aggressive Behavior, 10*(3), 253-267. doi: 10.1002/1098-2337(1984)10:3<253::Aid-Ab2480100309>3.0.Co;2-2

Raposa, E.B., Hammen, C.L., & Brennan, P.A. (2011). Effects of Child Psychopathology on Maternal Depression: The Mediating Role of Child-Related Acute and Chronic Stressors. *Journal of Abnormal Child Psychology, 39*(8), 1177-1186. doi: 10.1007/s10802-011-9536-0

Rothbaum, F., & Weisz, J.R. (1994). Parental caregiving and child externalizing behavior in nonclinical samples: a meta-analysis. *Psychological Bulletin, 116*(1), 55-74.

Schermerhorn, A.C., Cummings, E.M., DeCarlo, C.A., & Davies, P.T. (2007). Children's influence in the marital relationship. *Journal of Family Psychology, 21*(2), 259-269. doi: 10.1037/0893-3200.21.2.259

Schermerhorn, A.C., D'Onofrio, B.M., Turkheimer, E., Ganiban, J.M., Spotts, E.L., Lichtenstein, P., et al. (2011). A Genetically Informed Study of Associations Between Family Functioning and Child Psychosocial Adjustment. *Developmental Psychology, 47*(3), 707-725. doi: 10.1037/a0021362

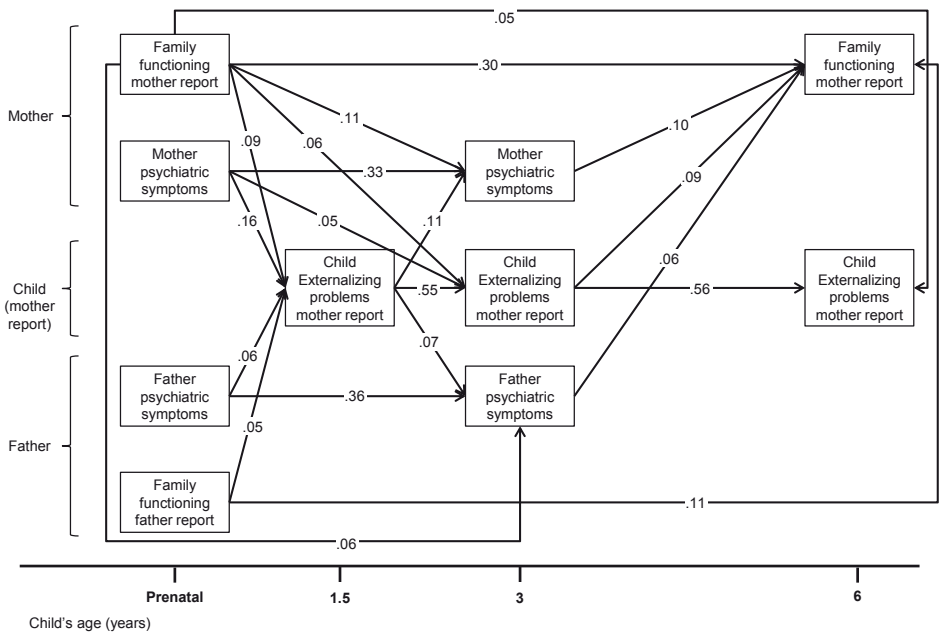
Sturge-Apple, M.L., Davies, P.T., & Cummings, E.M. (2010). Typologies of family functioning and children's adjustment during the early school years. *Child Development, 81*(4), 1320-1335. doi: 10.1111/j.1467-8624.2010.01471.x

Tiemeier, H., Velders, F.P., Szekely, E., Roza, S.J., Dieleman, G., Jaddoe, V.W., et al. (2012). The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(11), 1119-1135.e1117. doi: 10.1016/j.jaac.2012.08.021

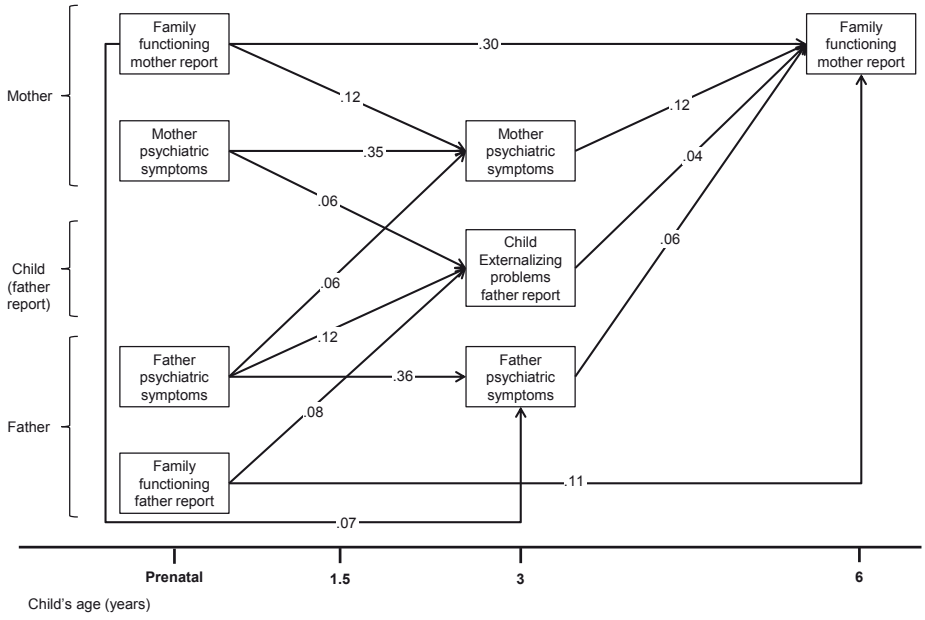
Vandervalk, I., de Goede, M., Spruijt, E., & Meeus, W. (2007). A longitudinal study on transactional relations between parental marital distress and adolescent emotional adjustment. *Adolescence, 42*(165), 115-136.

Velders, F.P., Dieleman, G., Henrichs, J., Jaddoe, V.W., Hofman, A., Verhulst, F.C., et al. (2011). Prenatal and postnatal psychological symptoms of parents and family functioning: the impact on child emotional and behavioural problems. *European Child & Adolescent Psychiatry, 20*(7), 341-350. doi: 10.1007/s00787-011-0178-0

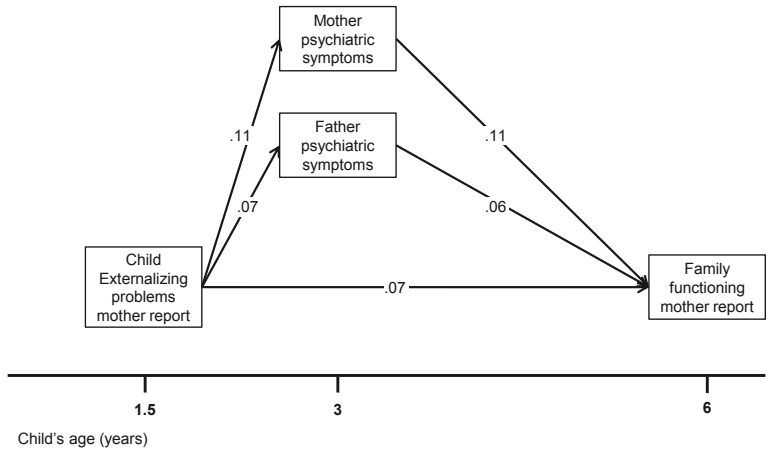
Yates, T.M., Obradovic, J., & Egeland, B. (2010). Transactional relations across contextual strain, parenting quality, and early childhood regulation and adaptation in a high-risk sample. *Development and Psychopathology, 22*(3), 539-555. doi: 10.1017/S095457941000026X



Supplementary Figure 1 Associations between child externalizing problems reported by the mother, parental psychiatric symptoms, and family functioning.



Supplementary Figure 2 Associations between child externalizing problems reported by the father, parental psychiatric symptoms, and family functioning.



Supplementary Figure 3 Parental psychiatric symptoms as mediators between child externalizing problems and family functioning.

Chapter 6

The stability of problem behavior across the preschool years: an empirical approach in the general population.

Basten, M., Tiemeier, H., Althoff, R.R., van de Schoot, R., Jaddoe, V.W.V., Hofman, A., Hudziak, J.J., Verhulst, F.C., & van der Ende, J.

Submitted for publication

ABSTRACT

This study examined the stability of internalizing and externalizing problems from age 1.5 to 6 years, while taking into account developmental changes in the presentation of problems. The study comprised a population-based cohort of 7,206 children. At ages 1.5, 3, and 6 years, primary caregivers reported on problem behavior using the Child Behavior Checklist/1.5-5 (CBCL/1.5-5). At each age we performed cross-sectional latent profile analysis on the CBCL/1.5-5 scales. Latent transition analysis (LTA) was applied to study the stability of problem behavior. Profiles of problem behavior varied across ages. At each age, 82-87% of children were free of problem behavior whereas approximately 2% showed a profile of co-occurring internalizing and externalizing problems. This combined profile was more severe (higher scores across scales) at 6 years than at earlier ages. A predominantly internalizing profile only emerged at 6 years, while a profile with externalizing problems and emotional reactivity was present at each age. LTA showed that, based on profiles at 1.5 and 3 years, it was difficult to predict what kind of profile a child would exhibit at 6 years. Children with a profile of co-occurring internalizing and externalizing problems early in life were most likely to show problem behavior at 6 years. This study shows that the presentation of problem behavior changes across the preschool period. Heterotypic continuity of problems is very common among preschoolers. Children with co-occurring internalizing and externalizing problems were most likely to show persisting problems and should therefore be target for intervention.

INTRODUCTION

The recognition that emotional and behavioral problems start at an early age has led to an increase in studies on preschool emotional and behavioral problems and its stability over time (Egger & Angold, 2006). Defining emotional and behavioral problems in preschoolers is however challenging, as behaviors that are considered "problematic" at older ages are part of normative development in early childhood (Carter et al., 2004). Developmental changes in the presentation of internalizing, externalizing and the co-occurrence of internalizing and externalizing problems across the preschool period need to be considered to improve our understanding of the continuity of problems among preschool children.

As with older children and adolescents, problem behavior among preschoolers can be divided into internalizing problems, such as anxiety and depression, and externalizing problems, including aggression, hyperactivity, and impulsivity (Achenbach & Rescorla, 2000; Carter et al., 2003; Sterba et al., 2007a). Several studies have examined the persistence of internalizing and externalizing problems across the preschool period and beyond by examining associations between levels of internalizing and externalizing problems measured at different ages. Substantial stability has been found (Campbell, 1995; Fischer et al., 1984; Keenan et al., 1998; Mathiesen & Sanson, 2000; Mesman et al., 2001; Mian et al., 2011). For example, Mesman et al. (2001) found that internalizing and externalizing problems at ages 2-3 years predicted the same type of problems at ages 10-11 years. Apart from showing the same type of problems across ages, also called homotypic stability, these studies found also heterotypic stability, that is, showing different types of problems across ages (Fischer et al., 1984; Mesman et al., 2001). In the study of Mesman et al. (2001) preschool levels of externalizing problems predicted higher levels of internalizing problems.

Stability has also been demonstrated in studies using latent class growth analyses. In these studies, groups of children have been identified with patterns of persisting internalizing problems or persisting externalizing problems over time (Fanti & Henrich, 2010; Sterba et al., 2007b; Tremblay et al., 2004). Although most of these studies focused on only one type of problems, Fanti and Henrich (2010) examined how latent class trajectories of internalizing problems from age 2 to 12 years co-occurred with latent class trajectories of externalizing problems. They identified groups of children with persistent internalizing problems over time, persistent externalizing problems over time, and persistent co-occurring internalizing and externalizing problems over time.

These association studies and latent class growth models have been highly informative on our understanding of the stability of problems across the preschool period and beyond. However, they give limited information at the level of the individuals. The identification of preschool

children who are most likely to have persisting problems is highly relevant for decisions about intervention and prevention. Therefore, the persistence of problems has also been studied categorically using symptom cut-points or diagnostic classifications (Briggs-Gowan et al., 2006; Bufferd et al., 2012; Campbell, 1995; Keenan et al., 1998; Lavigne et al., 1998; Luby et al., 2009; Mathiesen & Sanson, 2000; Speltz et al., 1999). For example, Briggs-Gowan et al. (2006) found that 50% of 12-to-40 month olds with high levels of parent reported externalizing problems, again showed high levels of externalizing problems one year later. Children with high levels of internalizing problems had a 38% chance to have internalizing problems after one year. Interestingly, children with co-occurring internalizing and externalizing problems were most likely to have persisting problems. Bufferd et al. (2012) showed significant persistence of attention deficit hyperactivity disorder, oppositional defiant disorder, and anxiety disorders from age 3 to age 6 years. Heterotypic continuity was also found in this study. For example, children meeting the criteria for an anxiety disorder at age 3 years were more likely to meet the criteria for depression and oppositional defiant disorder at age 6 years.

A major challenge for studies on the categorical stability of preschool problems is to distinguish deviant behavior from normal development (Carter et al., 2004). Longitudinal studies have shown that overall levels of externalizing problems decrease from ages 2 to 6 years (Fanti & Henrich, 2010; Gilliom & Shaw, 2004). This is explained by the recognition that externalizing behaviors such as oppositional behavior and temper tantrums are part of normal behavior when children are younger, and in many children these behaviors decrease over time. Some types of internalizing problems are also considered 'normal' at younger ages, such as separation anxiety. However, although some studies found a decreasing pattern of internalizing problems across the preschool period (Carter et al., 2010; Sterba et al., 2007b), others found an increase over time (Colder et al., 2002; Gilliom & Shaw, 2004). Little is known regarding the development of co-occurring internalizing and externalizing problems. One theory suggests that co-occurrence decreases with age as psychopathology becomes more differentiated (Nottelmann & Jensen, 1995). However studies on DSM disorders in preschoolers have found increases in the prevalence of comorbidity over time (Egger & Angold, 2006; Lavigne et al., 1998).

It has long been recognized that changes in the presentation of problem behavior across ages have to be taken into account to understand the stability of problems over time (Cicchetti & Toth, 1991; Sroufe & Rutter, 1984). However, most studies on the stability of problems in preschoolers have applied the same criteria to define problem behavior at each age. By using the same criteria or cut-points across different ages on the same instrument, the deviance from typical development is not taken into account appropriately. An alternative is to use age-specific cut-points on scales of problem behavior. For example, Briggs-Gowan et al. (2006) used standardized scores within 6-month age bands and set cut-points at the 90th percentile, which results in 10% of the children having problems at each age. With the use of these age-

specific cut-points it is assumed that the prevalence of problems is equal across ages, which is questionable. A third possibility is using different age-specific instruments to asses problem behavior (e.g. Keenan et al., 1998). A disadvantage of this approach is that differences between instruments limit the comparability over time.

An empirical way to study the individual stability of problem behavior, while taking into account developmental changes in the presentation of problem behavior, is by using latent transition analysis (LTA; Collins & Lanza, 2010). Latent transition analysis is a longitudinal extension of cross-sectional person centered methods such as latent class analysis (LCA) and latent profile analysis (LPA). LCA and LPA are methods to empirically identify homogeneous groups of individuals with similar profiles of problem behavior on a set of categorical variables (LCA) or dimensions (LPA). Changes in the presentation of problem behavior can be identified by comparing latent profiles derived at different ages. Subsequently, in latent transition analysis, children's transitions in profiles across ages can be examined.

An advantage of this method is that groupings are empirically based and not based on cut-points, which are to a certain degree arbitrary and, as described above, less developmentally sensitive. Another important advantage is that profiles can be estimated across the range of internalizing and externalizing problems. In this way, the stability of co-occurring internalizing and externalizing problems can be studied. This is highly relevant since co-occurrence is common among preschoolers (Egger & Angold, 2006) and has been shown to be related to higher persistence (Briggs-Gowan et al., 2006). Also heterotypic continuity across internalizing and externalizing problems can be examined.

Connell et al. (2008) previously used LTA to investigate the stability of internalizing and externalizing problems in preschoolers at 2, 3, and 4 years of age. This study was performed to examine family intervention effects among high risk children with behavior problems, family problems and low socio-economic status. At each age they identified four classes on dichotomized scales of the CBCL. These classes were labelled 'externalizing only', 'internalizing only', 'comorbid internalizing and externalizing', and 'normative'. Classes were assumed to be similar across ages, but this was not tested. Children in the 'externalizing only', 'internalizing only', and 'comorbid internalizing and externalizing' classes, who did not receive treatment, were likely to be in the same class after one year (transition probabilities ranged from 0.53-0.86; Connell et al., 2008). The selection of children at high risk may have influenced the identified classes (Angold et al., 1999) and the stability of class membership over time. Therefore it is unknown if these findings are generalizable to the general population.

Recently, our research group performed an LPA to empirically derive profiles of emotional and behavioral problems in 6 year old children from the general population (Basten et al., 2013).

Four distinct profiles were identified: 1) a profile with few problems, 2) a profile with moderate internalizing problems, 3) a profile with moderate externalizing problems and emotional reactivity, and 4) a combined profile with high levels of internalizing and externalizing problems, which was labeled 'dysregulation'. It is unknown if these distinctive and co-occurring profiles of internalizing and externalizing problems in the general population arise through the preschool period, or if a similar presentation can already be found in very young children.

The first aim of the current study was to investigate the architecture and the prevalence of profiles of internalizing and externalizing problems at the ages 1.5, 3, and 6 years in a large general-population sample using latent profile analysis. If the presentation of internalizing and externalizing problems changes during the preschool period, this may be reflected in the number of profiles that can be distinguished at different ages and the shape of these profiles. In addition, differences in the prevalence of the profiles may be identified. Since factor analytical work has shown that the distinction between internalizing and externalizing problems exist already at a very young age (Achenbach & Rescorla, 2000; Carter et al., 2003), we expected to find profiles with predominantly internalizing problems and profiles with predominantly externalizing problems to exist already at 1.5 years of age. We also expected to find a profile with co-occurring internalizing and externalizing problems at each age given the substantial correlations across both domains that has been found (Achenbach & Rescorla, 2000; Carter et al., 2003). Since levels of externalizing problems are higher in younger children (Fanti & Henrich, 2010; Gilliom & Shaw, 2004), we hypothesized profiles characterized by externalizing problems to be more prevalent at the beginning of the preschool period than at a later age.

Our second aim was to study the stability of internalizing and externalizing problems by examining children's transitions in profiles from 1.5 and 3 years to 6 years of age using LTA. Based on earlier findings on the stability of co-occurring internalizing and externalizing problems (Briggs-Gowan et al., 2006), we hypothesized that children with a profile of co-occurring internalizing and externalizing problems were more likely than children with problems on a single domain to have persisting problems.

Finally, we also studied gender differences in the stability of problems. Previous studies examining categorical stability across the preschool period found little gender differences (Briggs-Gowan et al., 2006; Bufferd et al., 2012; Lavigne et al., 1998). However, it is well known that gender differences in externalizing problems emerge across the preschool period, with externalizing problems becoming more prevalent in boys than in girls (Hay, 2007; Rutter et al., 2003). Based on this emerging gender difference in externalizing problems in the preschool period, boys were expected to have more persistent externalizing problems than girls.

METHODS

Setting and population

This study was embedded in the Generation R Study, a multi-ethnic population-based cohort from fetal life onwards in Rotterdam, the Netherlands. The Generation R Study has been described previously (Jaddoe et al., 2012; Tiemeier et al., 2012). Briefly, all pregnant women living in Rotterdam, with an expected delivery date between April 2002 and January 2006 were invited to participate. The study was approved by the Medical Ethics Committee of the Erasmus Medical Center, Rotterdam. Written informed consent was obtained from all adult participants and anonymity was guaranteed. At birth, 9,749 children participated in the study. Primary caregivers reported on child's problem behavior at ages 1.5 years (n=5,184), 3 years (n=4,928), and 5-to-7 years (n=6,131). In the present study we included 7,206 children for which at least one measurement was available (follow-up rate 74%). At age 3 years partner report on the child's problem behavior was also available in 4,010 children. At 5-to-7 years, the majority

Table 1 Sample characteristics

	N=7,206
Gender %	
Girls	49.6
Boys	50.4
Age at each wave, years, mean (SD)	
Age 1.5	1.5 (0.1)
Age 3	3.1 (0.1)
Age 6	6.0 (0.4)
Child ethnicity %	
Dutch	58.8
Other Western	8.9
Non-Western	31.0
Missing	1.3
Maternal education %*	
High	53.3
Medium	29.9
Low	14.8
Missing	2.0
Family income (net per month) %*	
> €3,200	41.2
€1,600 - €3,200	26.5
< €1,600	12.6
Missing	19.7

Note: * maternal education and family income were measured at age 6.

was 5 years old (58%) and some children were 6 (38%), or 7 (4%) years old. Because the mean age was 6.0 (SD=0.4) this wave was hereafter referred to as 'age 6'. Table 1 presents sample characteristics.

Child Behavior Checklist

We assessed problem behavior using the Child Behavior Checklist for ages 1.5 to 5 (CBCL/1.5-5; Achenbach & Rescorla, 2000). This preschool version was chosen at age 6 for continuity. At all ages the CBCL/1.5-5 was completed by the primary caregiver, which were mostly mothers (age 1.5 95% mothers; age 3 92.5% mothers; age 6 92.6% mothers). At age 3, the mothers' partners, most of whom were fathers (89.5%), reported on problem behavior of the child. The CBCL/1.5-5 consists of 100 problem items. Based on the behavior of the child in the preceding two months, the caregiver rated each item as 0 for not true, 1 for somewhat or sometimes true, and 2 for very true or often true. We used the empirically derived syndrome scales Emotionally Reactive, Anxious/Depressed, Somatic Complaints and Withdrawn, which are part of the internalizing domain, and Attention Problems and Aggressive Behavior, which are part of the externalizing domain. Good reliability and validity have been reported for the CBCL/1.5-5 (Achenbach & Rescorla, 2000) and the scales were found to be generalizable across 23 societies, including the Netherlands (Ivanova et al., 2010). At the third wave, for all scales Cronbach's alphas were the same in 5 year-old children and in children older than 5, indicating that problems were also reliably measured in children older than 5. We used T-scores based on multicultural norms (Achenbach & Rescorla, 2010).

Data analysis

Our first aim was to examine the development of profiles of problem behavior during the preschool period. To this goal, we examined profiles of problem behavior at ages 1.5 and 3 using cross-sectional latent profile analysis (LPA) on the CBCL/1.5-5 completed by the primary caregivers. LPA identifies homogeneous latent classes of subjects with similar profiles on a set of continuous variables. T-scores on the CBCL/1.5-5 scales were used as indicators. To guard against skewed variables, a maximum likelihood estimator with robust standard errors was used. We used five criteria to determine the number of profiles. The first two criteria were the Bayesian information criterion (BIC) and the Bootstrapped Likelihood-Ratio Test (BLRT) as these fit indices appeared to perform best in a simulation study (Nylund et al., 2007). For the BIC a lower value represents a better tradeoff between model fit and model complexity. The BLRT tests if the addition of a profile leads to a significant increase in model fit. Third, we examined entropy, a measure of how well children were classified. Entropy values approaching 1 indicate clear delineation of profiles. Fourth, profiles should include at least 1% of the sample. Fifth, an additional profile had to considerably differ in severity or had to have a different shape than the other profiles. This procedure was similar to the LPA that was previously performed at age 6 (Basten et al., 2013).

Next, we evaluated if profiles were equal across ages. The concept that a latent variable has the same measurement characteristics over time or across groups is known as measurement invariance (Collins & Lanza, 2010). To test measurement invariance we estimated four models: 1) a model where profiles were allowed to vary across ages; 2) a model with equal profiles across ages 1.5 and 3; 3) a model with equal profiles across ages 3 and 6; and 4) a model holding profiles equal across all ages. Differences in model fit between these four models were assessed by comparing the BICs. We also performed a measurement invariance test to examine if the profiles at age 3 based on the primary caregiver report were similar to profiles based on partner report.

Our second aim was to study the stability of problem behavior in children. Therefore we performed latent transition analysis (LTA; Collins & Lanza, 2010; Lanza & Collins, 2008; Meeus et al., 2011). LTA is a person-centered method for longitudinal data to study the stability and change of profile membership over time. LTA estimates transition probabilities from a particular profile at time *t* to another profile at time *t*+1. Homotypic stability of profile membership can be studied if profiles are measurement invariant over time. However, if profiles are not equal over time, the qualitative change in profiles should be taken into account for interpreting the transition probabilities (Collins & Lanza, 2010).

We examined gender differences in profile prevalence rates and transitions. At each age we assigned children to their most likely latent profile. This is justified if entropy is high (>.80; Clark & Muthen, 2009). We performed multinomial logistic regression analysis to test if gender was related to profile membership. Subsequently, we added gender as a covariate to the LTA model to obtain transition probabilities for boys and girls separately.

To deal with missing values in LTA, full-information maximum likelihood was used. Moreover, models were estimated on the basis of all information available from both complete cases (53.2%) and cases with 1 (27.9%) or 2 (18.9%) measurements. All analyses were performed in Mplus version 7 (Muthén & Muthén, 1998-2012). To examine possible biases of this method, we repeated LTA in the complete cases.

Non-response analysis

We compared prenatal child and maternal characteristics of the children included in the analysis (n=7,206) with those excluded because of no CBCL/1.5-5 available (n=2,543). Children of responding mothers were more likely to be Dutch (58.8% vs. 25.9%, χ^2=1761, df=3, p<0.001). Responding mothers were more likely to be higher educated (46.2% vs. 13.3% higher education, χ^2=1320, df=3, p<0.001) and to have a family income > €2,000 net per month (52.5% vs. 13.2%, χ^2=1464, df=3, p<0.001).

RESULTS

Creating profiles and testing measurement invariance

At age 6, a four-profile solution was considered the best fitting model (Basten et al., 2013). At ages 1.5 and 3 the BIC and the BLRT indicated that five profiles resulted in better model fit than four profiles (fit indices are reported in Supplementary Table S1). However, at age 1.5 the fifth profile consisted of only 2 participants with extreme scores. These measurements were considered outliers and were removed. After removal, we estimated a model with five profiles, but this time, the fifth profile had a shape similar to another profile, with only a slight difference in severity. Therefore, we chose a four-profile solution. At age 3, a model with five profiles was not the best option, as one of the profiles had a prevalence of less than 1%. Thus, as we did at age 1.5, we decided to use a four-profile solution at age 3.

The measurement invariance test showed that a model with varying profiles across all ages had a lower BIC (502,960) than models with equal profiles across ages 1.5 and 3 (BIC=503,398), across ages 3 and 6 (BIC=503,964), or across all ages (BIC=505,547). These results did not support the assumption of measurement invariance, indicating that profiles were different across ages. We also performed a measurement invariance test across informants at age 3. To this end, we built a model with four profiles on partner reported problem behavior at age 3 and compared this to the model based on primary caregiver report. The measurement invariance test showed that a model with varying profiles across informants had a higher BIC (BIC=241,011) than a model with equal profiles across informants (BIC=240,900). These results demonstrate that profiles at age 3 were similar for primary caregiver report (mainly mothers) and partner report (mainly fathers).

Figure 1 shows the profiles at ages 1.5, 3, and 6. We looked at similarities and differences of profiles across ages. At each age most children were in a profile without problems: profile 1.5A (81.8%), profile 3A (86.5%), and profile 6A (85.6%). These profiles were labeled 'No problems'. Additionally, at each age there was a profile with moderate externalizing problems and emotionally-reactive behavior (T-scores around 60) and a clear absence of anxious/depressed problems: profile 1.5B, profile 3B, and profile 6B. We labeled these profiles 'Externalizing/emotionally-reactive'. The prevalence of these profiles was higher at age 1.5 (11.1%) than at ages 3 (6.5%) and 6 (7.3%). The 'Internalizing' profile at age 6 (profile 6C; 5.3%), with moderate scores around 60 on all internalizing scales and no elevations on the externalizing scales, was not observed at earlier ages. Instead, at age 3 there was a profile 3C (4.8%) with only slightly higher scores on the internalizing scales than on the externalizing scales. This profile was labeled 'Mild internalizing'. At age 1.5 we found a profile 1.5C (5.4%) with mild problems on all scales and was therefore labeled 'Mild problems'. Finally, at each age there was a profile with moderate to high scores across all internalizing and externalizing scales: profile 1.5D (1.7%), profile 3D (2.2%),

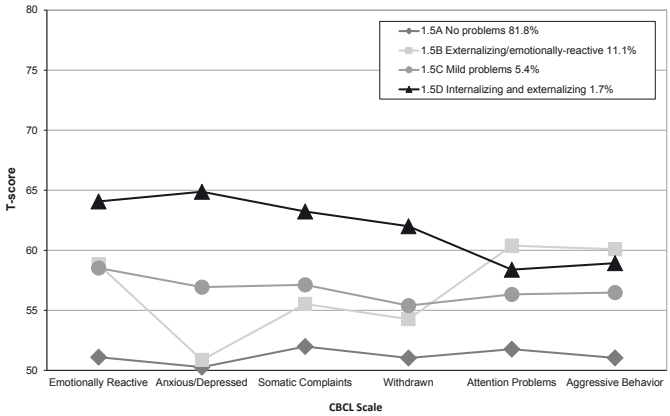


Figure 1a Latent profiles age 1.5

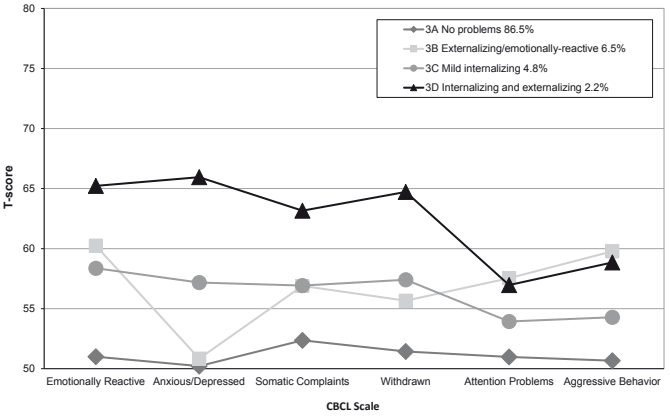


Figure 1b Latent profiles age 3

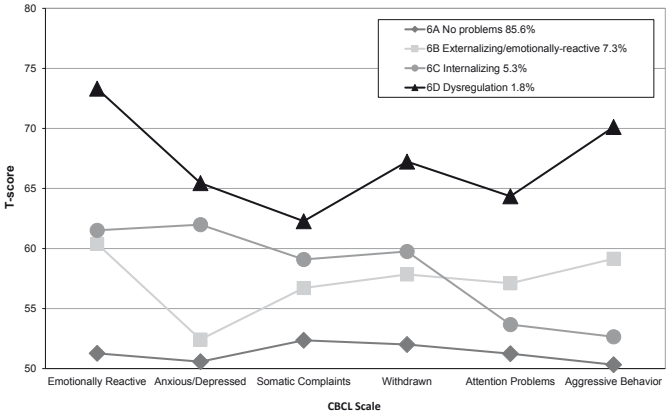


Figure 1c Latent profiles age 6

Figure 1 Mean T-scores for latent profile models at ages 1.5, 3 and 6 years.
Note: Latent profile model at age 6 adapted from Basten et al. (2013). CBCL = Child Behavior Checklist 1.5–5.

and profile 6D 'Dysregulation' (1.8%). Profiles 1.5D and 3D differed from the 'Dysregulation' profile at age 6 in that they scored lower on Emotionally Reactive, Attention Problems, and Aggressive behavior. Profiles 1.5D and 3D were labeled 'Internalizing and externalizing'.

Transitions over time

We performed latent transition analysis to examine the stability of problem behavior in children. Because profiles were not measurement invariant, transition probabilities do not represent homotypic stability (showing the same profile over time). Instead, the transition probabilities represent the likelihood to move from a certain profile at ages 1.5 or 3 to another profile at a later age. Table 2 shows the transition probabilities from age 1.5 to age 3 and from ages 1.5 and 3 to age 6. Children in the 'No problems' profile at age 1.5 were, with a transition probability of 0.89, very likely to be in the 'No problems' profile at age 6. Similarly, children in the 'No problems' profile at age 3 were likely to be in the 'No problems' profile at age 6 (probability=0.92). In contrast, children in the 'Internalizing and externalizing' profiles at ages 1.5 and 3 were less likely to be in the 'No problems' profile at age 6: the probability to move to the 'No problems' profile at age 6 was 0.57 for the 'Internalizing and externalizing' profile at age 1.5 and 0.32 for the 'Internalizing and externalizing' at age 3. In other words, the probabilities for children with combined internalizing and externalizing problems at age 1.5 or 3 to be in one of the three problem profiles at age 6 were 0.43 and 0.68 respectively.

Transition probabilities to move from one of the three problem profiles at age 1.5 to any specific problem profile at age 6 were all low (<0.20). From age 3 to age 6 the highest probability to move from one problem profile to any specific problem profile was found for children moving from profile 3B 'Externalizing/emotionally reactive' to the very similar profile 6B 'Externalizing/emotionally-reactive' at age 6 (probability=0.39). LTA in complete cases yielded almost identical transition probabilities (data not shown).

We also examined transitions conversely by investigating the previous profile membership for those children who were in one of the three problem profiles at age 6. To this aim, we calculated profile membership probabilities at ages 1.5 and 3 conditional on profile membership at age 6 (probabilities are shown in Supplementary Table S2). Children in the 'Dysregulation' profile at age 6 were most likely to have had any problems at younger ages. These probabilities were 0.72 (age 3) and 0.52 (age 1.5). In comparison, for children in the 'Externalizing/emotionally-reactive' profile and 'Internalizing' profile at age 6 the probabilities to have had any problems at age 3 were 0.52 and 0.49, respectively.

Gender differences

Boys were more likely to be in the 'Dysregulation' profile at age 6 (OR=2.04, p<0.001) than girls, while there was no relation between gender and the 'Internalizing and externalizing'

Table 2 Transition probabilities from age 1.5 to age 3, and from ages 1.5 and 3 to age 6 (N=7,206).

	Profiles age 3			
	3A No problems (n=6,070)	3B Externalizing/ emotionally-reactive (n=566)	3C Mild internalizing (n=363)	3D Internalizing and externalizing (n=178)
Profiles age 1.5				
1.5A No problems (n=5,815)	0.93	0.04	0.03	0.01
1.5B Externalizing/emotionally-reactive (n=847)	0.52	0.31	0.11	0.05
1.5C Mild problems (n=407)	0.51	0.16	0.22	0.12
1.5D Internalizing and externalizing (n=137)	0.31	0.15	0.17	0.37
	Profiles age 6			
	6A No problems (n=6,114)	6B Externalizing/ emotionally-reactive (n=560)	6C Internalizing (n=393)	6D Dysregulation (n=140)
Profiles age 1.5				
1.5A No problems (n=5,815)	0.89	0.06	0.04	0.01
1.5B Externalizing/emotionally-reactive (n=847)	0.70	0.17	0.09	0.05
1.5C Mild problems (n=407)	0.70	0.13	0.12	0.05
1.5D Internalizing and externalizing (n=137)	0.57	0.15	0.19	0.09
	Profiles age 6			
	6A No problems (n=6,114)	6B Externalizing/ emotionally-reactive (n=560)	6C Internalizing (n=393)	6D Dysregulation (n=140)
Profiles age 3				
3A No problems (n=6,070)	0.92	0.04	0.03	0.01
3B Externalizing/emotionally-reactive (n=566)	0.43	0.39	0.08	0.09
3C Mild internalizing (n=363)	0.60	0.12	0.23	0.05
3D Internalizing and externalizing (n=178)	0.32	0.15	0.35	0.18

Note: Profile sizes represent profile counts based on estimated model.

profiles at age 1.5 (OR=1.14, p=0.539) and age 3 (OR=1.26, p=0.237). Boys were also more likely to be in the 'Externalizing/emotionally-reactive' profile at age 6 (OR=1.86, p<0.001) and age 3 (OR=1.52, p<0.001), but not at age 1.5 (OR=1.11, p=0.232). Gender was not related to the other profiles.

We added gender to the LTA model to examine transition probabilities per gender (gender specific probabilities are shown in Supplementary Table S3). Most transition probabilities differed only slightly by gender. Boys in the profile 'Externalizing/emotionally-reactive' at age 1.5 and 3 appeared more likely than girls in these profiles to move again to the 'Externalizing/emotionally-reactive' profile at age 6. These probabilities were from age 3 to age 6: 0.44 for boys vs. 0.32 for girls. Examining transitions conversely (Supplementary Table S4), girls in the 'Dysregulation' profile at age 6 appeared more likely to have had any problems at younger age than boys. These probabilities were from age 6 to age 3: 0.94 for girls vs. 0.64 for boys.

DISCUSSION

This study examined the stability of internalizing and externalizing problems from age 1.5 to 6 years, while taking into account developmental changes in the presentation of problems. Using LPA, we showed that the presentation of internalizing and externalizing problems changed from 1.5 to 3 and to 6 years. Most notably were changes in the presentation of co-occurring internalizing and externalizing problems over time: a profile with co-occurring internalizing and externalizing problems was found at all ages but was characterized by more severe problems at 6 years than at 1.5 and 3 years. A profile with predominantly internalizing problems was only discernible at 6 years, while at earlier ages internalizing problems were accompanied by at least mild levels of externalizing problems. In contrast, a profile characterized by moderate externalizing problems and emotionally-reactive behavior was visible at all ages.

The lack of measurement invariance in profiles across ages in our study suggests that homotypic stability is rare in the preschool period and heterotypic stability is much more common. The predominance of heterotypic stability was further supported by the results from the LTA analysis. Furthermore, transition probabilities showed that, although children with problems at ages 1.5 and 3 were at increased risk to show problems again at 6 years, it was difficult to predict what kind of problem profile a child would exhibit at 6 years. The transition probabilities of having any problems across ages are highly similar to overall stability rates from previous studies (Briggs-Gowan et al., 2006; Bufferd et al., 2012; Lavigne et al., 1998). We found a 40% to 68% stability of any problems from 3 to 6 years, which was comparable to a stability of 50% of having any psychiatric disorder across this same age span reported by Bufferd et al. (2012). Heterotypic stability has also been identified by others (Briggs-Gowan et al., 2006; Bufferd et al., 2012; Lavigne et al., 1998; Mesman et al., 2001). Bufferd et al. (2012) found that magnitudes of odds ratios were highly similar for homotypic stability and heterotypic stability of DSM diagnoses. By using an empirical approach to define profiles of internalizing and externalizing problems, we found that heterotypic stability in the general population is even more common than expected based on previous studies.

At all ages a profile with moderate to high levels of co-occurring internalizing and externalizing problems was identified, but at 6 years this profile was characterized by more severe problems on the Emotionally Reactive, Attention Problems and Aggressive Behavior scales. From the viewpoint that co-occurrence of internalizing and externalizing problems stems from an underlying syndrome of poor self-regulation, we previously labeled this profile at 6 years 'dysregulation' (Basten et al., 2013). A possible explanation for the finding that the profile shows higher scores in 6 year-olds is that by this age children have entered school where self-regulatory skills are required. Problems in regulating emotions, attention and behavior might become more impairing and more visible for the environment at this age (see also Blair, 2002). The finding of a highly dysregulated group only at 6 years appears also in line with studies showing higher prevalence of comorbid DSM diagnoses at the end of the preschool period (Egger & Angold, 2006; Lavigne et al., 1998).

Another finding related to co-occurrence was that latent profiles at 1.5 and 3 years showed that internalizing problems were accompanied by at least mild forms of externalizing problems. A possible explanation for the absence of a profile with predominantly internalizing problems at these ages is that young children have limited ability to communicate about their emotions and might use also externalizing behavior to express their feelings (Gardner & Shaw, 2008). Based on factor analytical studies showing the distinction between internalizing and externalizing problems at early age (Achenbach & Rescorla, 2000; Carter et al., 2003), it is often assumed that children with only internalizing problems can be identified. However based on our results, we suggest that future studies should take into account that 1.5- to 3-year-old children with parent reported internalizing problems are also likely to have at least mild levels of externalizing problems.

Although much of the findings suggested heterotypic stability, there were some findings supporting homotypic stability. The profile externalizing/emotionally-reactive showed very similar profiles across ages. Furthermore, children in this profile at age 3 were more likely to move again to this profile at age 6 than moving to another problem profile. These findings are in line with a higher homotypic stability found for externalizing problems than for internalizing problems by others (Briggs-Gowan et al., 2006; Fischer et al., 1984). The prevalence of this class was higher at 1.5 years than at older ages which is in agreement with existing literature reporting that externalizing behavior is more common at early age (Gardner & Shaw, 2008).

Stability of any problems was highest for children with moderate to high levels of co-occurring internalizing and externalizing problems, with almost 70% of children in a co-occurring profile at age 3 having again problems at age 6. This has been previously found in preschool children (Briggs-Gowan et al., 2006). Studies in school-age children have shown that co-occurrence of internalizing and externalizing problems is a very strong risk factor for adult psychopathology

(Althoff et al., 2010; Sourander et al., 2007). These findings suggest that co-occurrence needs to be taken into account for decisions about prevention and intervention. In addition, other risk factors should be considered. Several biological and environmental factors have been found to play an important role in the stability and change of problems over time, such as family functioning, stressful life events and physical health problems (Briggs-Gowan et al., 2006; Campbell et al., 2000; Mesman & Koot, 2001). These factors, as well as levels of impairment, should also be taken into account to improve prediction of later problems.

A gradual emergence of a higher prevalence of boys in profiles characterized by externalizing problems was found, in line with existing literature (Hay, 2007; Rutter et al., 2003). Additionally, transition probabilities suggested that externalizing problems appear more stable in boys than in girls. Previous studies on categorical stability did not find these gender differences (Briggs-Gowan et al., 2006; Bufferd et al., 2012; Lavigne et al., 1998), which might be related to limited power. Hay (2007) proposes that these emerging differences are most likely related to earlier maturation of girls, boys' vulnerability, and differences in social influences. Another finding related to gender was that in the dysregulation profile at age 6, which included more boys than girls, girls were more likely to have had problems earlier in life than boys. This finding might be explained by the gender paradox, which describes that in disorders with an unequal gender ratio, members of the gender with the lower prevalence rate tend to be more seriously affected (Diamantopoulou et al., 2011; Loeber & Keenan, 1994).

Strengths of the current study were the large number of children, the population-based design and the use of multiple informants. Also, children were classified empirically and not on arbitrarily chosen cut-points. There were also limitations. At ages 1.5 and 6 years problem behavior was only reported by the primary caregiver. The measurement invariance test at age 3 showed that profiles were similar for primary caregivers and their partners. Unfortunately we could not test this for ages 1.5 and 6 years. We were also unable to examine differences in stability across informants. Another limitation is that at "age 6" children were actually 5-to-7 years old. To examine whether profiles were influenced by age differences at this wave, we added age as a covariate in the LPA (Basten et al., 2013). Model fit did not improve, suggesting that age differences had little effect on profiles. Finally, the participation rate in the present study was high (74%) but the possibility of selection bias remains, as the non-respondents had more often a lower socioeconomic status. Because low socioeconomic status is related to higher levels of problem behavior, the prevalence and persistence of problem behavior might have been higher in the non-response group.

In conclusion, we showed that in the general population the presentation of internalizing and externalizing problems changes during the preschool period. The identified profiles in the current study do not represent clinical diagnoses. However, our findings suggest the need

for developmentally sensitive methods for the assessment of psychopathology in preschoolers and the importance of taking into account co-occurrence of internalizing and externalizing problems. In addition, this study showed that heterotypic continuity of problems is very common among preschoolers and that children with high levels of co-occurring internalizing and externalizing problems are most likely to have persisting problems. Children with co-occurring problems thus deserve early intervention to prevent continuing problems for these children as they enter their school age period.

REFERENCES

Achenbach, T.M., & Rescorla, L.A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Achenbach, T.M., & Rescorla, L.A. (2010). *Multicultural Supplement to the Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Althoff, R.R., Verhulst, F.C., Rettew, D.C., Hudziak, J.J., & van der Ende, J. (2010). Adult outcomes of childhood dysregulation: a 14-year follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(11), 1105-1116. doi: 10.1016/j.jaac.2010.08.006

Angold, A., Costello, E.J., & Erkanli, A. (1999). Comorbidity. *Journal of Child Psychology and Psychiatry, 40*(1), 57-87.

Basten, M.M., Althoff, R.R., Tiemeier, H., Jaddoe, V.W., Hofman, A., Hudziak, J.J., et al. J. (2013). The dysregulation profile in young children: empirically defined classes in the generation R study. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(8), 841-850 e842. doi: 10.1016/j.jaac.2013.05.007

Blair, C. (2002). School readiness. Integrating cognition and emotion in a neurobiological conceptualization of children's functioning at school entry. *American Psychologist, 57*(2), 111-127.

Briggs-Gowan, M.J., Carter, A.S., Bosson-Heenan, J., Guyer, A.E., & Horwitz, S.M. (2006). Are infant-toddler social-emotional and behavioral problems transient? *Journal of the American Academy of Child and Adolescent Psychiatry, 45*(7), 849-858. doi: 10.1097/01.chi.0000220849.48650.59

Bufferd, S.J., Dougherty, L.R., Carlson, G.A., Rose, S., & Klein, D.N. (2012). Psychiatric disorders in preschoolers: continuity from ages 3 to 6. *American Journal of Psychiatry, 169*(11), 1157-1164. doi: 10.1176/appi.ajp.2012.12020268

Campbell, S.B. (1995). Behavior problems in preschool children: a review of recent research. *Journal of Child Psychology and Psychiatry, 36*(1), 113-149.

Campbell, S.B., Shaw, D.S., & Gilliom, M. (2000). Early externalizing behavior problems: toddlers and preschoolers at risk for later maladjustment. *Development and Psychopathology, 12*(3), 467-488.

Carter, A.S., Briggs-Gowan, M.J., & Davis, N.O. (2004). Assessment of young children's social-emotional development and psychopathology: recent advances and recommendations for practice. *Journal of Child Psychology and Psychiatry, 45*(1), 109-134.

Carter, A.S., Briggs-Gowan, M.J., Jones, S.M., & Little, T.D. (2003). The Infant-Toddler Social and Emotional Assessment (ITSEA): factor structure, reliability, and validity. *Journal of Abnormal Child Psychology, 31*(5), 495-514.

Carter, A.S., Godoy, L., Wagmiller, R.L., Veliz, P., Marakovitz, S., & Briggs-Gowan, M.J. (2010). Internalizing trajectories in young boys and girls: the whole is not a simple sum of its parts. *Journal of Abnormal Child Psychology, 38*(1), 19-31. doi: 10.1007/s10802-009-9342-0

Cicchetti, D., & Toth, S.L. (1991). A Developmental Perspective on Internalizing and Externalizing Disorders. *Internalizing and Externalizing Expressions of Dysfunction : Rochester Symposium on Developmental Psychopathology, Vol 2*, 1-19.

Clark, S., & Muthen, B. (2009). Relating Latent Class Analysis Results to Variables not Included in the Analysis. http://www.statmodel.com/download/relatinglca.pdf

Colder, C.R., Mott, J.A., & Berman, A.S. (2002). The interactive effects of infant activity level and fear on growth trajectories of early childhood behavior problems. *Development and Psychopathology, 14*(1), 1-23.

Collins, L.M., & Lanza, S.T. (2010). *Latent Class and Latent Transition Analysis with applications in the social, behavioral, and health sciences*. Hoboken, New Jersey: John Wiley & Sons.

Connell, A., Bullock, B.M., Dishion, T.J., Shaw, D., Wilson, M., & Gardner, F. (2008). Family intervention effects on co-occurring early childhood behavioral and emotional problems: a latent transition analysis approach. *Journal of Abnormal Child Psychology, 36*(8), 1211-1225. doi: 10.1007/s10802-008-9244-6

Diamantopoulou, S., Verhulst, F.C., & van der Ende, J. (2011). Gender differences in the development and adult outcome of co-occurring depression and delinquency in adolescence. *Journal of Abnormal Psychology, 120*(3), 644-655. doi: 10.1037/a0023669

Egger, H.L., & Angold, A. (2006). Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. *Journal of Child Psychology and Psychiatry, 47*(3-4), 313-337. doi: 10.1111/j.1469-7610.2006.01618.x

Fanti, K.A., & Henrich, C.C. (2010). Trajectories of pure and co-occurring internalizing and externalizing problems from age 2 to age 12: findings from the National Institute of Child Health and Human Development Study of Early Child Care. *Developmental Psychology, 46*(5), 1159-1175. doi: 10.1037/a0020659

Fischer, M., Rolf, J.E., Hasazi, J.E., & Cummings, L. (1984). Follow-up of a Preschool Epidemiological Sample - Cross-Age Continuities and Predictions of Later Adjustment with Internalizing and Externalizing Dimensions of Behavior. *Child Development, 55*(1), 137-150. doi: 10.2307/1129840

Gardner, F., & Shaw, D.S. (2008). Behavioral problems of infancy and preschool children (0-5). In M. Rutter (Ed.), *Rutter's Child and Adolescent Psychiatry* (5th ed.): Blackwell Publishing.

Gilliom, M., & Shaw, D.S. (2004). Codevelopment of externalizing and internalizing problems in early childhood. *Development and Psychopathology, 16*(2), 313-333.

Hay, D.F. (2007). The gradual emergence of sex differences in aggression: alternative hypotheses. *Psychological Medicine, 37*(11), 1527-1537. doi: 10.1017/S0033291707000165

Ivanova, M.Y., Achenbach, T.M., Rescorla, L.A., Harder, V.S., Ang, R.P., Bilenberg, N., et al. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1215-1224. doi: 10.1016/j.jaac.2010.08.019

Jaddoe, V.W., van Duijn, C.M., Franco, O.H., van der Heijden, A.J., van Iizendoorn, M.H., de Jongste, J.C., et al. (2012). The Generation R Study: design and cohort update 2012. *European Journal of Epidemiology, 27*(9), 739-756. doi: 10.1007/s10654-012-9735-1

Keenan, K., Shaw, D., Delliquadri, E., Giovannelli, J., & Walsh, B. (1998). Evidence for the continuity of early problem behaviors: application of a developmental model. *Journal of Abnormal Child Psychology, 26*(6), 441-452.

Lanza, S.T., & Collins, L.M. (2008). A new SAS procedure for latent transition analysis: Transitions in dating and sexual risk behavior. *Developmental Psychology, 44*(2), 446-456. doi: 10.1037/0012-1649.44.2.446

Lavigne, J.V., Arend, R., Rosenbaum, D., Binns, H.J., Christoffel, K.K., & Gibbons, R.D. (1998). Psychiatric disorders with onset in the preschool years: I. Stability of diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*(12), 1246-1254. doi: 10.1097/00004583-199812000-00007

Loeber, R., & Keenan, K. (1994). Interaction between conduct disorder and its comorbid conditions: Effects of age and gender. *Clinical Psychology Review, 14*, 497-523.

Luby, J.L., Si, X., Belden, A.C., Tandon, M., & Spitznagel, E. (2009). Preschool depression: homotypic continuity and course over 24 months. *Archives of General Psychiatry, 66*(8), 897-905. doi: 10.1001/archgenpsychiatry.2009.97

Mathiesen, K.S., & Sanson, A. (2000). Dimensions of early childhood behavior problems: stability and predictors of change from 18 to 30 months. *Journal of Abnormal Child Psychology, 28*(1), 15-31.

Meeus, W., Van de Schoot, R., Klimstra, T., & Branje, S. (2011). Personality types in adolescence: change and stability and links with adjustment and relationships: a five-wave longitudinal study. *Developmental Psychology, 47*(4), 1181-1195. doi: 10.1037/a0023816

Mesman, J., Bongers, I.L., & Koot, H.M. (2001). Preschool developmental pathways to preadolescent internalizing and externalizing problems. *Journal of Child Psychology and Psychiatry, 42*(5), 679-689. doi: 10.1017/S0021963001007351

Mesman, J., & Koot, H.M. (2001). Early preschool predictors of preadolescent internalizing and externalizing DSM-IV diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 40*(9), 1029-1036. doi: 10.1097/00004583-200109000-00011

Mian, N.D., Wainwright, L., Briggs-Gowan, M.J., & Carter, A.S. (2011). An Ecological Risk Model for Early Childhood Anxiety: The Importance of Early Child Symptoms and Temperament. *Journal of Abnormal Child Psychology, 39*(4), 501-512. doi: 10.1007/s10802-010-9476-0

Muthén, L.K., & Muthén, B.O. (1998-2012). *Mplus User's Guide* (Seventh Edition ed.). Los Angeles, CA: Muthén & Muthén.

Nottelmann, E.D., & Jensen, P.S. (1995). Comorbidity of Disorders in Children and Adolescents - Developmental Perspectives. *Advances in Clinical Child Psychology, 17*, 109-155.

Nylund, K.L., Asparouhov, T., & Muthén, B.O. (2007). Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study. *Structural Equation Modeling, 14*(4), 535-569.

Rutter, M., Caspi, A., & Moffitt, T.E. (2003). Using sex differences in psychopathology to study causal mechanisms: unifying issues and research strategies. *Journal of Child Psychology and Psychiatry, 44*(8), 1092-1115.

Sourander, A., Jensen, P., Davies, M., Niemela, S., Elonheimo, H., Ristkari, T., et al. (2007). Who is at greatest risk of adverse long-term outcomes? The Finnish From a Boy to a Man study. *Journal of the American Academy of Child and Adolescent Psychiatry, 46*(9), 1148-1161. doi: 10.1097/chi.0b013e3180986 1e9

Speltz, M.L., McClellan, J., DeKlyen, M., & Jones, K. (1999). Preschool boys with oppositional defiant disorder: Clinical presentation and diagnostic change. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(7), 838-845. doi: 10.1097/00004583-199907000-00013

Sroufe, L.A., & Rutter, M. (1984). The Domain of Developmental Psychopathology. *Child Development, 55*(1), 17-29. doi: 10.2307/1129832

Sterba, S., Egger, H.L., & Angold, A. (2007a). Diagnostic specificity and nonspecificity in the dimensions of preschool psychopathology. *Journal of Child Psychology and Psychiatry, 48*(10), 1005-1013. doi: 10.1111/j.1469-7610.2007.01770.x

Sterba, S.K., Prinstein, M.J., & Cox, M.J. (2007b). Trajectories of internalizing problems across childhood: heterogeneity, external validity, and gender differences. *Development and Psychopathology, 19*(2), 345-366. doi: 10.1017/S0954579407070174

Tiemeier, H., Velders, F.P., Szekely, E., Roza, S.J., Dieleman, G., Jaddoe, V.W., et al. (2012). The Generation R Study: A Review of Design, Findings to Date, and a Study of the 5-HTTLPR by Environmental Interaction From Fetal Life Onward. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(11), 1119-1135.e1117. doi: 10.1016/j.jaac.2012.08.021

Tremblay, R.E., Nagin, D.S., Seguin, J.R., Zoccolillo, M., Zelazo, P.D., Boivin, M., et al. (2004). Physical aggression during early childhood: trajectories and predictors. *Pediatrics, 114*(1), e43-50.

Supplementary Table S1 Fit statistics for latent profile models at ages 1.5, 3, and 6 years

	Number of Profiles	BIC	BLRT	Entropy	Smallest profile
Age 1.5 (n=5,182)	1	176,330	-	-	-
	2	167,397	<0.001	0.96	13.2%
	3	163,105	<0.001	0.96	4.3%
	4	158,942	<0.001	0.97	1.7%
	5	157,784	<0.001	0.98	1.7%
Age 3 (n=4,928)	1	165,393	-	-	-
	2	155,495	<0.001	0.98	8.7%
	3	151,292	<0.001	0.98	2.5%
	4	147,230	<0.001	0.99	2.2%
	5	145,126	<0.001	0.99	0.6%
Age 6* (n=6,131)	1	217,304	-	-	-
	2	204,285	<0.001	0.98	8.9%
	3	199,746	<0.001	0.97	2.8%
	4	196,759	<0.001	0.98	1.8%
	5	194,392	<0.001	0.99	0.9%

*Note:** Results were previously published in Basten et al. (2013). BIC = Bayesian information criterion, BLRT = Bootstrapped likelihood-ratio test.

Supplementary Table S2 Profile membership probabilities at ages 1.5 and 3 conditional on profile membership at age 6 (N=7,206).

	Profiles age 1.5			
	1.5A No problems (n=5,815)	1.5B Externalizing/ emotionally-reactive (n=847)	1.5C Mild problems (n=407)	1.5D Internalizing and externalizing (n=137)
Profiles age 6				
6A No Problems (n=6,114)	0.84	0.10	0.05	0.01
6B Externalizing/emotionally-reactive (n=560)	0.62	0.25	0.09	0.04
6C Internalizing (n=393)	0.62	0.19	0.13	0.07
6D Dysregulation (n=140)	0.48	0.29	0.14	0.09
	Profiles age 3			
	3A No problems (n=6,070)	3B Externalizing/ emotionally-reactive (n=566)	3C Mild internalizing (n=363)	3D Internalizing and externalizing (n=178)
Profiles age 6				
6A No Problems (n=6,114)	0.92	0.04	0.04	0.01
6B Externalizing/emotionally-reactive (n=560)	0.48	0.40	0.08	0.05
6C Internalizing (n=393)	0.51	0.12	0.21	0.16
6D Dysregulation (n=140)	0.28	0.37	0.12	0.23

Note: Profile sizes represent profile counts based on estimated model.

Supplementary Table S3 Transition probabilities per gender

BOYS (n=3,631)				
	Profiles age 3			
	3A No problems (n=3,023)	3B Externalizing/ emotionally-reactive (n=340)	3C Mild internalizing (n=176)	3D Internalizing and externalizing (n=92)
Profiles age 1.5				
1.5A No problems (n=2,886)	0.92	0.04	0.03	0.01
1.5B Externalizing/emotionally-reactive (n=462)	0.49	0.36	0.11	0.04
1.5C Mild problems (n=210)	0.52	0.18	0.17	0.13
1.5D Internalizing and externalizing (n=73)	0.33	0.16	0.14	0.37
	Profiles age 6			
	6A No Problems (n=2,988)	6B Externalizing/ emotionally-reactive (n=366)	6C Internalizing (n=185)	6D Dysregulation (n=92)
Profiles age 1.5				
1.5A No problems (n=2,886)	0.86	0.08	0.04	0.02
1.5B Externalizing/emotionally-reactive (n=462)	0.66	0.21	0.08	0.05
1.5C Mild problems (n=210)	0.69	0.16	0.10	0.06
1.5D Internalizing and externalizing (n=73)	0.56	0.18	0.16	0.10
	Profiles age 6			
	6A No Problems (n=2,988)	6B Externalizing/ emotionally- reactive (n=366)	6C Internalizing (n=185)	6D Dysregulation (n=92)
Profiles age 3				
3A No problems (n=3,023)	0.90	0.06	0.03	0.01
3B Externalizing/emotionally-reactive (n=340)	0.39	0.44	0.07	0.10
3C Mild internalizing (n=176)	0.63	0.14	0.19	0.05
3D Internalizing and externalizing (n=92)	0.34	0.18	0.31	0.18

Note: Profile sizes represent profile counts based on estimated model.

Supplementary Table S3 Transition probabilities per gender - continued

GIRLS (n=3,575)

	Profiles age 3			
	3A No problems (n=3,074)	3B Externalizing/ emotionally-reactive (n=224)	3C Mild internalizing (n=191)	3D Internalizing and externalizing (n=86)
Profiles age 1.5				
1.5A No problems (n=2,927)	0.94	0.03	0.03	0.00
1.5B Externalizing/emotionally-reactive (n=388)	0.55	0.26	0.12	0.07
1.5C Mild problems (n=197)	0.50	0.13	0.27	0.10
1.5D Internalizing and externalizing (n=64)	0.30	0.13	0.21	0.37

	Profiles age 6			
	6A No Problems (n=3,124)	6B Externalizing/ emotionally-reactive (n=207)	6C Internalizing (n=196)	6D Dysregulation (n=48)
Profiles age 1.5				
1.5A No problems (n=2,927)	0.91	0.04	0.04	0.01
1.5B Externalizing/emotionally-reactive (n=388)	0.73	0.12	0.11	0.04
1.5C Mild problems (n=197)	0.72	0.10	0.14	0.05
1.5D Internalizing and externalizing (n=64)	0.57	0.11	0.22	0.10

	Profiles age 6			
	6A No Problems (n=3,124)	6B Externalizing/ emotionally-reactive (n=207)	6C Internalizing (n=196)	6D Dysregulation (n=48)
Profiles age 3				
3A No problems (n=3,074)	0.94	0.03	0.03	0.00
3B Externalizing/emotionally-reactive (n=224)	0.50	0.32	0.10	0.08
3C Mild internalizing (n=191)	0.58	0.10	0.27	0.05
3D Internalizing and externalizing (n=86)	0.30	0.11	0.39	0.20

Note: Profile sizes represent profile counts based on estimated model.

Supplementary Table S4 Profile membership probabilities at 3 years and 1.5 years conditional on profile membership at 6 years per gender

BOYS (n=3,631)				
	Profiles age 1.5			
	1.5A No problems (n=2,886)	1.5B Externalizing/ emotionally-reactive (n=462)	1.5C Mild problems (n=210)	1.5D Internalizing and externalizing (n=73)
Profiles age 6				
6A No Problems (n=2,988)	0.84	0.10	0.05	0.01
6B Externalizing/emotionally-reactive (n=366)	0.61	0.26	0.09	0.04
6C Internalizing (n=185)	0.63	0.19	0.11	0.06
6D Dysregulation (n=92)	0.53	0.27	0.13	0.08
	Profiles age 3			
	3A No problems (n=3,023)	3B Externalizing/ emotionally-reactive (n=340)	3C Mild internalizing (n=176)	3D Internalizing and externalizing (n=92)
Profiles age 6				
6A No Problems (n=2,988)	0.91	0.04	0.04	0.01
6B Externalizing/emotionally-reactive (n=366)	0.48	0.41	0.07	0.04
6C Internalizing (n=185)	0.54	0.13	0.18	0.15
6D Dysregulation (n=92)	0.36	0.37	0.10	0.17

Note: Profile sizes represent profile counts based on estimated model.

Supplementary Table S4 Profile membership probabilities at 3 years and 1.5 years conditional on profile membership at 6 years per gender - continued

GIRLS (n=3,575)

	Profiles age 1.5			
	1.5A No problems (n=2,927)	1.5B Externalizing/ emotionally-reactive (n=388)	1.5C Mild problems (n=197)	1.5D Internalizing and externalizing (n=64)
Profiles age 6				
6A No Problems (n=3,124)	0.85	0.09	0.05	0.01
6B Externalizing/emotionally-reactive (n=207)	0.63	0.23	0.10	0.04
6C Internalizing (n=196)	0.60	0.20	0.14	0.07
6D Dysregulation (n=48)	0.35	0.33	0.19	0.13
	Profiles age 3			
	3A No problems (n=3,074)	3B Externalizing/ emotionally-reactive (n=224)	3C Mild internalizing (n=191)	3D Internalizing and externalizing (n=86)
Profiles age 6				
6A No Problems (n=3,124)	0.92	0.04	0.04	0.01
6B Externalizing/emotionally-reactive (n=207)	0.49	0.36	0.10	0.05
6C Internalizing (n=196)	0.48	0.11	0.25	0.16
6D Dysregulation (n=48)	0.06	0.40	0.19	0.35

Note: Profile sizes represent profile counts based on estimated model.

Chapter 7

Discussion

This thesis focuses on young children with severe emotional and behavioral problems. In school-age children and adolescents, the Child Behavior Checklist dysregulation profile (CBCL-DP) has been shown to be a useful instrument to study these severely disturbed children. This profile is based on three scales of the CBCL: Anxious/Depressed, Attention Problems, and Aggressive Behavior. High scores on these scales reflect poor regulation of emotion, attention, and behavior. Little is known about this profile in younger children. The aims of this thesis were 1) to explore whether a CBCL-DP could be identified in 5- to 7-year-old children; 2) to examine the correspondence between the CBCL-DP and other diagnostic approaches and informants of child emotional and behavioral problems; 3) to examine cognitive correlates of the CBCL-DP; 4) to study socioeconomic and family risk factors of the CBCL-DP; and 5) to study the development of dysregulated behavior across the preschool years. In this chapter, the main findings of this thesis are highlighted and interpreted in a broader context. Subsequently, methodological considerations are discussed and clinical and research implications are addressed.

MAIN FINDINGS

The CBCL dysregulation profile in young children

In chapter 2 we aimed to empirically identify the CBCL-DP in 5- to 7-year-old children. In school-age children, the CBCL-DP has been identified either by using cut-points on the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales or by performing latent class analysis (LCA) on the items from these three scales (Althoff et al., 2010b; Althoff et al., 2006; Althoff et al., 2010c). Other CBCL scales were not considered in these analyses. We were interested if we could identify a CBCL-DP with specifically high scores on the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales while examining a wide range of emotional and behavioral problems. We performed latent profile analysis (LPA) on six syndrome scales of the preschool version of the CBCL: Emotionally Reactive, Anxious/Depressed, Somatic Complaints, and Withdrawn, which are part of the internalizing domain, and Attention Problems, and Aggressive Behavior, which are part of the externalizing domain. We identified four profiles: 1) a profile with few problems (85.6%); 2) a profile with moderate levels of problems on the four internalizing scales (5.3%), which was labeled internalizing; 3) a profile with moderate levels of emotionally reactive behavior, attention problems, and aggressive behavior (7.3%), which was labeled externalizing/emotionally-reactive; and 4) a profile characterized by high levels of problems across the range of both internalizing and externalizing scales, which included 1.8% of the sample. We did not find a profile with only high scores on the Anxious/Depressed, Attention Problems and Aggressive Behavior scales. Instead, children with high scores on these three scales showed also high levels of problems on the other scales. Therefore we concluded that, at least for young children, the CBCL-DP should

not be restricted to these three scales only. In young children the CBCL-DP is characterized by high levels of problems across the range of both internalizing and externalizing problems.

After we performed this study, De Caluwe et al. (2013) also performed a latent profile analysis on the CBCL/6-18 syndrome scales to identify a CBCL-DP in a sample of school-age children and adolescents. These authors did not find a profile with only elevations on the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales either. Again, children with high scores on these three scales showed also severe problems on the other CBCL scales. These findings suggest that also in older children the CBCL-DP is characterized by high levels of problems across the range of internalizing and externalizing problems assessed with the CBCL.

An important question is whether the different definitions of the CBCL-DP that are being used result in the identification of the same children. I will discuss this question below in the section 'Defining dysregulation: cut-points, latent classes, or dimensions?'.

CBCL profiles and DSM diagnoses

In chapter 3 we studied the overlap between the empirically derived CBCL profiles and DSM-IV diagnoses assessed using the Diagnostic Interview Schedule for Children (DISC) young child version (Fisher & Lucas, 2006). We also examined associations between CBCL profiles and teacher and child reports of emotional and behavioral problems. Moderate overlap across the CBCL profiles and DISC DSM-IV diagnoses was found. In children with the CBCL-DP, 68% met criteria for at least one DSM-IV diagnosis, including externalizing disorders (36%) or comorbid internalizing and externalizing disorders (28%). Children with CBCL-DP showed also more internalizing and externalizing problems according to teacher report and child self-report. We concluded that children with CBCL-DP are also considered highly problematic based on DSM-IV classification, other informants, and in other settings. The CBCL internalizing profile showed limited overlap with DSM-IV internalizing disorders. This profile was however associated with child and teacher reported internalizing problems, while DSM-IV internalizing disorders were not. The CBCL externalizing profile overlapped with DSM-IV externalizing disorders and was associated with higher levels of child and teacher reported internalizing and externalizing problems.

Our study and others found substantial overlap between attention deficit hyperactivity disorder (ADHD) and CBCL-DP (Holtmann et al., 2008; Volk & Todd, 2007). The overlap between CBCL-DP and ADHD, has been of interest to several researchers. ADHD is also considered a disorder of self-regulation: children with ADHD do not only have problems with regulation of attention and behavior, but have often also emotion regulation disabilities (Barkley, 2011). In children with ADHD, the CBCL-DP captures those children with the most severe emotional problems (Peyre et al., 2012; Spencer et al., 2011). This was further supported by a recent study

using electroencephalography (EEG) that found that the EEG profile for children with ADHD and CBCL-DP corresponded with a profile that has been previously related to anxiety and mood disorders (McGough et al., 2013).

We did not study to what extent CBCL-DP overlaps with the new DSM-5 diagnosis disruptive mood dysregulation disorder (DMDD). DMDD describes children with severe temper outbursts and chronic irritability. Both the CBCL-DP and DMDD capture severly dysregulated children and are developed from the study of children with juvenile bipolar disorder. Dougherty et al. (2014) examined the overlap between DMDD and the CBCL-DP in a community sample of 6-year-old children. Since no validated instrument is yet available to identify DMDD, the diagnosis was constructed using psychiatric structured interview questions from the diagnoses oppositional defiant disorder (ODD) and depression that capture temper tantrums and irritable mood (Axelson et al., 2012; Copeland et al., 2013). The CBCL-DP was defined by a score of 180 or higher on the summed t-scores of the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales. Of all children with DMDD (prevalence 8.2%), 29% showed the CBCL-DP, while 36% of children with CBCL-DP showed DMDD. For this discussion, we also constructed the diagnosis DMDD using the DISC interview data. In the Generation R sample we found a prevalence of 0.4% (Rijlaarsdam, 2013). In our sample 45% (95% CI: 25%-66%) of children with DMDD were also in the CBCL-DP group, while of the children with CBCL-DP 12% (95% CI: 6%-21%) met a DMDD diagnosis. The results from Dougherty et al. (2014) and our data suggest limited overlap. However, the development of a valid interview tool to assess DMDD will be necessary before conclusions can be drawn.

Dysregulation and nonverbal intelligence

Different forms of psychopathology, including attention problems, aggressive behavior, and overall levels of psychopathology, are associated with a lower intelligence level (Goodman et al., 1995; Koenen et al., 2006; Kuntsi et al., 2004). In chapter 4 we examined the relation between empirically derived CBCL profiles and nonverbal intelligence. We found that children with CBCL-DP scored 11 points lower on a nonverbal intelligence test than children without problems and 7 points lower than children in the internalizing and externalizing/emotionally-reactive profiles. Children with the CBCL-DP scored 8 points lower than children without problems after adjustment for parental intelligence, parental psychiatric symptoms, socioeconomic status and perinatal factors. The internalizing profile was not related to nonverbal intelligence, while the externalizing/emotionally-reactive profile was mildly associated with lower nonverbal intelligence.

We examined the specificity of the relationship between CBCL-DP and nonverbal intelligence and found that the relationship is independent of the presence of ADHD and autism spectrum disorders. Children with CBCL-DP scored also 3 points lower than children with equal levels

of CBCL total problems, although this difference was not significant. Whether the relationship between CBCL-DP and nonverbal intelligence is specific or reflects only a global relationship between psychopathology and intelligence, these findings have important implications. Studying the most severely disturbed children who have the lowest nonverbal intelligence score might shed light on the underlying mechanisms in the association between child psychopathology and intelligence. Second, the lower nonverbal intelligence will likely put these children at risk for poor school performance.

Dysregulated behavior and family functioning

In chapter 2 we examined whether gender, ethnicity, maternal education, family income, and maternal and paternal psychiatric symptoms predicted membership to the CBCL profiles. We found that maternal and paternal psychiatric symptoms at 3 years were strongest predictors for the CBCL-DP. These findings suggest that parental psychiatric symptoms play a role in the development of dysregulated emotions and behavior. Four important mechanisms are described through which parental psychopathology may affect the development of the child (Connell & Goodman, 2002): 1) Genetic transmission; 2) fetal exposure to psychopathology related factors, such as increased maternal stress hormones, and maternal drugs and alcohol use; 3) exposure to parental maladaptive affect, behavior and cognitions in everyday life; and 4) environmental stressors associated with parental psychopathology, such as marital discord, poverty, and low social support.

In these mechanisms, the child's problems are considered to be a consequence of parental psychopathology. In chapter 5 we showed however that the association between parental psychiatric symptoms and child behavior problems is likely to be bidirectional. We found that prenatally assessed psychiatric symptoms in the parents predicted child externalizing problems at 1.5 years and child externalizing problems at 1.5 years of age predicted parental psychiatric symptoms at 3 years. Children's externalizing problems may increase parenting stress, decrease parents' self-efficacy or result in social isolation, which in turn may result in the development of psychiatric symptoms in parents (Donenberg & Baker, 1993; Raposa et al., 2011). Children's externalizing problems at 1.5 and 3 years predicted also lower family functioning at 5 to 7 years. These results are in line with family systems theory that suggest that all family members, including the child, influence the overall configuration of the family (Cox & Paley, 1997; Patterson, 1982). Children's externalizing problems may cause disagreement among family members in how to deal with the behavior of the child or family members may become very cautious to prevent negative behavior from the child. An accurate understanding how the child, the parents, and the family influence and are influenced by each other is key for the development of intervention strategies.

Stability of problem behavior in preschool children

Emotional and behavioral problems that arise early in life may have long lasting effects. Understanding the stability and change of problems over time is crucial for the development of screening strategies. In chapter 6 we examined the development of dysregulated behavior across the preschool years. We examined profiles of emotional and behavioral problems at ages 1.5, 3, and 5 to 7 years and studied children's transitions in profiles over time. In this study we found that profiles were different across ages. These findings demonstrate changes in the presentation of problems across the preschool years. We also examined the stability of problems over time, using latent transition analysis (LTA). We found that, based on profiles at 1.5 and 3 years, it was difficult to predict what kind of profile a child would exhibit at 5 to 7 years. Children with a profile with co-occurring internalizing and externalizing problems early in life were most likely to show problem behavior at later age. The changing patterns and the low transition probabilities showed that in young children continuity of problems is likely to be heterotypic. In other words, in children who are persistently problematic, the presentation of problems likely changes across ages.

Several studies have used the DSM-IV diagnostic categories to describe problems in preschool children (Bufferd et al., 2011; Egger & Angold, 2006; Lavigne et al., 1998). To examine whether the DSM diagnoses adequately describe problems in preschoolers, confirmatory factor analyses have been performed on the DSM-IV symptoms in 2- to 5-year-old children (Sterba et al., 2007) and in 4-year-old children (Strickland et al., 2011; Wichstrom & Berg-Nielsen, 2013). Based on these studies the authors concluded that the DSM-IV diagnoses adequately describe psychopathology in preschoolers and thus that the presentation of problems is the same in preschoolers as in school-age children and adolescents. The findings of these studies are however subject to circularity, because the symptom ratings were collected using diagnostic instruments organized around the diagnostic categories which the researchers aimed to validate (Uher & Rutter, 2012). In our study we used a more empirically based assessment of problems in preschoolers. Contrary to the findings based on the DSM, we found differences in the presentation of psychopathology across ages. Our findings suggest that age appropriate diagnostic classification of problems in preschoolers is needed.

In our study we used the same scales to assess profiles of emotional and behavioral problems at 1.5, 3, and 5 to 7 years. We assumed that these scales are measurement invariant across the preschool period. The identified changes in profiles may suggest that also the scale structure changes across the preschool period. The scales are developed using exploratory factor analysis in a sample of 1.5- to 5-year-old children (Achenbach & Rescorla, 2000). Ivanova et al. (2010) studied measurement invariance of the scales across 23 societies. An interesting next step would be to study measurement invariance across ages.

METHODOLOGICAL CONSIDERATIONS

Defining dysregulation: cut-points, latent classes, or dimensions?

In the current literature several definitions of the CBCL-DP are being used. In school-age children and adolescents, most often cut-points on the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales of the CBCL are used to define the CBCL-DP. Initially, the CBCL-DP was defined by t-scores equal or above 70 on the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales (Holtmann et al., 2007; Hudziak et al., 2005). Others used lower cut-points, for example t-scores of 60 were used by Meyer et al. (2009). Alternatively, Biederman and colleagues first summed the t-scores of the three scales and then set a cut-point. These authors proposed two definitions of varying severity: children with a sum score of 210 and higher were labeled severe dysregulation, and children with a sum score between 180 and 210 were considered as having deficient emotional self-regulation (DESR; Biederman et al., 2012; Spencer et al., 2011).

By using a cut-point approach children who fall just below the cut-points on one of the three scales are considered normal, even though their scoring pattern is very close to the CBCL-DP. To overcome this limitation, Althoff et al. (2006) proposed phenotypic refinement using person centered statistical methods, in which children are categorized based on their overall pattern of problems. These person centered methods derive groupings empirically and are therefore preferred above the rather arbitrarily chosen cut-points. Two person centered methods have been used to define the CBCL-DP: LCA on the items of Anxious/Depressed, Attention Problems and Aggressive Behavior scales by Althoff et al. (2006; 2010b; 2010c) and LPA on all CBCL syndrome scales in our study and by De Caluwe et al. (2013).

Although the use of person centered statistical methods is preferred because they result in more empirically based groupings, the application of these methods requires advanced statistical knowledge. In contrast, cut-points are easy to use in research and in clinical settings. If the use of certain cut-points results in the same groupings of children these cut-points may also be recommended for future studies.

For this discussion I examined the overlap between the CBCL-DP identified in our studies using LPA and the above described cut-point based definitions of the CBCL-DP. The results are presented in Table 1. The CBCL-DP definitions based on cut-points on the separate scales resulted in small groups of children. Almost all children fell in the LPA based CBCL-DP. The CBCL-DP based on LPA included more children. Most likely these children have scores just below the cut-points but have a very similar pattern and are therefore included in the LPA based profile.

The severe dysregulation definition, defined by Biederman and colleagues, also resulted in a small group of children who all fell in the LPA based CBCL-DP. Biederman's DESR definition captured most children in the LPA based CBCL-DP, but half of the children meeting the DESR definition fell outside the profile. This is explained by the fact that children with DESR do not necessarily have high scores on all three scales. Children with, for example, high t-scores of 65 on both the Attention Problems and Aggressive Behavior scales and a low t-score of 50 on the Anxious/Depressed scale are included in the DESR definition. In our study, these children fall in the CBCL externalizing/emotionally-reactive profile.

Table 1 Overlap between empirically derived dysregulation profile using latent profile analysis and cut-points based dysregulation profiles in the Generation R sample of 5- to 7-year-old children (N=6,131).

	Total study sample (N=6,131)	CBCL-DP based on LPA (n=110)	No CBCL-DP based on LPA (n=6,021)
Cut-point based CBCL-DP definitions*	n	n	n
Each syndrome scale t-score ≥70	6	6	0
Each syndrome scale t-score ≥60	53	51	2
Severe dysregulation: sum t-scores ≥ 210	23	23	0
DESR: sum t-scores <210 and ≥ 180	172	83	89

Note: * Definitions are based on the Anxious/Depressed, Attention Problems, and Aggressive Behavior syndrome scales of the CBCL. CBCL-DP = Child Behavior Checklist dysregulation profile; LPA = latent profile analysis; DESR = deficient emotional self-regulation.

These comparisons show that there is a large overlap across definitions, but there are also differences that may have an important impact in studying children with CBCL-DP. To further answer the question whether CBCL-DP definitions based on person centered methods result in more accurate groupings than CBCL-DP definitions based on cut-points, these definitions need to be compared on external validators, such as outcomes later in life. Also, the overlap between the LCA based and LPA based definitions of CBCL-DP, as well as their relations to external validators is an interesting topic for future research.

For this discussion, I was also interested in the overlap between the LPA based CBCL-DP and cut-point based groupings of co-occurring internalizing and externalizing problems. Children in our CBCL-DP scored high on all internalizing and externalizing syndrome scales. The LPA based CBCL-DP may therefore be highly overlapping with groupings of co-occurring internalizing and externalizing problems. Table 2 shows the overlap between the LPA based CBCL-DP and co-occurring internalizing and externalizing problems based on CBCL clinical cut-points and borderline cut-points. Clinical levels of co-occurring internalizing and externalizing problems were strongly overlapping with the LPA based CBCL-DP. Decreasing cut-points to borderline level resulted in a higher overlap with the LPA based CBCL-DP, but at the same

Table 2 Overlap between empirically derived Child Behavior Checklist dysregulation profile and groups of children with co-occurring internalizing and externalizing problems on the CBCL in the Generation R sample of 5- to 7-year-old children (N=6,131).

	Total study sample (N=6,131)	CBCL-DP based on LPA (n=110)	No CBCL-DP based on LPA (n=6,021)
Co-occurring internalizing and externalizing problems*	n	n	n
Clinical cut-points: t-scores >63	90	79	11
Borderline cut-point: t-scores ≥ 60	186	104	82

Note: * Definitions are based on the Internalizing and Externalizing broadband scales of the CBCL/1.5-5; CBCL-DP = Child Behavior Checklist dysregulation profile; LPA= latent profile analysis

time more children fell out the CBCL-DP group. Differences between definitions again reflect that cut-points are arbitrary, while the CBCL-DP takes the pattern of problems into account.

The high overlap between cut-point defined co-occurring internalizing and externalizing problems, suggests that previous results on co-occurring internalizing and externalizing problems may be applicable to children with dysregulation. This also means that children who were previously described as having co-occurring internalizing and externalizing problems, are now described as having 'dysregulation'. Is it desirable to rename this group of children? Giving a new name for an existing group can be very confusing. However, naming the problems in these children dysregulation is in agreement with the idea that the different types of problems in these children result from one underlying syndrome.

Finally, the CBCL-DP has also been studied dimensionally. Dimensional measures are highly attractive as they give the researcher much more power and flexibility in statistical analyses. A dimensional model assumes that self-regulation is a continuous trait. This is in line with other measures of poor self-regulation, such as irritability and mood lability (Stringaris, 2011; Stringaris & Goodman, 2009). Dimensional measures of CBCL-DP that are being used are: 1) the sum score of the t-scores of the three scales (Hudziak et al., 2005); 2) a latent factor based on the items of the three scales (Ayer et al., 2009); 3) the CBCL Posttraumatic stress problems scale, which has been found to measure dysregulation (Althoff et al., 2010a; Ayer et al., 2009); and a dysregulation scale that has been developed on the Strengths and Difficulties Questionnaire (Holtmann et al., 2011a).

Does a CBCL dysregulation scale measure other problems than the well-known scales of the CBCL? In Generation R the sum of the Anxious/Depressed, Attention Problems, and Aggressive Behavior items correlated 0.95 with the CBCL total problems score and 0.98 with the CBCL externalizing problems scale. This is to a large extent explained by the high number of overlapping items across scales. These data suggest that the dysregulation scale does not add extra information to the other scales of the CBCL. Another limitation of a dimensional mea-

sure of dysregulation is that a very anxious child, a very aggressive child, and a child with mild problems on all three scales, may end up with the same sum score. The goal of the development of the CBCL-DP was however to describe children with most severe problems in all three domains. It is unknown whether findings based on a dimensional measure of the CBCL-DP are applicable to these most severely disturbed children.

Person centered statistical methods

Latent class analysis (LCA) and latent profile analysis (LPA) are advanced statistical methods to empirically identify groups or classes of children with similar patterns on a set of indicators. In latent class analysis, the underlying grouping variable is based on categorical indicators, while in latent profile analysis dimensional indicators are used to estimate the latent grouping variable. LCA and LPA can be applied to group persons on a wide array of variables. These methods allow studying co-occurrence of different types of problems which is a common phenomenon in child psychiatry. Additionally, these methods can be used to identify homogeneous subtypes of broader phenotypes, such as subtypes of aggressive behavior (Ligthart et al., 2005). Once a latent class model is estimated, determinants of the identified classes can be studied or latent classes can be used as predictors of distal outcomes. In longitudinal studies, with repeated measurements of problems, latent classes can be estimated at different time points and compared over time. Subsequently, latent transition analysis, a longitudinal extension of LCA and LPA, can be applied to study the stability of class membership over time.

These statistical methods assume that a latent categorical variable underlies behavior. Thus, by using these methods, we treat psychopathology as a categorical phenomenon. Whether child emotional and behavioral problems should be considered continuously or categorically remains an important debate in child psychiatry (Coghill & Sonuga-Barke, 2012). Most types of psychopathology have been shown to have both continuous and categorical characteristics. Whether problem behavior is qualitatively different from normal behavior or not should however be distinguished from the practical need to categorise (Coghill & Sonuga-Barke, 2012). Even if problem behavior is a severe form of normal behavior, the study of categories will remain important in child psychiatry as clinicians have to make important decisions whether a child requires treatment or not. Studying psychopathology categorically has, however, disadvantages that also need consideration: categorisation results in a loss of information, decrease in statistical power, and may lead to a misestimation of the strength of relationships (von Eye & Bergman, 2003).

The selection of the sample may affect the structure and the prevalence of the latent classes (Lenzenweger, 2004). Classes that are highly dependent on selected samples contribute little to our general understanding of developmental psychopathology. Therefore, unselected samples are preferred and replication studies are needed to improve the generalizability of the findings.

Deciding on the number of classes, which is a main step in LCA and LPA, has also important implications for the study results. Several statistical fit indices have been developed and used to decide on the number of classes (Collins & Lanza, 2010; Nylund et al., 2007). These fit indices can be contradictive. Therefore, also the interpretability of classes has to be taken into account. The decision on the number of classes can be based on current theories concerning different subtypes or on findings from previous studies. In our thesis we decided that a class should include at least 1%. Classes smaller than 1% were considered too small for further analyses in our sample. Other studies with a smaller sample size have used a minimum of 5% (e.g. Meeus et al., 2011). Also, we decided that an additional profile should be qualitatively different from the other classes or differ substantially in severity. This criterion was based on the assumption that classes should present different subtypes of problems and not only severity differences. Taking into account the interpretability of the classes makes the decision on the number of classes a subjective matter. Describing the applied criteria is highly important to understand different findings across studies.

After deciding on the number of classes the validity of the identified latent classes needs to be established (Leoutsakos et al., 2010; von Eye & Bergman, 2003). This should be done by relating the classes to external variables that are not used to create the classes. The addition of covariates or outcomes to a latent class model may however impact on the latent class solution itself, because the latent class model and the relation between the latent variable and the covariate or outcome are estimated at the same time. To overcome this problem, we classified children based on their most likely latent class membership and used this categorical variable for further analyses. This method is only justified when entropy is high (0.98 in our study). Recently, several methods have been developed in which the latent class model is estimated independent of the outcome variable, while the uncertainty of the latent class model is taken into account in the estimation of the outcome variable, such as Lanza's method or the 3 step method in Mplus (Lanza et al., 2013; Tihomir & Muthen, 2013).

In this thesis we used LTA to study the stability of problem behavior over time. Collins and Lanza (2010) adviced to fix latent classes to be equal across ages whenever it is reasonable to do so. In this way homotypic stability of class membership can be studied. Also differences in class prevalences across time can be easily interpreted. A practical advantage is that fixing classes to be equal across time decreases the number of estimated parameters and therefore improves model identification. In our studies we found that the patterns of the classes were different across ages. Since these differences reflected in our view important developmental changes in the presentation of problem behavior, we allowed classes to differ in shape over time. In the interpretation of transition probabilities we took into account changes in profiles over time.

Assessing young children's emotional and behavioral problems: multi-informant approach

In adolescence and adulthood, self-report is a very important source of information. In young children self-report is less often used, because young children are often considered unable to reflect on their own emotions and behavior. Therefore, parents are the most important informants of young children's emotional and behavioral problems. In this thesis we relied predominantly on reports of primary caregivers (93% mothers), who spend the most time with their child under a variety of circumstances. We also used other sources of information, including the second caregiver, which was most often the father, and teacher report. Despite the young age of the child, we also assessed children's self-report using the Berkeley Puppet Interview. Psychometric studies in Generation R and in other samples of young children have shown that this interview gives valid and reliable information about the child's own perspective (Ablow et al., 2003; Ablow et al., 1999; Ringoot et al., 2013).

The use of multiple informants is recommended for several reasons. Each informant has its own interpretation of normal and abnormal behavior and experiences the child in different contexts. The agreement across informants supports the validity of the information and the consistency of children's problems across settings. Discrepancies between informants in their report on child's problem behavior are however large (Achenbach et al., 1987; De Los Reyes & Kazdin, 2005). Since there is not one golden standard in child psychiatry, a multi-informant approach is recommended for a more complete picture of the functioning of the child (Dirks et al., 2012; Kraemer et al., 2003).

In this thesis we used multiple informants to examine the validity of the CBCL profiles (chapter 3). We examined associations between CBCL profiles, based on primary caregiver, and continuous scales of teacher and child reported problems. A more advanced examination of cross-informant agreement would be to perform latent profile analysis on the scales of the TRF and the BPI to examine whether a dysregulation profile can also be identified on these instruments and to examine the overlap of profiles across informants. This has been previously done by Althoff et al. (2010b) in school-age children and adolescents. They identified a dysregulation profile on parent report (CBCL), teacher report (TRF), and child self-report (Youth Self Report Form; YSR). The overlap of the dysregulation profile across informants was low to moderate (kappa's 0.14-0.28), but comparable to previous findings on informant agreement in child psychiatry (De Los Reyes & Kazdin, 2005).

Using information from multiple informants is also recommended to prevent shared method variance. When both the determinant and outcome are reported by the same informant, part of the variance between the determinant and the outcome is the result of the characteristics of the informant. To prevent this sort of bias, we used maternal and paternal reports of parental

psychiatric symptoms, family functioning, and child problem behavior in studying the determinants of dysregulated behavior.

A single informant approach was used in this thesis to study the stability of problem behavior across the preschool period (chapter 6). To study the stability of problems, it is preferred to use the same informant over time, because otherwise the stability estimates will be diluted by the different perspectives of the informants. The use of the same informant over time will likely have inflated the stability of problems over time. Parents tendency to over or under report child's problem behavior, and parents tendency to maintain a consistent view of their child may have increased the stability estimates.

Examining child effects on the environment

Various aspects of the environment have been found to be associated with children's emotional and behavioral problems. These associations are most often interpreted as the environment having a negative influence on the child. However, in most cases the reverse might also be true. The child's problems may have a negative influence on the environment. Unfortunately, observational studies cannot determine whether relations are causal. The interaction between the child and the environment is highly complex and it is hard separate effects of the child on the environment and effects of the environment on the child.

In chapter 5 we aimed to study the bi-directional effects of child externalizing problems, parental psychiatric symptoms and family functioning. To make a causal effect of the parents and the family on the child as plausible as possible, we used measures of parental psychiatric symptoms and family functioning that were assessed before the birth of the child. These measures were completely independent of the child's behavior, which makes it more likely that associations between prenatal levels of parental psychiatric symptoms and family functioning and child externalizing problems were causal. We examined the effects of the child on the parents and the family while adjusting these effects for prenatal levels of parental psychiatric symptoms and family functioning. Although we found significant relationships, we cannot completely rule out that the identified effects of the child on the parents are actually effects of the parent on the child. After birth, psychiatric symptoms in the parents or family problems may have arisen that have elicited externalizing problems in the child.

Other studies examined child effects by testing the effect of the child's behavior at a given time t on parental psychopathology at time t+1, while controlling for parental psychopathology at time t (e.g. Fanti et al., 2013; Gross et al., 2008). Parental psychopathology at time t may already be influenced by the behavior of the young child. These analyses are therefore overadjusted. Despite these overadjustments, child effects on parental psychopathology have been found, which makes it likely that the child contributes to the well-being of the parents.

Randomized controlled trials are considered the golden standard with respect to causal inference. A few interesting experiments on the effects of child behavior have been done. For example, Pelham et al. (1997) asked parents to interact with 5- to 12-year-old boys who were trained to behave defiant or in a normal manner. Parents who had interacted with the defiant boys reported higher levels of depressive symptoms than those interacting with normal behaving children.

CLINICAL IMPLICATIONS

It is well recognized that the assessment of child's psychopathology requires a multi-informant and multi-method procedure. A psychiatric interview, to assess the presence of DSM diagnoses, is most often part of standard assessment procedures. Empirically derived syndromes on symptom checklists, such as the CBCL syndrome scales, provide information on the severity of problems, and tap into problems that are not considered by, for example DSM criteria, but have important implications for prognosis. Dimensional scores are also suitable to examine treatment effects and to make comparisons across ages and informants (Hudziak et al., 2007). Profile types, such as identified in this thesis, may offer a more comprehensive basis for classification and decision making than do individual syndromes (Achenbach, 1993).

The practical implication of the empirically derived profiles in this thesis can be established in several ways. The scoring of the CBCL is computerized and the output provides a profile of t-scores on the syndrome scales. The printout of a computer-scored profile of an individual child can be directly compared with the empirically derived profiles in our study. The clinician can compare patterns visually. Alternatively, an algorithm may be developed for the CBCL scoring system to compute the child's likelihood to belong to each profile.

The assessment of a child's profile on the CBCL may improve decision-making concerning further assessment and treatment. For example, if a young child's profile is very similar to the CBCL-DP, the clinician may decide to assess a child's intelligence level to see whether the child is at risk for poor academic achievement and may need extra support at school. Also, the poor outcomes of children with the CBCL-DP that have been found by others, including suicidality, substance abuse and depression (Althoff et al., 2010c; De Caluwe et al., 2013; Holtmann et al., 011b), demonstrate that the CBCL-DP is an important indicator for treatment.

Achenbach previously developed profiles on the CBCL/6-18 using cluster analysis (Achenbach, 1993). Unfortunately, these profiles have received little attention. This might be related to the lack of information about the added value of these profiles in decision making. Uher and Rutter (2012) stated "scientific classification is not valuable as an aim in itself, but it will become

valuable if it can help developing effective cures or improve the matching between patients and treatment options." To make the implementation of profiles fruitful, more research is needed that shows the predictive validity of the profiles concerning treatment outcomes and prognosis. Also, the added value to, for example, DSM diagnoses should be further examined. Only if these profiles have proven to be of additional value, assessment of profiles will be of interest for clinicians.

Finally, the findings in this thesis have implications for screening strategies in preschool children. Young children at high risk for psychopathology later in life may benefit from early detection and intervention. Several intervention techniques have been proven to be beneficial in young children (Shaw, 2013). Screening should be based on developmentally sensitive instruments to make adequate distinctions between normal and abnormal behavior given the age of the child. Since many children who show emotional or behavioral problems at young age have no problems at later ages, additional risk factors should be taken into account. We found that co-occurrence of internalizing and externalizing problems predicts continuing problems. Therefore, co-occurrence of internalizing and externalizing problems should be included as a risk factor. Other risk factors that predict continuity of problems should also be incorporated in a screening procedure, such as poor family functioning, and neighborhood stresses (Campbell et al., 2000).

FUTURE RESEARCH

Advances in molecular genetics, imaging and other techniques to assess biological risk factors, have generated much hope to help understanding psychopathology and improve classification (Kapur et al., 2012; Uher & Rutter, 2012). Unfortunately, until now these studies have not been very informative for classification. Therefore classification of psychopathology still largely depends on symptoms and is free of etiological assumptions. To improve research on biological mechanisms, phenotypic refinement is needed. The person centered methods applied in this thesis, might help in refining current categories and in the development of new categories.

The CBCL-DP may be a useful instrument to study the biological mechanisms underlying psychopathology. Family and molecular genetic studies have shown that most genetic factors that have been associated with psychopathology are not specific to current classification categories. (Cross-Disorder Group of the Psychiatric Genomics, 2013; Dean et al., 2010). Examining genetics of the most severely disturbed children who are at risk for several psychiatric disorders in adulthood may be a fruitful investigation. In a similar way the CBCL-DP may be used in brain imaging studies to improve our understanding of biological mechanisms that play a role in the development of psychopathology. In Generation R, all children with CBCL-DP were invited

for MRI studies to examine neurobiological underpinnings of CBCL-DP and differences in neurodevelopmental trajectories with typically developing children. The first results of these studies are expected soon.

Several studies have shown that CBCL-DP is a predictor of severe psychopathology later in life (Althoff et al., 2010c; Holtmann et al., 2011b; Meyer et al., 2009). Further understanding of determinants of the poor prognoses in these children is needed. However, not all children with dysregulation develop psychopathology in adulthood. Understanding risk factors as well as protective factors for poor outcomes later in life, will aid in developing intervention strategies for these children.

Finally, in studying the development of psychopathology, the interaction between the child and his or her environment should be examined. Psychopathology is not only the result of biological and environmental influences on the child. The child, from a very young age, influences and also selects his or her environment. At young age, studies should focus on the interaction within the family. At older ages interaction with peers and teachers becomes also highly important. Interaction between the child and parents or peers should be studied using observational measures in daily or laboratory settings. In addition, longitudinal studies with repeated measurements of child and environmental factors and the use of advanced statistical techniques are needed to understand this interaction.

REFERENCES

Ablow, J.C., Measelle, J.R., & Assessment, the MacArthur Working Group on Outcome Assessment (2003). *Manual for the Berkeley Puppet Interview: Symptomatology, social, and academic modules (BPI 1.0).* Pittsburgh, PA: University of Pittsburgh.

Ablow, J.C., Measelle, J.R., Kraemer, H.C., Harrington, R., Luby, J., Smider, N., et al. (1999). The MacArthur Three-City Outcome Study: evaluating multi-informant measures of young children's symptomatology. *Journal of the American Academy of Child and Adolescent Psychiatry, 38*(12), 1580-1590. doi: 10.1097/00004583-199912000-00020

Achenbach, T.M. (1993). *Empirically based taxonomy: How to use syndromes and profile types derived from the CBCL/4-18, TRF, and YSR.* Burlington, VT: University of Vermont Department of Psychiatry.

Achenbach, T.M., McConaughy, S.H., & Howell, C.T. (1987). Child adolescent behavioral and emotional problems - implications of cross-informant correlations for situational specifcity. *Psychological Bulletin, 101*(2), 213-232. doi: 10.1037/0033-2909.101.2.213

Achenbach, T.M., & Rescorla, L.A. (2000). *Manual for the ASEBA Preschool Forms & Profiles*. Burlington, VT: University of Vermont, Research Center for Children, Youth, & Families.

Althoff, R.R., Ayer, L.A., Rettew, D.C., & Hudziak, J.J. (2010a). Assessment of dysregulated children using the Child Behavior Checklist: a receiver operating characteristic curve analysis. *Psychological Assessment, 22*(3), 609-617. doi: 10.1037/a0019699

Althoff, R.R., Rettew, D.C., Ayer, L.A., & Hudziak, J.J. (2010b). Cross-informant agreement of the Dysregulation Profile of the Child Behavior Checklist. *Psychiatry Research, 178*(3), 550-555. doi: 10.1016/j.psychres.2010.05.002

Althoff, R.R., Rettew, D.C., Faraone, S.V., Boomsma, D.I., & Hudziak, J.J. (2006). Latent class analysis shows strong heritability of the child behavior checklist-juvenile bipolar phenotype. *Biological Psychiatry, 60*(9), 903-911. doi: 10.1016/j.biopsych.2006.02.025

Althoff, R.R., Verhulst, F.C., Rettew, D.C., Hudziak, J.J., & van der Ende, J. (2010c). Adult outcomes of childhood dysregulation: a 14-year follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(11), 1105-1116. doi: 10.1016/j.jaac.2010.08.006

Axelson, D., Findling, R.L., Fristad, M.A., Kowatch, R.A., Youngstrom, E.A., Horwitz, S.M., et al. (2012). Examining the proposed disruptive mood dysregulation disorder diagnosis in children in the Longitudinal Assessment of Manic Symptoms study. *Journal of Clinical Psychiatry, 73*(10), 1342-1350. doi: 10.4088/JCP.12m07674

Ayer, L., Althoff, R., Ivanova, M., Rettew, D., Waxler, E., Sulman, J., & Hudziak, J. (2009). Child Behavior Checklist Juvenile Bipolar Disorder (CBCL-JBD) and CBCL Posttraumatic Stress Problems (CBCL-PTSP) scales are measures of a single dysregulatory syndrome. *Journal of Child Psychology and Psychiatry, 50*(10), 1291-1300. doi: 10.1111/j.1469-7610.2009.02089.x

Barkley, R.A. (2011). Attention-deficit/hyperactivity disorder, self-regulation, and executive functioning. In K. D. Vohs & R. F. Baumeister (Eds.), *Handbook of self-regulation: research,theory, and applications* (2 ed.). New York: The Guilford Press.

Biederman, J., Spencer, T., Lomedico, A., Day, H., Petty, C.R., & Faraone, S.V. (2012). Deficient emotional self-regulation and pediatric attention deficit hyperactivity disorder: a family risk analysis. *Psychological Medicine, 42*(3), 639-646. doi: 10.1017/S0033291711001644

Bufferd, S.J., Dougherty, L.R., Carlson, G.A., & Klein, D.N. (2011). Parent-reported mental health in preschoolers: findings using a diagnostic interview. *Comprehensive Psychiatry, 52*(4), 359-369. doi: 10.1016/j.comppsych.2010.08.006

Campbell, S.B., Shaw, D.S., & Gilliom, M. (2000). Early externalizing behavior problems: toddlers and preschoolers at risk for later maladjustment. *Development and Psychopathology, 12*(3), 467-488.

Coghill, D., & Sonuga-Barke, E.J. (2012). Annual research review: categories versus dimensions in the classification and conceptualisation of child and adolescent mental disorders—implications of recent empirical study. *Journal of Child Psychology and Psychiatry, 53*(5), 469-489.

Collins, L.M., & Lanza, S.T. (2010). *Latent Class and Latent Transition Analysis with applications in the social, behavioral, and health sciences.* Hoboken, New Jersey: John Wiley & Sons.

Connell, A.M., & Goodman, S.H. (2002). The association between psychopathology in fathers versus mothers and children's internalizing and externalizing behavior problems: a meta-analysis. *Psychological Bulletin, 128*(5), 746-773.

Copeland, W.E., Angold, A., Costello, E.J., & Egger, H. (2013). Prevalence, comorbidity, and correlates of DSM-5 proposed disruptive mood dysregulation disorder. *American Journal of Psychiatry, 170*(2), 173-179. doi: 10.1176/appi.ajp.2012.12010132

Cox, M.J., & Paley, B. (1997). Families as systems. *Annual Review of Psychology, 48*, 243-267. doi: 10.1146/annurev.psych.48.1.243

Cross-Disorder Group of the Psychiatric Genomics (2013). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics, 45*(9), 984-994. doi: 10.1038/ng.2711

De Caluwe, E., Decuyper, M., & De Clercq, B. (2013). The child behavior checklist dysregulation profile predicts adolescent DSM-5 pathological personality traits 4 years later. *European Child & Adolescent Psychiatry, 22*(7), 401-411. doi: 10.1007/s00787-013-0379-9

De Los Reyes, A., & Kazdin, A.E. (2005). Informant discrepancies in the assessment of childhood psychopathology: A critical review, theoretical framework, and recommendations for further study. *Psychological Bulletin, 131*(4), 483-509. doi: 10.1037/0033-2909.131.4.483

Dean, K., Stevens, H., Mortensen, P.B., Murray, R.M., Walsh, E., & Pedersen, C.B. (2010). Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Archives of General Psychiatry, 67*(8), 822-829. doi: 10.1001/archgenpsychiatry.2010.86

Dirks, M.A., De Los Reyes, A., Briggs-Gowan, M., Cella, D., & Wakschlag, L.S. (2012). Annual research review: embracing not erasing contextual variability in children's behavior—theory and utility in the selection and use of methods and informants in developmental psychopathology. *Journal of Child Psychology and Psychiatry, 53*(5), 558-574. doi: 10.1111/j.1469-7610.2012.02537.x

Donenberg, G., & Baker, B.L. (1993). The Impact of Young-Children with Externalizing Behaviors on Their Families. *Journal of Abnormal Child Psychology, 21*(2), 179-198. doi: 10.1007/Bf00911315

Dougherty, L.R., Smith, V.C., Bufferd, S.J., Carlson, G.A., Stringaris, A., Leibenluft, E., & Klein, D.N. (2014). DSM-5 disruptive mood dysregulation disorder: correlates and predictors in young children. *Psychological Medicine*, 1-12. doi: 10.1017/S0033291713003115

Egger, H.L., & Angold, A. (2006). Common emotional and behavioral disorders in preschool children: presentation, nosology, and epidemiology. *Journal of Child Psychology and Psychiatry, 47*(3-4), 313-337. doi: 10.1111/j.1469-7610.2006.01618.x

Fanti, K.A., Panayiotou, G., & Fanti, S. (2013). Associating Parental to Child Psychological Symptoms: Investigating a Transactional Model of Development. *Journal of Emotional and Behavioral Disorders, 21*(3), 193-210. doi: 10.1177/1063426611432171

Fisher, P., & Lucas, C. (2006). *Diagnostic Interview Schedule for Children (DISC-IV) - Young Child*. New York, NY: Columbia University.

Goodman, R., Simonoff, E., & Stevenson, J. (1995). The impact of child IQ, parent IQ and sibling IQ on child behavioural deviance scores. *Journal of Child Psychology and Psychiatry, 36*(3), 409-425.

Gross, H.E., Shaw, D.S., & Moilanen, K.L. (2008). Reciprocal associations between boys' externalizing problems and mothers' depressive symptoms. *Journal of Abnormal Child Psychology, 36*(5), 693-709. doi: 10.1007/s10802-008-9224-x

Holtmann, M., Becker, A., Banaschewski, T., Rothenberger, A., & Roessner, V. (2011a). Psychometric validity of the strengths and difficulties questionnaire-dysregulation profile. *Psychopathology, 44*(1), 53-59. doi: 10.1159/000318164

Holtmann, M., Bolte, S., Goth, K., Dopfner, M., Pluck, J., Huss, M., et al. (2007). Prevalence of the Child Behavior Checklist-pediatric bipolar disorder phenotype in a German general population sample. *Bipolar disorders, 9*(8), 895-900. doi: 10.1111/j.1399-5618.2007.00463.x

Holtmann, M., Buchmann, A.F., Esser, G., Schmidt, M.H., Banaschewski, T., & Laucht, M. (2011b). The Child Behavior Checklist-Dysregulation Profile predicts substance use, suicidality, and functional impairment: a longitudinal analysis. *Journal of Child Psychology and Psychiatry, 52*(2), 139-147. doi: 10.1111/j.1469-7610.2010.02309.x

Holtmann, M., Goth, K., Wockel, L., Poustka, F., & Bolte, S. (2008). CBCL-pediatric bipolar disorder phenotype: severe ADHD or bipolar disorder? *Journal of neural transmission, 115*(2), 155-161. doi: 10.1007/s00702-007-0823-4

Hudziak, J.J., Achenbach, T.M., Althoff, R.R., & Pine, D.S. (2007). A dimensional approach to developmental psychopathology. *International Journal of Methods in Psychiatric Research, 16 Suppl 1*, S16-23. doi: 10.1002/mpr.217

Hudziak, J.J., Althoff, R.R., Derks, E.M., Faraone, S.V., & Boomsma, D.I. (2005). Prevalence and genetic architecture of Child Behavior Checklist-juvenile bipolar disorder. *Biological Psychiatry, 58*(7), 562-568. doi: 10.1016/j.biopsych.2005.03.024

Ivanova, M.Y., Achenbach, T.M., Rescorla, L.A., Harder, V.S., Ang, R.P., Bilenberg, N., et al. (2010). Preschool psychopathology reported by parents in 23 societies: testing the seven-syndrome model of the child behavior checklist for ages 1.5-5. *Journal of the American Academy of Child and Adolescent Psychiatry, 49*(12), 1215-1224. doi: 10.1016/j.jaac.2010.08.019

Kapur, S., Phillips, A.G., & Insel, T.R. (2012). Why has it taken so long for biological psychiatry to develop clinical tests and what to do about it? *Molecular Psychiatry, 17*(12), 1174-1179. doi: 10.1038/mp.2012.105

Koenen, K.C., Caspi, A., Moffitt, T.E., Rijsdijk, F., & Taylor, A. (2006). Genetic influences on the overlap between low IQ and antisocial behavior in young children. *Journal of Abnormal Psychology, 115*(4), 787-797. doi: 10.1037/0021-843X.115.4.787

Kraemer, H.C., Measelle, J.R., Ablow, J.C., Essex, M.J., Boyce, W.T., & Kupfer, D.J. (2003). A new approach to integrating data from multiple informants in psychiatric assessment and research: mixing and matching contexts and perspectives. *American Journal of Psychiatry, 160*(9), 1566-1577.

Kuntsi, J., Eley, T.C., Taylor, A., Hughes, C., Asherson, P., Caspi, A., & Moffitt, T.E. (2004). Co-occurrence of ADHD and low IQ has genetic origins. *American journal of medical genetics. Part B, Neuropsychiatric genetics, 124B*(1), 41-47. doi: 10.1002/ajmg.b.20076

Lanza, S.T., Tan, X.M., & Bray, B.C. (2013). Latent Class Analysis With Distal Outcomes: A Flexible Model-Based Approach. *Structural Equation Modeling-a Multidisciplinary Journal, 20*(1), 1-26. doi: 10.1080/10705511.2013.742377

Lavigne, J.V., Arend, R., Rosenbaum, D., Binns, H.J., Christoffel, K.K., & Gibbons, R.D. (1998). Psychiatric disorders with onset in the preschool years: I. Stability of diagnoses. *Journal of the American Academy of Child and Adolescent Psychiatry, 37*(12), 1246-1254. doi: 10.1097/00004583-199812000-00007

Lenzenweger, M.F. (2004). Consideration of the challenges, complications, and pitfalls of taxometric analysis. *Journal of Abnormal Psychology, 113*(1), 10-23. doi: 10.1037/0021-843X.113.1.10

Leoutsakos, J.M.S., Zandi, P.P., Bandeen-Roche, K., & Lyketsos, C.G. (2010). Searching for valid psychiatric phenotypes: discrete latent variable models. *International Journal of Methods in Psychiatric Research, 19*(2), 63-73. doi: 10.1002/Mpr.301

Ligthart, L., Bartels, M., Hoekstra, R.A., Hudziak, J.J., & Boomsma, D.I. (2005). Genetic contributions to subtypes of aggression. *Twin Research and Human Genetics, 8*(5), 483-491. doi: 10.1375/183242705774310169

McGough, J.J., McCracken, J.T., Cho, A.L., Castelo, E., Sturm, A., Cowen, J., et al. (2013). A potential electroencephalography and cognitive biosignature for the child behavior checklist-dysregulation profile. *Journal of the American Academy of Child and Adolescent Psychiatry, 52*(11), 1173-1182. doi: 10.1016/j.jaac.2013.08.002

Meeus, W., Van de Schoot, R., Klimstra, T., & Branje, S. (2011). Personality types in adolescence: change and stability and links with adjustment and relationships: a five-wave longitudinal study. *Developmental Psychology, 47*(4), 1181-1195. doi: 10.1037/a0023816

Meyer, S.E., Carlson, G.A., Youngstrom, E., Ronsaville, D.S., Martinez, P.E., Gold, P.W., et al. (2009). Long-term outcomes of youth who manifested the CBCL-Pediatric Bipolar Disorder phenotype during childhood and/or adolescence. *Journal of Affective Disorders, 113*(3), 227-235. doi: 10.1016/j.jad.2008.05.024

Nylund, K.L., Asparouhov, T., & Muthén, B.O. (2007). Deciding on the Number of Classes in Latent Class Analysis and Growth Mixture Modeling: A Monte Carlo Simulation Study. *Structural Equation Modeling, 14*(4), 535-569.

Patterson, G.R. (1982). *Coercive family process*. Eugene, Oregon: Castalia Publishing Company.

Pelham, W.E., Lang, A.R., Atkeson, B., Murphy, D.A., Gnagy, E.M., Greiner, A.R., et al. (1997). Effects of deviant child behavior on parental distress and alcohol consumption in laboratory interactions. *Journal of Abnormal Child Psychology, 25*(5), 413-424.

Peyre, H., Speranza, M., Cortese, S., Wohl, M., & Purper-Ouakil, D. (2012). Do ADHD Children With and Without Child Behavior Checklist-Dysregulation Profile Have Different Clinical Characteristics, Cognitive Features, and Treatment Outcomes? *Journal of Attention Disorders*. doi: 10.1177/1087054712452135

Raposa, E.B., Hammen, C.L., & Brennan, P.A. (2011). Effects of Child Psychopathology on Maternal Depression: The Mediating Role of Child-Related Acute and Chronic Stressors. *Journal of Abnormal Child Psychology, 39*(8), 1177-1186. doi: 10.1007/s10802-011-9536-0

Rijlaarsdam, J. (2013). *Social Disadvantage and Child Emotional and Behavioural Problems: At HOME in the Netherlands.* Erasmus Universiteit, Rotterdam, the Netherlands.

Ringoot, A.P., Jansen, P.W., Steenweg-de Graaff, J., Measelle, J.R., van der Ende, J., Raat, H., et al. (2013). Young children's self-reported emotional, behavioral, and peer problems: the Berkeley Puppet Interview. *Psychological Assessment, 25*(4), 1273-1285. doi: 10.1037/a0033976

Shaw, D.S. (2013). Future directions for research on the development and prevention of early conduct problems. *Journal of Clinical Child and Adolescent Psychology, 42*(3), 418-428. doi: 10.1080/15374416.2013.777918

Spencer, T.J., Faraone, S.V., Surman, C.B.H., Petty, C., Clarke, A., Batchelder, H., et al. (2011). Toward Defining Deficient Emotional Self-Regulation in Children with Attention-Deficit/Hyperactivity Disorder Using the Child Behavior Checklist: A Controlled Study. *Postgraduate Medicine, 123*(5), 50-59. doi: 10.3810/pgm.2011.09.2459

Sterba, S., Egger, H.L., & Angold, A. (2007). Diagnostic specificity and nonspecificity in the dimensions of preschool psychopathology. *Journal of Child Psychology and Psychiatry, 48*(10), 1005-1013. doi: 10.1111/j.1469-7610.2007.01770.x

Strickland, J., Keller, J., Lavigne, J.V., Gouze, K., Hopkins, J., & LeBailly, S. (2011). The structure of psychopathology in a community sample of preschoolers. *Journal of Abnormal Child Psychology, 39*(4), 601-610. doi: 10.1007/s10802-011-9487-5

Stringaris, A. (2011). Irritability in children and adolescents: a challenge for DSM-5. *European Child & Adolescent Psychiatry, 20*(2), 61-66. doi: 10.1007/s00787-010-0150-4

Stringaris, A., & Goodman, R. (2009). Mood lability and psychopathology in youth. *Psychological Medicine, 39*(8), 1237-1245. doi: 10.1017/S0033291708004662

Tihomir, A., & Muthen, B. (2013). Auxiliary variables in mixture modeling: 3-step approaches using Mplus. Retrieved from http://statmodel.com/download/3stepOct28.pdf website:

Uher, R., & Rutter, M. (2012). Basing psychiatric classification on scientific foundation: problems and prospects. *International Review of Psychiatry, 24*(6), 591-605. doi: 10.3109/09540261.2012.721346

Volk, H.E., & Todd, R.D. (2007). Does the Child Behavior Checklist juvenile bipolar disorder phenotype identify bipolar disorder? *Biological Psychiatry, 62*(2), 115-120. doi: 10.1016/j.biopsych.2006.05.036

von Eye, A., & Bergman, L.R. (2003). Research strategies in developmental psychopathology: dimensional identity and the person-oriented approach. *Development and Psychopathology, 15*(3), 553-580.

Wichstrom, L., & Berg-Nielsen, T.S. (2013). Psychiatric disorders in preschoolers: the structure of DSM-IV symptoms and profiles of comorbidity. *European Child & Adolescent Psychiatry*. doi: 10.1007/s00787-013-0486-7

SUMMARY

Child psychiatry continues to struggle how to describe children with severe emotional and behavioral problems. One of the recently developed methods to describe these children is the Child Behavior Checklist Dysregulation profile (CBCL-DP). The CBCL-DP is characterized by high scores on three syndrome scales of the CBCL: Anxious/Depressed, Attention Problems, and Aggressive Behavior. These three scales reflect poor regulation of emotions, attention, and behavior. Studies in school-age children and adolescents have shown that children with this profile show high levels of impairment and are at high risk for suicidality and psychopathology in adulthood. Little is known about the CBCL-DP in young children. The aim of the current thesis was to examine whether a CBCL-DP could be identified in 5- to 7-year-old children. Additionally, we examined determinants and correlates of the CBCL-DP in young children and studied the stability of dysregulated behavior across the preschool period. All studies in this thesis were performed in Generation R, a population-based multi-ethnic birth cohort in Rotterdam, the Netherlands.

In chapter 2 we examined whether we could identify a CBCL-DP in 5- to 7-year-old children. We used latent profile analysis, a person centered statistical method, to empirically identify groups of children with similar patterns of problems. Based on six internalizing and externalizing scales of the CBCL, we identified four profiles: a no problems profile (85.6%), an internalizing profile (5.3%), an externalizing/emotionally-reactive profile (7.3%), and a dysregulation profile (CBCL-DP). In contrast to school-age children and adolescents, children with the CBCL-DP did not only score high on the Anxious/Depressed, Attention Problems, and Aggressive Behavior scales, but scored also high on the other scales of the CBCL. Therefore we concluded that in young children the CBCL-DP is characterized by high scores across the range of internalizing and externalizing problems. We found that the CBCL-DP was associated with higher levels of parental psychiatric symptoms than the other three profiles.

In chapter 3 we examined the overlap between these empirically derived CBCL profiles and DSM-IV diagnoses. We also studied associations between both approaches and other informants of problem behavior. Children with CBCL-DP met criteria for one or more DSM-IV diagnoses in 67% of the cases. They were likely to meet criteria for externalizing disorders or comorbid internalizing and externalizing disorders. Children with the externalizing/emotionally reactive profile were likely to meet criteria for DSM-IV externalizing disorders, while the CBCL internalizing profile showed limited overlap with DSM-IV internalizing disorders. The CBCL profiles were associated with higher levels of internalizing and externalizing problems based on teacher and child report. The DSM-IV externalizing disorders were also related to teacher and child reported problems, while DSM-IV internalizing disorders were not. These

findings give indications how the empirically derived CBCL profiles can be an informative complement to standard psychiatric assessment.

In chapter 4 we studied the relationship between the CBCL-DP and nonverbal intelligence level. We found that children with the CBCL-DP scored 11 points lower on a nonverbal intelligence test than children without problems. This difference was only partly explained by socio-economic, parental and perinatal factors and was independent of the presence of attention deficit hyperactivity disorder and autism spectrum disorder. The CBCL externalizing/emotionally reactive profile was mildly associated with lower nonverbal intelligence level, while no association was found for the internalizing profile after adjustment for all covariates. The lower nonverbal intelligence level in children with the CBCL-DP is a risk factor for poor academic achievement.

In chapter 5 we studied the bidirectional relations between children's externalizing problems, parental psychiatric symptoms, and poor family functioning. Prenatal levels of parental psychiatric symptoms and poor family functioning, which could not have been influenced by the child, predicted children's externalizing problems at 1.5 and 3 years of age. Additionally, we found that children's externalizing problems at 1.5 and 3 years predicted higher levels of parental psychiatric symptoms and poor family functioning at 3 and 6 years. These child effects were independent of prenatal parental psychiatric symptoms, prenatal family functioning and socio-economic status. These results suggest that young children's externalizing problems can be a burden for the family.

In chapter 6 we studied the stability of emotional and behavioral problems from 1.5 and 3 years of age to 5 to 7 years of age. We performed latent profile analyses at each age and found that profiles differed across ages. These results showed that the presentation of problems changes across the preschool years. We also examined children's transitions in profiles over time. Based on profiles at 1.5 and 3 years, it was difficult to predict what type of problems children would exhibit at later ages. However, children with a profile of co-occurring internalizing and externalizing problems at 1.5 and 3 years were most likely to show continuing problems over time. These children may benefit from early intervention.

Chapter 7 describes the main findings of the thesis and major methodological issues concerning the studies described in this thesis. In addition, clinical implications and considerations for future studies are discussed.

SAMENVATTING

De kinder- en jeugdpsychiatrie blijft worstelen met de vraag hoe kinderen met ernstige emotionele en gedragsproblemen het beste gekarakteriseerd kunnen worden. Een recent ontwikkelde methode om deze kinderen te beschrijven is het Child Behavior Checklist dysregulatie profiel (CBCL-DP). Het CBCL-DP wordt gekenmerkt door hoge scores op drie syndroom schalen van de CBCL: Angstig/Depressief, Aandachtsproblemen, en Agressief Gedrag. Deze drie schalen weerspiegelen slechte regulatie van emoties, aandacht en gedrag. Studies bij schoolgaande kinderen hebben aangetoond dat kinderen die voldoen aan dit profiel zeer beperkt worden in hun dagelijks functioneren en een verhoogd risico hebben op suïcidaliteit en psychopathologie in de volwassenheid. Er is weinig bekend over het CBCL-DP bij jonge kinderen. Het doel van dit proefschrift was om te onderzoeken of een CBCL-DP kan worden geïdentificeerd bij 5- tot 7-jarige kinderen. Ook hebben we onderzoek gedaan naar hoe verschillende socio-economische factoren, gezinsfactoren en cognitieve factoren samenhangen met het CBCL-DP. Daarnaast hebben we onderzoek gedaan naar de stabiliteit van emotionele en gedragsproblemen bij jonge kinderen. Alle studies in dit proefschrift zijn uitgevoerd binnen Generation R, een grootschalig bevolkingsonderzoek naar de groei en ontwikkeling van kinderen geboren in Rotterdam.

In hoofdstuk 2 hebben we onderzocht of we een CBCL-DP konden identificeren bij 5- tot 7-jarige kinderen. Hiervoor hebben we gebruik gemaakt van latente profielanalyse. Dit is een statistische methode waarmee we op een empirische wijze groepen kinderen konden onderscheiden met vergelijkbare profielen van emotionele en/of gedragsproblemen. Op basis van zes internaliserende en externaliserende schalen van de CBCL, hebben we vier profielen geïdentificeerd: een profiel zonder problemen (85.6%), een internaliserend profiel (5,3%), een externaliserend/emotioneel-reactief profiel (7,3%) en een disregulatie profiel (CBCL-DP; 1.8%). In tegenstelling tot bevindingen bij schoolgaande kinderen en adolescenten, hadden jonge kinderen met het CBCL-DP niet alleen hoge scores op de Angstig/Depressief, Aandachtsproblemen en Agressief Gedrag schalen, maar scoorden ze ook hoog op de andere schalen van de CBCL. Hieruit hebben we geconcludeerd dat de CBCL-DP bij jonge kinderen wordt gekenmerkt door hoge scores over de hele range van internaliserende en externaliserende problemen. In dit hoofdstuk vonden we ook dat ouders van kinderen met het CBCL-DP, meer psychiatrische symptomen vertonen dan ouders van kinderen met de andere profielen.

In hoofdstuk 3 hebben we de overlap tussen deze empirisch verkregen CBCL profielen en de DSM-IV diagnoses onderzocht. Ook hebben we de CBCL profielen vergeleken met leerkracht en kind rapportages van probleemgedrag. Kinderen met het CBCL-DP voldeden in 67% van de gevallen aan de criteria voor één of meer DSM-IV diagnoses. Externaliserende stoornissen en comorbide internaliserende en externaliserende stoornissen kwamen vaak voor bij deze groep. Kinderen met het externaliserend/emotioneel-reactief profiel voldeden vaak aan de criteria

voor DSM-IV externaliserende stoornissen, terwijl het CBCL internaliserende profiel maar beperkte overlap vertoonde met DSM-IV internaliserende stoornissen. De CBCL profielen waren geassocieerd met hogere niveaus van internaliserende en externaliserende problemen gerapporteerd door de leerkracht en het kind zelf. Deze bevindingen bevestigen de validiteit van de CBCL profielen. Opvallend was dat de DSM-IV internaliserende stoornissen niet gerelateerd waren aan internaliserende problemen gerapporteerd door de leerkracht of het kind. De bevindingen uit dit hoofdstuk geven aanwijzingen hoe de CBCL profielen een informatieve aanvulling kunnen zijn in psychiatrisch onderzoek.

In hoofdstuk 4 hebben we de relatie tussen de CBCL-DP en non-verbale intelligentie bestudeerd. Wij vonden dat kinderen met het CBCL-DP gemiddeld 11 punten lager scoorden op een non-verbale intelligentietest dan kinderen zonder problemen. Dit verschil werd slechts gedeeltelijk verklaard door sociaal-economische, ouderlijke en perinatale factoren. Het externaliserende/emotioneel-reactief profiel was ook geassocieerd met een lager non-verbaal intelligentie niveau, terwijl er geen verband werd gevonden voor het internaliserende profiel. Het lagere non-verbale intelligentie niveau bij kinderen met het CBCL-DP is een risicofactor voor slechtere schoolprestaties.

In hoofdstuk 5 hebben we de bidirectionele relatie onderzocht tussen externaliserende problemen van het kind, psychiatrische klachten van de ouders, en gezinsfunctioneren. Psychiatrische klachten van de ouders en slecht functioneren van het gezin, beiden gemeten voor de geboorte van het kind, voorspelden meer externaliserende problemen bij het kind op 1,5- en 3-jarige leeftijd. Daarnaast voorspelden externaliserende problemen van het kind op 1,5 en 3 jaar meer psychiatrische symptomen bij de ouders en verminderd gezinsfunctioneren op 3 en 6 jaar. Deze effecten van het kind waren onafhankelijk van prenatale niveaus van psychiatrische symptomen van de ouders en gezinsfunctioneren. Deze resultaten suggereren dat externaliserende problemen bij jonge kinderen een last voor het gezin kunnen zijn.

In hoofdstuk 6 hebben we onderzoek gedaan naar de stabiliteit van emotionele en gedragsproblemen van 1,5 tot 5-7 jaar. Met behulp van latente profielanalyses vonden we op 1,5, 3 en 5-7 jaar verschillende profielen van emotionele en gedragsproblemen. Deze resultaten toonden aan dat de presentatie van problemen verandert tijdens de vroege ontwikkeling van het kind. Veel kinderen met problemen op jonge leeftijd, bleken later geen problemen meer te hebben. Echter, 1,5- en 3- jarige kinderen met een profiel dat werd gekenmerkt door zowel internaliserende als externaliserende problemen hadden de meeste kans op aanhoudende problemen op 5-7 jaar. Deze kinderen kunnen baat hebben bij vroege interventie.

AUTHOR AFFILIATIONS

Department of Child and Adolescent Psychiatry and Psychology, Erasmus University Medical Center, Rotterdam, The Netherlands
Althoff, R.R., Basten, M., van der Ende, J., Hudziak, J.J., Rijlaarsdam, J., Ringoot, A.P., Tiemeier, H., Verhulst, F.C., White, T.

Department of Epidemiology, Erasmus University Medical Center, Rotterdam, The Netherlands
Hofman, A., Jaddoe, V.W.V., Tiemeier, H.

Department of Medicine, College of Medicine, University of Vermont, Burlington, VT, USA
Hudziak, J.J.

Department of Methods and Statistics, Utrecht University, Utrecht, The Netherlands
van de Schoot, R.

Department of Paediatrics, Erasmus University Medical Center, Rotterdam, The Netherlands
Jaddoe, V.W.V.

Department of Pediatrics, College of Medicine, University of Vermont, Burlington, VT, USA
Althoff, R.R., Hudziak, J.J.

Department of Psychiatry, College of Medicine, University of Vermont, Burlington, VT, USA
Althoff, R.R., Hudziak, J.J.

Department of Psychiatry, Erasmus University Medical Center, Rotterdam, The Netherlands
Tiemeier, H.

Department of Psychology, University of Vermont, Burlington, VT, USA
Althoff, R.R.

Department of Radiology, Erasmus University Medical Center, Rotterdam, The Netherlands
White, T.

Optentia Research Program, Faculty of Humanities, North-West University, Mahikeng, South Africa
van de Schoot, R.

School of Pedagogical and Educational Sciences, Erasmus University Rotterdam, The Netherlands
Mileva-Seitz, V.R.

The Generation R Study Group, Erasmus University Medical Center Rotterdam, The Netherlands
Basten, M., Jaddoe, V.W.V., Mileva-Seitz, V.R., Rijlaarsdam, J., Ringoot, A.P., Trajanoska, K.

ABOUT THE AUTHOR

Maartje Basten was born on the 15th of July 1984 in Vierlingsbeek, the Netherlands. She graduated from secondary school in 2002 at the Elzendaal College in Boxmeer. She went on to study Human Movement Sciences at the University of Groningen and completed her Bachelor of Science Degree in 2005. Hereafter, Maartje moved to Amsterdam where she completed two Master of Science Degrees at the VU University: Human Movement Sciences, specialisation Psychomotor Therapy (2007; cum laude), and Clinical Psychology (2009; cum laude). In 2010, Maartje started the work described in this thesis at the Department of Child and Adolescent Psychiatry and Psychology of the Erasmus Medical Center in Rotterdam, in close collaboration with the University of Vermont, USA. In the course of her Ph.D., she obtained a Master of Science Degree in Epidemiology from the Netherlands Institute for Health Sciences (2012). In July 2014, she started as a research fellow at the Department of Psychology at the University of Warwick, UK. She is involved in a study of the long-term outcomes of preterm birth.

PHD PORTFOLIO

Name PhD Student:	Maartje Basten
Erasmus MC Department:	Child and Adolescent Psychiatry/Psychology
Research School:	Netherlands Institute for Health Sciences (NIHES)
PhD period:	March 2010 – July 2014
Promotors:	Prof. Frank C. Verhulst, Prof. James J. Hudziak, Prof. Henning Tiemeier

1. PHD TRAINING

	Year	Workload (ECTS)
Research Skills		
MSc Epidemiology, Netherlands Institute for Health Sciences	2010-2012	
Core Curriculum		
Study Design		4.3
Classical Methods for Data-Analysis		5.7
Methodologic Topics in Epidemiologic Research		1.4
Modern Statistical Methods		4.3
Public Health Research Methods		5.7
Erasmus Summer Programme		
Principles of Research in Medicine		0.7
Methods of Public Health Research		0.7
Topics in Meta-analysis		0.7
Genome Wide Association Analysis		1.4
Conceptual Foundation of Epidemiologic Study Design		0.7
Cohort Studies		0.7
Introduction to Public Health		0.7
Principles of Genetic Epidemiology		0.7
Primary and Secondary Prevention Research		0.7
Social Epidemiology		0.7
Markers and Prognostic Research		0.7
Advanced Short Courses		
Repeated Measurements in Clinical Studies		1.4
Missing Values in Clinical Research		0.7
Courses for the Quantitative Researcher		1.4
Psychiatric Epidemiology		1.1

Research skills (continued)		
Biomedical English Writing and Communication, Erasmus Medical Center Rotterdam	2011	4.0
The Big Mplus show, Utrecht University	2011	2
New Features of Mplus version 7, Utrecht University	2012	0.6
Meetings and Symposia		
Research Meetings, The Generation R Study Group	2010-2014	1.0
Symposium: 'Standardized assessment of child psychopathology: new developments.' Erasmus Medical Center Rotterdam	2011	0.3
Symposium: 'Sophia 150 years: children of the future' Erasmus Medical Center Rotterdam	2013	0.3
Symposium: 'Consortium on Individual Development, Kick off Symposium', Utrecht University. Poster presentation: 'Nonverbal intelligence in young children with Dysregulation'	2013	0.3
Symposium: 'Hans Ormel: A life in Epidemiology and Beyond', University Medical Center Groningen	2014	0.3
International conferences		
Conference of the Life History Research Society, Richmond, Surrey, UK. Oral communication: 'Patterns of emotional and behavioral problems at 18 months, 36 months and 6 years of age: a person-centered approach in a large population-based cohort.'	2012	1.0
60th Annual meeting of American Academy of Child and Adolescent psychiatry (AACAP), Orlando, USA. Poster presentation: 'Nonverbal intelligence in young children with dysregulation'.	2013	1.4

2. TEACHING ACTIVITIES

Lecturing		
Erasmus Summer Programme Teaching assistant 'Principles of research in medicine'	2013	1.4
Erasmus University Medical Center VO.3 Workshop 'Normal development of children'	2012	0.5
Supervising Master's theses		
Nicole van der Horst, 'Diurnal cortisol: a moderating factor in the association between attachment disorganization and aggression in early childhood?' Erasmus University Rotterdam, Medicine	2011	1.5
Noraly Heshof, 'The relation between maternal thyroid function during pregnancy and the presence of dysregulation in 5 to 8 year old children: the Generation R Study' Erasmus University Rotterdam, Medicine	2011	3

Supervising Master's theses (continued)

Devika Jhingur, 'Prenatal and postnatal dysregulation are associated with dysregulation in children at 3 years: Generation R Study' Leiden University, Child and Adolescent Psychology	2011	3
Lilian Waterlander, 'Executive functioning in young children with dysregulation' Leiden University, Clinical Neuropsychology	2013	3
Inge Merkelbach, 'Harsh parenting and child temperament as correlates of Disruptive Mood Dysregulation Disorder in a community sample', Erasmus University Rotterdam, Clinical Psychology	2013	3

DANKWOORD

De Generation R studie was niet mogelijk geweest zonder de medewerking van alle kinderen, hun moeders, vaders en leerkrachten. Daarvoor wil ik hen allen hartelijk bedanken. Ik hoop dat alle kinderen nog lang blijven deelnemen aan Generation R!

Graag wil ik mijn supervisoren Jan van der Ende, Henning Tiemeier, Frank Verhulst, Rob Althoff en Jim Hudziak bedanken voor hun begeleiding. Op de eerste plaats Jan, bedankt voor het delen van je expertise, je betrokkenheid en niet te vergeten je altijd aanwezige optimisme. Henning, door jou goede inzichten en epidemiologische kennis klopte ik steeds weer bij je aan. Bedankt dat je telkens weer ruimte hebt gemaakt om mee te denken. Beste Frank, je plaatste mijn onderzoeksbevindingen in een breder perspectief, hartelijk dank daarvoor. Dear Rob, working with you was very inspiring and fulfilling, thank you. Dear Jim, thank you for sharing all your great ideas during our meetings.

Een van de belangrijkste ingredienten voor plezier in het werk zijn prettige collega's en daar zijn er bij Generation R geweldig veel van. Graag bedank ik alle collega-promovendi voor de gezellige werksfeer en het delen van alle ups en downs van het promoveren. In het bijzonder dank aan mijn enthousiaste kamergenoten Nicole, Eszter, Laura, Eirini, Lisette en Annemarie, dank voor de gezelligheid en het vele meedenken! Ook dank ik Ank, Sabine, Jolien en Jolien voor de fijne samenwerking tijdens de cursussen, congressen, dataverzameling, Mplus analyses en data opschoning. Akhgar, Marina, and Ilse thanks for the good company, and Akhgar, for answering all my questions. En ook dank aan Inge, Fadila, Sandra, Dafna, Ryan, Nina, Andrea, Anne, Selma, Rianne, Rolieke, Fleur, Maartje, Viara, Pauline en Monica.

Dank aan alle medewerkers van het onderzoekscentrum. De bureaumedewerkers Patricia, Roos, Karin, Karien, Ronald, Claudia, Marjolein, Nathalia en Alwin, jullie staan altijd klaar, geweldig. Ook Laureen en Erica, bedankt voor alle goede zorgen. Tonya en Rens, dank voor jullie input als co-auteurs. Graag bedank ik de leden van de leescommissie Vincent Jaddoe, Judy Mesman en Lydia Arends voor het beoordelen van mijn proefschrift. En natuurlijk mijn paranimfen, Anneke en Femke, super fijn en leuk dat jullie naast mij willen staan bij de verdediging.

Dit proefschrift was er nooit gekomen zonder de steun van al mijn lieve familie en vrienden, bedankt voor het meeleven en de bemoedigende en relativerende woorden.

ACKNOWLEDGEMENTS

The Generation R Study is conducted by the Erasmus Medical Center in close collaboration with the School of Law and Faculty of Social Sciences of the Erasmus University Rotterdam, the Rotterdam Homecare Foundation, and the 'Stichting Trombosedienst & Artsen-laboratorium Rijnmond' (STAR) in Rotterdam. We gratefully acknowledge the contribution of all participating children and their families, general practitioners, midwives, and pharmacies in Rotterdam. The general design of the Generation R Study is made possible by the Erasmus Medical Center Rotterdam, the Erasmus University Rotterdam, the Netherlands Organization for Health Research and Development (ZonMw), the Netherlands Organization for Scientific Research (NOW), the Ministry of Health, Welfare, and Sport, and the Ministry of Youth and Families.

Studies presented in this thesis were conducted at the Department of Child and Adolescent Psychiatry and Psychology of the Erasmus Medical Center – Sophia Children's Hospital in Rotterdam.

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