RISK FACTORS FOR THE DEVELOPMENT AND OUTCOME OF CHILDHOOD PSYCHOPATHOLOGY

Laura W. Wesseldijk

Risk factors for the development and outcome of childhood psychopathology

Laura Wendelmoet Wesseldijk

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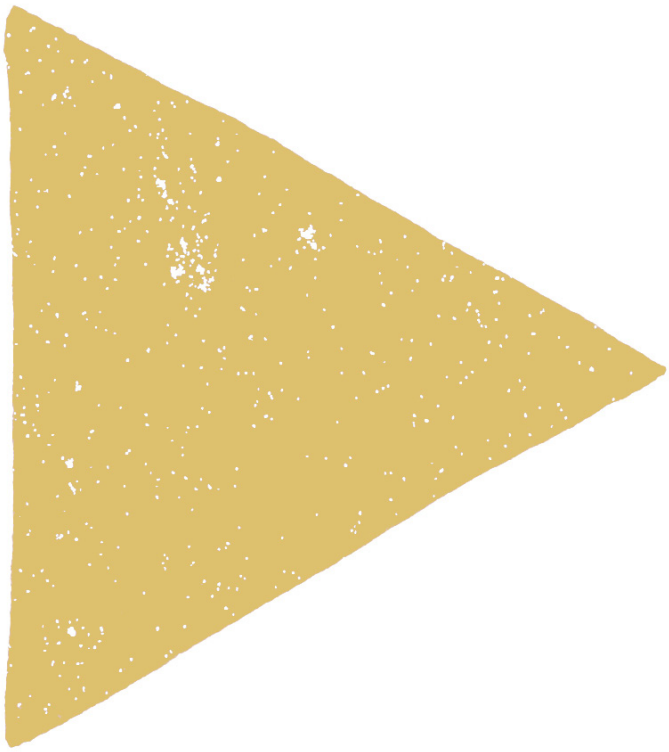
Risk factors for the development and outcome of childhood psychopathology

INTRODUCTION



Chapter 1

This thesis is about factors that influence the development and/or persistence of childhood psychopathology, including genetic as well as other familial factors. Risk factors for psychopathology are investigated in two different samples: a large population-based twin sample and a clinical sample of families with children with psychopathology.

Psychiatric disorders run in families. This can partly be explained by genetic factors. Earlier twin-family studies have estimated the heritability for childhood psychiatric disorders to range between 40% (for e.g. depression and anxiety) and 80% (for e.g. attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD)) [1-3]. In addition, familial or shared environmental factors, i.e., factors shared by children growing up in the same family, appeared to explain familial resemblance for psychiatric disorders or traits. Shared environmental influences accounted for around 10-30% of the variance in most of the psychiatric disorders or traits measured during childhood [4,5], except for ADHD, for which the effect of the shared environment has consistently been found to be negligible. Not only the resemblance, but also the frequently observed differences between family members can be due to genetic factors, since family members only share part of their genetic material (except for identical twins). Environmental factors that are unique to each member of a family, the so-called non-shared environment, explain the remaining part of the variation in psychiatric disorders.

Although the field of behavior genetics has a long history of twin- and family-studies into childhood psychopathology, several issues that might influence the estimates of genetic and environmental influences remain understudied.

1. Childhood psychopathology is often assessed by external informants, like mothers, fathers, or teachers. Studies on the genetic and environmental causes of individual differences in childhood psychopathology most frequently use either maternal or paternal ratings. However, each rater introduces some kind of rater bias, for example based on his or her own standards or own psychopathology. In twin studies, this so-called rater bias can resemble an effect of the shared environment [6]. Using multiple ratings simultaneously, e.g., both parents for both twins, is also possible [6-22] and results in more reliable estimates of the genetic and shared environmental influences on childhood psychopathology.

2. Different informant do not completely agree. Previous multiple rater studies showed that there are parental differences in the assessment of childhood

psychopathology. The parental agreement about the level of problems in their child (i.e., the correlation between the parental ratings) was not perfect (ranging between r=.60 and r=.75) and mother ratings were often found to be slightly higher than father ratings for internalizing and externalizing problems in their children. Differences in the scores depending on the informant assessing childhood psychopathology may lead to different conclusions in situations where scores are used to screen children for psychiatric disorders. It is still unclear whether differences in means between mother and father ratings depend on the child's gender or age and whether the mean discrepancies are the result of the gender of the informant or of different reasons, e.g. a different relationship with the child.

3. Age is also a factor that can modify the heritability of psychiatric disorders, which is not always taken into account. Genetic influences are often found to be smaller in childhood and increase with age, whereas shared environmental influences decrease with age [23]. Another issue is the explanation of stability over the ages, i.e. the factors that influence the persistence of psychopathology in childhood into adolescence and adulthood. Epidemiological studies have shown that around 50% of individuals with a childhood psychiatric disorder still fulfil the criteria of a psychiatric disorder in adulthood [24,25]. Earlier genetic longitudinal analyses have shown that for anxiety and depression [26-29], attention problems [30,31], and aggressive behavior [32] the persistence of the psychiatric problems into adulthood is mainly due to genetic effects and not to the shared environment. This has not been studied for other psychiatric symptoms in childhood.

There are also several understudied issues regarding the prevalences of parental psychopathology in families with children referred to a child and adolescent psychiatric outpatient clinic, and the association with the child's psychopathology, also over time. The significant genetic and shared environmental influences reported in twin-family studies imply that clinicians treating children with psychiatric disorders are likely to come across parents of children experiencing psychiatric symptoms themselves. Studies in clinical samples indeed found that parents whose children are evaluated for psychiatric disorders at a mental health clinic report high levels of internalizing [33-47] and externalizing psychiatric problems themselves [48-52]. The prevalence rates varied between 18% and 68%. Studies also showed that parental psychiatric symptoms influenced the course of childhood psychopathology and outcome of the child's treatment [47,53-72]. Issues that are understudied are:

1. Resemblance in spouses for psychopathology. Having two parents with psychopathology, as opposed to one, can make the shared environment more unfavorable with a greater impact on outcome [73], but it is unknown whether parents of children referred to a clinic are more often both affected than parents in the general population.

2. The comorbidity of psychiatric disorders. The majority of the earlier research in clinical samples focused on a single psychiatric disorder, but familial resemblance for psychopathology is often not confined to the disorder of the index subjects [74,75]. Assessing a broad range of psychopathology in parents with offspring suffering from various internalizing and externalizing disorders can provide better insight into associations between parent-offspring psychopathology.

3. Paternal psychopathology and father-offspring associations. Although it is known that paternal psychopathology is associated with offspring psychopathology [76,77] as well as with maternal psychopathology for internalizing problems [see for reviews 78,79,80], earlier studies mostly analyzed maternal psychiatric symptoms or included far fewer fathers than mothers.

Data

In this thesis, I investigate genetic and familial risk factors for psychopathology and its outcome in two samples: a large population-based twin sample and a clinical sample of families with children with psychopathology. Both samples are described briefly below. A more extensive description of the clinical data collection procedures, response rates and the measurement instruments used are described in the Appendix.

A. The Twin Sample. Since the establishment in 1987, the Netherlands Twin Register (NTR) has on a regular basis collected information on, among other things, mental health problems in children, adolescents and adults [81-83]. As data have been collected over a period of 27 years, the NTR has come to have a unique large longitudinal twin dataset with information available on psychiatric symptoms across different ages. For my thesis project I analyzed psychiatric symptoms in 12,310 7 year-old, 9,783 9-10 year-old, 6,839 13-18 year-old, and 7,909 19-65 year-old twin pairs, and in 2,784 parents of twins. The NTR has measures available on childhood psychopathology from different informants (i.e. mothers, fathers, teachers and self-reports).

B. The Clinical Sample. Data from families with a child with psychopathology were collected in four different child and adolescent outpatient clinics in Amsterdam and Rotterdam, the Netherlands (de Bascule, GGZ inGeest and UvA Minds in Amsterdam and the Erasmus University Medical Center-Sophia Children's Hospital (EUMC) in Rotterdam). Data were collected on the child's, mother's and father's psychopathology at time of the first assessment in the clinics (N=1,942 families, N=1,850 mothers and N=1,399 fathers). The same surveys assessing the child's and parents' psychiatric symptoms were collected approximately one to five years later for three clinics (N=794 families, N=742 mothers, N=440 fathers). In Appendix I, I describe the part of this data collection that was performed for the NWO TOP project: "Genetic influences on stability and change in psychopathology from childhood to young adulthood."

Content of this thesis

In this thesis I focus on the outstanding issues described above regarding the influences of genetic and shared environmental factors on childhood psychopathology and the clinical implications. I take into account that data from children are collected from different informants and test for effects of genotype x age interaction. The analyses include one- and two generation designs, using the classical twin design of mono- and dizygotic twins and parent-offspring designs. The first part of this thesis focuses on the heritability and assessment of childhood psychopathology, utilizing the large population-based twin sample from the NTR. The second part of this thesis describes studies into familial factors associated with childhood psychopathology and its outcome, utilizing data from a clinical sample of families with children with psychopathology. In the discussion I will put the results in the context of the implications for psychiatric outpatient clinics treating children with psychiatric disorders and provide recommendations for future research. A brief description of the chapters in this thesis is provided below.

Part I: Childhood psychopathology: assessment and heritability

Chapter 2 presents a twin study which investigates what the influences of genetic and shared environmental factors are on affective, anxiety, somatic, ADHD, oppositional-defiant, conduct and obsessive-compulsive problems in 7-year-olds while analyzing mother and father ratings simultaneously. This chapter also describes differences in parental assessment of their children's psychiatric problems and whether this depends on gender of the child.

Chapter 3 seeks to answer two questions: 1) whether informant discrepancies depend on the gender or age of the child or on the psychiatric symptoms assessed and 2) whether differences in maternal and paternal reports on childhood psychopathology are due to the gender of the informant. We provide an overview of the informant discrepancies between maternal and paternal ratings, but also between female and male teacher ratings of a broad range of childhood psychiatric symptoms in 5, 7, 10 and 12 year-old boys and girls. If male and female means differ as much as mothers' and fathers', these differences could be due to gender of the informant. It was further tested whether gender of the child interacts with gender of the informant.

Chapter 4 describes the results from a genetic longitudinal analysis which reveals the genetic architecture of childhood and adolescent conduct problems and adult antisocial personality problems when taking into account genotype x age interaction. Conduct problems in children, defined by repetitive and persistent behaviors that violate the rights of others or societal norms or rules [84], are known to be relatively stable and can predict antisocial personality problems in adults and related problems, such as crime and conviction [24,85-87]. We undertook this study to estimate the influences of the genetic, shared and non-shared environmental factors on variation in conduct problems in 9-10 year-olds, 13-18 year-olds and on antisocial personality problems in 19-65 year-olds. We further estimated the contribution of genetic and environmental factors on the persistence of conduct problems from childhood into adolescence and adulthood. Possible gender differences in the etiology of conduct and antisocial personality problems were also examined.

Part II: Aggregation of psychopathology in a clinical sample of children and their parents

Chapter 5 focuses on spousal resemblance, we investigate whether psychiatric symptoms in partners are associated. We evaluate whether parents of children referred to a child and adolescent psychiatric outpatient clinic are more alike in psychiatric symptoms than parents of children in the general population (i.e. the parents of twins registered with the NTR), within and across multiple internalizing and externalizing psychiatric symptoms.

Chapter 6 provides the prevalence rates of several psychiatric symptoms in both mothers and fathers of children that are evaluated for psychiatric disorders at

psychiatric outpatient clinics. In addition, this chapter investigates parent-offspring associations, both within and across internalizing and externalizing symptoms. We seek to address the question whether the parental prevalence rates and associations with their offspring psychopathology are similar in mothers and fathers. The associations are analyzed separately for boys and girls, while controlling for spousal resemblance for psychiatric symptoms.

Chapter 7 reports on a study that aims to identify the parents at the highest risk for psychopathology themselves when their child is evaluated for psychiatric disorders by exploring the predictive validity of various risk factors on multiple parental psychiatric symptoms. We examine whether family (relationship status), parental (e.g. education level, occupational status, age and gender) and offspring characteristics (e.g. age, kind of psychiatric diagnosis and comorbidity) predict depressive, anxiety, ADHD, avoidant personality and antisocial personality symptom scores in mothers and fathers.

Chapter 8 describes the results of a longitudinal analysis which examines the effect of several internalizing and externalizing parental psychiatric symptoms present when their child is evaluated in a psychiatric outpatient clinic on the child's outcome of psychopathology. We evaluate predictions of the child's depressive, anxiety, ADHD, oppositional-defiant or conduct problems at follow-up by the parental depressive, anxiety, avoidant personality, ADHD and antisocial personality problems at baseline in a model that also includes the parent-offspring associations at baseline, predictions of parental psychiatric symptoms at follow-up and the child's symptom score at baseline. Analyses are performed separately for mothers and fathers.

Chapter 9 concludes with a summary of the results of the studies described in this thesis and a discussion on the implications for psychiatric outpatient clinics treating children with psychiatric disorders and recommendations for future research.

PSYCHOPATHOLOGY IN 7-YEAR-OLD CHILDREN: DIFFERENCES IN MATERNAL AND PATERNAL RATINGS AND THE GENETIC EPIDEMIOLOGY

Chapter 2

Abstract

The assessment of children's psychopathology is often based on parental report. Earlier studies have suggested that rater bias can affect the estimates of genetic, shared environmental and unique environmental influences on differences between children. The availability of a large dataset of maternal as well as paternal ratings of psychopathology in 7-year old children enabled 1) the analysis of informant effects on these assessments, and 2) to obtain more reliable estimates of the genetic and non-genetic effects. DSM-oriented measures of affective, anxiety, somatic, attention-deficit/hyperactivity, oppositional-defiant, conduct, and obsessive-compulsive problems were rated for 12,310 twin pairs from the Netherlands Twin Register by mothers (N=12,085) and fathers (N=8,516). The effects of genetic and non-genetic effects were estimated on the common and rater-specific variance. For all scales, mean scores on maternal ratings exceeded paternal ratings. Parents largely agreed on the ranking of their child's problems (r .60-.75). The heritability was estimated over 55% for maternal and paternal ratings for all scales, except for conduct problems (44-46%). Unbiased shared environmental influences, i.e. on the common variance, were significant for affective (13%), oppositional (13%) and conduct problems (37%). In clinical settings, different cutoffs for (sub)clinical scores could be applied to paternal and maternal ratings of their child's psychopathology. Only for conduct problems, shared environmental and genetic influences explain an equal amount in differences between children. For the other scales, genetic factors explain the majority of the variance, especially for the common part that is free of rater bias.

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Introduction

Many childhood psychiatric disorders, including attention deficit hyperactivity disorder (ADHD), behavioral disorders and anxiety disorders, are already prevalent at age 7. Pooled prevalence rates across countries at this age are estimated in a meta-analysis at 3.4% for ADHD, 3.6% for oppositional defiant disorder (ODD), 2.1% for conduct disorder (CD) and 6.5% for anxiety disorders [88]. There are no pooled world-wide prevalences for obsessive-compulsive disorder (OCD), the estimated prevalence rates in children vary between 1% and 7% across countries [89,90]. In the current study, performed in a large sample of Dutch 7-year old twins, we investigated whether there are differences in paternal and maternal ratings of their child's psychopathology. Next, contributions of genetic, shared familial and unshared environmental factors on the differences between children in psychopathology as assessed by mothers and fathers were estimated.

Measures of childhood psychopathology below age 12 are often based on reports from mothers and/or fathers. The outcome of these assessments can depend on the rater. Earlier studies in 7-year-old children have found maternal ratings to be higher than paternal ratings [7,8,11,91-95]. The ranking of the children's problems has also been found to vary between fathers and mothers resulting in correlations of .60 between maternal and paternal ratings [95,96].

Several twin studies have investigated parental ratings of childhood psychopathology and estimated the influences of additive genetic (A), common environmental (C) factors shared by children growing up in the same household, and non-shared environmental (E) factors [1,4]. As monozygotic (MZ) twin pairs share almost all of their genetic material, while dizygotic (DZ) twin pairs share on average 50%, a higher MZ than DZ twin correlation indicates that A plays a role in differences between children. If the DZ twin correlation is higher than half of the MZ twin correlation, C, representing environmental influences that create resemblance among siblings, may also be of influence. The remaining part of the variance is attributed to E, representing environmental influences that create differences among siblings and measurement error. Genetic factors have been consistently reported to have an influence on differences between children in psychiatric disorders or symptoms. In addition, usually C was found to explain additional variation, except for ADHD [1,4].

Most estimates of A and C were based on studies that analyzed reports of one rater in which the assessments can partly reflect characteristics of the rater. A rater may systematically over or underestimate certain behavior in children and when

the same rater assesses behavior in multiple children, the extent to which they resemble each other thus can in part be due to rater characteristics [97]. In genetic epidemiological analyses, this bias will create an effect that resembles an effect of common environment (C) as this bias results in a higher resemblance in MZ as well as in DZ twins [6]. In studies that include reports of multiple raters, e.g., both parents for both twins, an unbiased estimate of the effect of shared environmental factors on childhood psychopathology can be obtained by estimating the effect of C on the part of the variance the parents agree upon. Previous multiple-rater studies in 7-year-old twins [6-11] showed that rater bias might account for around 10 to 30% of the phenotypic variance. These studies focused on broad measures of internalizing and externalizing measures or on anxious depression, thought problems and aggression. Such estimates are lacking for measures of childhood psychopathology that reflect symptoms associated with common psychiatric disorders as defined by the DSM-IV [98]. The effects of genetic and environmental factors on psychopathology have been shown to vary with age and so could the effects of rater bias [1,4,6,23]. It is therefore important to analyze groups of children with a narrow age range, when considering the impact of rater bias.

Here, we analyze data on childhood psychopathology in a large sample of twins whose parents participate in the Netherlands Twin Register (NTR). Data were collected close to their 7th birthday in 12,310 twin pairs of which 8,480 twin pairs (67.4%) have ratings available from both parents. We analyzed the DSM-oriented affective, anxiety, somatic, attention-deficit/hyperactivity, oppositional-defiant, conduct and obsessive-compulsive problems scales of the Child Behavior Checklist (CBCL) [99]. The CBCL was originally developed to assess behavioral and emotional problems across a series of empirically defined scales based on exploratory (EFA) and confirmatory (CFA) factor analysis [99,100]. In contrast, items defining DSM-oriented scales were selected when 14 out of 22 experienced child psychiatrists and psychologist judged the item to be highly consistent with the relevant DSM-IV diagnostic category [99,101]. A limited number of studies is available for the DSM-oriented scales. In one study in 398 Italian twin pairs [102], the heritability for five DSM scales (i.e. affective, anxiety, attention, oppositional-defiant and conduct problems) varied between 34% and 74% in twins aged 8-11 and between 53% and 82% in twins aged 12-17. Significant effects of C were found for affective (39%) and anxiety (30%) problems in children aged 8-11. A recent Chinese twin study [103] in 658 twin pairs aged 6-18 reported modest genetic influences (19-37%) and substantial influences of C (54-67%) for the affective, anxiety and somatic DSM-oriented CBCL scales. Chen et al. [103] discussed that these discrepancies in genetic

and environmental estimates across studies could be due to context differences, or to the broad age ranges and reports of one rater analyzed. For the obsessive-compulsive scale of the CBCL, analyzing maternal and paternal ratings yielded heritability estimates between 46% and 59% for boys and girls and an effect of C between 10% and 15% in 8.083 twin pairs at age 7 [9].

We investigated whether parents differ in the assessments of their children, whether parental agreement depends on the child's gender and to what extent differences between children are explained by genetic, shared and non-shared environmental factors by simultaneously analyzing maternal and paternal ratings of mono- and dizygotic twins.

Methods

Subjects

All participants were registered by their parents with the Netherlands Twin Register (NTR) shortly after birth [82,83]. When the twins were 1, 2, 3, 5, 7, 10 and 12 years old, parents received a survey from the NTR. The first twins were registered in 1987 and recruitment and data collection is ongoing. For the current study, data of 7-years-old twins from birth cohorts 1986-2005 were analyzed. The surveys were mailed to the parents close to the twin's 7th birthday and reminders were sent after 2 to 4 months resulting in a response rate of 55% [82]. The final sample contained 2,079 monozygotic male (MZm), 2,324 monozygotic female (MZf), 2,086 dizygotic male (DZm), 1,924 dizygotic female (DZf) and 3,897 dizygotic opposite-sex twin pairs (DOS). More mothers (N=12,085) than fathers (N=8,516) completed the survey. For the same-sex twin pairs, zygosity was determined by DNA polymorphisms for 1,752 pairs, and otherwise by items in the survey about physical resemblance. Zygosity determination based on items about physical resemblance and DNA polymorphisms are in agreement in more than 93% of the twin pairs [104].

Measures

Children's behavioral and emotional problems were assessed using the Child Behavior Checklist (CBCL) [99]. The CBCL is a rating scale for parents of children from 6 to 18 years old. It contains 118 specific items that are rated on a three-point scale (0 to 2; not true, somewhat true, very true). We analyzed variation among children's behavioral and emotional problems using the DSM-oriented CBCL scales that are consistent with diagnostic categories of the American Psychiatric

Association's [1994] Diagnostic and Statistical Manual, 4th Edition (DSM-IV), namely the DSM-oriented affective, anxiety, somatic, attention-deficit/hyperactivity, oppositional-defiant, conduct and obsessive compulsive problems scales. Good validity for the DSM-oriented scales of the CBCL was reported in a US sample, with 80% of referred and non-referred children classified correctly and correlations with DSM-IV diagnostic categories ranging between .43 and .80 [99]. In a sample of Dutch children, the anxiety problems scale moderately predicted the presence or absence of a clinical DSM-IV anxiety disorder diagnosis, while the affective problem scale closely predicted DSM-IV major depression [105]. In 2001, Nelson et al. [101] created the obsessive-compulsive DSM-oriented scale after CFA and Andersen, Bilenberg [106] confirmed high sensitivity and moderate specificity. Internal consistency in our sample, as reflected by Cronbach's α, was on average .63, ranging from .49 to .76, which is comparable to findings in Spanish validation studies [107,108].

Genetic epidemiological analyses and multiple rater models

Since MZ twins share (nearly) all their genetic material, while DZ twins share, on average, 50% of their segregating genes, a higher phenotypic MZ twin correlation indicates that genetic factors play a role. If the DZ twin correlation is higher than half of the MZ twin correlation, shared environmental effects also are of importance. If the MZ twin correlation is more than twice as high than the DZ twin correlation, it is inferred that non-additive genetic factors contribute to the phenotypic variance, in addition to additive genetic factors. Finally, the remaining part of the variance is attributed to non-shared environment effects and measurement error. This information can be captured in structural equation modelling, where the variance is decomposed into additive (A) and non-additive (D) genetic, shared environmental (C) and non-shared environmental (E) components. Since C and D have an opposing effect on the DZ twin correlations, their effects cannot be estimated simultaneously in the classical twin design. Based on the observed correlation pattern, an ACE or ADE model is tested. When ratings from mothers and fathers are available, it is possible to decompose the variances of the two ratings into a part the parents agree upon, the common part, and into two uncorrelated parts reflecting the disagreement, the rater-specific parts using the psychometric model (Figure 1) [97]. These common and rater-specific parts of the variance can be further decomposed in variance explained by A, C or D, and E. For the common part, information comes from the cross-twin-cross-rater-correlations, i.e., the correlations between the maternal ratings of twin 1 and the paternal ratings of twin 2. Rater bias is excluded from the common

part, but is contained in the rater-specific shared environmental influence (Cm and Cf). Therefore, C on the common part is an unbiased estimate of the effect of shared environmental factors. Furthermore, whether the rater-specific parts also reflect true behavior of the child is inferred from the significance of the genetic influences on these rater-specific parts (Am and Af), as it is unlikely that measurement error leads to an estimation of genetic influences [109].

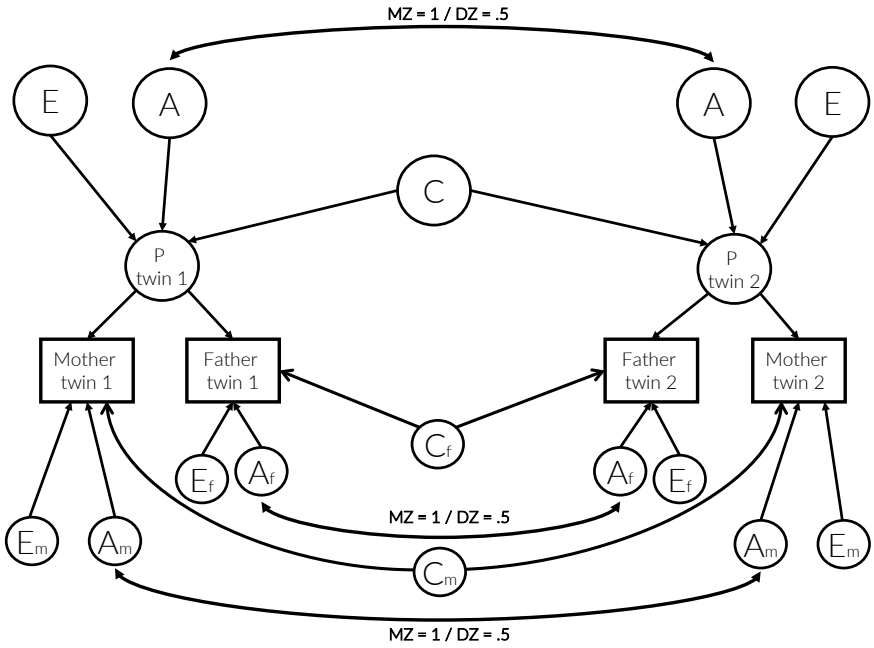


Figure 1. The psychometric model. Maternal and paternal ratings are linear functions of the latent phenotypes of the twins (P twin 1 and P twin 2), and rater specific variance (Am, Cm, Em, Af, Cf, and Ef). When constraining Am and Af to zero, the model represents a restricted rater bias model with Cm and Cf representing mother's and father's bias and Em and Ef representing residual error.

The DSM-oriented scales were highly skewed, as is usual given the relatively large number of subjects with no or little psychiatric symptoms in population based cohorts. Treating the scores as normally distributed variables would result in parameter bias and it is therefore recommended to categorize the data and fit a threshold model [110]. Dividing the data using the clinical cut-off scores consistent with the DSM-IV diagnostic categories would neglect the variation between individuals below the diagnostic threshold; previous work suggested no etiological demarcation between variation within the normal variation and at the extreme end [111]. In addition, dividing the data into 3 approximately equally sized groups instead of 2 groups yields more power [112]. Therefore, the scores were divided into three (low, middle and high) groups, and analyzed as categorical data with two thresholds [110]. In the threshold model, it is assumed that the categorical trait has an underlying continuous distribution of liability [113]. Data from boys and girls were divided into three more or less equally sized groups (percentages of children in the first two groups are shown in Table 1). As can be seen in the table, for each scale, the groups included children with identical problems scores for paternal and maternal ratings (see Table 1). Consequently, differences in thresholds for boys and girls and paternal and maternal ratings reflect differences in prevalence rates of 0, 1 or 2 scores.

The analyses were performed in OpenMx [114]. In the baseline model, we estimated the thresholds for maternal and paternal ratings in boys and girls and the polychoric correlations, reflecting the correlations on the liability distribution. In addition to the correlations between paternal and maternal ratings, twin correlations for the maternal and the paternal ratings and the cross-twin-cross rater correlations were estimated for MZm, DZm, MZf, DZf and DOS twin pairs. Sex differences in prevalence were analyzed by testing whether the thresholds could be constrained to be equal for mother and father ratings and for boys and for girls per rater. Next, we tested whether the parental agreement depended on zygosity or sex of the offspring, i.e., is parental agreement similar in MZ and DZ twins, and in boys and girls. Lastly, sex differences in the correlations were analyzed by constraining correlations between same-sex male and female twin pairs to be equal. This provides a test of quantitative sex differences in genetic architecture. To investigate qualitative sex effects, i.e. whether different genes operate in boys and girls, correlations between DZ same-sex and DOS twins were constrained to be equal [115]. The fit of these models was compared to the more general model.

Significance testing was based on the likelihood ratio test, where the negative log-likelihood (-2LL) of the constrained model is subtracted from the -2LL of the more general saturated model. The difference between the -2LL of the two models follows a χ^2 distribution with degrees of freedom (df) equal to the amount of constraints. If the difference in fit is significant, the more saturated model should be retained. If the difference in fit is not statistically significant, the constrained model should be retained to achieve the best fitting and most parsimonious model.

Based on these outcomes, the psychometric model as explained above and depicted in Figure 1 was applied to the data to estimate the influences of A, C (or D) and E on the common and rater specific parts. 95% confidence intervals were calculated to evaluate whether common and rater-specific A, C or D were significant and whether estimates were similar in mothers and fathers.

Results

Descriptives

The thresholds for boys and girls of maternal and paternal ratings in the 7-year-old Dutch twins are presented in Table 1. The mean problem scores of the untransformed data and their standard deviations are given in the Supplementary Material, Table 1. In the model as estimated in OpenMx, including thresholds and correlations, mothers scored higher than fathers as reflected by the lower thresholds for the former ($p<.001$ for all scales) (Supplementary material, Table 2). Furthermore, significant differences between boys and girls in the thresholds were observed ($p<.001$ for all scales, $p=0.03$ for anxiety problems). Overall, girls scored higher on the affective, anxiety, somatic and OCD scales and boys on the ADHD, ODD and CD scales.

Table 1. The thresholds (Th1 and Th2) for the liability distributions of maternal (M) and paternal (F) ratings on the different DSM-oriented CBCL scales in boys and girls.

	Affective		Anxiety		Somatic		ADHD		Opp-def		Conduct		Obsessive-compulsive	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Boys														
Th1	-.09	.08	-.16	-.04	.32	.51	-.20	-.11	-.35	-.20	-.23	-.14	.07	.23
Th2	.53	.76	.50	.61	.92	1.14	.56	.47	.50	.64	.28	.38	.72	.91
Girls														
Th1	-.14	-.01	-.21	-.07	.20	.43	.15	.22	-.13	.02	.15	.20	.02	.21
Th2	.51	.71	.46	.60	.79	1.05	.89	.78	.79	.91	.72	.76	.73	.92

ADHD: Attention deficit/hyperactivity disorder.

Correlations between parents and between twins

The cross-rater correlations varied between 0.60 and 0.75 for both boys and girls within MZ and DZ twins (Table 2). The correlations were fairly similar for all scales. The parental agreement did neither depend on the zygosity of the twins ($p > 0.05$ for all scales), nor on sex except for CD where agreement was higher in boys ($p < .001$ for CD, $p > .01$ for the other scales) (Supplementary material, Table 2). Overall, parental agreement is similar in boys and girls and in MZ and DZ twins.

Furthermore, Table 2 shows the polychoric twin correlations for the maternal and paternal ratings. The MZ correlations were always higher than the DZ correlations, indicating that additive genetic factors play a role. With the exception of ADHD, the DZ twin correlations were higher than half of the MZ twin correlations which suggests influences from C. The MZ correlations for ADHD were more than twice as large as the DZ twin correlations, pointing to a role for D, besides A. The cross-twin-cross-rater correlations were higher for MZ than for DZ twins, implying that the common part of the variance is also influenced by genetic factors. There were no significant differences ($p > .01$ for all scales) between the correlations of the same-sex male and female twin pairs (quantitative sex differences), or between the DZ same-sex and DOS twins for any of the scales (qualitative sex differences) (Supplementary material, Table 2).

Genetic and environmental influences on psychopathology

Rater-specific genetic influences were significant for all DSM-oriented scales ($p < .001$) (Supplementary material, Table 2). This indicates that in addition to a common phenotype assessed by mother and father, the unique part of each parent's ratings reflects true behavior of the child.

Table 2. Polychoric cross-rater correlations for boys and girls within MZ and DZ twins, polychoric twin correlations of the maternal (M) and paternal (F) ratings, and cross-twin-cross-rater correlations for the DSM-oriented CBCL scales.

	Affective		Anxiety		Somatic		ADHD		Oppositional defiant		Conduct		Obsessive-compulsive	
Cross-rater	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
MZ	0.66	0.67	0.66	0.64	0.68	0.66	0.75	0.72	0.74	0.69	0.67	0.61	0.62	0.62
DZ	0.66	0.64	0.64	0.65	0.68	0.67	0.74	0.73	0.70	0.67	0.68	0.63	0.64	0.60
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
MZm	0.80	0.82	0.74	0.77	0.71	0.73	0.82	0.79	0.84	0.88	0.88	0.91	0.68	0.74
DZm	0.47	0.49	0.39	0.42	0.44	0.38	0.26	0.26	0.55	0.55	0.67	0.66	0.40	0.37
MZf	0.80	0.80	0.75	0.80	0.74	0.74	0.80	0.81	0.82	0.84	0.87	0.88	0.67	0.70
DZf	0.48	0.49	0.40	0.48	0.48	0.40	0.23	0.25	0.54	0.57	0.68	0.70	0.32	0.33
DOS	0.50	0.50	0.46	0.49	0.45	0.44	0.27	0.34	0.55	0.54	0.63	0.66	0.40	0.39
Cross-twin cross-rater														
MZm	0.54		0.49		0.47		0.62		0.65		0.60		0.44	
DZm	0.30		0.23		0.22		0.14		0.35		0.43		0.19	
MZf	0.53		0.49		0.46		0.59		0.58		0.54		0.40	
DZf	0.31		0.25		0.21		0.08		0.33		0.40		0.12	
DOS	0.31		0.27		0.25		0.17		0.33		0.41		0.20	

ADHD: Attention deficit/hyperactivity disorder.

Table 3 shows the overall heritability estimate and the overall effects of shared and non-shared environment (A, C/D and E contributions to the common plus maternal or paternal rater-specific part) on the left. The individual parameter estimates and their confidence intervals of the A, C/D and E contributions to the common and rater-specific variance are displayed in the middle. The two columns on the right give the total percentage of variance explained by the common part and the standardized parameter estimates of A, C or D and E solely on the common part of the DSM-oriented CBCL-scales. This C estimate is unbiased. As an example, for affective problems, combining genetic influences on the commonly assessed part with the genetic influence on the maternal rater-specific part results in a heritability estimate of 62% using maternal ratings (43 [Acommon] + 19 [Am] in Table 3). The commonly assessed part of affective problems explains 65% (43 [A] + 9 [C] + 13 [E]) of the total variance and the contribution of C on the commonly assessed part is 14% (9 [Ccommon] / 65 [A+C+E common]) (shown under estimates on the % common in Table 3).

ADHD yielded the highest heritability with estimates of 81% and 80% for maternal and paternal ratings. For all other scales, except CD, adding the common and rater-specific parts resulted in heritability estimates between 54% and 64% (bold in Table 3). For CD, lower heritability estimates were reported, namely 44% and 46%. For all scales, higher genetic influences were found on the commonly assessed variance (ranging between 52% and 82%) than on either the maternal or paternal ratings (ranging between 44% and 80%). The larger contribution of genetic effects to the common part of the ratings is due to lower contributions of C. Based on the 95% confidence intervals, differences in rater-specific genetic influences between parents were observed for somatic problems, ODD and OCD, with significantly higher estimates for father ratings than for mother ratings. For the remaining scales, the rater-specific genetic influences were equal between fathers and mothers, resulting in equal total heritability estimates for the parents. Furthermore, significant rater-specific C, which includes rater bias, was found for all scales (ranging between 7 and 20%), except for ADHD for which the effect of D was estimated. Rater-specific C was smaller for the affective, anxiety and OCD problems scale (8-13%) than for the somatic, ODD, and CD problems scale (10-20%). Maternal-specific C was significantly higher for somatic, ODD and OCD problems than paternal-specific C. The estimates of the proportion of the common variance explained by C was significant for affective (14%), ODD (13%) and CD problems (37%) (Table 3). Recall that this estimation of C is free of rater bias.

Table 3. The estimates of the total additive genetic (A) (depicted in bold), shared (C) or non-additive genetic (D) and non-shared environmental (E) contributions to the common plus the rater-specific part for the maternal and paternal ratings are on the left side of the table. The parameter estimates [confidence intervals] of the A, C/D and E contributions to the common and rater-specific parts are in the middle. The last two columns give the total percentage of variance explained by the common part and the standardized parameter estimates of A, C or D and E on solely the common part of the DSM-oriented CBCL-scales. The reliable shared environmental effect is underlined.

		Maternal ratings	Paternal ratings	Common part	Rater-specific mother's part	Rater-specific father's part	Total % common	Estimates on the % common
Affective	A	62	62	43 [40-49]	19 [14-24]	19 [14-23]	65	66
	C	17	18	9 [4-11]	8 [4 -13]	9 [7-14]		<u>14</u>
	E	20	19	13 [11-13]	7 [5-9]	6 [4-8]		20
Anxiety	A	63	64	46 [41-51]	17 [11-22]	18 [12-23]	64	72
	C	11	14	2 [0-7]	9 [4-12]	12 [7-17]		<u>3</u>
	E	26	22	16 [15-17]	10 [8-11]	6 [4-8]		25
Somatic	A	55	64	47 [45-49]	8 [2-11]	17 [15-20]	68	69
	C	18	10	0 [0-0]	18 [18-20]	10 [7-10]		<u>0</u>
	E	28	27	21 [19-21]	7 [4-7]	6 [5-8]		31
ADHD	A	23	22	2 [0-12]	21 [19-23]	20 [19-22]	73	3
	D	58	58	58 [48-60]	0 [0-0]	0 [0-0]		79
	E	19	19	13 [13-15]	6 [5-7]	6 [4-8]		18
Oppositional defiant	A	56	61	50 [49-55]	6 [4-6]	11 [10-14]	69	72
	C	27	24	9 [6-11]	18 [17-21]	15 [13-17]		<u>13</u>
	E	17	14	10 [9-11]	7 [6-8]	4 [3-5]		15

Conduct	A	44	46	34 [29-39]	10 [6-14]	12 [7-17]	65	52
	C	44	43	24 [21-28]	20 [15-24]	19 [15-23]		37
	E	12	10	7 [6-9]	5 [4-7]	3 [2-5]		11
Obsessive-compulsive	A	54	63	41 [39-44]	13 [6-18]	22 [15-29]	62	66
	C	13	7	0 [0-0]	13 [10-17]	7 [2-13]		0
	E	33	29	21 [19-23]	12 [10-15]	8 [5-11]		34

ADHD: Attention deficit/hyperactivity disorder.

Discussion

We provided an overview of maternal and paternal symptom scores and the genetic, shared, and unshared environmental contributions to individual variation in DSM-oriented problem scales measured at age 7: affective, anxiety, somatic, attention-deficit/hyperactivity (ADHD), oppositional-defiant (ODD), conduct (CD), and obsessive-compulsive (OCD) problems. Maternal ratings exceeded paternal ratings of child psychopathology for all scales, regardless of the child's sex. Furthermore, parents agreed to a large extent (correlations between 0.60 and 0.75) on the ranking of the problems in their children. Differences in the unique rater parts were explained by significant genetic influences as well as by rater bias. Hence, parents assess unique aspects of their child's behavior, but are also somewhat biased in their assessment. Regarding the contributions of genetic and environmental effects, the following points are noteworthy: the estimates of A, C or D and E were comparable in boys and girls and largely comparable across raters, heritability estimates were generally around 60%. Estimates were comparable over scales, except for ADHD which was also influenced by D, and for CD which yielded lower heritability estimates and higher estimates for the influence of C. On the common part unbiased shared environmental influences were significant for affective problems (13%), ODD (13%) and CD (37%). This signifies that for the remaining scales, it is possible that the common environmental effects as found in our and previous studies on the rater specific parts of the parental ratings or on reports of one rater are due to rater bias.

In this study, the correlations between parental measures are quite large, this indicates that parents generally agree on the ranking of their child. However, scores on maternal ratings were, on average, higher than scores on paternal ratings for all problem scales, i.e., mothers report on average more behavioral and emotional problems of their children than fathers did. This is in agreement with prior studies in 7-year-old children using different scales of the CBCL [7,8,11,92,93]. Since the cut-offs for subclinical or clinical scores as defined in the manual are the same for maternal and paternal ratings, children rated by their mother will more often pass the threshold than children rated by their father due to this difference between raters. This is especially important in situations where these scores are used to screen children for psychiatric symptoms, for example, to decide which children may benefit from an intervention, either prevention or treatment or to decide which children are eligible for inclusion in research studies. Consequently, it could be considered to apply different cut-offs for (sub)clinical scores for reports from mothers and fathers. Furthermore, our findings confirm that relying on a single parent for rating probably

results in biased estimates of the influences of C [6-11]. We report reliable influences of C, free of rater bias, for affective problems, ODD and CD in 7-year olds only. Our C estimates were smaller than reported by Spatola et al. [102] in Italian twins aged 8-11 and Chen et al. [103] in Chinese twins aged 6-18, which can be explained by the fact that we used a smaller age range and multiple informants. Neither did we find a significant effect of C for OCD on the common part like van Grootheest et al. [9], who also used the common perception shared by both parents, not confounded by rater bias, to estimate a unbiased C of 10% on OCD in 7-year-old twins. However, our study used a larger sample size and categorized the data. Derks et al. [110] showed that the use of categorized data leads to unbiased estimates of genetic and environmental effects in L-shaped distributed data.

Furthermore, we found a high contribution of C (37%) on CD, which is discrepant with the two earlier studies that estimated C on the DSM-oriented CD scale [102,116]. Besides rater bias, there are two other biases that can confound C; namely imitation among twins and assortative mating. When twins imitate one another more than other siblings do, this can result in higher estimates of C, as this behavior increases the correlations of both monozygotic and dizygotic twins, but affects the dizygotic variances to a greater extent [117,118]. This can be detected by analyzing whether there are differences in the MZ and DZ thresholds [117]. This was not the case in our sample for CD ($p=0.78$). Assortative mating, the tendency for people to mate with those who are more similar to themselves, can lead to an increase in genetic similarity in dyzygotic twins, but not in monozygotic twins (as they already share 100% of their genes), which can also confound C. Spousal resemblance has been reported for scores on the DSM-oriented scales in a population-based sample, but not to a greater extent for antisocial problems than for other psychopathologies [119] and therefore cannot explain the high contribution of C solely on CD. Future research on the role of C on CD in young children is therefore recommended. Genetically informative designs, such as children-of-twins or adoption studies are most suitable since these designs offer possibilities to account for genotype-environment correlations [120,121].

This study has several strengths and weaknesses. The distribution of the different CBCL DSM-oriented scales were highly skewed, and we therefore analyzed the data using a threshold model, resulting in lower statistical power compared to an analysis of continuous data [110]. However, the parameter estimates in a threshold model are more accurate than in an analysis of continuous data [122]. While scores on the CBCL DSM-oriented scales are associated with the presence or absence of

DSM diagnoses [99], they are not the same. Therefore, the heritability estimates apply only to the questionnaire scales. The major strength of this study is that we have fully explored informant effects and the influence of genetic and environmental factors on the rarely studied DSM-oriented scales of the CBCL in a large 7-year-old twin sample.

To conclude, this study shows that, besides the substantial genetic influence on the common and rater-specific parts for all scales, there appears to be a reliable effect of C only for affective, ODD and CD problems and not for anxiety, somatic and OCD problems. Additionally, fathers and mothers assess their child's psychopathology differently and this should be evaluated when using parental reports.

Supplement to chapter 2

Table 1. Mean and standard deviations of the maternal (M) and paternal (F) ratings on the different DSM-oriented CBCL scales in boys and girls.

	Affective		Anxiety		Somatic		ADHD		Oppositional defiant		Conduct		Obsessive-compulsive	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Boys														
Means	1.20	0.93	1.23	1.01	0.71	0.51	2.50	2.21	2.57	2.25	1.76	1.49	0.98	0.76
SD	1.67	1.42	1.58	1.36	1.22	0.99	2.31	2.11	2.06	1.95	2.38	2.09	1.51	1.27
Girls														
Means	1.25	0.97	1.28	1.04	0.84	0.58	1.82	1.63	2.08	1.84	0.99	0.89	0.99	0.74
SD	1.69	1.43	1.56	1.34	1.31	1.04	2.01	1.86	1.86	1.76	1.62	1.50	1.48	1.23

ADHD: Attention deficit/hyperactivity disorder.

Table 2. Test statistics of the bivariate model fitting analyzing the rater and gender effects, the psychometric model and the rater bias model. The saturated model included all correlations reported in Table 2. The more restricted models were compared to this model. In model 6 the correlations between monozygotic males (MZm) and females (MZf) and the dizygotic males (DZm) and females (DZf) were constrained to be equal (quantitative sex differences), and in model 7 it was tested whether the dizygotic same-sex (DZ) and opposite-sex (DOS) correlations could be constrained to equal (qualitative sex differences).

			-2LL	df	Compared to	X^2	P-value
Affective	1	Saturated	75488.05	40959	-	-	
	2	Equal thresholds father mother	75839.84	40963	1	351.80 (4)	<.001
	3	Equal thresholds boys and girls	75511.67	40963	1	23.61 (4)	<.001
	4	Parental agreement across zyg	75489.64	40961	1	1.60 (2)	0.45
	5	Parental agreement across sex	75489.77	40962	4	0.12 (1)	0.73
	6	MZm=Mzf & DZm = DZf	75493.62	40968	5	3.85 (6)	0.70
	7	DZ=DOS	75494.64	40971	6	1.02 (3)	0.80
	89	Psychometric model	75494.64	40971	-	-	-
		Am and Af constrained to 0	75628.6	40973	8	133.97 (2)	<.001
Anxiety	1	Saturated	77968.84	41049	-	-	-
	2	Equal thresholds father mother	78159.90	41053	1	191 (4)	<.001
	3	Equal thresholds boys and girls	77979.24	41053	1	10.41 (4)	0.03
	4	Parental agreement across zyg	77969.82	41051	1	0.98 (2)	0.61
	5	Parental agreement across sex	77969.90	41052	4	0.08 (1)	0.78
	6	MZm=Mzf & DZm = DZf	77974.40	41058	5	4.50 (6)	0.61
	7	DZ=DOS	77982.29	41061	6	7.90 (3)	0.05
	89	Psychometric model	77982.29	41061	-	-	-
		Am and Af constrained to 0	78091.7	41063	8	109.41 (2)	<.001

Somatic	1	Saturated	65198.48	40387	-	-	
	2	Equal thresholds father mother	65645.15	40391	1	446.67 (4)	<.001
	3	Equal thresholds boys and girls	65260.85	40391	1	62.37 (4)	<.001
	4	Parental agreement across zyg	65198.61	40389	1	0.13 (2)	0.94
	5	Parental agreement across sex	65199.47	40390	4	0.87 (1)	0.35
	6	MZm=Mzf & DZm = DZf	65206.23	40396	5	6.67 (6)	0.34
	7	DZ=DOS	65210.61	40399	6	4.38 (3)	0.22
	89	Psychometric model	65211.35	40399	-	-	-
		Am and Af constrained to 0	65266.22	40401	8	54.87 (2)	<.001
ADHD	1	Saturated	73282.32	41031	-	-	-
	2	Equal thresholds father mother	73521.55	41035	1	239.23 (4)	<.001
	3	Equal thresholds boys and girls	73812.43	41035	1	530.11 (4)	<.001
	4	Parental agreement across zyg	73282.66	41033	1	0.34 (2)	0.84
	5	Parental agreement across sex	73284.21	41034	4	1.54 (1)	0.21
	6	MZm=Mzf & DZm = DZf	73294.54	41040	5	10.33 (6)	0.11
	7	DZ=DOS	73300.78	41043	6	6.24 (3)	0.10
	89	Psychometric model	73336.9	41043	-	-	-
		Am and Af constrained to 0	73470.2	41045	8	133.30 (2)	<.001
Oppositional defiant	1	Saturated	74038.30	41027	-	-	-
	2	Equal thresholds father mother	74281.41	41031	1	243.11 (4)	<.001
	3	Equal thresholds boys and girls	74394.69	41031	1	356.39 (4)	<.001
	4	Parental agreement across zyg	74044.16	41029	1	5.86 (2)	0.05
	5	Parental agreement across sex	74051.05	41030	4	6.89 (1)	0.01
	6	MZm=Mzf & DZm = DZf	74060.66	41036	5	9.61 (6)	0.14
	7	DZ=DOS	74061.13	41039	6	0.48 (3)	0.92
	89	Psychometric model	74061.13	41039	-	-	-
		Am and Af constrained to 0	74104.59	41041	8	43.46 (2)	<.001

Conduct	1	Saturated	70398.71	40957	-	-	-
	2	Equal thresholds father mother	70463.16	40961	1	64.44 (4)	<.001
	3	Equal thresholds boys and girls	71249.75	40961	1	851.03 (4)	<.001
	4	Parental agreement across zyg	70399.92	40959	1	1.20 (2)	0.55
	5	Parental agreement across sex	70413.14	40960	4	13.23 (1)	<.001
	6	MZm=Mzf & DZm = DZf	70423.13	40966	5	9.98 (6)	0.13
	7	DZ=DOS	70433.41	40969	6	10.28 (3)	0.02
	89	Psychometric model	70433.62	40969	-	-	-
		Am and Af constrained to 0	70536.03	40971	8	102.42 (2)	<.001
Obsessive-compulsive	1	Saturated	73790.27	40660	-	-	-
	2	Equal thresholds father mother	74115.01	40664	1	324.74 (4)	<.001
	3	Equal thresholds boys and girls	73807.62	40664	1	17.34 (4)	<.001
	4	Parental agreement across zyg	73791.37	40662	1	1.11 (2)	0.57
	5	Parental agreement across sex	73794.66	40663	4	3.28 (1)	0.07
	6	MZm=Mzf & DZm = DZf	73802.06	40669	5	7.41 (6)	0.29
	7	DZ=DOS	73805.56	40672	6	3.50 (3)	0.32
	89	Psychometric model	73811.38	40672	-	-	-
		Am and Af constrained to 0	73893.64	40674	8	82.26 (2)	<.001

ADHD: Attention deficit/hyperactivity disorder.

DIFFERENCES IN MALE AND FEMALE ASSESSMENTS OF CHILDHOOD PSYCHOPATHOLOGY IN PARENTAL AND TEACHER RATINGS OF 5, 7, 10 AND 12 YEAR-OLD BOYS AND GIRLS

Chapter 3

Abstract

Both parental and teacher ratings can be used to assess childhood psychopathology. Previous studies have suggested that mothers and fathers systematically differ in their assessments. We aim to extend this knowledge by exploring informant discrepancies (i.e., mean differences) in problem scores not only between paternal and maternal ratings but also between male and female teacher ratings, while taking gender of the child, age of the child and behavioral domain into account. The Devereux Child Behavior scales were analyzed for 16,568 five year-old boys and girls and the DSM-oriented scales of the Child Behavior Checklist and of the Teacher Report Form for 14,573 seven year-old, 12,299 ten year-old and 10,104 twelve year-old boys and girls. The influence of gender of the informant was analyzed by multivariate ANOVA's per age group. Overall, significant differences in scores of childhood psychopathology were observed between mothers and fathers. For 5 year-olds, paternal ratings exceeded the maternal ratings, while for 7, 10 and 12 year-olds maternal ratings exceeded the paternal ratings. In contrast, female and male teacher ratings only differed in 12 year-old boys with female teachers reporting more problems. Researchers and clinicians should be aware that the systematic interparental informant discrepancies in the assessment of childhood psychopathology are present at all ages of the child, for boys and girls and across all behavioral domains. These discrepancies cannot be ascribed to gender, since they were not seen in female and male teacher ratings. Further research should investigate which factors may explain the differences in parental ratings.

Based on: Wesseldijk LW, Bartels M, de Zeeuw EL, van Beijsterveldt CEM, Boomsma DI, Middeldorp CM. Differences in male and female assessments of childhood psychopathology in parental and teacher ratings of 5, 7, 10 and 12 year-old boys and girls. Submitted.

Introduction

When assessing emotional and behavioral problems in children, different informants, e.g., mothers, fathers, teachers, can provide information. To interpret the information from these raters, either for clinical or for research purposes, it is important to know whether informants differ in the assessment of childhood psychopathology and into factors that can cause informants to systematically differ in their assessment. One of these factors could be gender of the informant. This paper reports on differences between mothers and fathers and between male and female teachers in the assessments of childhood psychopathology while taking into account the age and gender of the child.

A meta-analysis of interparental agreement on emotional and behavioral problems in children by Duhig et al. [95] was the first to describe informant discrepancies, i.e. mean differences between informants. In their meta-analysis of 25 studies (total N=60) no significant discrepancies between mother and father ratings were observed in any of the behavioral domains, although mothers tended to report more problems than fathers. Later studies mostly observed significantly higher maternal than paternal scores for of all kinds of internalizing [9,13,19,93,94,99,123-131] and externalizing [10,19,91,92,99,123-136] problems in 6 to 18 year-old children. Only two studies did not find a significant mean difference between mother and father ratings [12,137] and two reported higher paternal than maternal scores [17,138]. The latter two studies are the only two that analyzed ratings of 5 to 6 year-old children, which suggests that age of the child might influence the informant discrepancies.

Overall, the findings suggest that mothers systematically report more emotional and behavioral problems in their children than fathers do. It is unclear whether this gender difference is also observed in teacher ratings of childhood psychopathology. A lot of research has been conducted on the influence of gender of the teacher on educational achievement in children (see for a literature review and a large study in Dutch primary school children: Coenen, Van Klaveren [139]), but to our knowledge only a few studies have examined whether male and female teachers differ in their assessment of childhood psychopathology. One study reported no difference between male and female teachers in the assessment of attention-deficit/hyperactivity (ADHD) [140]. Rietveld et al. [141] reported female teachers' ratings to exceed male teacher ratings for internalizing problems in 10 and 12 year-olds, but not for externalizing problems and not for 7 year-olds. Three other studies reported no consistent differences between male and female teachers, but if

differences were found female teacher ratings exceeded male teacher ratings [142,143]. All in all, studies on differences between male and female teachers in the assessment of childhood psychopathology are limited and the available findings are contradictory, possibly due to the small sample sizes. Moreover, knowledge is lacking on factors that may influence gender differences in ratings, either parental or teacher, such as age of the child, gender of the child and the behavioral domain assessed.

The purpose of this study is to provide an overview of the discrepancies between maternal and paternal ratings of a broad range of childhood psychopathology as measured by the Devereux Child Behavior (DCB) instrument in 5 year-old boys and girls and by the Child Behavior Checklist (CBCL) in 7, 10 and 12 year-old boys and girls and between female and male teacher ratings of childhood psychopathology as measured by the Teacher Report Form (TRF) across 7, 10 and 12 year-old children.

Methods

Participants

Since 1987, parents can register their twins shortly after birth with the Netherlands Twin Register (NTR). Parents of twins then receive a survey including questions on their twin's problem behavior when the twins are 5, 7, 10 and 12 year-old [82]. The surveys about 5 year-old twins are sent to mothers since 1994 and include a two page section for fathers. These surveys are available for participating twins with birth year 1986 to 2008. The surveys about 7 year-old twins are sent to both parents since 1995, and available for birth year 1986 to 2006. No data were collected for birth year 2000, and only partly for birth years 2000 and 2002, due to a shortage of staff and a transition to a new administration database. Surveys on 9/10 year-old twins are collected since 1997 for birth year 1986 to 2004, except for twins from birth year 1998 and partly for year 1999. Until 2008, the survey 9/10 was sent to both parents around the 10^{th} birthday of the twins, from 2009 onwards the survey is sent only to the mother of the twins around their 9^{th} birthday, including a section for father reports. Surveys for the 12 year-old twins are collected since 1999 and are available for birth years 1986-2001. Until 2007 this survey was sent to both parents, but from 2008 onwards the survey is sent only to mothers, including a section for father reports. Since 1999, if parents of twins gave their consent, teacher(s) of twins aged 7, 10 and 12 are approached to complete a survey including similar questions

on problem behavior [82]. Teacher reports for 7 year-old twins are available for birth years 1992-2008, for 9/10 year-old twins for birth years 1989-2006, and for 12 year-old twins for 1986-2003. From 2007 onwards, teachers of the registered 7, 10 and 12 year-old twins are also approached to report on siblings of twins. In addition, teacher data were collected in a two small sub-groups of 5 year-olds; one group with twins born in 1990-1991 [144] and the second group with twins born in 2002-2003.

Ratings on emotional and behavioral problems by at least one informant were available for 33,837 five year-old children, 29,890 seven year-old children, 24,969 nine to ten year-old children and 20,214 twelve year-old children. The aim of the current study was to compare problem behavior scores between female and male informants, i.e. mother vs. father rated and female vs. male teacher rated. Since scores of related children are not independent from each other, testing differences in scores in a sample containing twins and siblings can result in biased test-statistics (Rebollo et al., 2006). Therefore, per age group, we selected children that were unrelated to each other. We started with the group of children that were rated by a male teacher, since this is the smallest group and randomly selected one child per family. Next, data from these children and the children related to the selected child were removed in the remaining groups (i.e. female teacher, mother and father). We repeated this procedure for children with reports available from a female teacher and from parents only. In these groups, we randomly selected one child from each family. Our final sample sizes of children rated by mother, father, female teacher and male teacher per age group and by gender of the child are shown in Table 1. We excluded the teacher ratings for the 5 year-old children (n=530) from the analyses, due to the limited availability of ratings from male teachers (n=30). Note, there are fewer ratings from male teachers available for younger than for older aged children, because the lower grades in Dutch schools are more often taught by female teachers [145,146].

Measures

In 5 year-old children, problem behavior was assessed by a selection of 42 items of the Devereux Child Behavior (DCB), a rating scale for parents of young children that might be related to cognitive development. Items are scored on a 5-point scale (never to very frequently) [147,148]. We analyzed the problem scales: aggressive behavior, anxiety problems, attention problems and emotional liability [17]. In 7, 10 and 12 year-old children, behavior was assessed with instruments belonging to the Achenbach System of Empirically Based Assessment (ASEBA) including the Child Behavior Check List (CBCL) and the Teacher Report Form (TRF) [99]. The CBCL is a rating scale for parents of children from 6 to 18 years old, containing 118 questions

that are rated on a 3-point scale (not true, somewhat true, very true). The TRF is a similar instrument for teachers and contains 112 questions on the child's functioning in school as seen by the teacher. We analyzed the DSM-oriented affective (N items CBCL: 12, TRF:10), anxiety (N items CBCL: 6, TRF:6), somatic (N items CBCL: 7, TRF:7), attention-deficit/hyperactivity (N items CBCL: 5, TRF:13), oppositional-defiant (N items CBCL: 5, TRF:5) and conduct problem (N items CBCL: 16, TRF:103) scales [99]. The problem scales of the CBCL and TRF reflect similar emotional and behavioral problems in children, but are different in item quantity and content and scores can therefore not be directly compared.

Statistical analyses

The Statistical Package for the Social Sciences (SPSS, version 23) was used to calculate means and standard deviations of the different problem scales in 5, 7, 10 and 12 year-old boys and girls per informant (mother, father, female teacher and male teacher). The parental and teacher ratings at the different ages were separately analyzed for boys and girls by multivariate ANOVAs to examine the influence of the informant's gender on the childhood's problem scales while controlling for associations between the problem scales. Additionally, we tested whether the gender of the child interacted with gender of the informant. To correct for multiple testing a two-tailed p-value of <0.01 was used as a threshold for statistical significance. Partial eta squared, provided by SPSS by default, ($\mathbf{SSeffect/(SSeffect + SSerror))}$ is provided as an effect size for the multivariate ANOVAs.

Results

Figures 1 and 2 display the means of the female and male parental and teacher ratings. All means and standard deviations are given in the Supplementary Material, Table 1 and 2.

5 year-old children

Tested by the MANOVA, the influence of the informant's gender on parental ratings of psychopathology was significant in boys and girls with paternal ratings higher than maternal ratings (Table 1). Interaction between gender of the informant and gender of the child was not significant. The effect sizes ranged from 0.001 (aggressive and attention problems in boys) to 0.003 (anxiety problems in girls). Figure 1 shows that paternal and maternal ratings did not differ for anxiety problems and emotional liability assessed in boys.

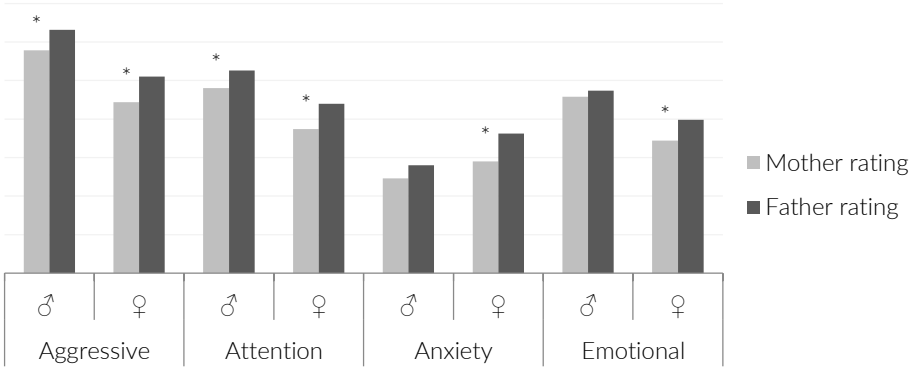


Figure 1. Means of the mother and father ratings of the Devereux Child Behavior problem scales across 5 year-old boys (♂) and girls (♀). * = Significant difference ($p < 0.01$) between mother and father ratings.

7 year-old children

The influence of the informant's gender on rating psychopathology in 7 year-old children was significant for parents for boys and girls, but not for teachers (Table 1). Neither for parents nor for teachers was the interaction between gender of the informant and gender of the child significant. The effect sizes ranged from 0.004 (anxiety and conduct problems in boys and ADHD and oppositional-defiant problems in girls) to 0.014 (somatic problems in both boys and girls) for parents. Maternal ratings were significantly higher than paternal ratings in all problem scales, except for conduct problems rated in girls (Figure 2a). The female teacher ratings exceeded the male teacher ratings only for attention deficit/hyperactivity disorder (ADHD) in boys (Figure 2a) with an effect size of 0.003.

Figure 2a, 2b and 2c. Means of the female and male parental (mother and father) ratings of the problem scales of the Child Behavior Checklist and the female and male teacher ratings of the problem scales of the for 7 year-old (a), 10 year-old (b) and 12 year-old (c) boys (♂) and girls (♀).* = Significant difference ($p < 0.01$) between the raters. ADHD: Attention deficit/hyperactivity disorder. Opp-defiant: Oppositional defiant disorder. Note, the parental and teacher ratings cannot be directly compared.

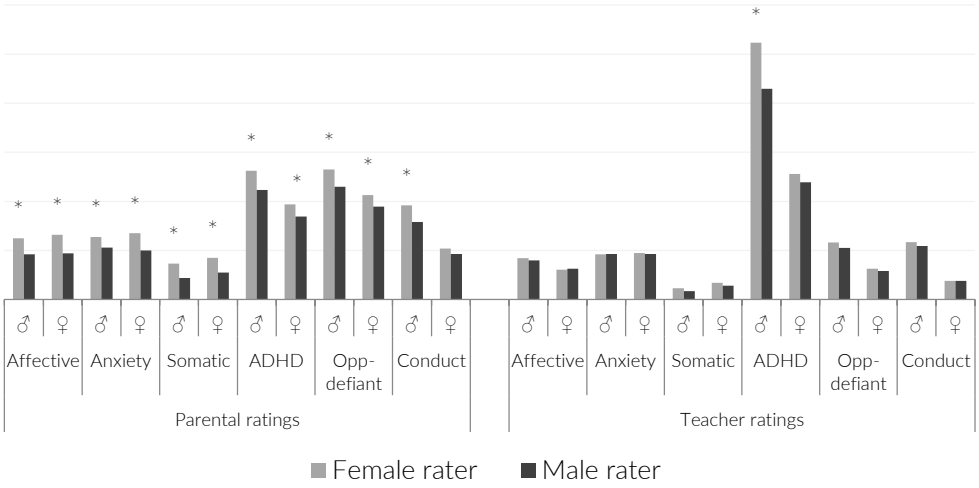


Figure 2a

10 year-old children

The influence of the informant's gender on rating psychopathology in 10 year-old children was significant for parents for boys and girls, but not for teachers (Table 1). Interaction between gender of the informant and gender of the child was not significant for parents or teachers. The effect sizes ranged from 0.003 (somatic problems in boys) to 0.011 (affective problems in boys) among parental ratings. Figure 2b shows that mothers rated their children significantly higher than fathers on all problem scales, except on the ADHD scale in girls. Female teacher ratings only exceeded male teacher ratings for somatic problems in girls (effect size 0.002) and affective problems and ADHD in boys (effect size 0.003) (Figure 2b).

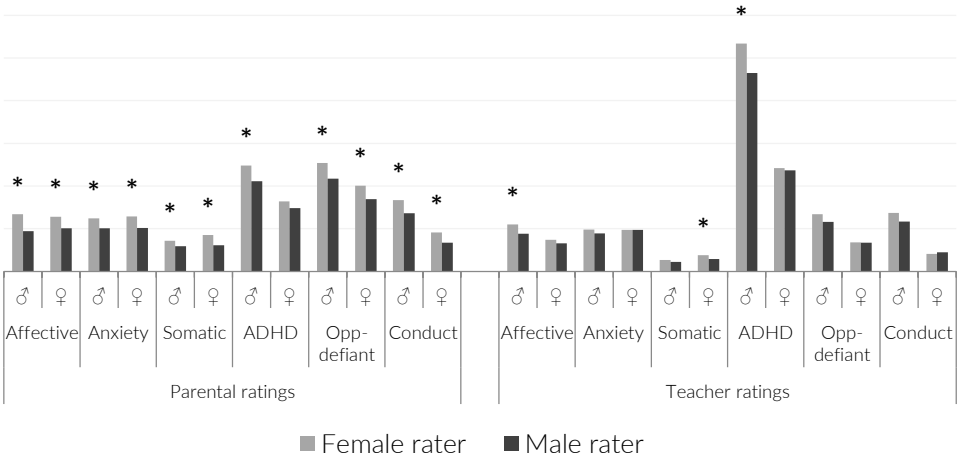


Figure 2b

12 year-old children

The influence of the informant's gender on rating psychopathology in 12 year-old children was significant for parents for boys and girls, and for teachers for boys, but not for girls (Table 1). However, the interaction between gender of the informant and child was not significant for teachers or parents. The effect sizes ranged from 0.003 (anxiety and conduct problems in boys) to 0.01 (somatic problems in boys) for parents and between 0.003 (somatic problems in both boys and girls) and 0.005 (affective problems in boys) for teachers. Figure 2c shows that, with the exception of ADHD for boys and girls, all maternal ratings were significantly higher than paternal ratings. The female teacher ratings exceeded the male teacher ratings for affective problems in boys, anxiety problems in girls and somatic problems in both boys and girls (Figure 2c).

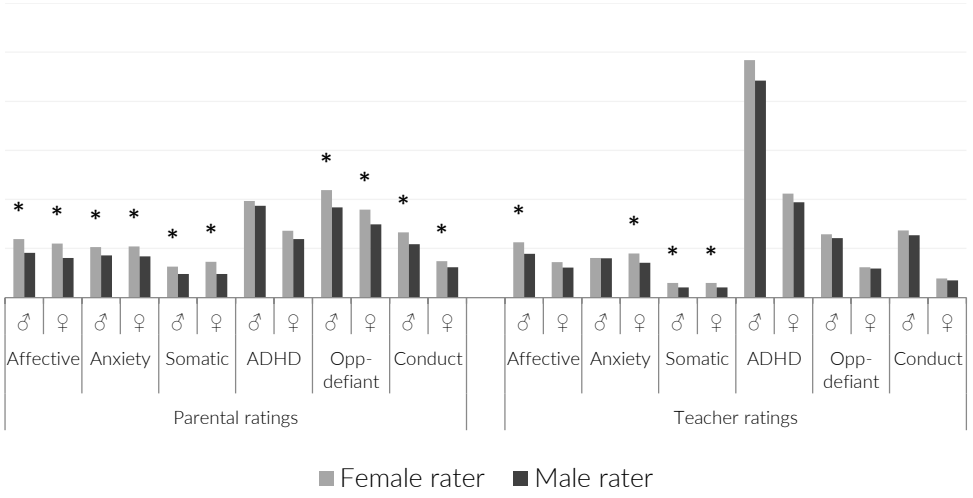


Figure 2c

Table 1. Sample sizes of the mother, father, female and male teacher ratings and test statistics for the multivariate analyses of childhood psychopathology ratings predicted by gender of the informant for parents and teachers for boys and girls separately.

	N parental sample		N teacher sample		F (df)		Partial η2	
	Mother	Father	Female	Male	Parents	Teachers	Parents	Teachers
Boys								
5y	4,589	3,610	252	13	4.06 (4)*		.002	
7y	2,585	1,442	2,863	378	12.78 (6)**	2.23(6)	.019	.004
10y	1,907	1,015	2,178	994	6.41(6)**	2.55 (6)	.013	.005
12y	1,748	860	1,263	1,141	5.23 (6)**	3.70 (6)*	.012	.009
Girls								
5y	4,713	3,656	248	17	9.71(4)**		.005	
7y	2,540	1,468	2,905	392	15.44(6)**	.81 (6)	.023	.002
10y	1,945	1,051	2,190	1,019	7.10 (6)**	2.04 (6)	.014	.004
12y	1,743	941	1,282	1,126	5.98 (6)**	2.10 (6)	.014	.005

* p< .01, **p<0.001.

Discussion

This study provided an overview of the informant discrepancies between maternal and paternal ratings and between female and male teacher ratings of a broad range of childhood psychopathology in 5, 7, 10 and 12 year-old boys and girls. Overall, significant differences in scores of childhood psychopathology were observed between mothers and fathers in 5, 7, 10 and 12 year-old boys and girls, but only between female and male teachers in 12 year-old boys. In 5-year old children, paternal scores for aggressive, attention, anxiety and emotional problems in their child were higher than maternal scores. At all other ages, maternal scores exceeded paternal scores for affective, anxiety, somatic, attention-deficit/hyperactivity (ADHD), oppositional-defiant (ODD), conduct (CD) problems in their child. As gender of the informant only consistently influenced parental ratings and not teacher ratings, it can be concluded that gender of the informant cannot fully explain that mothers systematically rate their 7, 10 and 12 year-old child's behavioral problems as more severe than fathers. It is of note that the differences between mothers and fathers are similar for boys and girls and for all behavioral domains.

The systematic mean differences between maternal and paternal ratings imply that it should be taken into account whether the mother or the father provided the information on psychiatric symptoms since their ratings are not interchangeable. Therefore, research studies should collect information on which parent provides informant on the child's psychiatric symptoms. Even though the parental mean discrepancies are small, there is a higher chance for 7, 10 or 12 year-old children rated by their mother to score above the subclinical cut-off score than for children rated by their father. For example, in our sample of 4,027 7 year-old boys, 21% more boys scored in the subclinical range for anxiety when considering maternal ratings (7.6% versus 9.2%). The same holds for externalizing problems such as, for example, oppositional-defiant problems, where 47.7% more boys scores in the subclinical range for oppositional-defiant problems when considering maternal ratings (9.6% versus 6.5%). In line with earlier studies [17,138], the opposite holds for 5 year-old boys and girls, with father ratings leading to more subclinical scores than mother ratings. However, the parental discrepancy is smaller than for 7, 10 and 12 year-old boys and girls, as shown by the effect sizes. An explanation for this contrast is the difference in measurement instruments. However, similar results were reported for the Strength and Difficulties Questionnaire (SDQ) in 4 to 5 year-old children [138,149]. As for teacher ratings, gender of the informant is only significant in 12 year-old boys, but differences between female and male teacher ratings are very

small, almost negligible. All in all, both researchers and clinicians should be most aware of the systematic interparental informant discrepancies in the assessment of childhood psychopathology, as well as of the effect of the age of the child on the discrepancies.

Other factors that we examined are gender of the child and the behavioral domain assessed. Though the effect sizes of the mean differences between the maternal and paternal ratings are small, for the internalizing psychiatric symptom scales (i.e. affective, anxiety and somatic problems), the informant discrepancies are about as large and sometimes even larger than the mean differences between boys and girls on the psychiatric symptom scales, a difference which has received much attention in the literature. This is not the case for the externalizing psychiatric symptom scales (i.e. ADHD, oppositional defiant and conduct problems), where mean symptom score differences between boys and girls are larger than the maternal and paternal mean differences. However, the effect sizes for both internalizing and externalizing psychiatric symptom scales are roughly similar. It can be concluded that interparental informant discrepancies are not only systematically present at all ages of the child, in both boys and girls, but also are consistent across all behavioral domains.

De Los Reyes [150] outlined the main theories on why informant discrepancies in general exist. First, so-called informant-biases, such as mood influences or different motivations to report certain behavior, might cause mean differences between informants. Another explanation is that the informant discrepancies are due to measurement error. However, the most widely accepted explanation is that informant discrepancies reflect differences in behavior of the child across different settings. This is in line with the lack of discrepancy between female and male teachers in their assessment, as they observe the child in a similar environment. Nevertheless, none of the above hypotheses, nor gender of the informant can fully explain the systematic mean differences observed between maternal and paternal ratings of childhood psychopathology. To interpret group differences with respect to sum scores, a necessary condition is that the measurement instrument is measurement invariant, i.e. it measures the same underlying trait across groups [151,152], i.e., across female and male informants. Studies that looked at measurement invariance for CBCL problem scales, across gender of the child [153], gender and age of the child [154], low or high birth weight [155] and gender of the child and parent across time [156], generally conclude that the scales assess the same concepts across the groups.

This study has several strengths and weaknesses. Since the DCB and the CBCL are different instrument, we cannot definitely conclude that age plays a role in informant discrepancies. Furthermore, there were fewer ratings from male teachers available for younger than for older aged children and this might have influenced the results. However, a post-hoc power analysis in G*Power [157] revealed that for the 7 year-old boy sample, which had the lowest availability of male teacher ratings (n=378), the sample had enough power (99%) to detect a mean difference between female and male teachers of a small effect size (Cohen's d = .05). The major strength of this study is that we have explored the effects of gender of the informant, gender of the child, age of the child and behavioral domain on informant discrepancies when rating childhood psychopathology, either by parents or teachers, in large samples.

To conclude, this study shows that there are systematic mean differences between maternal and paternal reports when rating childhood psychopathology in 5, 7, 10 and 12 year old boys and girls. Fathers rate the psychopathology of their 5 year-old children higher than mothers, while at all other ages mothers rate the psychiatric symptoms of their child higher than fathers. As there were no systematic mean differences between female and male teacher ratings, gender of the informant cannot fully explain the interparental informant discrepancies. Clinicians and researchers, when using ratings from different informants, should take into account that mother and father ratings of childhood psychopathology are not interchangeable.

Supplement to chapter 3

Table 1. Means and standard deviations of the female and male parental (mother and father) ratings of the problem scales of the Child Behavior Checklist and the female and male teacher ratings of the problem scales of the Teacher Report Form across 7, 10 and 12 year-old boys and girls.

	Affective		Anxiety		Somatic		ADHD		Opp-defiant		Conduct	
	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Parents												
7 year-olds												
Boys	1.25*	0.92	1.27*	1.06	0.73*	0.44	2.62*	2.23	2.65*	2.30	1.92*	1.58
	(1.71)	(1.46)	(1.61)	(1.45)	(1.27)	(0.90)	(2.39)	(2.09)	(2.10)	(1.97)	(2.50)	(2.15)
Girls	1.32*	0.94	1.35*	1.00	0.85*	0.55	1.94*	1.69	2.13*	1.89	1.04	0.93
	(1.75)	(1.40)	(1.64)	(1.30)	(1.33)	(0.98)	(2.09)	(1.92)	(1.89)	(1.78)	(1.68)	(1.57)
10 year -olds												
Boys	1.34*	0.94	1.24*	1.01	0.72*	0.59	2.48*	2.11	2.54*	2.17	1.67*	1.36
	(1.95)	(1.57)	(1.64)	(1.43)	(1.24)	(1.14)	(2.34)	(2.22)	(2.15)	(2.00)	(2.42)	(2.01)
Girls	1.28*	1.01	1.29*	1.02	0.85*	0.61	1.64	1.48	2.01*	1.69	0.91*	0.67
	(1.81)	(1.60)	(1.63)	(1.41)	(1.34)	(1.08)	(1.88)	(1.81)	(1.86)	(1.76)	(1.57)	(1.26)
12 year-olds												
Boys	1.19*	0.91	1.03*	0.86	0.63*	0.48	1.97	1.87	2.19*	1.84	1.33*	1.09
	(1.87)	(1.67)	(1.56)	(1.41)	(1.16)	(0.98)	(2.12)	(2.01)	(2.06)	(1.92)	(2.21)	(1.83)
Girls	1.10*	0.81	1.04*	0.84	0.73*	0.48	1.36	1.19	1.79*	1.49	0.74	0.62
	(1.76)	(1.40)	(1.45)	(1.29)	(1.25)	(0.91)	(1.79)	(1.58)	(1.80)	(1.66)	(1.52)	(1.21)

Teachers												
7 year-olds												
Boys	0.84	0.80	0.92	0.93	0.23	0.17	5.23*	4.29	1.16	1.05	1.17	1.09
	(1.49)	(1.40)	(1.46)	(1.34)	(0.73)	(0.63)	(5.78)	(4.96)	(1.81)	(1.70)	(2.48)	(2.40)
Girls	0.61	0.63	0.95	0.93	0.34	0.28	2.56	2.39	0.63	0.58	0.38	0.38
	(1.25)	(1.28)	(1.43)	(1.34)	(0.88)	(0.79)	(3.90)	(4.08)	(1.28)	(1.28)	(1.25)	(1.31)
10 year-olds												
Boys	1.10*	0.88	0.98	0.89	0.27	0.22	5.34*	4.65	1.34	1.16	1.37	1.17
	(1.76)	(1.45)	(1.50)	(1.43)	(0.80)	(0.81)	(5.70)	(5.46)	(1.97)	(1.73)	(2.74)	(2.38)
Girls	0.74	0.66	0.97	0.97	0.38*	0.29	2.42	2.37	0.68	0.67	0.41	0.45
	(1.43)	(1.32)	(1.54)	(1.50)	(0.98)	(0.82)	(3.84)	(3.78)	(1.37)	(1.35)	(1.30)	(1.26)
12 year-olds												
Boys	1.13*	0.89	0.81	0.80	0.30*	0.21	4.84	4.42	1.29	1.21	1.37	1.27
	(1.68)	(1.49)	(1.34)	(1.34)	(0.87)	(0.74)	(5.50)	(5.30)	(1.92)	(1.93)	(2.76)	(2.62)
Girls	0.72	0.61	0.90*	0.71	0.30*	0.21	2.12	1.94	0.62	0.59	0.39	0.35
	(1.39)	(1.20)	(1.47)	(1.23)	(0.82)	(0.74)	(3.50)	(3.30)	(1.35)	(1.22)	(1.26)	(1.04)

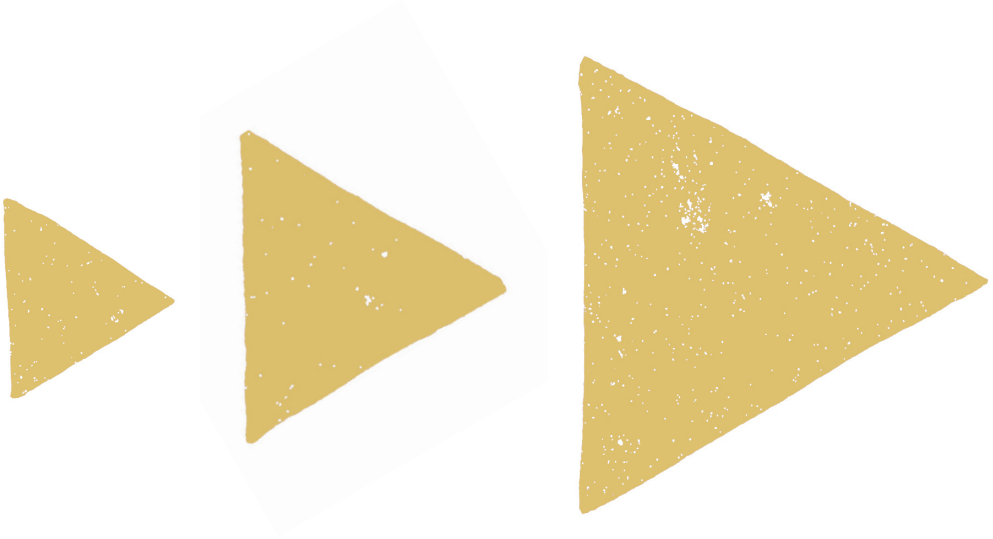
* = Significant difference ($p < 0.01$). ADHD: Attention deficit/hyperactivity disorder. Opp-defiant: Oppositional defiant disorder.

Table 2. Means and standard deviation (SD) for mother (M) and father (F) ratings of the Devereux problem scales across 5 year-old boys and girls.

	Aggressive behavior		Attention problems		Anxiety problems		Emotional lability	
	Mother	Father	Mother	Father	Mother	Father	Mother	Father
Boys	12.39*	12.66	11.90*	12.13	10.73	10.90	11.79*	11.87
	(3.87)	(3.84)	(3.62)	(3.39)	(3.35)	(3.20)	(3.61)	(3.31)
Girls	11.72*	12.05	11.37*	11.70	10.95*	11.31	11.22*	11.49
	(3.38)	(3.57)	(3.48)	(3.28)	(3.33)	(3.30)	(3.32)	(3.23)

* = Significant difference ($p < 0.01$) between the maternal and paternal ratings. ADHD: Attention deficit/hyperactivity disorder. Opp-defiant: Oppositional defiant disorder.

GENETIC AND ENVIRONMENTAL INFLUENCES ON CONDUCT AND ANTISOCIAL PERSONALITY PROBLEMS IN CHILDHOOD, ADOLESCENCE AND ADULTHOOD



Chapter 4

Abstract

Conduct problems in children and adolescents can predict antisocial personality disorder and related problems, such as crime and conviction. We sought an explanation for such predictions by performing a genetic longitudinal analysis. We estimated the effects of genetic, shared environmental, and unique environmental factors on variation in conduct problems measured at childhood and adolescence and antisocial personality problems measured at adulthood and on the covariation across ages. We also tested whether these estimates differed by sex. Longitudinal data were collected in the Netherlands Twin Register over a period of 27 years. Age appropriate and comparable measures of conduct and antisocial personality problems, assessed with the Achenbach System of Empirically Based Assessment, were available for 9,783 9-10 year-old, 6,839 13-18 year-old, and 7,909 19-65 year-old twin pairs respectively, 5,114 twins have 2 or more assessments. At all ages, men scored higher than women. There were no sex differences in the estimates of the genetic and environmental influences. During childhood, genetic and environmental factors shared by children in families explained 43% and 44% of the variance of conduct problems, with the remaining variance due to unique environment. During adolescence and adulthood, genetic and unique environmental factors equally explained the variation. Longitudinal correlations across age varied between .20 and .38 and were mainly due to stable genetic factors. We conclude that shared environment is mainly of importance during childhood, while genetic factors contribute to variation in conduct and antisocial personality problems at all ages, and also underlie its stability over age.

Based on: Wesseldijk LW, Bartels M, Vink JM, van Beijsterveldt CEM, Ligthart, L, Boomsma DI, Middeldorp CM (2017). Genetic and environmental influences on conduct and antisocial personality problems in childhood, adolescence and adulthood. European Child & Adolescent Psychiatry, 1-10.

Introduction

Conduct problems in children and adolescents and antisocial personality problems in adults involve a variety of repetitive and persistent behaviors that violate the rights of others or societal norms or rules, such as aggression to people, destruction of property, theft or violations of rules [84]. Conduct problems during childhood may be the developmental precursor for adult antisocial personality problems and are significantly associated with adverse adult outcomes related to health, crime and conviction, and financial and personal functioning [24,85-87,158]. World-wide, childhood and adolescent conduct problems and adult antisocial personality problems pose a challenge to societies and health care, with prevalence rates ranging between 1 and 4% in the general population [159-161]. It is important to get insight into risk factors for conduct and antisocial personality problems, especially into the factors influencing the stability over age. We therefore present a longitudinal twin study (N = 17,513 twin pairs) following twins from age 9 until adulthood (30 years on average).

Twin studies allow the estimation of influences of genetic, shared and unique environmental factors on individual differences in behavior and on stability over ages. Most twin studies performed cross-sectional analyses on conduct and antisocial personality problems. Meta-analyses of these studies have estimated the proportion of the variation explained by genetic factors to be between 32% and 60% for children, between 45% and 50% for adolescents and one meta-analysis provided a heritability estimate of 49% for adults [1,4,162,163]. The contribution of the shared environment, also referred to as the 'common' familial environment, has been estimated at between 10% and 20% in childhood, between 10% and 17% in adolescence and 14% in adulthood [1,4,162,163]. In twin studies, the remaining variation that is not due to genetics or the shared environment is attributed to unique environmental influences, which also includes measurement error. Thus, all meta-analyses agree upon the importance of genetic factors, and also agree upon a lower estimate for the contribution of shared environment.

Longitudinal twin studies on conduct and antisocial personality problems reported stability over ages to be mainly due to genetic factors [164], and three studies reported an additional small influence of the shared environment on the stability across ages [165-167]. However, research on antisocial personality problems in later adulthood, i.e. above 24 years old, is underrepresented. Furthermore, the sex differences in prevalences for conduct and antisocial personality problems [166,168] lead to questions whether the influence of genetic and environmental influences also are different for males and females (i.e., quantitative sex differences) and whether

there the same or different genes play a role (i.e., qualitative sex differences). Some twin studies have reported qualitative sex differences for conduct and antisocial problems [166,169], while others have not [115,165,167,170-172], just as some studies have detected quantitative sex differences [165,167,169,171,173], and others have not [163,166,170,172,174]. As the effect of sex might differ across age, we hope to address this question by analyzing large samples of twins ranging from 9 to 65 years old.

The aim of the present study was to elucidate the genetic architecture of conduct and antisocial personality problems by analyzing a large longitudinal dataset with observations of 9-10 year-old twins (childhood), 13-18 year-old twins (adolescence), and 19- 65 year-old twins (adulthood). The data, collected over a 27 year period in the Netherlands Twin Register, offer the opportunity to examine the following questions: 1) what is the heritability of conduct problems in childhood and adolescence and of antisocial personality problems in adulthood? 2) What is the longitudinal stability across age and which factors contribute to the stability? 3) Do genetic and environmental factors interact with sex? We analyzed the DSM-oriented conduct problems scales of the Child Behavior Checklist (CBCL) and the Youth Self-Report (YSR) and the antisocial personality problem scale of the Adult Self-Report (ASR) belonging to the Achenbach System of Empirically Based Assessment (ASEBA), that consist of similar sets of items across ages [99,175].

Methods

Subjects

The Netherlands Twin Register (NTR) includes a register for young twins, the YNTR [82], and for adult twins, the ANTR [81]. Since 1986, parents can register their young twins shortly after birth with the YNTR and will then receive a survey when their twins are around 1, 2, 3, 5, 7, 10 and 12 years old. Between 2005 and 2013, twins themselves were asked to complete a survey when they reached ages 14 and 16 years. At the age of 18 years, twins enrol into the ANTR. The ANTR started in 1991 by recruiting adolescent twins and their family members through city councils and subsequently added adults through volunteer registration [81]. The NTR data collection is prospective, with data collected when twins reach a particular age. Therefore, more data are available from twin pairs at younger ages in the YNTR. Due to financial constraints, there was no data collection of the survey for 10 year-olds in 2008 [82]. Until 2008, the survey for 10 year-olds was mailed to both parents of

twins around the 10th birthday of the twins. From 2009, the survey was mailed around the 9th birthday of the twins. For the current study, maternal ratings of 9-10 year-old young twins from birth cohorts 1986-2004 were included. Average age was 10 years. The sample included 60 pairs between age 8.7 - 9 years and 10 pairs who had reached age 12 years when their parents completed the survey, throughout the paper we refer to this group as 9-10 year-olds. Paternal reports were not included; an earlier study of these twins at age 7 showed that heritability estimates for conduct problems did not differ between paternal and maternal reports [130]. For the 13-18 year-old adolescent twins self-report data from birth cohorts 1986-1999 were analyzed. Self-report data from 19-65 year-old adult twins were collected in the ANTR in 1997, 2000, 2009-2012 or 2013-2014. If adolescent twins had completed multiple surveys, the survey completed by both twins closest to age 16 was selected. For adult twins, a preference was given to the survey that was completed by both twins, closest to age 40. The final sample contained 17,513 twin pairs, including 9,783 child twin pairs (9,702 complete and 81 incomplete twin pairs on average 10 years), 6,839 adolescent twin pairs (5,107 complete and 1,732 incomplete twin pairs, on average 15.77 years) and 7,909 adult twin pairs (4,752 complete and 3,157 incomplete twin pairs on average 29.39 years). Table 2 presents sample sizes per zygosity-by-sex group. There were 3,283 complete and 694 incomplete twin pairs with data in childhood and adolescence. Between adolescence and adulthood the overlap was 1,135 complete and 1,163 incomplete twin pairs. For 1,412 complete and 1,253 incomplete twin pairs, the NTR had data in childhood and adulthood. Overall, there were 985 complete and 1,913 incomplete twin pairs with data available in childhood, adolescence and adulthood.

Phenotypes

Conduct and antisocial personality problems were measured with the age appropriate versions of the questionnaires belonging to the Achenbach System of Empirically Based Assessment (ASEBA), i.e., the Child Behavior Checklist (CBCL), the Youth Self-Report (YSR) and the Adult Self-Report (ASR). In all three instruments, items are rated on a three-point scale (0 to 2; not true, somewhat true, very true). The conduct problem scales of the CBCL and YSR are based on a similar set of items, that only differ in the phrasing depending on whether the parent is asked to rate his or her child ("Gets in many fights") or whether the adolescent is asked to rate his or her own behavior ("I get in many fights") (see Supplementary Table 1 for the items included). Items of the ASR used to calculate antisocial personality problems in adults differ between versions over the years of data collection. For this study, we summed the

15 items that were available for all ASR questionnaires obtained in the NTR from 1997 until 2013 (see Supplementary Table for the items included). Petersen et al. [176] showed for externalizing problems measured by the CBCL, YSR and ASR that there is theoretical and empirical support for construct validity invariance, and therefore for examining these measurements over time.

Statistical analyses

Mean age was calculated in SPSS (version 21). Average symptoms scores and their standard deviations were calculated using OpenMx [114]. The scores for childhood and adolescent conduct and adult antisocial personality problems were highly skewed, as is common for psychiatric symptoms in population-based samples. Therefore, to obtain accurate parameter estimations, the scores were divided into three roughly equal sized categories (low, middle and high scores), and analyzed as categorical data with two thresholds [110]. In a threshold model, where the mean of the distribution is standardized at zero and the standard deviation one, it is assumed that the categorical trait has an underlying continuous distribution of liability [113] and polychoric correlations between twins reflect the correlations in liability. Polychoric twin correlations were estimated for MZm, DZm, MZf, DZf and DOS pairs for childhood, adolescence and adulthood using structural equation modeling in OpenMx [114]. With the full information maximum likelihood option, all available data were analyzed, including the data from the incomplete twin pairs. We estimated the 95% confidence interval around the correlations in OpenMx [177]. Sex differences in the prevalence of conduct and antisocial problems behavior at each age were investigated by testing whether thresholds could be constrained to be equal across sex. Next, we tested for quantitative sex effects on twin correlations by constraining the correlations of the male same-sex MZ and DZ twin pairs to be equal to the correlations of the female same-sex MZ and DZ twin pairs respectively. If these constraints are not allowed, this indicates that the contribution of genetic and environmental influences may differ in males and females. Lastly, to investigate whether different genes or different shared environmental factors operate in males and females, we tested whether the correlation for DZ same-sex and DOS twins could be constrained as a function of the DZ same-sex correlations.

Based on the outcomes of these analyses, we proceeded with the longitudinal analyses. First, the correlations between twin1 and twin2 across the three ages (i.e. cross-twin-cross-age correlations) were calculated. Next, in a genetic structural equation model, the observed phenotypic variance in each age group as well as the phenotypic covariance across age was partitioned into additive genetic

(A), common environmental (C) and non-shared environmental (E) components [178]. MZ twins share (nearly) all their genetic material [179,180], while DZ twins share, on average, 50% of their segregating genes. Therefore, a higher MZ than DZ twin correlation indicates that genetic factors play a role. When the DZ twin correlations are higher than half of the MZ twin correlation, there is resemblance among twins from the same family that is attributable to common environmental influences shared by children from the same family. Variation that is not due to genes or the common environment shared by twins is attributed to unique environment. In a similar vein, the genetic, shared environmental, and unique environmental influences to the stability of conduct and antisocial personality problems across the ages were estimated based on the cross-twin-cross-age correlations [109]. We derived the estimates for the heritability, the environmental effects, and the correlations between the genetic and environmental factors across the ages from the cross-twin-cross-age correlations after testing for the significance of A and C by the likelihood-ratio test by comparing an ACE model to an AE model for children, adolescents and adults. In the likelihood ratio test, the negative log-likelihood (-2LL) of the more constrained submodel is subtracted from the -2LL of the more general model. The difference between the two models follows a χ^2 distribution where the number of df (degrees of freedom) is equal to the difference in df between the two models. Constraints were retained when they did not significantly deteriorate the fit ($p < 0.01$ due to multiple testing), so that the most parsimonious model is selected.

Results

Descriptives

Table 1 provides the mean ages, standard deviations, and age ranges of the twins included in the childhood and adolescent conduct problems groups and in the adult antisocial personality problems group. The untransformed mean symptom scores, standard deviations, and the two thresholds for the liability distributions for the three age groups are given for boys and girls separately. As expected, at all ages, males scored higher, which is reflected by significant differences in the thresholds ($p<.001$, model 2 in Table 3).

Table 1. Mean age, standard deviations (SD) and age range for children, adolescents and adults. Childhood conduct problems were measured by the CBCL, adolescent conduct problems were measured by the YSR and adult antisocial personality problems were measured by the ASR. The lower part shows the untransformed mean symptom scores, the standard deviations (SD) and thresholds (Th1 and Th2) based on an underlying normal distribution of liability estimated for the three age groups and separately for males and females.

	Conduct problems								Antisocial personality problems			
	Children, CBCL				Adolescents, YSR				Adults, ASR			
Mean age (SD)	10.00 (0.44)				15.77 (1.31)				29.39 (11.12)			
Min-Max	8.71 - 12.98				13.00 - 18.00				18.00 - 64.98			
	M	SD	Th1	Th2	M	SD	Th1	Th2	M	SD	Th1	Th2
Males	1.57	2.39	-.10	.42	3.10	2.58	-.57	.38	1.84	2.24	-.45	.62
Females	0.85	1.53	.28	.82	2.38	2.23	-.22	.73	1.51	1.90	-.33	.80

CBCL: Child Behavior Checklist, YSR: Youth Self Report, ASR: Adult Self Report.

Twin correlations

Polychoric twin correlations and their 95% confidence intervals are shown in Table 2. For all three age groups, MZ correlations were higher than DZ correlations, suggesting that additive genetic factors play a role. The DZ correlations were larger than half the MZ correlations during childhood, suggesting shared environmental effects. During adolescence and adulthood, the DZ correlations were larger than half of the MZ correlations for males, but not for females. However, further testing showed that there were no significant differences ($p > .01$) between the correlations for same-sex male and female twin pairs (i.e. there were no quantitative sex differences), or between the DZ same-sex and DOS twins (i.e. there were no qualitative sex differences) as can be seen from Model 3 and 4 in Table 3. MZ and DZ correlations in the most parsimonious model are depicted in the middle of Table 2. The phenotypic correlation between childhood and adolescent conduct problems was .20, between adolescent conduct problems and adult antisocial personality problems .38 and between childhood conduct problems and adult antisocial personality problems .22. Table 2 also gives the cross-twin-cross-age correlations for the MZ twins (below the diagonal) and the DZ twins (above the diagonal). These cross-twin-cross-age correlations were higher for MZ twins than for DZ twins, indicating that genetic factors influence the stability of conduct and antisocial personality problems across the ages.

Table 2. Samples sizes and the polychoric twin correlations per age-by-zygosity-by-sex group, as well as correlation estimates constrained to be the same across sex (for MZ and DZ twin pairs). The overlapping sample sizes across age and the cross-twin-cross-age correlations are depicted at the bottom of the table, where the MZ correlations are below the diagonal and the DZ correlations above the diagonal.

	Conduct problems				Antisocial personality problems	
	Children		Adolescents		Adults	
	N	Twin correlation	N	Twin correlation	N	Twin correlation
MZM	1656	0.90 (0.87-0.91)	1012	0.47 (0.40-0.54)	1057	0.44 (0.35-0.51)
DZM	1587	0.68 (0.64-0.72)	928	0.32 (0.22-0.41)	763	0.34 (0.22-0.45)
MZF	1880	0.85 (0.83-0.88)	1429	0.52 (0.45-0.57)	2388	0.41 (0.35-0.46)
DZF	1466	0.66 (0.61-0.71)	1201	0.27 (0.18-0.35)	1481	0.22 (0.14-0.29)
DOS	3194	0.65 (0.61-0.68)	2269	0.21 (0.14-0.27)	2220	0.24 (0.14-0.34)
MZ		0.88 (0.86-0.89)		0.50 (0.45-0.54)		0.42 (0.37-0.46)
DZ		0.66 (0.63-0.69)		0.25 (0.20-0.29)		0.25 (0.19-0.31)
Children	9783	-		0.11 (0.09-0.11)		0.11 (0.09-0.11)
Adolescents	3977	0.18 (0.17-0.19)	6839	-		0.16 (0.13-0.16)
Adult	2665	0.22 (0.21-0.23)	2298	0.30 (0.30-0.31)	7909	-

Table 3. Model fitting statistics for the three age groups. For each model, the negative log-likelihood (-2LL) is given, with the number of degrees of freedom (df). The more restrained models are compared to models containing a larger number of parameter dizygotic same-sex (DZ) and opposite-sex (DOS) correlations were constrained to be equal (qualitative sex differences).

			Estimated parameters	-2LL	df	Compared to	X^2	P-value
Children	1	Saturated	9	34417.66	19476	-	-	-
	2	Equal thresholds across sex	7	34896.08	19478	1	478.43 (2)	< 0.001
	3	MZm=Mzf & DZm = DZf	7	34427.56	19478	1	9.91 (2)	0.01
	4	DZ=DOS	6	34429.02	19479	3	1.46 (1)	0.23
Adolescents	1	Saturated	9	25285.53	11937	-	-	-
	2	Equal thresholds across sex	7	25541.73	11939	1	256.21 (2)	< 0.001
	3	MZm=Mzf & DZm = DZf	7	25287.28	11939	1	1.75 (2)	0.42
	4	DZ=DOS	6	25290.91	11940	3	3.63 (1)	0.06
Adults	1	Saturated	9	23338.24	11092	-	-	-
	2	Equal thresholds across sex	7	23378.17	11094	1	39.93 (2)	< 0.001
	3	MZm=Mzf & DZm = DZf	7	23341.73	11094	1	3.49 (2)	0.18
	4	DZ=DOS	6	23341.75	11095	3	0.02 (1)	0.89

Genetic and environmental influences

An AE model yielded a worse fit than the ACE model in childhood ($p<0.001$), while in adolescence and adulthood the AE model did not lead to a deterioration in fit compared to an ACE model (adolescents: $p=.55$, adults: $p=.46$). The estimates of the proportions of variance explained by genetic and environmental factors, their standard errors and the genetic and unique environmental correlations across childhood and adolescent conduct problems and adult antisocial personality problems of the final longitudinal model are reported in Table 4.

Genetic (43%) and shared environmental (44%) factors were equally important contributors to individual differences in conduct problems measured in 9-10 year-old twins. During adolescence the effect of the shared environment disappeared and genetic influences explained 49% the variance. Roughly similar results were obtained in adulthood, with a heritability estimate of 43%. The effect of the unique environment increased from 13% in childhood to 51% in adolescence and 57% in adulthood. Genetic and non-shared environmental influences accounted for 91% and 9%, respectively, for the stability between childhood and adolescent conduct problems. Genetic and non-shared environmental influences accounting for 96% and 4% for the stability between childhood conduct problems and adult antisocial personality problems. Lastly, genetic and non-shared environmental influences accounting for 80% and 20% for the stability between adolescent conduct problems and adult antisocial personality problems. These findings correspond with genetic correlations of .39 between childhood and adolescent conduct problems, of .67 between adolescent conduct problems and adult antisocial personality problems and of .49 between childhood conduct problems and adult antisocial personality problems (Table 4). The non-shared environmental correlations ranged between .03 and .14. Thus, there is considerable genetic continuity, especially between adolescent conduct problems and adult antisocial personality problems.

Table 4. Standardized estimates of additive genetic (A) and common and unique environmental (C and E) influences and their 95% confidence intervals (CI). Below the diagonal the genetic correlations between the phenotypes assessed in children, adolescents and adults are given, above the diagonal, the unique environmental correlations between the three different ages are presented for the most parsimonious longitudinal model.

	Model	A	C	E	Correlations		
					Children	Adolescents	Adults
Children	ACE	43% (38-44%)	44% (39-45%)	13% (12-14%)	-	.07	.03
Adolescents	AE	49% (45-51%)	-	51% (50-55%)	.39	-	.14
Adults	AE	43% (39-44%)	-	57% (53-61%)	.49	.67	-

Discussion

Our aim was to explore the genetic architecture of conduct and later antisocial personality problems in childhood, adolescence problems, and adulthood in a unique longitudinal twin dataset, collected over a period of over 27 years. At all ages, we observed the expected sex differences in mean symptom scores, with males scoring higher than females (differences in mean scores equalled about half the standard deviation for children and adolescents and a sixth of the standard deviation for adults). However, no quantitative or qualitative sex differences in genetic architectures were found, i.e. the proportions of variance explained by the genome did not differ between sexes and the same genes seemed to be expressed in males and females. Across ages, we found large differences in the influences of shared and unique environmental factors on variation in conduct and later antisocial personality problems. In 9-10 year-olds, genetic and shared environmental factors were equally important, explaining 43% and 44% of the individual differences in conduct problems. During adolescence and adulthood the effect of the shared environment on individual differences in conduct and antisocial personality problems was non-significant and the genetic and unique environmental effects accounted for 49% and 51% in adolescents and 43% and 57% in adults. The phenotypic correlations across the ages varied between 0.20 and 0.38, showing childhood and adolescent conduct problems and adult antisocial personality problems are moderately stable. The genetic correlations were substantial across the ages; namely .39 between childhood and adolescent conduct problems, .67 between adolescent conduct problems and adult antisocial personality problems and .49 between childhood conduct problems and adult antisocial personality problems. The unique environmental correlations were far lower, ranging between .03 and .14.

In line with earlier studies, the heritability of childhood and adolescent conduct problems and adult antisocial personality problems is substantial (between 43 and 49%) [1,4,23,162,163,181] and genetic factors are the main contributor to covariation across the ages [164-167]. In agreement with an earlier study in 7-year-old Dutch twins, the influence of the shared environment on conduct problems in childhood was large (44%) [130]. Strikingly, the shared environmental effect was non-significant during adolescence and adulthood, while the sample sizes (6,839 adolescent twin pairs and 7,909 adult twin pairs, overlap of 3,977 twin pairs) were sufficiently large to detect shared environmental influences [122,182]. This is a different finding than reported by some earlier studies on conduct problems, which found small, at max 23%, but significant shared environmental influences on

adolescent conduct problems and adulthood antisocial personality problems [1,4,23,162-167,183] and on the stability between the ages [165-167]. This difference might be due to differences in the assessment of the phenotype, or may reflect country-shared environment interactions. In Dutch twins, the decrease in the influence of C after childhood has also been reported for anxiety problems [184] and obsessive compulsive problems [185].

How should we interpret the disappearance of the shared environmental influences? It could mean that the shared environment is not of importance anymore after childhood for example because the span of control of the parents decreases. We speculate that the shared environmental factors that explain differences in conduct problems during childhood may include factors that have a protective effect that lose their influence during adolescence due to the changed parental role. This speculation is based on the finding that inadequate parental monitoring is a risk factor for the development of child and adolescent conduct problems [186] Parental monitoring often decreases from childhood to adolescence as a natural development in the process of raising children [187-191]. A recent study in children of twins confirmed that parental knowledge of their children's whereabouts, activities, and behaviors is a parental influence that diminishes adolescent externalizing behavior after accounting for genetic influences [192]. Continued parental monitoring and parental knowledge may not only be effective during childhood (when the shared environment plays such an important role), but as well during adolescence.

Future research on environmental factors should consider that environmental factors can be correlated with an individual's genotype, i.e. gene-environment correlations. This describes the process whereby an individual's exposure to an environmental factor depends on the individual's genotype. For example, a preference for peers with externalizing problems can be associated with a genetic predisposition for externalizing problems. For future research on environmental influences on conduct problems, children-of-twins and adoption studies are genetically informative designs that offer possibilities to account for such gene-environment correlations [120,121].

Another factor, apart from age, that could explain the observed differences in environmental influences throughout development may be the change in rater. Typically, psychopathology in childhood is assessed by parents, whereas in adolescence and adulthood self-ratings are feasible. During childhood, both twins within a twin pair were rated by their mother in our study, whereas in adolescence and adulthood the twin and co-twin rated themselves; i.e. there were two raters per

pair. This change in the number of raters can influence estimates of heritability and the shared environment, as Kan et al. [12] demonstrated. When both twins are rated by the same informant, any rater specific variance is added to the genetic and the shared environmental influences. However, when each twin is rated by a different informant, the rater specific variance is added to the unique environmental effect, resulting in a decrease in both the heritability and the shared environmental estimate. In our current study, we observed only a decrease in the amount of variance explained by shared environment and no decrease in heritability. Thus, our results suggest that the contribution of shared environmental influences may truly decreases with age. A change of rater also raises the question whether the parental and self-reports are measurement invariant, i.e. whether they measure the same underlying trait across age [152]. As shown in Supplementary Table 1, the items included in the CBCL and YSR to assess conduct problems are highly similar. However, highly similar items do not necessarily imply that the items have identical meaning for mothers and adolescents. To our knowledge no study has addressed construct validity invariance for the conduct problem scales of the CBCL and YSR. However, Petersen et al. [176] argued on the basis of five conditions, that there is theoretical and empirical support for construct validity invariance for the externalizing scales of the CBCL and YSR, a scale including all items used in the conduct problem scales (CBCL: 16 out of 33, YSR: 17 out of 30) that were used in the current study [31]. As 1) the measures were derived empirically, 2) showed a similar factor structure across time, 3) showed strong cross-time consistency, 4) strong convergent and discriminant validity over time with respect to internalizing problems and 5) the items showed high internal consistency at each age, they concluded that examining the changes in externalizing problems as measured in the CBCL and YSR over time is permitted. Therefore, it seems unlikely that measurement non-invariance between mothers and adolescents fully explains the difference in the estimates for the contribution of C.

Besides the effect of age and the change of rater, the influence of the behavior of one twin on the behavior of the other twin, may have become stronger during adolescence. If an increase in problems in one twin, causes a decrease in the behavior of the other twin (contrast effect) this can result in an underestimation of the shared environment during adolescence. Twin contrast effects can be detected by analyzing whether there are prevalence differences between the MZ and DZ twins [117,118]. We did not observe such differences as a function of zygosity: 44.43% of the 9-10 year-old MZ boys scored 'low' on conduct problems, compared to 43.64% of the DZ boys (for girls, MZ: 60.6% vs. DZ: 62.17%). For adolescent MZ boys, 29.81% scored 'low' versus 26.76% of the DZ boys (for girls, MZ: 44.43% vs.

DZ: 40.13%) and for adult males, 36.32% scores 'low' versus 31.21% of the DZ males (for females, MZ: 37.45% vs. DZ: 36.32%). These were the largest differences that were observed and none were significant ($p<0.01$ due to multiple testing). For 'middle' and 'high' scores the differences in prevalence between MZ and DZ twins were even smaller. Thus, contrast effects between twins also do not appear to have caused an underestimation of the shared environmental influence in any of the age groups.

A limitation of the present study is that the ASEBA questionnaire symptom scores were skewed, as is common for psychiatric symptom scales. We therefore analyzed the data with a threshold model, which resulted in more accurate parameter estimates, but in lower statistical power [32]. This was balanced by the large samples, which also provided the opportunity to fully explore sex effects.

In conclusion, this study confirms a substantial genetic influence on conduct and antisocial personality problems across age, and an important contribution of the shared environment on childhood conduct problems. There is a moderate stability in conduct problems and antisocial personality problems across the lifespan and genetic factors are the main contributor to this stability over the ages. These findings show the important role of genetic factors across the lifespan and of the shared environment during childhood on conduct problems.

Supplement to chapter 4

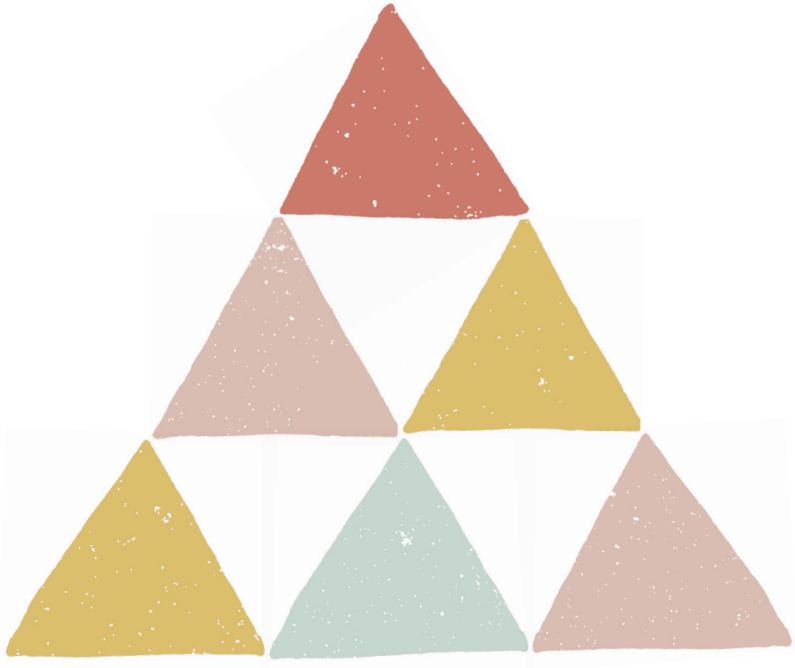
Table 1. The list of items included in the sum score of conduct problems as measured in the Child Behavior Checklist (CBCL) and Youth Self-Report (YSR) and of antisocial personality problems as measured in the Adult Self-Report (ASR).

CBCL and YSR	ASR
Mean to others	I am mean to others
Damage or destroy things belonging to others	I damage or destroy things belonging to others
Lacks guilt	I get along badly with my family
Gets in fights	I get in many fights
Hang around people who get in trouble	I hang around people who get in trouble
Lies/cheats	I lie or cheat
Physically attacks people	I physically attack people
Leaves home	My behavior is irresponsible
Sets fire	I do things that may cause me trouble with the law
Stealing from home	I steal
Stealing outside home	I argue a lot
Swearing	I have a hot temper
Threatens to hurt people	I threaten to hurt people
Truant	I fail to pay my debts or meet other financial responsibilities
Breaks rules**	I break rules at work or elsewhere
Vandalism*	
Cruel to animals*	

*only CBCL ** only YSR.

Aggregation of psychopathology in a clinical sample of children and their parents

SPOUSAL RESEMBLANCE IN PSYCHOPATHOLOGY: A COMPARISON OF PARENTS OF CHILDREN WITH AND WITHOUT PSYCHOPATHOLOGY



Chapter 5

Abstract

Background: Spouses resemble each other for psychopathology, but data regarding spousal resemblance in externalizing psychopathology, and data regarding spousal resemblance across different syndromes (e.g. anxiety in wives and attention deficit/hyperactivity disorder (ADHD) in husbands) are limited. Moreover, knowledge is lacking regarding spousal resemblance in parents of children with psychiatric disorders. We investigated and compared spousal resemblance within and across internalizing and externalizing symptom domains in parents of children with and without psychopathology. *Methods:* Symptoms of depression, anxiety, avoidant personality, ADHD, and antisocial personality were assessed with the Adult Self Report in 728 mothers and 544 fathers of 778 children seen in child and adolescent psychiatric outpatient clinics and in 2,075 mothers and 1,623 fathers of 2,784 children from a population-based sample. Differences in symptom scores and spousal correlations between the samples were tested. *Results:* Parents in the clinical sample had higher symptom scores than in the population-based sample. In both samples, correlations within and across internalizing and externalizing domains of psychopathology were significant. Importantly, correlations were significantly higher in the clinical sample (p=0.03). Correlations, within and across symptoms, ranged from 0.14 to 0.30 in the clinical sample and from 0.05 to 0.23 in the population-based sample. *Conclusions:* This large study shows that spousal resemblance is not only present within but also across symptom domains. Especially in the clinical sample, ADHD symptoms in fathers and antisocial personality symptoms in mothers were correlated with a range of psychiatric symptoms in their spouses. Clinicians need to be alert of these multiple affected families.

Based on: Wesseldijk LW, Dieleman GC, Lindauer RJ, Bartels M, Willemsen G, Hudziak JJ, Boomsma DI, Middeldorp CM (2016). Spousal resemblance in psychopathology: A comparison of parents of children with and without psychopathology. European Psychiatry, 34, 49-55.

Introduction

There are several important clinical implications of spousal resemblance in psychopathology, as already discussed by Galbaud du Fort et al. [193]. Firstly, due to the heritability of psychiatric disorders, children of parents with psychiatric symptoms have a higher risk to develop psychopathology. Furthermore, the family environment might become more unfavorable for a child when both parents suffer from psychiatric symptoms. In addition, parental psychopathology may also negatively affect the course and outcome of the treatment for a child with psychiatric symptoms [194-197]. Having two parents with psychopathology, as opposed to one, might have an even greater impact on the child's treatment effects [73]. Still, knowledge is lacking regarding spousal resemblance within, but especially across internalizing and externalizing symptom domains in parents of children that are evaluated at a child and adolescent psychiatry outpatient clinic.

So far, resemblance between spouses has been frequently observed for mood disorders, in particular depression or related traits [see for reviews 78,79,80]. Other psychiatric disorders or traits, such as anxiety disorders or symptoms, alcohol or substance use, and antisocial or borderline personality traits have been less extensively investigated, but showed similar results [198-207]. Spousal resemblance across disorders has also been reported, e.g, for major depression and alcohol abuse [79,193,205,207-209], as well as asymmetry with respect to sex. For example, maternal anxiety has recently been found to be associated with paternal attention deficit hyperactivity disorder (ADHD) [50], but paternal anxiety not with maternal ADHD. Furthermore, major depression in wives was associated with antisocial personality disorder in husbands but not vice versa [193,199]. However, most of the studies investigating spousal resemblance across psychiatric disorders in clinical samples were restricted to only two or three diagnoses. Also, ADHD has been understudied, since it has only recently been acknowledged that ADHD can persist into adulthood [204,210]. Moreover, in a very large study in the entire Danish population between 18 and 70 years (N=3,204,633), the risk to get a psychiatric disorder was increased in all spouses of individuals with a psychiatric disorder, but incidence rate ratios were more than twice as large among individuals with schizophrenia compared to other more mild psychiatric disorders [207]. Studies in other population-based samples have reported spousal resemblance by estimating correlations between and across traits in husbands and wives and these tend to be around 0.1 to 0.2 [202-204,206,209]. In clinical samples, spousal correlations range between 0.2 and 0.4 [50,198,211]. Clinical studies, however, mostly report odds

ratios to quantify resemblance, making a direct comparison of the results of clinical and population-based samples difficult. Still it is hypothesized that spousal resemblance might, in general, be more prevalent for the more severe psychiatric disorders. This hypothesis, though, has not yet been statistically tested and confirmed.

In the current study, we investigated spousal resemblance for psychiatric symptoms in a large sample of parents of children with psychopathology and for the first time statistically compared spousal resemblance in this clinical population to spousal resemblance in a population-based sample. We investigated a broad range of symptom domains, including ADHD and antisocial personality problems, which have been less often investigated in spousal resemblance studies than mood disorders. We hypothesized that, for all symptom domains, spousal resemblance will be higher in the clinical population following the earlier observations of higher spousal resemblance in clinical samples or for the more severe psychiatric disorders [50,198,207,211]. In an at-risk clinical sample, i.e. parents of children with psychopathology, there are several reasons why spousal resemblance for psychiatric symptoms may be higher than in a population-based sample. First, spouses might both be exposed stress, such as having a child suffering from psychiatric symptoms or experiencing financial problems, which can increase the risk for psychiatric symptoms in parents. Another possibility is that due to the heritability of psychiatric symptoms, the parents of children with psychopathology are more vulnerable to develop psychiatric problems themselves. Finally, parents who suffer from psychiatric symptoms might more easily recognize these symptoms in their partner or children and seek treatment. As having two parents afflicted with psychopathology, as opposed to one, can have a greater impact on the child's treatment effects, it is important for clinicians to know the patterns of the, possibly higher, resemblance in psychiatric symptoms between the parents of the children they evaluate, so that they can timely offer an intervention targeted at the parents. This study informs clinical practice by providing information on the co-occurrence of internalizing and externalizing psychiatric symptoms in parents of children with psychopathology.

Methods

Participants

Clinical sample

Data have been collected in three child and adolescent outpatient clinics in The Netherlands (two in Amsterdam and one in Rotterdam), all mainly treating children with ADHD (35.2%), autism spectrum disorders (21.8%), behavioral disorders (9.7%), anxiety disorders (20%) and/or depressive disorders (8.2%). Note, due to co-morbidity the diagnoses are not mutually exclusive.

A total of 1,272 parents (728 mother and 544 fathers) of 778 children participated in this study. In Amsterdam, first, a pilot study was carried out to examine how many parents are at risk for a psychiatric disorder at the moment of the first assessment of their child at a child and adolescent psychiatric outpatient clinic. Out of the 176 mothers and 122 fathers of 191 children that completed the Adult Self Report [175], 38.2% of the mothers and 31.5% of the fathers scored in the (sub)clinical range on at least one of the syndrome scales. Consequently, assessment of parental problems and offering further assessment and, if necessary, subsequent treatment became the standard procedure. The total Amsterdam sample consists of 395 mothers and 262 fathers from 425 families, after exclusion of 35 families who did not consent for the use of the data for research. In the Rotterdam outpatient clinic, data were collected as part of the standard clinical procedure from the start. Data were available for 333 mothers and 282 fathers from 353 families. In 70% of the families in Amsterdam and in 60% of the families in Rotterdam, at least one parent completed the survey. Age and educational achievement were significantly higher in the parents from Amsterdam than from Rotterdam and were included as covariates. This difference is in line with the already known regional differences in educational achievement in the Netherlands, with people in Rotterdam having on average a lower education than in Amsterdam [212]. The appendix provides a detailed description of the two study samples. The Amsterdam and Rotterdam studies were approved by the Central Ethics Committees of the participating institutions.

Population-based sample

Parents of twins registered with the Netherlands Twin Register (NTR) [81,83] completed the same questionnaires as the parents in the clinical sample to assess their psychiatric symptoms. Fathers and mothers in a similar age range as the parents

in the clinical sample were included, i.e., fathers between 29 and 68 years and mothers between 27 and 60 years. The final NTR sample consisted of 2,784 families with data available for 914 complete spouse pairs, 1,161 mothers and 709 fathers. All data, i.e. from complete and incomplete spouse pairs, were analyzed.

The twin population from the NTR is representative of the general Dutch population regarding the presence of psychiatric disorders. Eight percent of the twins aged 14 to 16 years reported to have received treatment for psychiatric problems over the last four years. This is largely comparable to the general Dutch population in which 5% of the children aged 0 to 18 received treatment over the last year [213]. The higher percentage in the twins can be explained by the differences in age between the two populations, 14-16 years compared to 0 to 18 years.

Measures

Psychiatric symptoms in parents were measured with the Adult Self Report (ASR), belonging to the Achenbach System of Empirically Based Assessment (ASEBA) [214]. The ASR is a questionnaire for adults from 18 to 59 years and consists of 120 items that are rated on a three-point scale (0 to 2; not true, somewhat true, very true). The DSM-oriented scales [175] depressive problems, anxiety problems, avoidant personality problems, ADHD problems, and antisocial personality problems were analyzed. Several studies have reported the reliability and validity of the ASR [215,216]. The questionnaire was available for parents both on paper and online.

Educational achievement was defined in three categories: low (1 to 3; primary school, lower vocational schooling, lower secondary schooling), intermediate (4 to 5; intermediate vocational schooling, intermediate/higher secondary schooling) and high educational achievement (6 to 7; higher vocational schooling, university).

Statistical analyses

Since the distribution of the psychiatric symptom scales was skewed, a square root transformation was performed improving the normality distribution. To investigate differences in age and education between fathers and mothers and between the clinical and population-based sample, independent sample t-tests and chi square tests were carried out in R (version 3.1.1). The effects of age and education on the ASR scores and differences in ASR scores between the clinical and population-based sample were tested in a regression analysis in SPSS (version 21) with sample, age and education included as fixed effects.

Spousal correlations were estimated and compared between the clinical and the population- based sample using structural equation modeling in OpenMx [114]. With the full information maximum likelihood option, all available information was analyzed, including data from incomplete spousal pairs. This provides better estimates than analyzing complete pairs only [217]. In the first most general model, means, standard deviations, and correlations were estimated separately for mothers and fathers in the clinical and the population-based sample. Age and education were included as fixed effects (covariates) on the scores. Next, more restricted models were tested against the most general model with a likelihood-ratio test, comparing the goodness of fit of the restricted model with the goodness of fit of the more general model. If the difference in fit is not statistically significant, the restricted model, which has fewer free parameters due to constraints, should be accepted. A significant test statistic (at $p < 0.05$ level) indicates that constraining the parameters results in a worsening of fit, thus that the more general model should be retained. First, the clinical and the population-based samples were compared. Differences between the two samples were tested for all scales simultaneously for 1) the standard deviations, 2) the within person or "phenotypic" correlations among scales, and 3) the spousal correlations between and across scales. Second, post hoc tests were carried out to investigate asymmetry with respect to sex in spousal resemblance. It was tested whether the correlation between the maternal score on scale X and the paternal score on scale Y could be constrained to be equal to the correlation between the maternal score on scale Y and the paternal score on scale X. These post hoc tests were based on visual inspections of the correlational patterns.

Results

Descriptives

Characteristics of the parents in the clinical (n=1,272) and population-based samples (n=3,698) are shown in Table 1. Both in the clinical and the population-based sample, the fathers were significantly older than the mothers (t=13.25 (521), p<.001 and t=-26.98 (1065), p<.001, respectively) and significantly higher educated (χ^2_4= 186.57, p=<.001 and χ^2_4=242.52, p<.001). Comparing the clinical and the population-based samples showed that the mothers were higher educated in the clinical sample compared to the mothers in the population-based sample (χ^2_4=23.83, p<.001). Fathers were similarly educated in the clinical and the population-based sample (χ^2_4= 5.08, p=.08). Further, parents in the population-sample were older than the parents in de clinical sample (mothers: t= -33.61 (2870), p<.001, fathers: t=-32.34 (2276),

p<.001), but parental age at child birth hardly differed between the two samples (Table 1).

Table 1. Characteristics of parents in the clinical and population-based samples.

	Mothers		Fathers	
	Clinical sample (n=728)	Population-based sample (n=2,075)	Clinical sample (n=544)	Population-based sample (n=1,623)
Age (Mean (SD))	41.80 (6.80) *	50.20 (5.50) *	44.69 (7.03) *	55.27 (6.61) *
Parent's age at childbirth (Mean (SD))	30.38 (6.48) *	29.43 (3.72) *	33.61 6.65) *	31.23 (3.99) *
Education achievement (n (%))				
Low	189 (25.5%) *	686 (32.9%) *	157 (26.2%)	443 (26.6%)
Intermediate	264 (35.6%) *	777 (37.2%) *	193 (32.2%)	460 (27.6%)
High	289 (38.9%) *	625 (29.9%) *	249 (41.6%)	764 (45.8%)

Age was a continuous variable measured in years. Educational achievement was a categorical variable with categories: low, intermediate and high. * = significant difference (p< .05) between the clinical and population-based sample.

Means

Table 2 shows the mean psychiatric symptom scores for the parents in the clinical and population-based sample. While controlling for the effects of age and education, mothers in the clinical sample scored significantly higher on depression, anxiety, avoidant problems and ADHD than mothers in the population-based sample. Fathers in the clinical sample had significantly increased scores for depression, anxiety, ADHD and significantly decreased scores for antisocial personality problems compared to fathers in the population based sample. The regression analyses to test for the effects of age and education showed significant coefficients for education ranging from -0.12 to -0.06, confirming the protective effect of a higher education (Appendix). Table 3 shows the test statistics of the comparisons between the standard deviations between the clinical and the population-based sample. Comparing model 2, with the standard deviations constrained to be equal across the samples, to the most general model 1, revealed that the clinical sample had significantly higher standard deviations although the differences are small.

Table 2. Mean symptom scale scores (standard deviations) of the square root transformed scores in the clinical and population-based sample.

	Mothers		Fathers	
	Clinical sample (n=728)	Population-based sample (n=2,075)	Clinical sample (n=544)	Population-based sample (n=1,623)
Depression	1.92 (1.14)**	1.66 (1.03)**	1.48 (1.06)**	1.22 (0.97)**
Anxiety	1.92 (0.82)**	1.80 (0.80)**	1.60 (0.84)*	1.41 (0.87)*
Avoidant	1.38 (0.88)*	1.26 (0.85)*	1.18 (0.90)	1.14 (0.86)
ADHD	1.98 (1.03)**	1.75 (0.94)**	1.86 (1.05)*	1.71 (0.97)*
Antisocial	1.26 (0.82)	1.28 (0.78)	1.37 (0.90)*	1.50 (0.78)*

* = significant difference (p<.01) in mean scores between the clinical and population-based sample. ** = significant difference (p<.001) in mean scores between the clinical and population -based sample. ADHD: Attention deficit/hyperactivity disorder (ADHD).

Table 3. Test statistics for the comparisons of the models to explore the differences between the clinical and population-based sample.

	Estimated parameters	-2LL	df	Compared to	X^2	P-value
1. Saturated clinical and population-based sample	170	56145.78	24640	-	-	-
2. Equal standard deviations between the clinical and population-based sample	160	56187	24650	1	41.22 (10)	< .00
3. Equal correlation matrices within mothers between the clinical and population-based sample	160	56159.29	24650	1	13.51 (10)	0.20
4. Equal correlation matrices within fathers between the clinical and population-based sample	160	56169.46	24650	1	23.68 (10)	0.01
5. Equal correlation matrices across mothers and fathers between the clinical and population-based sample	145	56185.61	24665	1	39.83 (25)	0.03

Note: All models are compared to model 1. Likelihood ratio tests are performed. The negative log-likelihoods (-2LL) of the models (2-5) are subtracted from the -2LL of the saturated model (1). The difference between the -2LL of the two models follows a χ^2 distribution with degrees of freedom (df) equal to the difference in the numbers of parameters in the two models.

Correlations

Table 4 shows the within-person correlations for psychiatric symptoms in the clinical sample and in the population-based sample for mothers (below the diagonal) and fathers (above the diagonal). Within-person correlations for psychiatric symptoms varied between 0.37 and 0.70 in mothers and between 0.33 and 0.65 in fathers in the clinical sample and between 0.35 and 0.64 in mothers and between 0.33 and 0.58 in fathers in the population-based sample. Table 3 shows that the within-person correlations among the different psychiatric symptom scales in mothers were similar across the samples (model 3), while the within person correlations in fathers were significantly higher in the clinical than in the population-based sample (model 4).

Correlations between spouses within the internalizing and externalizing symptom domains were between 0.22 and 0.28 in the clinical sample (Table 5, upper part). Correlations across symptoms ranged from 0.14 to 0.30. All correlations were significantly higher than 0 as shown by the confidence intervals. The spousal correlations for the five psychiatric symptom scales in the population-based sample ranged from 0.09 to 0.23 within scales (Table 5, lower part). Correlations across symptom scales ranged from 0.05 to 0.16. Again, all correlations were significant, with the exception of paternal anxiety with maternal ADHD. It becomes clear from Table 5 that the within and across symptom correlations in the population-based sample are lower, sometimes almost twice as low, than in the clinical sample.

In model 5, the correlations between the parents were constrained to be equal within and across the psychiatric symptoms in the clinical and in the population-based sample. Comparing model 5 to model 1 confirmed that the spousal correlations significantly differed between the clinical and the population-based sample (Table 3).

Table 4. Within-person correlations [confidence intervals] for psychopathology in the clinical sample (upper part) and the population-based sample (lower part). Within-mother correlations below the diagonal, within-father correlations above the diagonal.

	Clinical sample				
	Depression	Anxiety	Avoidant	ADHD	Antisocial
Depression		0.65 [0.60,0.70]	0.58 [0.52,0.63]	0.58 [0.52,0.63]	0.40 [0.32,0.46]
Anxiety	0.70 [0.66,0.73]		0.50 [0.43,0.56]	0.47 [0.40,0.53]	0.33 [0.26,0.41]
Avoidant	0.60 [0.56,0.65]	0.55 [0.49,0.60]		0.44 [0.37,0.51]	0.33 [0.26,0.41]
ADHD	0.57 [0.52,0.62]	0.48 [0.42,0.53]	0.47 [0.41,0.52]		0.58 [0.52,0.63]
Antisocial	0.45 [0.39,0.50]	0.37 [0.30,0.43]	0.40 [0.34,0.46]	0.50 [0.44,0.55]	
	Population-based sample				
	Depression	Anxiety	Avoidant	ADHD	Antisocial
Depression		0.56 [0.53,0.59]	0.58 [0.57,0.61]	0.54 [0.53,0.57]	0.41 [0.37,0.44]
Anxiety	0.64 [0.62,0.64]		0.45 [0.42,0.49]	0.46 [0.42,0.50]	0.33 [0.31,0.37]
Avoidant	0.61 [0.61,0.62]	0.50 [0.47,0.53]		0.45 [0.41,0.49]	0.36 [0.33,0.40]
ADHD	0.54 [0.53,0.57]	0.42 [0.39,0.45]	0.45 [0.41,0.48]		0.48 [0.44,0.51]
Antisocial	0.40 [0.37,0.43]	0.35 [0.31,0.38]	0.36 [0.35,0.39]	0.43 [0.40,0.46]	

ADHD: Attention deficit/hyperactivity disorder.

Table 5. Spousal correlations [confidence intervals] for psychopathology in the clinical sample (upper part, N=494 for complete spouse pairs) and the population-based sample (lower part, N=914 for complete spouse pairs).

		Mothers clinical sample (n=728)				
		Depression	Anxiety	Avoidant	ADHD	Antisocial
Fathers clinical sample (n=544)	Depression	0.26 [0.17,0.34]	0.19 [0.10,0.27]	0.24 [0.16,0.32]	0.18 [0.09,0.27]	0.30 [0.22,0.38]
	Anxiety	0.23 [0.14,0.31]	0.24 [0.15,0.32]	0.18 [0.10,0.27]	0.13 [0.04,0.22]	0.20 [0.11,0.29]
	Avoidant	0.20 [0.12,0.28]	0.18 [0.10,0.26]	0.22 [0.14,0.30]	0.16 [0.07,0.24]	0.22 [0.13,0.30]
	ADHD	0.30 [0.22,0.38]	0.24 [0.16,0.32]	0.30 [0.22,0.38]	0.25 [0.16,0.33]	0.29 [0.21,0.37]
	Antisocial	0.22 [0.13,0.30]	0.20 [0.12,0.28]	0.16 [0.07,0.25]	0.14 [0.05,0.23]	0.28 [0.20,0.36]
		Mothers population-based sample (n=2,075)				
		Depression	Anxiety	Avoidant	ADHD	Antisocial
Fathers population-based sample (n=1,623)	Depression	0.16 [0.11,0.23]	0.14 [0.08,0.20]	0.14 [0.12,0.21]	0.08 [0.01,0.14]	0.09 [0.02,0.15]
	Anxiety	0.15 [0.09,0.21]	0.23 [0.17,0.29]	0.07 [0.05,0.13]	0.07 [0.00,0.13]	0.05 [-0.01,0.12]
	Avoidant	0.13 [0.07,0.18]	0.16 [0.10,0.22]	0.14 [0.07,0.20]	0.09 [0.03,0.15]	0.10 [0.04,0.15]
	ADHD	0.12 [0.06,0.18]	0.15 [0.09,0.21]	0.13 [0.07,0.18]	0.09 [0.02,0.15]	0.12 [0.06,0.18]
	Antisocial	0.09 [0.02,0.15]	0.09 [0.03,0.15]	0.08 [0.03,0.14]	0.09 [0.03,0.15]	0.10 [0.04,0.16]

ADHD: Attention deficit/hyperactivity disorder.

Next, we performed post-hoc tests to investigate the asymmetry with respect to sex in spousal resemblance in the clinical sample. Based on visual inspection of the correlations, we tested whether 1) the correlations between paternal ADHD and all maternal scales were higher than the correlations between maternal ADHD and all paternal scales and 2) the correlations between maternal antisocial personality problems and all paternal scales were higher than the correlations between paternal antisocial personality problems and all maternal scales. The two post-hoc tests showed that paternal ADHD indeed was significantly higher correlated with all five maternal symptom clusters than vice versa (χ^2_4= 14.91, p <.001). The same held for antisocial personality problems in mothers and all five symptom clusters in fathers (χ^2_4= 10.21, p = 0.04). Asymmetry with respect to sex was non-significant in the population-based sample, neither for paternal ADHD with the five maternal symptom clusters (χ^2_4= 3.73, p =.44), nor for maternal antisocial personality problems with all five paternal symptom clusters (χ^2_4= 2.90, p =.57).

Discussion

In this study, we investigated spousal resemblance within and across internalizing and externalizing symptom domains and for the first time statistically compared resemblance in a large sample of parents of children with psychopathology with spousal resemblance in a population-based sample. Spousal correlations were generally significant within and across internalizing and externalizing symptom domains in both the clinical and population-based sample. Moreover, as hypothesized, spousal resemblance was clearly higher in the at-risk population of parents. We further observed significant asymmetry with respect to sex in the clinical and not in the population-based sample. Paternal ADHD correlated higher with maternal internalizing and externalizing symptom scores than maternal ADHD with paternal symptom scores and maternal antisocial personality problems correlated higher with paternal internalizing and externalizing symptom scores than vice versa. Parents of children with psychopathology also had higher symptom scores than parents in the population-based sample, as expected and in line with previous studies [33-40,47,48].

For clinical practice, these findings imply that parents have a significantly higher risk for psychopathology when their child is seen in a child and adolescent psychiatric outpatient, and that, if one parent suffers from psychiatric symptoms, chances are increased that their spouse also suffers from psychiatric symptoms, either in a similar or different symptom domain. Especially in the clinical sample,

spousal correlations across symptom domains were of similar magnitude as the spousal correlations within symptom domains. Clinicians should be aware of this great variety in spousal resemblance for psychopathology between parents. Besides the negative effects of psychiatric symptoms on the parent's own daily functioning, the course and outcome of the treatment for a child can be negatively influenced when both parents are afflicted with psychopathology [73].

Spousal resemblance can be due to different processes, including phenotypic assortment, social homogamy and marital interaction [201]. Assortative mating implies the tendency for people to start long-term relationships with those who are more similar to themselves than with those who are not [218]. When this co-occurrence is due to phenotypic assortment, partner selection is based directly on the partner's phenotype. Social homogamy refers to the tendency for individuals to have partners with similar social backgrounds [219]. Marital interaction refers to the mutual influences or the sharing of the same environmental factors between spouses living together [220]. In this study we cannot differentiate between phenotypic assortment, social homogamy and marital interaction as the cause of spousal resemblance, but for psychiatric disorders phenotypic assortative mating has been indicated as causes for spousal resemblance [79,201,208].

As discussed in the introduction, several mechanisms may underlie the higher spousal correlations within and across internalizing and externalizing symptom domains in the clinical population. As we observed significant correlations across the symptom domains, we tested whether co-morbidity could underlie the higher spousal correlations observed in the clinical sample. If individuals with higher scores on depression also report higher anxiety scores, it follows that, in case of a significant spousal correlation for depression, spousal correlations are probably also significant between depression and anxiety [221]. If co-morbidity is higher in the clinical sample than in the population-based sample, this can result in higher across-symptom domain spousal correlations. We have explored this mechanism by comparing the within-person correlations across the internalizing and externalizing scales, between the two samples. These correlations were only significantly different for fathers, and not for mothers, and the differences were small. This indicates that co-morbidity does not play an important role in explaining the higher correlations.

Another explanation for the higher spousal resemblance, as mentioned in the introduction, could be that parents in the at-risk sample are more exposed to stress. Living with and caring for a person with psychiatric symptoms is known to be a stressful experience and stress might evoke the development of psychiatric

symptoms [205,222,223]. In this sample, both parents are exposed to the stress of a child suffering from psychiatric symptoms. A recent study by van Steijn et al. [224] highlighted the increased burden of raising a child with autism spectrum disorder and/or ADHD and its relationship with parental autism spectrum disorder, ADHD, depressive symptoms and levels of stress. The other possibility is that the family members are all exposed to the same stressors, such as financial problems, which can increase the risk for psychiatric symptoms in parents as well as in children.

A different explanation for the higher spousal resemblance in the clinical sample is the influence of genetic factors, if the parents are biological parents. Excluding the data from 29 non-biological mothers, 30 non-biological fathers in the clinical sample (N=40 pairs) and 5 non-biological mothers and 7 non-biological fathers in the population-based sample (N=11 pairs) led to similar spousal correlations in both samples, with a maximum difference of 0.01. This suggests that both genetic and environmental influences seem to underlie the higher spousal resemblance in psychopathology, as the exclusion of non-biological parents did not lead to an increase in the spousal correlations, especially in the clinical sample, within and across the symptom domains. The above described stressful environment as a consequence of the problems of the child might pull the trigger of these more genetically vulnerable parents, resulting in higher spousal correlations in parents of clinically referred children in comparison to parents of the children in the population-based sample. Vice versa, children of parents who both have a psychiatric disorder also have the highest genetic risk to suffer from psychiatric disorders themselves [74]. This could also result in an overrepresentation of these families in a clinical sample. Finally, parents who suffer from psychiatric symptoms might more easily recognize these symptoms in their children and seek treatment.

Longitudinal studies can partly unravel the role of these mechanisms. Earlier studies have, for example, already indicated that the course of psychiatric symptoms in children and parents are associated [194-197], suggesting that family members influence each other's symptoms.

We also showed asymmetry with respect to sex in the spousal correlations in the clinical sample which was not apparent in the population-based sample. These results confirmed and extended the findings of Segenreich et al. [50] as paternal ADHD problems were more strongly associated with all five psychiatric symptom scales in mothers than the other way around. Contrary to the findings of Galbaud du Fort et al. [193] we reported paternal depressive problems to be significantly more strongly associated with maternal antisocial personality problems (0.30), than vice

versa (0.22). An explanation for this difference might be the low prevalence of mothers with antisocial personality problems in the study sample of Galbaud du Fort et al. [193], who gave sex specific population prevalence rates for psychiatric symptoms as an explanation for their finding. This asymmetry with respect to sex together with the high correlations found across the five psychiatric symptom scales between parents can influence the risk for co-morbidity of psychiatric symptoms in the offspring of children with two affected parents.

There are several limitations and strengths of this study. First, even though we reached a family-response rate around 65% in the clinical samples, there are still parents whom we did not reach. Middeldorp et al. [225] conducted a non-response analysis in the clinical sample and found that families in which only mothers completed the questionnaire were exposed to less favorable circumstances than families in which both parents, or only father completed the questionnaires. This may point to non-response bias with fathers who are more at risk for psychiatric symptoms being less likely to participate. However, part of the families in which only the mother completed the questionnaires are single-parent families (without a father) which are known to be at a higher risk for unfavorable circumstances [225]. Secondly, the parents of children in the population-based sample were significantly older than the parents in the clinical sample, which might have influenced the spousal correlations due to effects of marital interaction. However, van Grootheest et al. [201] examined the effects of length of the relationship on spousal resemblance for obsessive-compulsive, anxious, and depressive symptoms and did not find any evidence for higher spousal resemblance in longer relationships. A major strength of this study is that we have reached a large number of fathers for the screening procedure for psychiatric symptoms.

To summarize, this study shows that parents whose children are evaluated at a child and adolescent outpatient clinic have an increased risk to both suffer from a variety of psychiatric symptoms, with correlations across symptom domains of similar magnitude as the correlations within symptom domains. Therefore, it is important to encourage mothers as well as fathers to visit the outpatient clinic along with the child and to offer screening of parental symptoms and treatment in case of psychiatric complaints.

Supplement to chapter 5

Table 1. Description of the study samples from Amsterdam and Rotterdam.

	Amsterdam	Rotterdam
Age (Mean (SD))		
Mothers	43.05 (7.05)*	40.34 (6.19)*
Fathers	46.44 (7.15)*	43.08 (6.52)*
Education achievement (n (%))		
Mothers		
Low	76 (19.2%)*	113 (32.6%)*
Intermediate	119 (30.1%)*	145 (41.8%)*
High	200 (50.6%)*	89 (25.6%)*
Fathers		
Low	49 (18.5%)*	108 (32.3%)*
Intermediate	75 (28.3%)*	118 (35.3%)*
High	141 (53.2%)*	108 (32.3%)*
Symptom scores (Mean (SD))		
Mothers		
Depression	1.95 (1.19)	1.89 (1.07)
Anxiety	1.92 (0.86)	1.63 (0.72)
Avoidant	1.29 (0.89)*	1.49 (0.86)*
Attention deficit/hyperactivity disorder	1.95 (1.05)	2.01 (1.01)
Antisocial	1.30 (0.85)	1.22 (0.79)
Fathers		
Depression	1.44 (1.09)	1.51 (1.04)
Anxiety	1.57 (0.87)	1.63 (0.82)
Avoidant	1.12 (0.93)	1.24 (0.89)
Attention deficit/hyperactivity disorder	1.79 (1.12)	1.92 (0.98)
Antisocial	1.41 (1.01)	1.34 (0.78)

* = significant difference (p< .05) between the Amsterdam and Rotterdam sample.

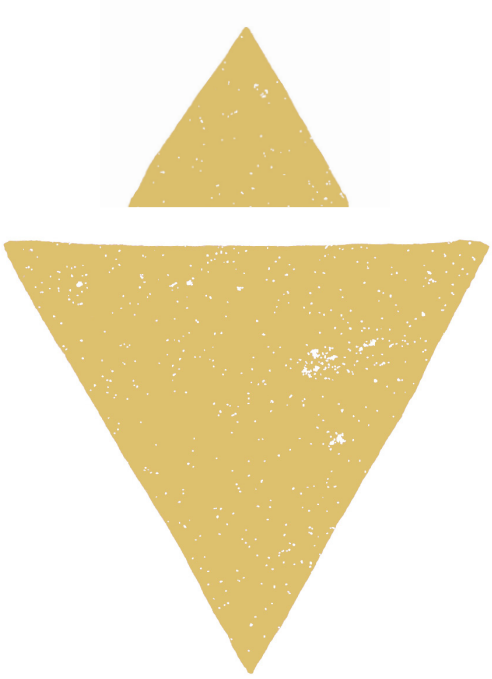
Table 2. Regression coefficients (beta's) for age and education of the square root transformed scores in the clinical and population-based sample.

	Mothers				Fathers			
	Clinical sample		Population-based sample		Clinical sample		Population-based sample	
	Beta's for age	Beta's for education	Beta's for age	Beta's for education	Beta's for age	Beta's for education	Beta's for age	Beta's for education
Depression	-0.01	-0.09	0.00	-0.06*	-0.00	-0.10	0.00	-0.08*
Anxiety	-0.01	-0.07	0.01*	-0.06*	-0.00	0.04	-0.00	-0.04
Avoidant	-0.01*	-0.12*	0.01*	-0.08*	0.00	-0.01	0.00	-0.03
ADHD	-0.01	-0.03	0.00	-0.05	-0.00	-0.10	0.00	-0.05
Antisocial	0.01	-0.03	0.00	-0.03	-0.00	-0.10*	-0.00	-0.02

* = significant regression coefficient (p< .05). ADHD: Attention deficit/hyperactivity disorder (ADHD).

Aggregation of psychopathology in a clinical sample of children and their parents

PARENTS OF CHILDREN WITH PSYCHOPATHOLOGY: PSYCHIATRIC PROBLEMS AND THE ASSOCIATION WITH THEIR CHILD'S PROBLEMS



Chapter 6

Abstract

Knowledge is lacking regarding current psychopathology in parents whose children are evaluated in a psychiatric outpatient clinic. This especially accounts for fathers. We provide insight into the prevalence rates of parental psychopathology and the association with their offspring psychopathology by analyzing data on psychiatric problems collected in 701 mothers and 530 fathers of 757 referred children. Prevalence rates of parental psychopathology were based on (sub)clinical scores on the Adult Self Report (ASR). Parent-offspring associations were investigated in multivariate analyses taking into account co-morbidity. Around 20% of the parents had a (sub)clinical score on internalizing problems and around 10% on Attention Deficit Hyperactivity (ADH) problems. Prevalence rates did not differ between mothers and fathers. Parent-offspring associations did not differ between girls and boys. Maternal anxiety was associated with all offspring problem scores. In addition, maternal ADH problems were associated with offspring ADH problems. Paternal anxiety and ADH problems scores were specifically associated with offspring internalizing and externalizing problem scores, respectively. Associations with offspring psychopathology were of similar magnitude for mothers and fathers and were not influenced by spousal resemblance. Our study shows that both fathers and mothers are at increased risk for psychiatric problems at the time of a child's evaluation and that their problems are equally associated with their offspring problems. The results emphasize the need to screen mothers as well as fathers for psychiatric problems. Specific treatment programs should be developed for these families in especially high need.

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Introduction

It is well established that psychiatric disorders run in families. Moreover, the increased risk for psychopathology in parents or children is not confined to the disorder of, respectively, the children or the parents, but also extends to other disorders [74,75]. These findings were mostly observed using a lifetime history of psychiatric illness approach. However, since ongoing psychopathology in parents can influence the course and treatment outcome of psychopathology in children [47,53,54,226,227], knowledge about parental psychiatric problems at the time a child is suffering from a psychiatric disorder is also important. So far, it has been shown that parents whose children are evaluated for psychiatric disorders at a child and adolescent psychiatric outpatient clinic, are at higher risk for internalizing problems and disorders, such as anxiety and depression. Prevalence rates range from 18% to 68% [33-40,48,50]. Far less information is available on parental externalizing problems and disorders, such as Attention Deficit Hyperactivity Disorder (ADHD) and antisocial personality disorder, but the risk also seems increased [33,34,39,48].

Information on paternal psychopathology is further lacking. In many of the former studies far fewer fathers than mothers were included and in four the data were restricted to mothers [33,35,36,39]. Still, several studies have indicated that paternal psychopathology is also associated with offspring psychopathology [77]. In addition, paternal psychopathology may influence the association between maternal and offspring symptoms due to spousal resemblance. Kim-Cohen et al. [199] found that the association between maternal depression and offspring externalizing problems was diminished, although still significant, when paternal antisocial personality disorder was included in the analysis. In contrast, Marmorstein et al. [228] observed no attenuation of the effects of either major depression in mothers or antisocial personality in fathers on major depression and conduct disorder in their offspring.

Finally, the majority of these studies selected children with specific diagnoses, i.e. depression [33,38], anxiety [34,35], or ADHD / conduct disorder (CD) [36,37,48,50]. Given that family studies clearly indicate that the associations between family members are not confined to the disorders of the probands, only an offspring population with a broad range of psychopathology provides good insight into the association between psychopathology of parents and children.

The current study provides prevalence rates of current psychiatric problems in mothers as well as fathers of children suffering from various psychiatric disorders.

In addition, the associations between parental and offspring problems in these families are reported. Internalizing as well as externalizing problem scales were assessed in a large sample of parents at the time of the first appointment of their child in a child and adolescent psychiatric outpatient clinic. Similar problem scales were measured in parents and children. The associations between the parental and offspring problem scores were analyzed within and across the different syndrome scales and the analyses were performed separately for boys and girls. Finally, we investigated whether the maternal and paternal problems were independently associated with offspring problems or whether these associations were partly explained by spousal resemblance for psychiatric problems.

Methods

Participants

Data have been collected in three child and adolescent outpatient clinics in The Netherlands (two in Amsterdam and one in Rotterdam). In these clinics, parents already rated the children's problems using the Child Behavior Checklist (CBCL) [99] as part of the standard clinical procedure at the first assessment. Families with children aged between 6 and 18 years were included. In Amsterdam, first, a pilot study was carried out to examine how many parents are at risk for a psychiatric disorder at the moment of the first assessment of their child at a child and adolescent psychiatric outpatient clinic. Out of the 176 mothers and 122 fathers of 191 children that completed the Adult Self Report (ASR) [175], 38.2% of the mothers and 31.5% of the fathers scored in the (sub)clinical range on at least one of the syndrome scales. Consequently, assessment of parental problems and, if necessary, further assessment and subsequent treatment, became the standard procedure. The total Amsterdam sample consists of 363 mothers and 235 fathers from 389 families, after exclusion of 35 families without consent for the use of the data for research and of 26 non-biological parents. The study was approved by the Central Ethics Committee on Research Involving Human Subjects of the VU University Medical Centre, Amsterdam. In the Rotterdam outpatient clinic, data were collected as part of the standard clinical procedure from the start. If parents reported (sub)clinical problems, psychopathology was further assessed, and, if necessary, parents were referred to adult mental health services. Data were available for 338 mothers and 295 fathers from 368 families, after exclusion from 29 non-biological parents. Family response rates, i.e., the percentage of families in which at least one parental questionnaire was

completed, were 70% in the Amsterdam and 60% in the Rotterdam samples. In total, data were analyzed from 701 mothers and 530 fathers from 757 families.

The most common diagnoses in children in the Amsterdam and Rotterdam cohort were ADHD (40% and 30%), autism spectrum disorders (18% and 26%), behavioral disorders (11% and 9%), anxiety disorders (17% and 24%) and depressive disorders (12% and 4%). These disorders are not mutually exclusive, i.e., children can have more than one diagnosis. The parental scores in the Amsterdam and Rotterdam cohort did not differ for the ASR syndrome scales [119]. The parents from the Amsterdam cohort were on average 3 years older and higher educated [119]. This latter difference is in line with the known regional differences in educational achievement in the Netherlands, with people in Rotterdam having on average a lower education than in Amsterdam [212]. The children in the Amsterdam cohort were also on average 1.5 years older than the children in the Rotterdam dam cohort. Parental and offspring age and parental education were included as covariates in the analyses.

Measures

Demographical information on age, sex and educational achievement was obtained from the questionnaire. Educational achievement was analyzed in three categories, i.e. low (at most lower secondary schooling), intermediate (at most higher secondary schooling) and high educational achievement.

Behavioral and emotional problems in parents and children were measured with the age-appropriate version of the questionnaires belonging to the Achenbach System of Empirically Based Assessment (ASEBA), i.e., the Child Behavior Checklist (CBCL) [99] and the Adult Self Report (ASR) [175]. In both generations, the DSM-oriented syndrome scales were analyzed. For the children, the depressive, anxiety, attention deficit/hyperactivity (ADH), oppositional defiant and conduct problem scales were included and for the parents depressive, anxiety, avoidant personality, ADH, and antisocial personality problem scales.

For both the CBCL and the ASR, thresholds for (sub)clinical scores for each sex are provided in the manual. The thresholds for the subclinical and clinical scores reflect the 93rd and 97th percentile respectively in men and women of the general population.

Analyses

To investigate potential response bias, we analyzed whether the children's scores differed according to the participation of the parents. We made four groups of children for boys and girls: 1) none of the parents participated, 2) both parents participated, 3) father participated, and 4) mother participated. Differences in mean syndrome scale scores between the four groups were analyzed with an ANOVA.

Based on the thresholds provided in the manual, the prevalence rates of fathers and mothers with (sub)clinical scores were calculated for each scale. These prevalence rates give an indication of how many parents are likely to suffer from clinically relevant psychiatric symptoms.

All other analyses were carried out on the continuous scores of the DSM-oriented scales so that all available information on individual variation was used. Pearson's correlations between parental and offspring problem scores were calculated within and across syndrome scales. This was followed by a multivariate multi-group analysis in Mplus in which the problem scores in boys and girls were predicted by the maternal problem scores or the paternal problem scores (see Figure 1). First, the analyses were performed separately for girls and boys. Next, it was tested whether there were sex differences by constraining the beta's to be equal over the sexes. In these analyses, we made optimal use of the available parental data since measures from families in which only one parent participated were also included. However, these analyses do not take into account spousal resemblance for psychopathology, which has been detected in the current sample with correlations varying between 0.13 and 0.30 within and across the syndrome scales [119]. To investigate whether the effects of maternal and paternal psychopathology can be explained by spousal resemblance, we also tested a model in which both the maternal and paternal scores were included that had a marginally significant effect ($p<0.10$) in the first analyses. If these effects remain similar in the order of magnitude and significance, spousal resemblance does not explain the association with childhood psychopathology. Age from parents and children and parental education were included as covariates.

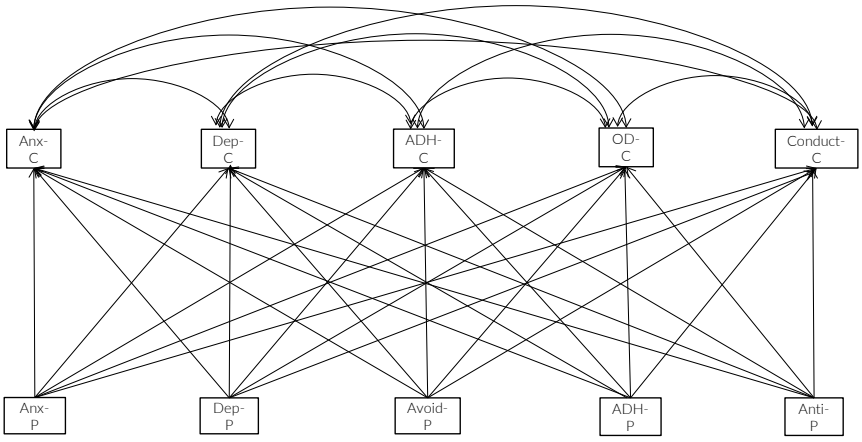


Figure 1. The multivariate model: The childhood problems scores (C) are correlated. The parental (P) problem scores predict each childhood problem score. The model was analyzed for maternal and paternal problem scores separately. ADH: Attention Deficit/Hyper Activity, Anti: Antisocial personality, Anx: Anxiety, Avoid: Avoidant personality, Dep: Depressive, OD: Oppositional Defiant problems

Results

Descriptives of participants and prevalence rates of parental psychiatric problems

Children in our sample scored higher than children from a population based sample [99] and their scores follow the well-known pattern of girls scoring higher on internalizing problems and boys on externalizing problems (Table 1). Table 2 shows the mean CBCL scores for the four possible response patterns in the families: 1) both parents, 2) mother, 3) father or 4) none of the parents completed the ASR. Children whose parents did not participate did not generally score higher than children of whom both parents participated. Only two of the ten analyses showed a significant between group difference in mean scores, i.e., for depressive and conduct problems in girls. This appeared to be due to the group of girls of whom only the mother completed the ASR. These girls scored higher than the girls in the other three groups. Further analyses comparing the families in which one or two parents completed the ASR revealed that factors associated with psychopathology were more prevalent in the families in which only the mother completed the ASR. These were more often broken or single parent families (65% compared to 37% of the families in which the

father completed the ASR and to 15% in the families in which both parents completed the ASR) and the level of education of the mother was lower (43% in the lowest category compared to 26% and 21%).

Around 25% of the parents had a (sub)clinical score on one of the analyzed scales (Table 1). A (sub)clinical score on depressive problems was most prevalent with 13% of the fathers and 15% of the mothers scoring above the threshold (Table 1). These rates are clearly higher than the rate of 7% (sub)clinical scores in the general population on which the cut-offs are based [175]. The percentages are also higher for avoidant personality and ADH problems. In total, 20% of the mothers and 18% of the fathers had a (sub)clinical score on the internalizing scales anxiety, depressive or avoidant personality problems. There were no significant differences between mothers and fathers.

Table 1. Mean (SD) age and scores on the DSM oriented syndrome scales in girls and boys (top) and mean age (SD), education (%) and number of parents (%) with a score in the (sub)clinical range (bottom).

	Girls (n=296)	Boys (n=375)
Age	11.7 (3.4)	10.5 (3.2)
Depression	7.1 (4.6)	5.4 (4.0)
Anxiety	4.5 (3.1)	3.6 (2.7)
ADH	5.4 (3.7)	7.2 (3.6)
Oppositional defiant	3.7 (2.8)	4.2 (2.5)
Conduct	3.5 (4.2)	4.4 (4.2)
	Mothers (n=701)	Fathers (n=530)
Age	41.9 (6.4)	44.9 (6.7)
Parental education: low/middle/high	26/ 58/ 16	27/ 57/ 19
Depression	107 (15.3)	67 (12.7)
Anxiety	52 (7.4)	32 (6.1)
Avoidant personality	59 (8.4)	55 (10.4)
ADH	71 (10.2)	49 (9.3)
Antisocial personality	36 (5.1)	34 (6.4)
Total	174 (24.8)	127 (24)

ADH: Attention Deficit/Hyper Activity.

Table 2. Mean problem scores (SD) in boys and girls of whom 1. no parents participated (No), 2. both parents participated (M+F), 3. only father participated (F), 4. only mother participated (M).

	Girls				Boys			
	No (114)	M+F (205)	F (13)	M (85)	No (167)	M+F (264)	F (24)	M (98)
Dep	6.3 (4.7)	6.7 (4.4)	6.7 (4.3)	8.6 (4.8)*	5.6 (4.1)	5.3 (3.9)	5.5 (4.3)	5.6 (4.1)
Anx	3.7 (2.8)	4.6 (3.1)	4.4 (2.4)	4.5 (3.0)	3.7 (2.7)	3.8 (2.7)	2.7 (2.1)	3.3 (2.6)
ADH	5.5 (3.8)	5.2 (3.6)	5.2 (4.1)	6.0 (3.9)	7.4 (3.7)	7.3 (3.6)	6.3 (3.7)	7.5 (3.6)
OD	3.4 (2.7)	3.6 (2.6)	2.9 (1.9)	4.3 (3.1)	4.2 (2.8)	4.1 (2.6)	4.1 (2.5)	4.6 (2.6)
Conduct	3.7 (4.4)	2.9 (3.6)	3.0 (3.5)	5.1 (5.6)*	4.9 (4.9)	4.2 (4.1)	5.5 (5.7)	4.8 (4.1)

*P<.005, ADH: Attention Deficit/Hyperactivity problems, Anx: anxiety problems, Dep: depressive problems, OD: oppositional defiant problems.

Parent-offspring associations

Table 3 shows the correlations between the parental and offspring problem scores, separately for girls and boys and mothers and fathers. Almost all parent-offspring correlations were significant and ranged between 0.15 and 0.25. A notable exception was anxiety problem scores in girls which were neither associated with paternal ADH nor with maternal and paternal antisocial personality problem scores. This was also seen in boys, but only for maternal and not for paternal problem scores. Another notable exception were conduct problem scores in boys, which were not associated with any of the paternal internalizing problem scores.

Subsequently, we performed the multivariate analyses predicting the offspring scores by maternal or paternal problem scores. Constraining the regression coefficients to be equal for boys and girls revealed no significant differences in the effects of the maternal (p=0.99) and paternal scores (p=0.90) on childhood psychopathology.

The results of the multivariate analyses indicate that the significant correlations found in the univariate analyses are mainly due to the high with-in person correlations for the problem scores. It becomes clear from Table 4 that in the analyses of the maternal problem scores, anxiety was associated with all offspring psychopathology with larger effect sizes for childhood anxiety and depression (~0.20) than for the externalizing problem scores (~0.15). In addition, maternal ADH was associated with offspring ADH with an effect size of 0.20. In the analyses of the paternal problem scores, anxiety was also associated with childhood internalizing psychopathology (effect sizes ~0.20), but not with externalizing psychopathology.

Paternal ADH was associated with childhood ADH and OD (effect sizes ~0.20). There were no significant associations with childhood conduct problems.

The multivariate analyses including the maternal and paternal problems scores with a p-value below 0.10 did not show substantial differences in the results. This indicates that the predictions as found in the separate analyses of the maternal and paternal problem scores not due to spousal resemblance in psychiatric problems.

Table 3. Correlations between parental and offspring problem scores (M = maternal and P = paternal). In bold the significant correlations (p<0.05).

		Mother					Father				
		Dep	Anx	Avoid	ADH	Anti	Dep	Anx	Avoid	ADH	Anti
Dep	Girls	**.27**	**.28**	**.25**	**.17**	**.12**	**.30**	**.27**	**.12**	**.23**	**.20**
	Boys	**.22**	**.30**	**.22**	**.20**	**.18**	**.31**	**.36**	**.25**	**.27**	**.19**
Anx	Girls	**.16**	**.26**	**.28**	**.18**	.08	.13	**.21**	**.14**	.04	-.03
	Boys	**.13**	**.23**	**.19**	.10	.01	**.25**	**.33**	**.18**	**.25**	**.16**
ADH	Girls	**.18**	**.21**	**.18**	**.25**	**.14**	**.26**	.11	**.15**	**.32**	**.17**
	Boys	**.15**	**.19**	**.14**	**.27**	**.13**	**.12**	**.13**	.05	**.20**	.03
OD	Girls	**.23**	**.23**	**.18**	**.23**	**.20**	**.32**	**.22**	**.20**	**.32**	**.21**
	Boys	**.16**	**.21**	**.15**	**.16**	**.16**	**.14**	**.17**	.08	**.25**	**.15**
Conduct	Girls	**.15**	**.17**	.10	**.19**	**.15**	**.26**	.10	**.18**	**.22**	**.18**
	Boys	**.18**	**.21**	.10	**.17**	**.17**	.10	.10	.10	**.16**	**.13**

ADH: Attention Deficit/Hyperactivity, Anti: Antisocial personality, Anx: anxiety, Avoid: Avoidant personality, Dep: depressive, OD: oppositional defiant problems.

Table 4. Standardized regression coefficients for the multivariate analyses with childhood psychopathology predicted by maternal (top) or paternal problem scores (bottom). Bold are the regression coefficients with a p-value below 0.05.

		Childhood Dep			Childhood Anx			Childhood ADH			Childhood OD			Childhood Conduct		
		Beta	S.E.	P	Beta	S.E.	P	Beta	S.E.	P	Beta	S.E.	P	Beta	S.E.	P
Mother	Dep	-0.04	0.07	0.58	**-0.15**	**0.07**	**0.04**	-0.09	0.07	0.15	-0.02	0.07	0.79	0.004	0.07	0.95
	Anx	**0.21**	**0.06**	**<0.001**	**0.25**	**0.06**	**<0.001**	**0.15**	**0.06**	**0.02**	**0.15**	**0.06**	**0.01**	**0.14**	**0.06**	**0.02**
	Avoid	**0.13**	**0.06**	**0.02**	**0.22**	**0.05**	**<0.001**	0.01	0.05	0.84	0.01	0.05	0.86	-0.07	0.06	0.23
	ADH	0.04	0.05	0.38	0.04	0.05	0.43	**0.24**	**0.05**	**<0.001**	0.07	0.05	0.16	0.08	0.06	0.16
	Anti	0.01	0.05	0.88	-0.09	0.05	0.06	-0.02	0.05	0.61	0.09	0.05	0.06	0.08	0.05	0.07
Father	Dep	0.14	0.08	0.09	-0.02	0.08	0.84	0.11	0.07	0.16	0.05	0.08	0.50	0.09	0.08	0.27
	Anx	**0.18**	**0.06**	**0.01**	**0.25**	**0.07**	**0.001**	-0.004	0.07	0.95	0.06	0.06	0.34	-0.04	0.06	0.56
	Avoid	-0.02	0.05	0.63	0.05	0.06	0.44	-0.04	0.06	0.50	-0.03	0.06	0.62	0.03	0.07	0.63
	ADH	0.04	0.07	0.55	0.04	0.07	0.55	**0.23**	**0.06**	**<0.001**	**0.20**	**0.06**	**0.001**	0.09	0.08	0.25
	Anti	0.05	0.07	0.45	-0.06	0.07	0.43	-0.09	0.05	0.10	0.02	0.06	0.67	0.06	0.06	0.31

ADH: Attention Deficit/Hyper Activity, Anti: Antisocial personality, Anx: Anxiety, Avoid: Avoidant personality, Dep: Depressive, OD: Oppositional Defiant problems.

Discussion

This study shows that parents whose children suffer from a variety of psychopathology have a higher risk of experiencing depressive, avoidant personality, and ADH problems than adults in the general population. In contrast to what is found in epidemiological studies in the general population, prevalence rates did not differ between sexes, i.e., mothers and fathers were equally affected with internalizing and ADH problems. Regarding the parent-offspring associations in problem scores at the time of a child's diagnostic evaluation in a child and adolescent psychiatric outpatient clinic, the similarities over the sexes are striking. The associations are not different for boys and girls and maternal problems are as associated with offspring problems as paternal problems. The only difference is that maternal anxiety is associated with all childhood problem scores while paternal anxiety is only associated with childhood internalizing problems. Childhood externalizing problems are associated with paternal ADH problems and childhood ADH problems are associated with maternal ADH problems.

Overall, our results indicate the usefulness of screening parents on psychopathology when their child is evaluated at a child and adolescent psychiatric outpatient clinic. For mothers, this screening should focus on internalizing problems, irrespective of the offspring psychopathology, and on ADH problems when the child experiences ADH problems. For fathers, the focus should be on internalizing problems when children are presented with internalizing problems and on ADH problems when children are presented with externalizing problems. Treatment programs should be developed specifically focused on these multiple affected families. The similarities in the results of mothers and fathers, both for the prevalence rates and for the associations with the offspring problems indicate the need to include fathers in such a screening and subsequent treatment.

Prevalence rates

The higher rates of (sub)clinical scores on the internalizing syndrome scales in fathers and mothers (20%) are in line with other studies investigating current symptoms at the time of the first assessment of a child in an outpatient psychiatric clinic, although the percentages observed in the current study are somewhat lower compared to the previous studies [33-40,48,50]. In addition, we found that parents of children with psychopathology have a higher prevalence rate of (sub)clinical ADH problems, as suggested by one other study in mothers [50]. The equal rates of (sub)clinical scores on antisocial personality problems in comparison to the general population are in

contrast to one earlier study investigating parental antisocial personality [48]. The lack of increased antisocial personality problems and the somewhat lower percentages of internalizing problems may be related to the sample of children in which the data were collected. Most of the previous studies selected children based on one or two diagnoses, i.e. depression, or ADHD and/or conduct disorder. In the study showing higher rates of antisocial personality disorder in parents, for example, this was only true for children with conduct disorder with or without ADHD and not for children with only ADHD. Only two studies included children with a broad range of psychopathology, just as in the current study [39,40]. The prevalence rate for parental internalizing disorders was comparable to ours in one study (18%), but a lot higher (57%) in the other study. Part of the difference with the latter study could be due to the demographic characteristics of the included parents. The sample of the study with similar estimates to ours is more comparable regarding socio-economic status and age of the parents. Future studies collecting data in families of children evaluated in a general child and adolescent outpatient clinic may shed more light on these large differences and identify which parents are especially at risk for psychopathology.

Parent-offspring associations in problem scores

The specificity observed in the father-offspring associations and the lack of associations with maternal externalizing problem scores may seem in contrast to large family studies which indicate that children of parents with psychopathology are not only at risk for the disorder of the parent, but for a broad range of disorders and vice versa [74,75]. One of these studies did not take the frequent co-morbidity of psychiatric disorders into account [74] which can result in significant correlations across disorders as illustrated by the many significant correlations in the univariate analyses in the current study. Three other important differences are that these family studies 1) investigated lifetime disorders in 2) population based samples and 3) did not stratify their analyses by sex [74,75]. The differences with the current results are therefore difficult to interpret.

The strength of the predictions of the offspring problem scores were similar for the paternal and the maternal problem scores (effect sizes ~0.20) and were not attenuated in the analyses including the problem scores of both parents simultaneously. This indicates that psychopathology in fathers and mothers is equally associated with offspring psychopathology agreeing with previous findings as summarized in a review on the influence of paternal psychopathology on their offspring [77]. By simultaneously analyzing the predictions of offspring scores by

maternal and paternal problem scores, we also showed that the contributions of the parents are independent of each other, thus not due to spousal resemblance which is also present in the current study population (correlations within and across syndrome scales varying between 0.13 and 0.30 [119]). This has already been suggested before by studies focusing on depression and/or antisocial personality [199,228,229]. These results underline the importance of involving fathers in research.

Limitations

A few limitations should be kept in mind. Although this sample has one of the largest numbers of fathers included, the participation rate in fathers was still lower than in mothers. Our non-response analyses suggested that families in which only the mothers participated were exposed to less favorable circumstances than the families in which both parents or only the father participated. This pattern of partly non-response in the fathers could have led to an underestimation of the prevalence rates for psychopathology in fathers. It should still be kept in mind that part of these families are single parent families who are known to be at higher risk for adverse events.

It could be considered a limitation that all problem scores were based on parental ratings, either of the child (CBCL) or of the parents (ASR), and not on a more objective measure, such as clinical diagnosis. However, both the CBCL and the ASR problem scores are associated with psychiatric diagnoses. This has been repeatedly demonstrated for the CBCL [see e.g. 230,231]. Further, a study in a subsample of the parents with a (sub)clinical score has shown that 71% and 74% of respectively these fathers and mothers have a lifetime psychiatric mood or anxiety disorder according to the Composite International Diagnostic Interview (CIDI) [232] or ADHD according to the Conners' Adult ADHD Rating Scales (CAARS) [233]. The advantage of analyzing continuous scores is that they capture more information on the individual variation in the presence of psychiatric problems. This signifies that, for example, subclinical comorbid symptoms that do not fulfill the criteria for a DSM-IV diagnosis are reflected in a higher than average problem score. A strength is that the CBCL and the ASR are specifically designed to measure similar constructs over ages, which make them particularly suitable for studying associations between children and parents.

The disadvantage of having one parental measure, instead of two, of the child's psychopathology is that it has been suggested that parental problems can influence the ratings of their child's problems. In 75% of the cases, the questionnaire

was rated by the mother. Studies investigating the influence of parental mood symptoms on the assessment of their children yielded discrepant results (see Maoz et al. [234] for an overview). Overall, it is probably safest to say that parental mood symptoms may increase the parental report of children's problems, but only to a small extent. Our finding that the association between paternal psychopathology and offspring psychopathology is of similar magnitude as the association with maternal psychopathology suggests that shared measurement variance is not of major influence to our results.

It is not possible to draw any conclusions about the mechanisms underlying the association between parental and offspring problems. Twin studies have shown that differences in the susceptibility for psychiatric disorders or traits are substantially explained by genetic factors with an average heritability of 46% [1]. For childhood phenotypes, in contrast to adult phenotypes, an effect of the shared familial environment has also been found with estimates ranging from 10% to 30% in meta-analyses of several measures of internalizing and externalizing problems [4]. For ADHD and related traits, shared environmental influences are consistently found to be absent [4]. Thus, in general, transmission of psychopathology from parents to children can go through genetic as well as environmental factors. Other study designs, such as adoption studies or extended twin designs (including parents of the twins or children of the twins) can further disentangle to what extent the association between parental and offspring psychopathology is due to genetic or environmental effects. A review of children-of twins studies indicates that both effects can play a role, depending on the phenotype under investigation [120].

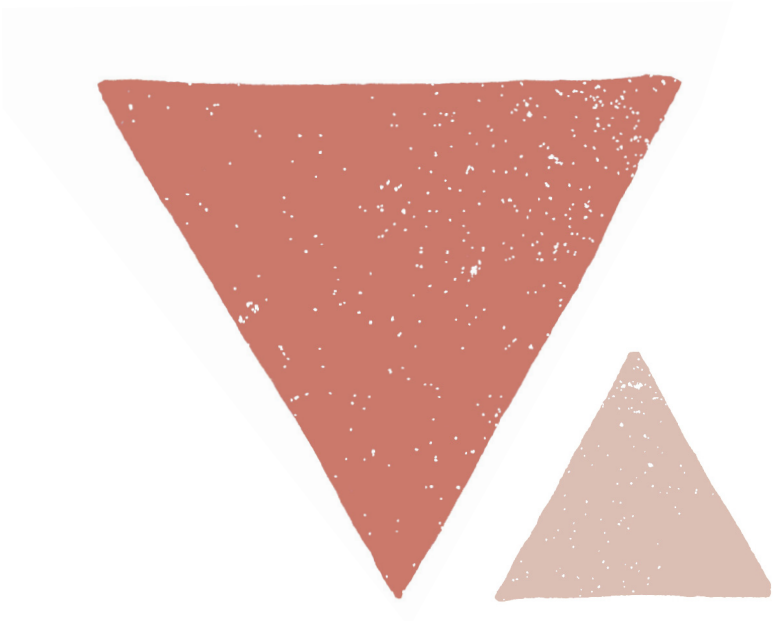
Our findings also do not imply a direction of effect, i.e., the association between parental and offspring problems is not necessarily entirely explained by the transmission of problems from parents to children. It has been shown that a successful depression treatment in mothers also results in a decrease of psychiatric problems in children [227]. However, the reverse has also been found, mothers whose daughters were treated for depression also showed an improvement of their depressive symptoms [196]. It should be noted that still a large group of children and mothers had continuing symptoms despite treatment of the mothers or daughters. Longitudinal studies are needed to elucidate in which families it is sufficient to only treat the admitted patient and in which families, all affected members should be treated at once.

Future steps

This study confirms that part of the families seen in a child and adolescent psychiatric outpatient clinic is in especially high need as not only the child, but also one or both parents are affected. Future studies, involving both mothers and fathers, are warranted to further investigate the associations between parent and offspring problems, not only concurrently but also longitudinally, and to develop specific treatment programs for these families. The question also arises what the prevalence rates are of psychiatric problems in children whose parents are evaluated in a psychiatric outpatient clinic. There have been several family studies investigating offspring psychopathology in parents with psychopathology. However, these mainly focused on lifetime disorders in the offspring [235]. Knowledge is lacking regarding current psychopathology at the time a parent is evaluated for a psychiatric disorder. A study similar to ours, but performed in an adult psychiatric outpatient clinic and focusing on the current problems of the children can indicate for which disorders these children are at risk and inform further treatment studies.

Aggregation of psychopathology in a clinical sample of children and their parents

WHICH PARENTS ARE AT RISK FOR PSYCHOPATHOLOGY? A STUDY IN FAMILIES WITH CHILDREN WITH PSYCHOPATHOLOGY



Chapter 7

Abstract

Background: Parents of children with psychopathology are themselves at increased risk for psychiatric symptoms. We study in a clinical sample of families with children with psychopathology, whether parental symptom scores can be predicted from offspring psychiatric diagnoses or other child, parent and family characteristics. *Methods:* Depressive, anxiety, avoidant personality, attention deficit/hyperactivity (ADHD), and antisocial personality symptoms were measured with the Adult Self Report in 1,805 mothers and 1,361 fathers of 1,866 children with a psychiatric diagnosis as assessed in a child and adolescent psychiatric outpatient clinic. A multivariate model, including all parental symptom scores as dependent variables, was used to simultaneously test the predictions of offspring psychiatric diagnosis (e.g., depression, ADHD, anxiety etc.), child's comorbidity, child's age, parental age, parental educational attainment, employment, and relationship status. *Results:* 35.7% of mothers and 32.8% of fathers scored (sub)clinical for at least one symptom domain, mainly depressive, ADHD or, only in fathers, avoidant personality problems. Parental psychiatric symptoms were generally predicted by unemployment. Parental depressive and ADHD problems were further predicted by offspring depression and offspring ADHD respectively, in addition to not being together with the other parent. Finally, parental avoidant personality symptoms were predicted by offspring pervasive developmental disorders. *Conclusions:* Without implying causality, these results show that in families with children referred to mental health clinics, parental symptom scores are associated with adverse circumstances and with similar psychopathology in their child. This signifies that some children are at a double disadvantage, with more severely affected parents and a more adverse home environment.

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Introduction

Parents whose children suffer from psychiatric symptoms are at an increased risk for psychiatric symptoms themselves. Prevalence rates for parental psychopathology, at the time their child has been referred to a mental health clinic, vary between 18% and 68% [33-40,42,44-50,64,225,236-241]. The majority of these studies focused on parental anxiety and depressive symptoms or disorders, but some also showed increased rates of parental attention-deficit/hyperactivity disorder (ADHD) and antisocial personality disorder. It has been further observed that parental symptoms are not always equivalent to their child's psychiatric problems, e.g. parents can suffer from depressive symptoms while their child has been diagnosed with autism spectrum disorder (ASD), anxiety, ADHD, schizophrenia, oppositional-defiant, or conduct symptoms [34-37,39,40,44-46,48-50,225,236-241]. Aside from the increased burden these symptoms cause in the parents, they can also negatively affect the course of psychiatric problems and outcome of treatment in their child [47,53-55,68,196,226,227,242,243]. These effects might even be long term. Epidemiological studies have shown that around 50% of individuals with a childhood psychiatric disorder still fulfill the criteria of a psychiatric disorder in adulthood and a family history of psychiatric disorders is one of the risk factors for persistence [24,25].

The increased risk for parental psychiatric symptoms is for a large part explained by the heritability of psychiatric disorders [1], which causes psychiatric disorders to run in families. The heritability of psychiatric disorders ranges from 40% (for depression and anxiety) to 80% (for e.g. ADHD and ASD). In addition, the burden of caring for a child with psychopathology can trigger psychiatric symptoms in parents. The observed differences in heritability and potential differences in parental burden per childhood psychopathology may result in variation in risk for the different parental psychiatric disorders and per offspring type of psychopathology. In a study comparing families with children with ASD, ASD + ADHD, or ADHD, depressive scores were found to be highest in the parents of children with ASD, or ASD and ADHD [240]. In a comparison of parents of children with a pure anxiety disorder to parents of children with pure ASD, pure ADHD-combined type, or pure ADHD inattentive type, no differences were found in the level of parental internalizing and externalizing symptoms [241]. The total problem scores were higher in parents of children with the ADHD inattentive type than in parents of children with an anxiety disorder [241]. Parental psychopathology may also be associated with the severity of the offspring symptoms. Parenting stress, which is related to parental

psychopathology [240,241], was observed to be higher when children with ADHD also had comorbid diagnoses, indicating higher severity [244]. This effect was not seen in families with children with comorbid ADHD and ASD [240].

General risk factors known to increase psychopathology, such as financial problems, divorce, being a single parent, or unemployment probably play a role in the prediction of parental psychiatric symptoms in these families as well [245,246]. Furthermore, characteristics of parent and child, like gender and age, might influence the likelihood of parental psychiatric symptoms. A recent large national-claim database study in the United States found the incidence of depression in parents of children diagnosed with autism spectrum disorder to increase with age of the child [238], but the age of children with anxiety disorders was not found to influence parental internalizing and externalizing problem scores [241].

No earlier studies have examined the relationship between, on the one hand, family, parent and child characteristics, including multiple child's psychiatric disorders and comorbidities, and, on the other hand, a broad range of parental psychiatric symptoms. However, information on these factors is relatively easy acquired during child evaluations at mental health clinics. If these characteristics are predictive of parental psychiatric symptoms, they provide valuable information on whether additional care should be provided to the parents, which may also improve the treatment outcome of the child. This study aims to explore risk factors for parental psychiatric symptoms at the time a child is assessed for psychiatric disorders. We assessed psychiatric symptoms in 1,805 mothers and 1,361 fathers from 1,866 children at the time their child was evaluated in a mental health clinic. The majority of the children were diagnosed with ADHD, autism spectrum disorders, or internalizing disorders. We examined whether family (relationship status), parental (education level, occupational status, age and gender) and offspring characteristics (age, kind of psychiatric diagnosis, and comorbidity) predicted depressive, anxiety, ADHD, avoidant personality, and antisocial personality symptom scores in parents.

Methods

Participants and recruitment

Participants came from four child and adolescent psychiatric outpatient clinics in The Netherlands (de Bascule, GGZ inGeest and UvA Minds in Amsterdam and the Erasmus University Medical Center-Sophia Children's Hospital (EUMC) in Rotterdam). In the Netherlands, children are referred to a child and adolescents psychiatric

outpatient clinic by their general practitioner. The four clinics offer mental health care to children who have a range of psychiatric problems such as depression, anxiety, autism spectrum disorder, ADHD, and behavioral disorders. The average age of the children (60.4% boys) was 11 years at first referral and the average age of the mothers and fathers was 43 and 46 years-old, respectively (Table 1).

Data were collected between April 2010 and December 2016. In all clinics, the parents of the child were asked to rate their child's problems as part of the first assessment. If possible, both parents were asked to complete the questionnaires. Only parents who did not have a sufficient knowledge of the Dutch language were excluded from participation. All studies were approved by the Central Ethics Committees of the participating institutions. Table 1 of the Supplementary material provides details on the four different study samples. For the current study, families were selected if the parental survey was filled in by the biological parent. We excluded data of children who did not fulfill the criteria of a psychiatric diagnosis after assessment (n=30). In total, data were analyzed for 1,805 mothers (96.73%) and 1,361 fathers (72.94%) from 1,866 unrelated children.

Measures

Demographic information regarding the child's age, the parent's age, parent's education level, employment, and relationship status was collected from a questionnaire that was administered before the first visit. Parental education level was defined in three categories: low (primary school, lower vocational schooling and lower secondary schooling), middle (intermediate vocational schooling and intermediate/higher secondary schooling) and high (higher vocational schooling, university and post graduate). Parents were employed or unemployed (yes/no). Relationship status was coded as being together with other biological parent yes/no and 'no' includes single parenthood from birth onwards or being divorced later on.

Parental psychiatric symptoms were measured with the Adult Self Report (ASR), which is part of the Achenbach System of Empirically Based Assessment (ASEBA) [175]. In the ASR, adults rate 120 items on a three-point scale (0 = not true, 1= somewhat true, 2= very true). The ASR offers, besides the commonly used empirical scales, DSM-oriented scales that are associated with the presence or absence of DSM diagnoses [215,216]. We analyzed the following DSM-oriented scales: depressive symptoms, anxiety symptoms, avoidant personality symptoms, ADHD symptoms, and antisocial personality symptoms.

DSM diagnoses in children were assessed by a multi-disciplinary team of clinicians based on the information obtained from the parents and child in diagnostic interviews and in the questionnaires collected before the first assessments combined with the teacher reports on the child's psychiatric problems and sometimes observations in the classroom. The diagnoses were categorized following the DSM–IV diagnostic categories [98]: attention deficit/hyperactivity disorders (ADHD), pervasive developmental disorders (PDD), disruptive behavior disorders, depressive disorders, anxiety disorders, tic disorders, eating disorders and, disorder of infancy, childhood, or adolescence not otherwise specified (NOS). We analyzed post-traumatic stress disorder as a separate category, i.e. not included in anxiety disorders, in line with the DSM-5. Adjustment disorder with mixed anxiety and depressed mood was added to depressive disorders. Adjustment disorder with disturbance of conduct was added to disruptive behavior disorders. This left 151 children with a diagnosis that could not be categorized (e.g. selective mutism or somatization disorder), who are listed as "other". A binary measure of comorbidity was constructed based on whether the child received one or more DSM diagnoses.

Analyses

As dichotomizing the parental scores into a normal and (sub)clinical score results in a loss of information on the variation and thereby in a loss of statistical power [112], the continuous symptom scores were analyzed. To get a first impression of the associations between the family, child, and parent characteristics, and the parental psychiatric symptoms, we calculated the means and standard deviations for the maternal and paternal psychiatric problem scales by the different childhood diagnoses, comorbidity within the child, parental education level, parental employment status, and, relationship status. A t-test was carried out to test whether the mean maternal and paternal psychiatric symptom scores significantly differed in their mean psychiatric symptom scores.

Next, we performed a multivariate multiple regression analysis in Mplus, in which all maternal and paternal symptom scores were predicted by all child's psychiatric diagnostic categories (i.e., depression yes/no, adhd yes/no etc.), comorbidity (yes/no), the age of the child, the age of the parent, the education level of the parent (low-middle-high), employment of the parent (yes/no), and the relationship status of the biological parents (yes/no). To control for associations between psychiatric symptoms and for spousal resemblance, we allowed the parental symptom scores to correlate within the parent and across mothers and fathers [119] (see Figure 1). Since the thirteen predictors were correlated, we used the software

'matSpD' to calculate that a p-value of <0.004 as a threshold for statistical significance is appropriate to correct for multiple testing [247,248].

Results

Descriptives of the parents and children

Characteristics of the parents and children are shown in Table 1. In the children, boys mainly received a diagnoses of ADHD (52%), PDD (23.2%), or an anxiety disorder (17%), while girls were mostly diagnosed with anxiety disorder (32.3%), ADHD (30%), PDD (11.2%), or a depressive disorder (10.3%). Since the numbers of children with tic and eating disorders were low, these categories were not included as predictors in the analyses. The group of "other" diagnoses was not included as a predictor either, due to the variety among the diagnoses. In the parents, 35.7% of the mothers and 32.8% of the fathers scored in the (sub)clinical range on at least one of the psychiatric symptom domains at time of the first assessment of their child. The highest percentages of parents scoring above the threshold were for depressive problems, ADHD and, in fathers only, avoidant personality problems with percentages varying between 11% and 15%.

Table 1. Descriptives of parental and offspring characteristics. Parental mean (SD) age, education level (%), employment status (%), relationship status (%) and number of parents (%) with a score in the (sub)clinical range are displayed at the top. Mean age (SD) and DSM diagnoses for the children (%) are displayed at the bottom.

	Mothers (N=1,805)	Fathers (N=1,361)
Mean age (SD)	43.50 (6.22)	46.22 (6.47)
Education level (n(%))		
Low	262 (15.1%)	219 (16.9%)
Intermediate	475 (27.3%	344 (26.6%)
High	1000 (57.6%)	730 (56.5%)
Employment status		
Yes	1407 (78.6%)	1219 (90.6%)
No	384 (21.4%)	127 (9.4%)
Relationship status		
Yes	1201 (67.9%)	1072 (78.8%)
No	568 (32.1%)	289 (21.2%)
(Sub)clinical range total (n(%))	643 (35.7%)	451 (32.8%)
Per analyzed domain:		
Depressive	263 (14.6%)	176 (12.8%)
Anxiety	129 (7.2%)	83 (6.0%)
Avoidant	130 (7.2%)	156 (11.3%)
ADHD	232 (12.9%)	156 (11.3%)
Antisocial	125 (6.9%)	103 (7.5%)
	Boys (N=1,127)	Girls (N=739)
Mean age (SD)	10.80 (3.12)	12.00 (3.59)
DSM diagnosis (n(%))		
ADHD	586 (52%)	224 (30.3%)
PDD	262 (23.2%)	83 (11.2%)
Disruptive behavior	61 (5.4%)	44 (6%)
Depression	54 (4.8%)	76 (10.3%)
Anxiety	192 (17%)	239 (32.3%
Trauma	45 (4%)	52 (7%)
Tic	13 (1.2%)	5 (.7%)
Eating disorders	4 (.4%)	37 (5%)
NOS	67 (5.9%)	45 (6.1%)
Other	78 (6.9%)	71 (9.6%)
More than 1 diagnoses	242 (21.5%)	143 (19.2%)

Employment status: having a job yes/no. Relationship status: together with biological parent yes/no (where 'no' includes single parenthood from birth onwards or being divorced later on). ADHD: Attention deficit/hyperactivity disorders. PDD: Pervasive Developmental disorders.

Predictions

Figures 2a and 2b depict the mean maternal and paternal scores on the different psychiatric symptom scales by child's diagnosis versus all other diagnoses. Figures 2c displays the mean maternal and paternal scores by education level of the parent, employment, relationship status, and the child's comorbidity. Mothers' psychiatric symptom scores were higher than fathers' ($p < .01$, with the exception of avoidant symptoms $p = .07$), but the effects of the predictors were similar in direction and magnitude in mothers and fathers (see Figures 2). Therefore, in the multivariate model the beta's were constrained to be equal for mothers and fathers (see Figure 1).

The multivariate analysis showed that parents who are unemployed have increased scores for depressive symptoms, anxiety symptoms, avoidant personality symptoms and ADHD (Table 2). Parents who are not together with the biological parent have increased scores for depressive symptoms and ADHD. Age of the child or parent did not significantly predict the risk for any of the parental psychiatric symptoms, nor did parental education level. Some childhood diagnoses predicted specific parental psychiatric symptoms. Offspring ADHD predicted parental ADHD, offspring depression predicted parental depressive symptoms, and offspring PDD predicted parental avoidant personality symptoms. Anti-social personality symptoms were not predicted by any offspring diagnosis and there weren't any significant predictions by offspring trauma, disorder of infancy, childhood, or adolescence NOS or child comorbidity.

Table 2. Standardized regression coefficients for the multivariate multi-group analysis with the parental psychiatric symptom scales predicted by the child diagnoses, comorbidity (yes/no), age of the child and parent, education level of the parent (low-middle-high) and relationship (yes/no together) and employment status (yes/no employed).

	Depressive		Anxiety		Avoidant		ADHD		Antisocial	
	β	SE	β	SE	β	SE	β	SE	β	SE
Child diagnosis										
ADHD	.76	.30	.19	.22	.07	.18	1.17*	.34	.15	.20
PDD	.60	.30	.34	.22	.63*	.20	.54	.34	-.05	.20
Disruptive	.61	.47	.73	.30	.05	.32	.24	.53	.29	.36
Depression	1.65*	.43	.58	.28	.37	.25	.76	.49	.24	.32
Anxiety	.38	.29	.37	.28	.15	.19	.09	.33	-.37	.20
Trauma	.81	.54	.27	.37	.21	.33	.05	.52	.13	.32
NOS	.60	.41	.44	.30	.17	.25	-.05	.44	-.19	.28
Comorbidity	-.52	.29	.02	.21	-.07	.19	-.07	.34	.21	.21
Characteristics										
Child age	.02	.03	.05	.02	.01	.02	.02	.03	-.01	.02
Parent age	.01	.02	-.01	.01	.00	.01	-.01	.02	.03	.01
Education level	-.14	.12	.04	.08	.-.15	.07	.08	.12	.03	.07
Employment	-1.36*	.29	-.82*	.19	-.80*	.17	-.87*	.28	-.28	.16
Relationship	-.96*	.23	-.37	.14	-.16	.13	-1.02*	.24	-.46	.18

*p< 0.004. ADHD: Attention deficit/hyperactivity disorders. PDD: Pervasive Developmental disorders. NOS: Disorders of infancy, childhood, or adolescence Not Otherwise Specified.

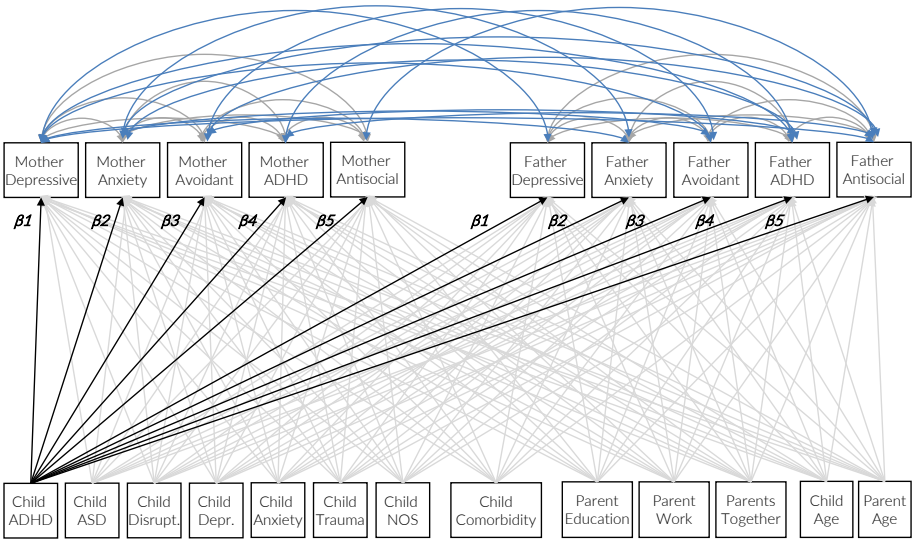


Figure 1. The multivariate model: the psychiatric symptom scores are correlated within the parent and between mothers and fathers. The child's diagnoses, comorbidity and the demographic variables (i.e. education level, employment and relationship status and age of the child and parent) predict the parental psychiatric symptom scales. The beta's were constrained to be equal for mothers and fathers (β1- β5). ADHD: Attention deficit/hyperactivity disorders. PDD: Pervasive Developmental disorders. Disrupt: Disruptive Behavior disorders. Depr: Depressive disorders. NOS: Disorders of infancy, childhood, or adolescence Not Otherwise Specified.

Figure 2a and b. Means of the maternal (figure 2a) paternal (figure 2b) psychiatric symptom scores of the Adult Self Report by child's diagnosis versus all other diagnoses. ADHD: Attention deficit/hyperactivity disorders. PDD: Pervasive Developmental disorders. Disruptive: Disruptive Behavior disorders. NOS: Disorders of infancy, childhood, or adolescence Not Otherwise Specified.

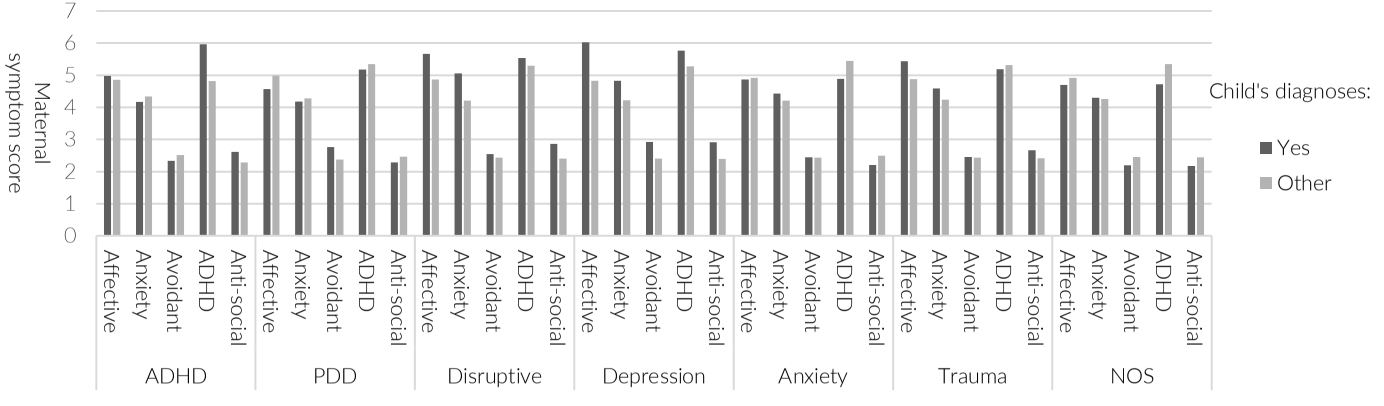


Figure 2a

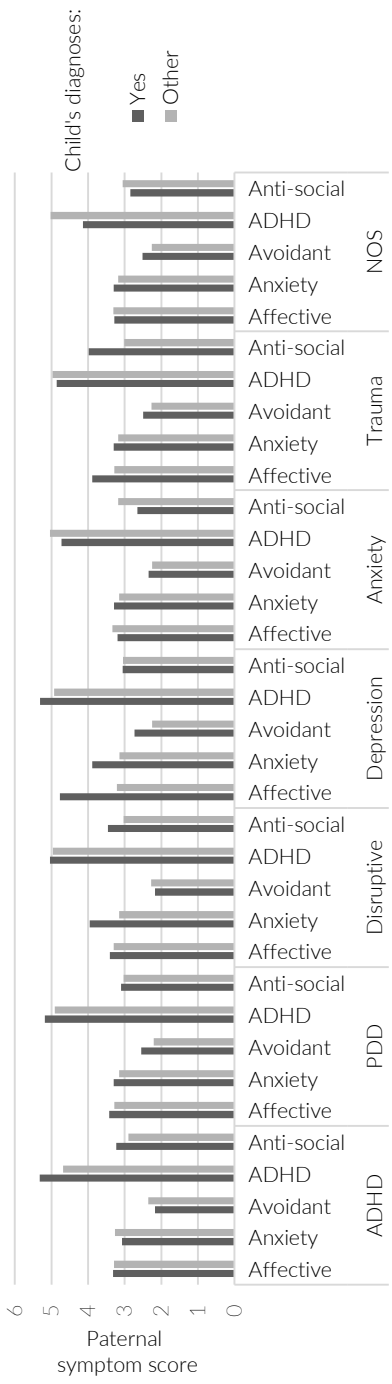
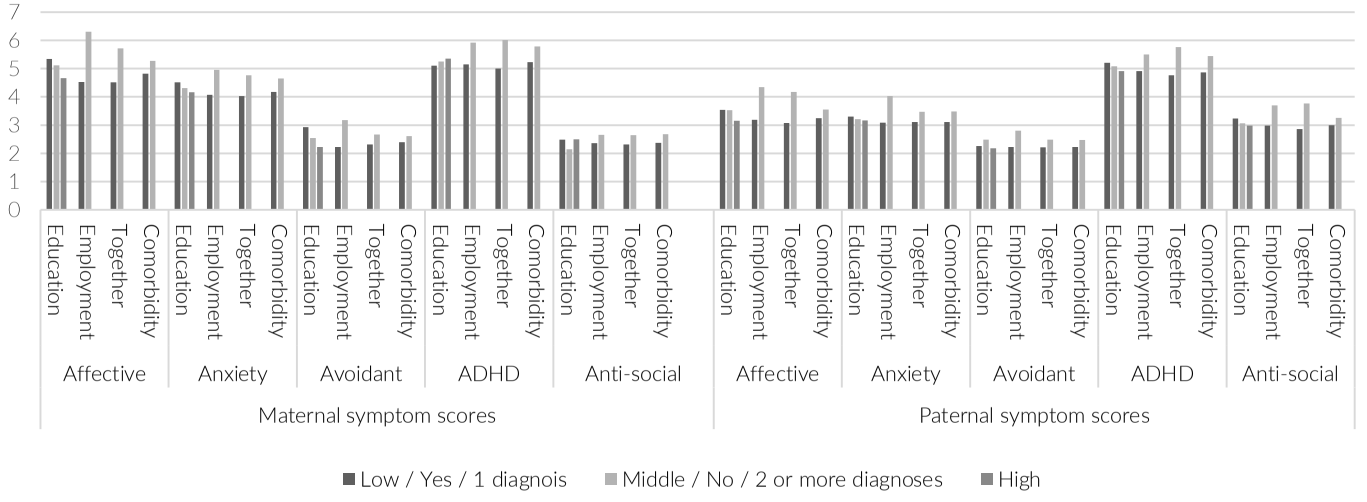

Child's diagnoses:
Yes
Other
Anti-social
ADHD
Avoidant
Anxiety
Affective
NOS
Trauma
Anxiety
Depression
Disruptive
PDD
ADHD
6
5
4
3
2
1
0
Paternal
symptom score

Figure 2b

Figure 2c. Means of the maternal paternal psychiatric symptom scores of the Adult Self Report by education level (low, middle, high), work status (yes/no), whether the biological parents of the child are together (yes/no) and by the child's comorbidity. ADHD: Attention deficit/hyperactivity disorders.



Discussion

This is, to our knowledge, the first study to examine which factors predict a broad range of maternal and paternal psychiatric symptoms scores in families with children assessed for psychopathology in an outpatient psychiatric clinic. 35.7% of the mothers and 32.8% of the fathers of clinically referred children scored in the (sub)clinical range for one of the psychiatric symptom scales, mainly depressive, ADHD or, in fathers, avoidant personality symptoms. Results further showed the importance of family risk factors (namely employment and relationship status) for parental psychopathology, and of child's diagnoses of ADHD, depression and pervasive developmental disorders, specifically on parental ADHD, depressive symptoms and avoidant personality symptoms respectively. Our findings indicate that a group of children is especially disadvantaged since they live in adverse family circumstances and their mothers and fathers also suffer from psychopathology.

This study, including the largest sample of fathers so far (72.94% of the children had father data), confirms again the necessity of parental screening of both mothers and fathers when a child is referred to a mental health clinic [119,225]. Our findings on the associations of parental symptom scores with family circumstances (employment and relationship status) were also in line with previous research [245,246], indicating how problems can accumulate in families. Furthermore, we found parental symptom scores to be predicted by similar psychopathology in their child, regarding depression, ADHD and parental avoidant personality symptoms. Contrary to the study by van Steijn et al. [240], offspring pervasive developmental disorders did not predict depressive symptoms in parents. However, avoidant personality symptoms, that we found to be predicted by offspring PDD, were not included in the former study and are also associated with depressive symptoms. Future studies should clarify whether PDD in offspring is indeed mainly related to avoidant personality problems instead of depression.

In contrast to an earlier study on parents of children with PDD [238], but in line with study on parents of children with anxiety disorders [241], we did not find an effect of the age of the child on parental psychopathology. It could be that the age effect is confined to parents of children with PDD as parents become more aware of the continuing disabilities when their child becomes older. In the current analysis, this effect would then be diluted by the lack of the effect of the child's age for other disorders (e.g. anxiety disorders).

The predictions were tested on the continuous symptom scores. As a sensitivity analysis, we additionally performed univariate logistic regression analyses including all variables from the multivariate analyses (the 7 child psychiatric diagnoses, comorbidity, child age and gender, parent age and gender, parental relationship status and occupational status) as predictors for parental (sub)clinical scores yes/no. In these analyses only the prediction of a parental score in the (sub)clinical range for ADHD by the offspring ADHD diagnosis showed a significant effect (see Supplementary Table 2), in addition to the significant effects of unemployment and not being together. The absence of significant effects of offspring depression and ASD could well be due to the loss of statistical power in analysing dichotomous variables.

This study has several strengths, such as the large sample size overall and, in particular the inclusion of a large group of fathers, the broad assessment of psychiatric symptoms in the parents, the inclusion of children with various psychiatric diagnoses, and the use of a statistical method that takes into account the associations between psychiatric symptoms. There are also several limitations. Although response rates were fairly high (at least 60%, after the pilot study), not all parents reported on their psychiatric symptoms. The percentage of employed mothers and fathers in our sample was higher than in the general Dutch population (mothers: 67.9% vs. 61.6%, fathers: 90.6% vs.71%), while the percentage of parents not being together (32.1% in case of mothers participation, 21.2% for fathers) was lower than the 39.6% divorce rate in the Netherlands [249,250]. This may suggest a response bias in our sample, which has most likely led to an underestimation of the prevalence rates for parental psychopathology. Psychiatric diagnoses in the children were mostly based on clinician's views and not on standardized interviews, although, if indicated, the Autism Diagnostic Observation Schedule (ADOS) and the Autism Diagnostic Interview (ADI) were used [251,252]. Next, we did not differentiate between childhood psychiatric disorders in boys or girls, due to our sample size (e.g., paternal psychiatric symptom ratings were only available for 23 girls with disruptive behavior disorder). However, a visual inspection of the means of the parental psychiatric symptom scores by child's diagnosis, comorbidity and family characteristics for boys and girls separately showed no consistent gender differences.

We would like to emphasize that our findings do not imply causal effects. The association between unemployment and parental psychiatric symptoms could evenly be due to the severity of the child's problems which resulted in the parent both having to quit the job and suffering from psychopathology. Moreover, parent

and offspring psychopathology are mutually associated. Remission of maternal depression has a positive effect on their children's psychiatric symptoms [227] and treatment of a child's psychopathology has a positive effect on mother's depressive symptoms [196]. A longitudinal study in a population based sample showed that the child's mental health status at 5 and at 14 years independently predicted maternal mental health 21 years post birth of the child, while adjusting for environmental risk factors and mother's prenatal mental health [253]. Future experimental and longitudinal studies can provide more insight into the direction of effect.

Still, our results do indicate which families with children with psychopathology are at a higher risk of having affected parents. Since parental psychopathology can influence treatment outcome [47,53-55,68,196,226,227,242,243], it is likely that providing additional care and treatment to these parents is beneficial for the children. Overall, we now know that parents experience higher rates of psychiatric symptoms and that holds for both mothers and fathers. The associations between parent and offspring psychopathology have also been shown to be similar in magnitude for mothers and fathers [225]. Furthermore, previous analyses in part of this sample showed that parents of a child with psychopathology are more alike regarding their psychiatric symptoms than parents in the general population, i.e. if one of the parents suffers from psychiatric symptoms the other parent has an increased chance of psychopathology [119]. We now add that the circumstances of a family, i.e. employment and relationship status, are associated with increased risk for parental psychopathology in addition to specific predictions by offspring psychopathology. Future research should investigate how the mothers, fathers, and children in these multiple affected families, can be helped most effectively. For example, is it more effective to treat the psychopathology of the child in order to reduce the psychopathology of the parent, or to treat the psychopathology of the parent to reduce the psychopathology of the child, or is it more effective to treat the psychopathology of the family member affected him/herself? This again argues for bridging the gap between child psychiatry and adult psychiatry and establish clinics that are able to provide integrated care for the whole family.

Supplement to Chapter 7

Table 1. Descriptives of the sample per child and adolescent psychiatry outpatient clinic. Mean (SD) age, education level (%), employment status (%), relationship status (%) and mean (SD) symptom scores for mothers and fathers per psychiatric symptom scale. ADHD: Attention deficit/hyperactivity disorders.

	Bascule (N=183)	GGZ inGeest (N=410)	UvA Minds (N=919)	Rotterdam (N=354)
Age (Mean (SD))				
Children	10.83 (3.82)	11.70 (3.77)	11.55 (3.03)	10.33 (3.24)
Mothers	42.42 (6.48)	42.92 (7.04)	45.04 (5.46)	40.35 (5.68)
Fathers	45.92 (6.67)	47.10 (6.68)	47.34 (5.98)	42.76 (6.20)
Education level (n (%))				
Mothers				
Low	38 (22.6%)	56 (15%)	71 (8%)	101 (31.6%)
Intermediate	54 (32.1%)	107 (28.7%)	191 (21.5%)	130 (40.6%)
High	76 (45.2%)	210 (56.3%)	628 (70.6%)	89 (27.8%)
Fathers				
Low	24 (21.8%)	35 (15.2%)	83 (12%)	104 (32.7%)
Intermediate	31 (28.2%)	68 (29.4%)	155 (22.4%)	110 (34.6%)
High	55 (50%)	128 (55.4%)	455 (65.7%)	104 (32.7%)
Employment status (n (%))				
Mothers employed	117 (69.6%)	280 (72.7%)	749 (81.9%)	275 (81.6%)
Fathers employed	96 (85%)	209 (87.4%)	659 (91.5%)	305 (92.4%)
Relationship status (n (%))				
Biological parents together	123 (69.1%)	227 (58.4%)	620 (67.5%)	264 (77.9%)
Symptom scores (Mean (SD))				
Mothers				
Depression	5.28 (4.72)	5.27 (4.94)	4.78 (4.02)	4.66 (4.23)
Anxiety	4.66 (3.07)	4.37 (3.07)	4.18 (2.63)	4.17 (2.62)
Avoidant	2.48 (2.40)	2.50 (2.63)	2.24 (2.24)	2.87 (2.48)
ADHD	5.04 (4.03)	5.12 (4.29)	5.56 (4.46)	4.99 (4.08)
Antisocial	2.39 (2.36)	2.50 (2.55)	2.52 (2.62)	2.08 (1.99)
Fathers				
Depression	3.44 (4.36)	3.01 (3.13)	3.32 (3.36)	3.46 (3.48)
Anxiety	3.28 (2.64)	2.98 (2.18)	3.14 (2.41)	3.42 (2.51)
Avoidant	2.40 (2.66)	1.95 (2.28)	2.33 (2.40)	2.35 (2.41)
ADHD	4.86 (4.73)	4.28 (4.19)	5.30 (4.14)	4.73 (3.76)
Antisocial	3.30 (3.99)	3.06 (3.07)	3.23 (2.88)	2.47 (2.51)

Table 2: The percentage of parents with a score in the (sub)clinical range per psychiatric symptom scale (italic) by the child diagnosis (bold) / all other child diagnoses.

	ADHD	**PDD**	**Disruptive**	**Depression**	**Anxiety**	**Trauma**	**NOS**
	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No	Yes / No
Depressive	14.3% / 13.4%	13.6% / 13.9%	16% / 13.7%	20.8% / 13.3%	13.3% / 14%	22.2% / 13.4%	10.2% / 14%
Anxiety	6.5% / 6.9%	6.8% / 6.6%	8% / 6.6%	12.3% / 6.3%	6.8% / 6.6%	11.1% / 6.5%	5.1% / 6.8%
Avoidant	8.9% / 9.1%	11.1% / 8.5%	7.4% / 9.1%	11.3% / 8.8%	9.3% / 8.9%	9.8% / 9%	6.6% / 9.1%
ADHD	15.2% / 9.8%*	12.7% / 12.1%	9.3% / 12.4%	17.5% / 11.8%	10.7% / 12.7%	12.2% / 12.4%	7.7% / 12.5%
Antisocial	9% / 5.7%	6.1% / 7.4%	10.5% / 7%	9.4% / 7%	4.7% / 8%	10.5% / 7%	6.1% / 7.2%

*p<0.004. ADHD: Attention deficit/hyperactivity disorders. PDD: Pervasive Developmental disorders. Disruptive: Disruptive Behavior disorders. NOS: Disorders of infancy, childhood, or adolescence Not Otherwise Specified.

THE LONGITUDINAL ASSOCIATION BETWEEN PARENTAL AND CHILDREN'S PSYCHIATRIC SYMPTOMS. A NATURALISTIC CLINICAL STUDY

Chapter 8

Abstract

Background: Parental psychiatric symptoms may negatively affect the outcome of children's psychiatric symptoms. Studies have so far mainly focused on the effects of maternal depression. We studied the effect of a broad range of psychiatric symptoms in both mothers and fathers on the child's outcome. *Methods:* Internalizing and externalizing psychiatric symptoms were assessed in 742 mothers, 440 fathers and their 811 children at the first evaluation in a child and adolescent psychiatric outpatient clinic and at follow-up (on average 1.7 years later). It was tested whether the child's symptom scores at follow-up were predicted by the parental symptoms scores at baseline, parental scores at follow-up and the child's score at baseline. The model also included the associations between parent and offspring scores at baseline as well as gender and age of the child, and time of follow-up. *Results:* Children whose parents scored above the (sub)clinical threshold at baseline had higher symptom scores at baseline and at follow-up. Offspring follow-up scores were most strongly predicted by offspring baseline scores, in addition to predictions by parental psychiatric symptoms at follow-up. Offspring symptom scores at follow-up were not predicted by parental scores at baseline, with the exception of maternal ADHD symptoms at baseline predicting lower child's ADHD symptoms at follow-up. *Conclusions:* The higher symptom scores at follow-up in children of parents with psychopathology are explained by higher symptom scores at baseline and by parental symptoms at follow-up. Parental treatment may improve the outcome for these children that are at risk for persisting symptoms.

Based on: Wesseldijk LW, Dieleman GC, van Steensel FJA, Blijenberg EJ, Bartels M, Boomsma DI, Bögels SM, Middeldorp CM. The longitudinal association between parental and children's psychiatric symptoms. A naturalistic clinical study. To be submitted.*

*Based on data from GGZ inGeest, UvA Minds and the Erasmus University Medical Center-Sophia Children's Hospital

Introduction

Parents whose children are evaluated for a psychiatric disorder at a child and adolescent psychiatric outpatient clinic, have shown increased prevalence rates of psychiatric disorders, varying between 18% and 68% at the time of the first assessment (see [225] for an overview of the literature). A next question is whether parental psychiatric symptoms have an effect on the outcome of the children's psychiatric symptoms.

This question has been most extensively addressed for maternal depressive symptoms, which appeared to be associated with a worse treatment outcome for the child's depression [196,254], as well as for anxiety problems [see for review: 53], conduct problems [60,66], externalizing problems [54,68], and attention deficit hyperactivity disorder (ADHD) [64,69]. Fewer studies focused on other psychiatric symptoms or on paternal symptoms. Similar associations as for maternal depression were reported between maternal anxiety symptoms and the outcome of youth anxiety problems [61,63,255,256], between non-specified maternal mental health problems and youth total, internalizing, and externalizing problems [47], between parental ADHD and the outcome of youth ADHD [70], and between parental health (including depression and anxiety) and youth outcomes regarding autism spectrum disorder [see for review: 71]. In contrast, two longitudinal studies did not find an effect of maternal anxiety or a broad measure of parental psychopathology on the child's anxiety outcome [257] and some even reported a positive influence of parental anxiety on the outcome of anxiety in the child [258,259].

Studies that separately analyzed paternal psychiatric symptoms reported paternal substance abuse to be associated with poorer treatment response for youth conduct problems [66], and paternal anxiety [56,59,61,256] or depression [59] with poorer treatment response in youth with anxiety. Paternal ADHD appeared to be associated with a smaller decrease in children's behavioral problems, but not ADHD [57]. Samples of fathers were smaller and responses rates were lower compared to mothers. One study in 3,200 children referred to child and adolescent psychiatric clinics rated treatment outcome as improved, stable or got worse according to the clinician. They included around 2,000 fathers [260] and found a history of paternal anxiety to positively influence treatment outcome in the child, while maternal or paternal depression, substance use, bipolar, ADHD, or maternal anxiety had no effect.

Overall, previous studies have indicated that parental psychopathology is negatively associated with the child's outcome, but findings are not entirely consistent and mostly limited to the effect of maternal psychopathology. Furthermore, most studies investigated a single psychiatric disorder in parents, thus not taking comorbidity into account. Our previous research showed that part of the significant associations between parental and offspring symptom scores found in univariate analyses, disappeared in a multivariate analysis, indicating that they were explained by the correlations within parental symptoms scores [225]. This may also explain longitudinal associations, e.g., the associations between maternal depression and the outcome of offspring externalizing disorders can also be due to co-morbid maternal disorders. Another outstanding question is whether the effect of parental symptoms at the start of the treatment on offspring outcome is due to a long-term effect of parental psychopathology at baseline or whether it can be ascribed to parental symptoms at the time of the follow-up. This has been rarely addressed by earlier studies with one exception [255], who found an association between lower maternal anxiety at baseline and a better outcome of youth anxiety.

The current naturalistic study aimed to investigate the association between both maternal and paternal psychiatric symptoms at baseline with offspring symptoms at follow-up, while taking into account co-morbidity and parental symptoms at follow-up. Therefore, we analyzed data from 742 mothers and 440 fathers and their 811 children who were assessed on a broad range of internalizing and externalizing psychiatric symptoms at the time of the child's evaluation at a child and adolescent psychiatric outpatient clinic and at follow-up 1 to 5 years later. Analyses were performed separately for mothers and fathers.

Methods

Participants

Data were obtained between April 2010 and December 2016 in three child and adolescent psychiatric outpatient clinics in The Netherlands (GGZ inGeest and UvA Minds in Amsterdam and the Erasmus University Medical Center-Sophia Children's Hospital (EUMC) in Rotterdam) (see Wesseldijk et al., submitted for a detailed description of the samples). Parents were asked to complete a survey about their own and their child's psychiatric symptoms before the first visit to the child and adolescent psychiatry outpatient clinics. Parents who were not sufficiently fluent in Dutch were excluded from participation. Families that completed the survey and

gave their consent were approached between one to five years later to complete the same survey assessing their child's and their own psychiatric symptoms (the average follow-up time varied between 1.06 years (SD = .64) at the UvA Minds clinic, 1.90 years (SD =.45) at the GGZ inGeest and 4.66 years (SD = .49) in the Erasmus EUMC sample). From the 1,771 families with surveys available at baseline, follow-up data were received from 811 families (a family-response rate of 45.8%). Sixty-three percent of the children in the families that participated in the follow-up were boys (N girls 303, N boys 508, N mothers 742, N fathers 440). When the families first entered the clinic, the girls were on average 11.9 years (SD = 3.5) and boys 10.9 years (SD = 3.0), during follow-up the girls were on average 13.9 years (SD = 3.5) and boys 12.47 years (SD = 3.1). The mothers, fathers and children of the families that did not participate in the follow-up measurement showed a similar psychiatric symptom scores at baseline compared to the mothers, fathers and children of the families who did participate in the follow-up (see Supplementary Table 1).

As this is a naturalistic follow-up study, children as well as parents received treatment as the clinicians and families deemed appropriate. Treatment for children generally included parental guidance, cognitive behavioral treatment, mindfulness and medication. Parents could be directed for individual treatment.

Measures

Demographic information regarding the child's age, gender and the parents' education level, employment and relationship status were collected in a survey administered before the first visit. Education level was defined in three categories: low (primary school, lower vocational schooling and lower secondary schooling), middle (intermediate vocational schooling and intermediate/higher secondary schooling) and high (higher vocational schooling, university and post graduate). Parents were either employed or unemployed (yes/no). Relationship status was coded as being together with biological parent (yes/no). A measure of time between baseline and follow-up was constructed by subtracting the date on which the second survey was completed from the date on which the first survey was administered.

Psychiatric symptoms in children and parents were measured with the age-appropriate version of questionnaires belonging to the Achenbach System of Empirically Based Assessment (ASEBA) i.e., the Child Behavior Checklist (CBCL, [99]) and the Adult Self Report (ASR, [175]). In both questionnaires, emotional and behavior problems are rated on a three-point scale (0 to 2; not true, somewhat true, very true). The CBCL depressive, anxiety, attention deficit/hyperactivity (ADHD),

oppositional-defiant and conduct problems and the ASR depressive, anxiety, avoidant personality, ADH, and antisocial personality problems DSM-oriented scales were analyzed. These are associated with the presence or absence of DSM diagnoses, and good validity has been reported [99,105,215,216].

Analyses

We calculated the mean maternal, paternal, and child psychiatric symptom scores at baseline and follow-up using SPSS (version 24). For the children, we calculated these scores separately for children whose parents scored below or above the (sub)clinical threshold at baseline and tested this difference with t-tests. Next, we calculated an effect size (Cohen's d) for the mean difference in the child's psychiatric symptom scores at baseline and follow-up for the two groups of children. As psychiatric symptoms in a parent can influence the ratings of their child's psychiatric symptoms [261], we investigated the other parent's ratings of the child's psychiatric problems as well.

We used Mplus to examine which factors are associated with the children's symptom scores at follow-up. Per CBCL psychiatric symptom scale, we tested in the model, as shown in Figure 1, whether the child's psychiatric symptom score at follow-up is predicted by parental psychiatric symptoms at baseline (β12s in the Figure) and follow-up (β22s in the Figure). As parental and offspring psychiatric symptoms at baseline are also associated, these predictions were also part of the model (β11s in the Figure). Thus, we investigated longitudinal associations, i.e., between parental symptoms at baseline and offspring symptoms at follow-up, and concurrent associations, i.e., the predictions of the offspring symptoms at baseline and follow-up by parental symptoms at baseline and follow-up respectively. We further included the child's psychiatric symptom score at baseline, since this is a known predictor of outcome. Regression analyses were performed to decide which demographic variables should be included as covariates. These showed that parental education level, employment, and relationship status were not associated with offspring symptoms at follow-up, thus were not added. Gender and age of the child and time of follow-up were added to the model. The older the child, the worse the child's depressive, anxiety and conduct problems at follow-up (coefficients ranged between .08 and .12, $p<.05$) and the more time between baseline and follow-up the higher the child's depressive, anxiety, ADHD and conduct problems (coefficients ranged between .31 and .32, $p<.05$). Since length of follow-up time also differed between the clinics, we checked whether the latter effect could be ascribed to differences between clinics instead of time of follow-up. This doesn't seem to be the

case, as mean scores at baseline and follow-up did not systematically differ between the different psychiatric outpatient clinics (Supplementary Table 2).

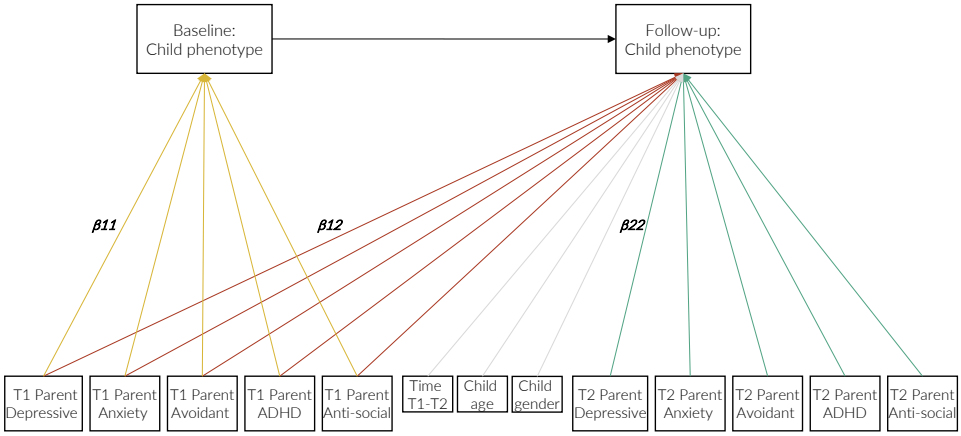


Figure 1. Model in which the child's psychiatric symptom score at follow-up is predicted by the child's psychiatric symptom score and the parental psychiatric symptom scores at baseline (β12s, red) and by the parental psychiatric symptoms at follow-up (β22s, blue). The child's psychiatric symptom score at baseline is also predicted by the parental psychiatric symptom scores at baseline (β11s, yellow). In addition, the length of the follow-up, the child's age and gender are included as predictors. ADHD: Attention deficit/hyperactivity disorders.

To be able to see whether effects differed between parents, analyses were carried out separately for mothers and fathers. A model incorporating the effects of both mothers and fathers simultaneously would have been preferable, as that would also account for spousal resemblance [119]. However, due to the necessity of complete data for predictors in a regression model, this would have led to a large loss of maternal data given that fewer fathers participated. Instead, we additionally performed the five analyses including all maternal and paternal psychiatric symptoms at baseline and follow-up simultaneously as predictors (n= 334 families) to investigate whether any associations were not better explained by association with the symptoms of the other parent.

In our main analyses we tested 11 correlated predictors (the parental psychiatric symptom scores at baseline and follow-up and the child's symptom score at baseline) and therefore used a p-value of .007, calculated by the software 'matSpD' [247,248], as the threshold for statistical significance.

Results

Parental and offspring symptom scores at baseline and follow-up

The mean symptom scores for mothers and fathers at baseline and follow-up are shown in Table 1. All parental mean scores significantly decreased over time ($p<.001$).

To get an impression of the relationship between parental and offspring scores, we calculated the offspring mean scores at baseline and follow-up for the children whose father or mother scored in the normal range and for the children whose parent scored above threshold at baseline for each parental scale and tested whether they significantly differed (Table 2). In general, offspring symptom scores were on average higher if a parent scored above threshold. At baseline, this was seen for the majority of the symptom scores. At follow-up, offspring symptom scores were mostly higher for the scales that measured similar symptoms as the scale for which the parent scored above threshold at baseline, and not for the other scales. Since parental psychopathology can influence the assessment of their child, mean scores were also calculated for the ratings performed by the other parent. This revealed a similar pattern, although the differences between offspring whose parents scored within the normal and in the (sub)clinical range were smaller (see Supplementary Table 3). Table 3 shows that all children, on average, improve, and children with parents scoring above threshold for any of the psychiatric symptoms at baseline do not show less improvement as expressed in the effect sizes of the mean differences between baseline and follow-up.

Predictions

Table 4 shows the standardized regression coefficients as estimated in the model shown in Figure 1. The child's psychiatric symptom scores at follow-up were most strongly predicted by the child's psychiatric symptom score at baseline (coefficients ranged between .37 and .67). Further, several parental symptom scores were significantly associated with concurrently measured offspring symptom scores, i.e., both parental and offspring scores measured at baseline (β11s in Figure 1) or both measured at follow-up (β22s in Figure 1). At baseline, maternal anxiety symptoms predicted offspring depressive, anxiety, oppositional-defiant and conduct problems (coefficients ranged between .17 and .37). Paternal anxiety problems predicted depressive and anxiety problems in the child and paternal ADHD predicted ADHD symptoms (coefficients ranged between .25 and .42). At follow-up, maternal anxiety

symptoms predicted offspring depressive, anxiety and ADHD and maternal ADHD problems predicted offspring anxiety, ADHD and conduct problems (coefficients ranged between .10 and .20). Paternal antisocial personality problems at follow-up predicted conduct problems in the child at follow-up (β=.26). Parental symptom scores at baseline did not predict offspring scores at follow-up, with the exception of maternal ADHD predicting lower ADHD scores in the child (β=-.12). There were fewer significant predictions by paternal symptoms scores than by maternal scores. This can be explained by the smaller sample size of fathers, as the coefficients were mostly of similar magnitude. Moreover, concurrent parent-offspring associations were smaller at follow-up (β22s) than at baseline (β11s)

Table 1. Demographic characteristics and psychiatric symptom scores of the parents at baseline and follow-up.

	Mothers (N=742)		Fathers (N=440)	
Mean age (SD) at baseline	44.4 (6.1)		47.0 (6.2)	
Mean age (SD) at follow-up	46.1 (5.9)		48.5 (6.5)	
Education level (n(%))				
Low	71 (9.8%)		42 (10.2%)	
Intermediate	190 (26.1%)		90 (21.8%)	
High	467 (64.1%)		281 (68%)	
Employment status				
Yes	604 (82.2%)		391 (92.2%)	
No	131 (17.8%)		33 (7.8%)	
Relationship status				
Yes	507 (68.7%)		359 (82%)	
No	231 (31.3%)		79 (18%)	
	Baseline	Follow-up	Baseline	Follow-up
Depressive	4.88 (4.33)	3.80 (3.85)	3.29 (3.36)	2.68 (3.20)
Anxiety	4.22 (2.75)	3.35 (2.64)	3.18 (2.42)	2.40 (2.29)
Avoidant	2.45 (2.42)	1.98 (2.26)	2.26 (2.37)	1.91 (2.23)
ADHD	5.31 (4.34)	4.36 (3.94)	4.93 (4.07)	4.10 (3.66)
Antisocial	2.44 (2.51)	1.65 (1.94)	3.02 (2.80)	2.41 (2.79)

All mean scores significantly differed between baseline and follow-up (p<.001). ADHD: Attention deficit/hyperactivity disorder.

Table 2. Means (SDs) of the child's psychiatric symptom scores at baseline and follow-up for children of parents whose mother's (upper part of the table) or father's (lower part of the table) psychiatric symptom score was in the normal or (sub)clinical range at baseline.

	Parental depressive		Parental anxiety		Parental avoidant		Parental ADHD		Parental antisocial	
	normal	(sub)clinical	normal	(sub)clinical	normal	(sub)clinical	normal	(sub)clinical	normal	(sub)clinical
Mother	N = 1258	N= 212	N = 1366	N = 101	N = 1372	N = 97	N = 1277	N = 193	N = 1364	N = 106
Child baseline:										
Depressive	5.55	7.79***	5.70	8.27***	5.71	8.26***	5.63	7.50***	5.73	7.78***
	(4.07)	(4.55)	(4.12)	(4.61)	(4.14)	(4.54)	(4.17)	(4.17)	(4.19)	(4.03)
Anxiety	3.77	4.75***	3.78	5.61***	3.81	5.35***	3.80	4.64***	3.84	4.77***
	(2.80)	(2.80)	(2.79)	(2.71)	(2.80)	(2.77)	(2.82)	(2.73)	(2.81)	(2.83)
ADHD	6.33	7.03***	6.38	7.16*	6.39	7.10	6.21	7.93***	6.34	7.69***
	(3.61)	(3.52)	(3.59)	(3.81)	(3.60)	(3.59)	(3.56)	(3.53)	(3.59)	(3.57)
ODD	3.81	4.50***	3.84	4.84***	3.85	4.75***	3.80	4.61***	3.82	5.09***
	(2.67)	(2.52)	(2.65)	(2.57)	(2.65)	(2.56)	(2.64)	(2.63)	(2.63)	(2.72)
Conduct	3.51	4.45***	3.56	4.77**	3.56	4.89***	3.49	4.67***	3.52	5.23***
	(3.64)	(4.14)	(3.66)	(4.42)	(3.69)	(4.07)	(3.63)	(4.21)	(3.66)	(4.22)
Child follow-up:	N = 614	N = 93	N = 666	N = 41	N = 664	N = 43	N = 624	N = 83	N =663	N = 44
Depressive	3.25	4.82***	3.38	4.78*	3.32	5.65***	3.37	4.16	3.36	4.93*
	(3.55)	(3.61)	(3.55)	(3.99)	(3.53)	(3.92)	(3.55)	(3.87)	(3.55)	(3.96)
Anxiety	2.25	3.08**	2.27	3.78***	2.26	3.93***	2.33	2.57	2.31	3.02
	(2.43)	(2.70)	(2.42)	(3.05)	(2.41)	(3.00)	(2.48)	(2.53)	(2.48)	(2.50)
ADHD	4.95	5.57	5.06	4.59	4.97	5.93	4.88	6.17***	5.00	5.43
	(3.38)	(3.36)	(3.39)	(3.26)	(3.35)	(3.84)	(3.27)	(3.98)	(3.40)	(3.10)
ODD	2.40	2.73	2.44	2.33	2.39	3.20 *	2.41	2.64	2.40	3.02
	(2.34)	(1.98)	(2.31)	(1.97)	(2.29)	(2.29)	(2.28)	(2.38)	(2.27)	(2.57)
Conduct	2.20	2.15	2.21	1.98	2.17	2.56	2.09	2.99 **	2.14	2.98
	(3.11)	(2.60)	(3.08)	(2.38)	(3.06)	(2.90)	(2.92)	(3.81)	(3.04)	(2.94)

Father										
Child baseline:	N = 859	N= 126	N = 923	N = 60	N = 876	N = 109	N = 870	N = 115	N = 907	N = 78
Depressive	4.30	7.39***	4.51	7.60***	4.45	6.61***	4.48	6.27***	4.52	6.73***
	(3.66)	(4.32)	(3.80)	(4.05)	(3.78)	(4.18)	(3.81)	(4.10)	(3.77)	(4.56)
Anxiety	3.11	4.60***	3.18	5.08***	3.14	4.59***	3.17	4.31***	3.22	4.21***
	(2.51)	(2.51)	(2.52)	(2.48)	(2.52)	(2.49)	(2.52)	(2.63)	(2.57)	(2.21)
ADHD	5.67	6.83***	5.75	6.82*	5.74	6.46*	5.58	7.65***	5.69	7.30***
	(3.40)	(3.44)	(3.42)	(3.37)	(3.40)	(3.53)	(3.40)	(3.02)	(3.43)	(3.05)
ODD	3.37	4.20***	3.43	4.13	3.39	4.12**	3.37	4.29***	3.37	4.74***
	(2.56)	(2.31)	(2.55)	(2.28)*	(2.56)	(2.27)	(2.53)	(2.51)	(2.54)	(2.22)
Conduct	3.12	4.05**	3.21	3.67	3.15	3.95*	3.08	4.44***	3.03	5.72***
	(3.38)	(3.43)	(3.41)	(3.12)	(3.38)	(3.40)	(3.35)	(3.51)	(3.22)	(4.30)
Child follow-up:	N = 360	N = 51	N = 386	N = 25	N = 358	N = 53	N = 360	N = 51	N = 373	N = 32
Depressive	2.95	4.61***	3.09	4.28	2.98	4.36**	3.01	4.20*	3.11	3.78
	(3.37)	(3.54)	(3.42)	(3.41)	(3.35)	(3.75)	(3.37)	(3.70)	(3.50)	(2.34)
Anxiety	2.07	2.71	2.10	2.88	2.06	2.71	2.04	2.88*	2.12	2.44
	(2.30)	(2.18)	(2.29)	(2.24)	(2.28)	(2.31)	(2.27)	(2.35)	(2.32)	(1.97)
ADHD	4.43	6.31***	4.57	6.16*	4.53	5.57*	4.44	6.24***	4.56	5.84*
	(3.30)	(3.14)	(3.33)	(2.98)	(3.34)	(3.18)	(3.27)	(3.39)	(3.35)	(2.84)
ODD	2.31	3.20**	2.37	3.24	2.37	2.77	2.34	2.98	2.32	3.59**
	(2.27)	(2.19)	(2.26)	(2.39)	(2.30)	(2.06)	(2.27)	(2.24)	(2.25)	(2.24)
Conduct	1.92	3.02**	2.02	2.58	2.05	2.09	2.04	2.16	1.93	3.56**
	(2.65)	(3.08)	(2.76)	(2.14)	(2.80)	(2.20)	(2.79)	(2.28)	(2.62)	(3.47)

*** p<.001, ** p<.01, * p<.05. ADHD: Attention deficit/hyperactivity disorder. ODD: Oppositional defiant disorder.

Table 3. Means (SDs) of the child's psychiatric symptom scores at baseline and at follow-up for children whose mother or father scored in the normal range or in the (sub)clinical range on at least one of the syndrome scales at baseline. The effect size (d) for the mean difference at baseline and follow-up is given by whether the parents scored in the normal or (sub)clinical range.

	Maternal psychiatric score						Paternal psychiatric score					
	normal			(sub)clinical			normal			(sub)clinical		
	Baseline	Follow-up	d	Baseline	Follow-up	d	Baseline	Follow-up	d	Baseline	Follow-up	d
Child score:	N = 949	N = 464		N= 528	N = 248		N = 643	N = 275		N = 344	N = 138	
Depressive	5.19 (4.02)	3.07 (3.56)	0.53	7.14 (4.26)	4.21 (3.54)	0.69	3.96 (3.55)	2.91 (3.57)	0.30	6.08 (4.10)	3.62 (3.08)	0.60
Anxiety	3.64 (2.82)	2.16 (2.44)	0.53	4.43 (2.76)	2.76 (2.52)	0.61	2.84 (2.40)	1.95 (2.30)	0.37	4.17 (2.62)	2.52 (2.22)	0.63
ADHD	6.01 (3.53)	4.73 (3.30)	0.36	7.20 (3.61)	5.65 (3.49)	0.43	5.28 (3.30)	4.16 (3.21)	0.34	6.83 (3.43)	5.67 (3.33)	0.34
ODD	3.60 (2.64)	2.29 (2.28)	0.50	4.46 (2.60)	2.73 (2.30)	0.67	3.04 (2.52)	2.08 (2.16)	0.38	4.30 (2.39)	3.07 (2.35)	0.51
Conduct	3.16 (3.36)	1.99 (2.88)	0.35	4.51 (4.17)	2.59 (3.29)	0.46	2.72 (3.16)	1.73 (2.54)	0.32	4.23 (3.64)	2.69 (2.96)	0.42

ADHD: Attention deficit/hyperactivity disorders. ODD: Oppositional-defiant disorder.

Table 4. Standardized regression coefficients (SEs) obtained in the model (Figure 1) in which the child's psychiatric symptom score at follow-up was predicted by the child's psychiatric symptom score at baseline (T1), the parental psychiatric symptoms at baseline (β12s) and the parental psychiatric symptoms at follow-up (β22s).The child's psychiatric symptom score at baseline was also predicted by all parental psychiatric symptom scores at baseline (β11s).

	Child psychiatric problems outcome														
	Depressive			Anxiety			ADHD			Oppositional-defiant			Conduct		
	β11	β12	β22	β11	β12	β22	β11	β12	β22	β11	β12	β22	β11	β12	β22
Mothers															
T1 Child	.43* (.03)			.37* (.03)			.59* (.03)			.54* (.03)			.48* (.03)		
Depressive	.13 (.07)	-.06 (.06)	.09 (.06)	-.06 (.05)	-.05(.04)	-.03 (.04)	.05 (.06)	-.02 (.05)	.00 (.05)	.00 (.05)	-.02 (.03)	.05 (.04)	-.06 (.06)	-.08 (.05)	-.02 (.05)
Anxiety	.25* (.09)	-.08 (.07)	.20*(.07)	.37*(.06)	.08 (.05)	.19*(.05)	-.05 (.08)	-.03 (.06)	.18*(.06)	.17* (.06)	-.11 (.05)	.08 (.05)	.24* (.08)	.02 (.06)	.14 (.06)
Avoidant	.06 (.09)	.05 (.08)	.06 (.08)	.07 (.06)	-.01(.05)	.11 (.06)	.03 (.08)	-.08 (.07)	.09 (.07)	-.01 (.06)	-.03 (.05)	.01 (.05)	-.09 (.08)	-.13 (.06)	.12 (.07)
ADHD	.02 (.05)	-.07 (.05)	.10 (.05)	-.01 (.03)	-.08(.03)	.10*(.03)	.10 (.04)	-.12* (.04)	.19*(.04)	.01 (.03)	-.06 (.03)	.05 (.03)	.00 (.04)	-.05 (.04)	.13* (.04)
Antisocial	.17 (.08)	-.02 (.06)	.08 (.08)	.04 (.06)	-.02(.04)	.06 (.05)	.04 (.07)	.01 (.05)	.05 (.07)	.12 (.05)	.05 (.04)	.11 (.05)	.18 (.07)	.04 (.05)	.07 (.07)
Fathers															
T1 Child	.44* (.04)			.48*(.04)			.67* (.04)			.55* (.04)			.52* (.03)		
Depressive	.09 (.09)	-.08 (.07)	.16 (.08)	-.10 (.06)	-.11(.05)	.14 (.06)	-.03 (.08)	05 (.06)	.00 (.07)	-.05 (.06)	.04 (.04)	-.04 (.05)	.04 (.07)	.01 (.05)	-.06 (.06)
Anxiety	.42* (.12)	-.13 (.09)	.22 (.10)	.37* (.07)	-.01(.06)	.11 (.07)	.21 (.10)	-.10 (.08)	.16 (.08)	.20 (.07)	-.03(.06)	.20 (.06)	.17 (.09)	.05 (.07)	.16 (.07)
Avoidant	.02(.11)	-.11 (.09)	.22 (.10)	.08 (.07)	-.02(.06)	.05 (.07)	-.14 (.09)	-.13 (.08)	.15 (.08)	-.04 (.07)	-.10(.06)	-.04 (.06)	-.17 (.09)	-.09 (.07)	.01 (.07)
ADHD	.13 (.07)	-.11 (.07)	.04 (.07)	.10 (.04)	-.01(.04)	-.00 (.05)	.25* (.06)	-.07 (.05)	.13 (.06)	.06 (.05)	.01(.04)	.06 (.04)	.12 (.06)	-.05 (.05)	.03 (.05)
Antisocial	-.05 (.09)	.09 (.08)	.03 (.07)	-.03 (.06)	.04 (.05)	.02 (.05)	.04 (.08)	-.01 (.06)	.08 (.06)	.14 (.06)	-.05(.05)	.14 (.05)	.14 (.07)	-.09(.06)	.26* (.06)

*p< 0.007. ADHD: Attention deficit/hyperactivity disorders.

The results of the analyses including maternal and paternal psychiatric symptom scores simultaneously were similar, although fewer parent-offspring associations were significant probably because of the smaller sample size. In this analysis, no parental psychiatric symptoms at baseline predicted the child's outcomes. The standardized regression coefficients for the different regression analyses are given in the Supplementary Table 4 (coefficients ranged between .25 and .35 at baseline and between .17 and .29 at follow-up). These results indicate that the associations found in the former analyses cannot be explained by resemblance between parents.

Discussion

We examined, in a clinical sample, the impact of several internalizing and externalizing parental psychiatric symptoms on the outcome of the child's psychiatric symptoms. We looked at longitudinal associations, i.e., between parental symptoms at baseline and offspring symptoms at follow-up. We also included concurrent associations in the model, i.e., the predictions of the offspring symptoms at baseline and follow-up by parental symptoms at baseline and follow-up respectively. In addition, predictions of the offspring symptoms at baseline were included and comorbidity in parental symptoms was taken into account. Our results indicate that children referred to psychiatric outpatient clinics whose parents scored in the (sub)clinical range at baseline scored higher at baseline and at follow-up (Table 2), although the differences were smaller at follow-up. The improvement between baseline and follow-up, as expressed in effect sizes, was not smaller in children whose parents scored above threshold compared to children whose parents scored in the normal range (Table 3). Our model showed that the higher scores at follow-up were not explained by long-term effects of parental psychiatric symptom scores at baseline. Instead, the child's follow-up scores were for the largest part predicted by the child's symptom score at baseline, in addition to predictions of concurrently measured parental psychiatric symptoms at follow-up. Thus, apart from parental psychopathology being associated with higher offspring scores at baseline, there was no extra effect of parental symptoms at baseline that predicts a worse outcome in these children. However, parental symptoms at follow-up did have an additional effect on offspring symptoms at follow-up, although these concurrent associations were smaller than at baseline.

Our results suggest that longitudinal predictions of parental psychopathology as found previously may be explained by persistent parental psychopathology, which

was not accounted for in earlier analyses. Only one study also included an association between parental psychopathology at follow-up with child's scores at follow-up [255]. They reported an association between maternal anxiety at baseline and higher scores in mother-reported child anxiety, but not in clinician-rated child anxiety. Another study also included the maternal symptoms at follow-up in the analysis, by testing the difference between children's externalizing symptoms at follow-up in children whose mothers were not depressed, whose mothers were only depressed at baseline and whose mothers were depressed at baseline and follow-up [68]. The children in the latter group showed the highest scores in line with the concurrent associations at follow-up in our model.

Baseline child's symptoms were also not always incorporated in a similar way as in the current study. Sometimes, a child's change score was analyzed as outcome measure [60,69,70,260] or whether or not remission of a diagnosis was achieved [59,61]. These analyses do not account for the higher symptom scores at baseline in children whose parents have psychopathology. A quantitative measure of the child's psychiatric symptoms at baseline and follow-up provides the most information on how factors influence outcome.

Similar to the previous analyses of parent-offspring associations at baseline in a sample partly overlapping with the current one, the prediction model showed that parent-offspring associations were mainly driven by parental anxiety or ADHD [225]. Moreover, we found that concurrent parent-offspring associations were less strong at follow-up than at baseline, which may be explained by the strong predictions of the child's baseline symptoms on the child's score at follow-up. Lastly, there were some differences between the patterns of predictions by paternal and maternal symptom scores, but apart from that, the associations were of similar magnitude for mothers and fathers.

It could be that parent-offspring associations for psychopathology are influenced by spousal resemblance for psychiatric symptoms [119]. A study on the association between maternal depression and childhood conduct problems, for example, showed that this association was partly explained by paternal antisocial personality problems [199]. However, our additional analyses including the maternal and paternal symptoms simultaneously in the model showed that spousal resemblance for psychiatric symptoms did not explain the effects as found in the separate analyses.

The only longitudinal significant prediction from parental symptoms to offspring outcome was maternal ADHD symptoms at baseline predicting lower ADHD scores in their children at follow-up. An earlier study by Brammer et al. [262] found reductions in parental ADHD to predict a reduction in the child's ADHD symptoms, however, only among non-ADHD youth and they examined ADHD symptom change instead of outcome. Our finding may be driven by an improvement in maternal ADHD symptoms with as a consequence more focused and less impulsive behavior of the mother which in turn helps the child to reduce its ADHD symptoms. The direction of the effect could also go the other way around, i.e. the child's improvement may reduce maternal ADHD symptoms. However, the effect was relatively small. Future studies should provide further insight into the association between parental ADHD and offspring ADHD over time and clarify whether there are relevant implications for the treatment of youth ADHD.

The results should be considered in view of several limitations. First, to analyze the largest possible sample, we used the report on the child's psychopathology of the parent that also reported on his or her own symptoms. Psychiatric symptoms in the parent, however, can influence the ratings of their child's psychiatric symptoms [261]. We also had reports from the other parent about the child's psychiatric symptoms and Supplementary Table 3 showed that similar differences are seen in offspring symptom scores depending on the other parent scoring below or above the (sub)clinical thresholds, although the differences are smaller. Second, although the sample size was large, around 50% of the families were lost to follow-up. Comparison of mothers, fathers and child's symptoms scores at baseline showed no differences between families who did or did not participate at follow-up (see Supplementary Table 1). This suggests that participation is not associated to maternal, paternal or offspring psychopathology at baseline. It is still possible that symptoms at follow-up, either of the parents or children, were associated with drop-out. Third, we modelled the predictions of several internalizing and externalizing parental psychiatric symptoms on the outcome of the child's psychiatric symptoms as the sample was ascertained for psychiatric symptoms in children. This does not preclude that the effect could go the other way around, i.e. children's symptoms may also influence parental psychopathology. It has, for example, been found that a decrease in offspring anxiety symptoms is related to a decrease in maternal anxiety symptoms [255]. Our findings also do not imply causality. Both parental and offspring psychopathology could be influenced by continuing adverse family circumstances, such as financial or marital problems

Findings from the present study have important clinical implications. They show that children of parents with psychopathology, which is around 30% of children referred to community services (Wesseldijk et al., submitted), are at risk for continuing higher levels of psychiatric symptoms. Improvement is not smaller relative to children whose parents score in the normal range, but should be even larger because of the higher scores at baseline. Future studies should focus on how the treatment of children with more severe symptoms could be adapted to improve their prognosis. Given the continuing associations with parental psychopathology, both in mothers and fathers, one way could be to treat the parental symptoms and investigate whether this is also beneficial for the child.

Supplement to Chapter 8

Table 1. Means and standard deviations of the maternal and paternal psychiatric symptoms scores of the Adult Self Report (ASR) and of their child's psychiatric scores of the Child Behavior Checklist (CBCL) at baseline depending on whether or not parents participated in the follow-up.

	Mothers		Fathers	
	Baseline without follow-up	Baseline score with follow-up	Baseline without follow-up	Baseline score with follow-up
ASR				
Depressive	5.03 (4.57)	4.70 (4.03)	3.29 (3.35)	3.30 (3.37)
Anxiety	4.30 (2.92)	4.12 (2.54)	3.18 (2.47)	3.18 (2.36)
Avoidant	2.49 (2.49)	2.40 (2.33)	2.13 (2.31)	2.38 (2.42)
ADHD	5.38 (4.38)	5.24 (4.29)	4.69 (4.02)	5.16 (4.11)*
Antisocial	2.43 (2.56)	2.45 (2.45)	2.93 (2.74)	3.11 (2.86)
CBCL				
Depressive	6.03 (4.29)	5.76 (4.16)	4.62 (3.81)	4.77 (3.94)
Anxiety	4.02 (2.83)	3.79 (2.81)	3.33 (2.57)	3.29 (2.56)
ADHD	6.36 (3.63)	6.50 (3.60)	5.54 (3.46)	6.05 (3.37)*
ODD	3.93 (2.65)	3.88 (2.65)	3.51 (2.54)	3.47 (2.55)
Conduct	3.76 (3.78)	3.58 (3.73)	3.17 (3.39)	3.36 (3.49)

*p< 0.05. ADHD: Attention deficit/hyperactivity disorder. ODD: Oppositional defiant disorder.

Table 2. Means and standard deviations of the maternal and paternal psychiatric symptoms scores of the Adult Self Report (ASR) and of their child's psychiatric scores of the Child Behavior Checklist (CBCL) at baseline and follow-up per psychiatric outpatient clinic. Means at the three clinics were compared per psychiatric symptom scale for mothers and fathers separately at baseline and at follow-up with univariate ANOVAs. ADHD: Attention deficit/hyperactivity disorders. ODD: Oppositional-defiant disorder.

	Baseline						Follow-up					
	Mothers			Fathers			Mothers			Fathers		
	Uva Minds	GGZ ingeest	Erasmus	Uva Minds	GGZ ingeest	Erasmus	Uva Minds	GGZ ingeest	Erasmus	Uva Minds	GGZ ingeest	Erasmus
ASR												
Depressive	4.74	5.31	4.74	3.33	3.13	3.35	3.62^	4.68	3.75	2.70	2.95	2.24
	(4.02)	(4.97)	(4.30)	(3.36)	(3.29)	(3.43)	(3.59)	(4.74)	(3.95)	(3.29)	(3.27)	(2.38)
Anxiety	4.16	4.40	4.16	3.14	3.07	3.35	3.27	3.70	3.42	2.36	2.53	2.55
	(2.64)	(3.10)	(2.60)	(2.41)	(2.28)	(2.54)	(2.56)	(3.07)	(2.52)	(2.35)	(2.01)	(2.23)
Avoidant	2.23^	2.52	2.92	2.33	1.94	2.35	1.81	2.34	2.43	1.88	1.93	2.10
	(2.24)	(2.64)	(2.53)	(2.39)	(2.27)	(2.38)	(2.11)	(2.68)	(2.37)	(2.24)	(2.22)	(2.17)
ADHD	5.52	5.11	5.02	5.26*	4.23	4.68	4.39	4.64	3.93	4.22	4.35	3.08
	(4.47)	(4.25)	(4.07)	(4.14)	(4.10)	(3.76)	(3.94)	(4.15)	(3.69)	(3.82)	(3.46)	(2.52)
Antisocial	2.52^	2.54	2.11	3.21^	3.13~	2.44	1.77^	1.66	1.07	2.60^	2.15	1.43
	(2.63)	(2.61)	(2.01)	(2.86)	(3.11)	(2.26)	(1.95)	(2.07)	(1.58)	(2.91)	(2.73)	(1.60)
CBCL												
Depressive	5.65^	6.21	6.43	4.56	5.20	4.96	3.13^	4.08	4.83	2.91	3.84	3.82
	(4.09)	(4.56)	(4.22)	(3.85)	(4.09)	(3.72)	(3.28)	(3.84)	(4.71)	(3.14)	(3.47)	(4.79)
Anxiety	3.78^	3.61~	4.79	3.17^	3.36	4.12	2.12^	2.34~	3.65	2.02^	1.84	2.98
	(2.79)	(2.70)	(2.90)	(2.56)	(2.27)	(2.83)	(2.21)	(2.52)	(3.29)	(2.18)	(2.12)	(2.84)
ADHD	6.57*	5.63~	6.89	5.99*	4.67~	6.23	4.88	5.32	5.80	4.55	5.42	4.41
	(3.58)	(3.16)	(4.13)	(3.39)	(3.06)	(3.77)	(3.24)	(3.16)	(4.41)	(3.14)	(2.90)	(4.55)
ODD	3.87	3.78	4.18	3.43	3.40	3.97	2.38	2.65	2.66	2.41	2.62	2.13
	(2.63)	(2.72)	(2.64)	(2.58)	(2.51)	(2.34)	(2.20)	(2.47)	(2.66)	(2.24)	(2.41)	(2.42)
Conduct	3.51^	3.74	4.19	3.28	3.22	3.31	1.99^	2.63	3.06	1.91	2.64	2.18
	(3.56)	(3.77)	(4.37)	(3.42)	(3.46)	(3.58)	(2.77)	(3.28)	(4.14)	(2.78)	(2.97)	(3.10)

(p<.01); * indicates a difference between Uva Minds and GGZinGeest, ^ between Uva Minds and Erasmus and ~ between GGZ inGeest and Erasmus.

Table 3. Means (SDs) of the child's psychiatric symptom scores at baseline and follow-up for children of parents whose mother's (upper part of the table) or father's (lower part of the table) psychiatric symptom score was in the normal or (sub)clinical range at baseline. The difference with Table 2 in the main text is that the offspring symptoms are assessed by the other parent.

	normal	(sub)clinical	normal	(sub)clinical	normal	(sub)clinical	normal	(sub)clinical	normal	(sub)clinical
	Maternal depressive		Maternal anxiety		Maternal avoidant		Maternal ADHD		Maternal antisocial	
Child score father rated										
Child at baseline:	N = 852	N = 127	N = 915	N = 62	N = 924	N = 54	N = 845	N = 134	N = 903	N = 76
Depressive	4.52	6.10***	4.62	6.32***	4.61	6.72***	4.64	5.22	4.66	5.49
	(3.82)	(4.15)	(3.83)	(4.58)	(3.87)	(3.86)	(3.90)	(3.84)	(3.85)	(4.34)
Anxiety	3.26	3.83*	3.26	4.53***	3.27	4.56***	3.35	3.27	3.32	3.53
	(2.56)	(2.66)	(2.54)	(2.84)	(2.55)	(2.70)	(2.61)	(2.38)	(2.56)	(2.76)
ADHD	5.78	6.18	5.80	6.34	5.81	6.33	5.71	6.63**	5.77	6.65*
	(3.43)	(3.47)	(3.42)	(3.69)	(3.42)	(3.66)	(3.41)	(3.52)	(3.43)	(3.40)
ODD	3.43	3.91*	3.48	3.61	3.45	4.19*	3.45	3.74	3.42	4.32**
	(2.55)	(2.51)	(2.55)	(2.52)	(2.57)	(2.09)	(2.53)	(2.69)	(2.54)	(2.38)
Conduct	3.16	3.82*	3.20	3.89	3.22	3.67	3.12	4.05**	3.17	4.16*
	(3.39)	(3.56)	(3.41)	(3.61)	(3.41)	(3.59)	(3.31)	(3.95)	(3.36)	(3.99)
Child at follow-up:	N = 369	N = 45	N = 390	N = 24	N = 389	N = 96	N = 363	N = 51	N = 378	N = 36
Depressive	3.04	3.89	3.15	2.95	3.08	4.00	3.06	3.65	3.07	3.86
	(3.41)	(3.54)	(3.44)	(3.37)	(3.47)	(2.80)	(3.44)	(3.33)	(3.41)	(3.68)
Anxiety	2.10	2.38	2.12	2.33	2.07	3.08*	2.12	2.20	2.05	2.97*
	(2.31)	(2.10)	(2.30)	(2.01)	(2.24)	(2.81)	(2.28)	(2.33)	(2.24)	(2.62)
ADHD	4.49	5.38	4.60	4.33	4.54	5.32	4.48	5.33	4.49	5.64*
	(3.32)	(3.03)	(3.31)	(3.21)	(3.30)	(3.22)	(3.31)	(3.19)	(3.30)	(3.21)
ODD	2.34	2.84	2.44	1.75	2.34	3.28*	2.37	2.61	2.32	3.25*
	(2.25)	(2.44)	(2.30)	(1.78)	(2.26)	(2.48)	(2.25)	(2.47)	(2.20)	(2.88)
Conduct	1.97	2.49	2.05	1.67	1.95	3.20*	1.91	2.88*	1.96	2.69
	(2.62)	(3.27)	(2.75)	(1.74)	(2.60)	(3.86)	(2.57)	(3.40)	(2.62)	(3.40)

	Paternal depressive		Paternal anxiety		Paternal avoidant		Paternal ADHD		Paternal antisocial	
Child score mother rated	N = 970	N = 138	N = 1035	N = 71	N = 990	N = 118	N = 981	N = 127	N = 1026	N = 82
Child at baseline:										
Depressive	5.56	7.15***	5.65	7.34***	5.63	6.81**	5.65	6.55*	5.68	6.66*
	(4.04)	(4.44)	(4.10)	(4.26)	(4.05)	(4.56)	(4.11)	(4.17)	(4.06)	(4.81)
Anxiety	3.84	4.36***	3.85	4.62*	3.84	4.39*	3.86	4.22	3.91	3.83
	(2.84)	(2.71)	(2.83)	(2.80)	(2.82)	(2.89)	(2.83)	(2.82)	(2.83)	(2.95)
ADHD	6.38	6.84**	6.40	6.89	6.48	6.06	6.31	7.38**	6.40	6.85
	(3.65)	(3.57)	(3.66)	(3.42)	(3.68)	(3.36)	(3.65)	(3.49)	(3.66)	(3.41)
ODD	3.84	4.16***	3.85	4.28	3.90	3.70	3.83	4.25	3.83	4.45*
	(2.64)	(2.55)	(2.64)	(2.26)	(2.66)	(2.39)	(2.64)	(2.53)	(2.64)	(2.40)
Conduct	3.49	3.68***	3.51	3.42	3.56	3.05	3.47	3.84	3.45	4.27
	(3.77)	(3.19)	(3.76)	(2.85)	(3.75)	(3.27)	(3.72)	(3.56)	(3.73)	(3.35)
Child at follow-up:	N = 503	N = 70	N = 538	N = 35	N = 510	N = 63	N = 500	N = 73	N = 528	N = 45
Depressive	3.34	4.03***	3.41	3.66	3.43	3.40	3.41	3.53	3.31	4.76**
	(3.65)	(3.31)	(3.64)	(3.11)	(3.66)	(3.19)	(3.67)	(3.19)	(3.60)	(3.43)
Anxiety	2.24	2.73**	2.29	2.43	2.31	2.25	2.26	2.55	2.27	2.60
	(2.41)	(2.43)	(2.45)	(1.85)	(2.45)	(2.19)	(2.44)	(2.26)	(2.43)	(2.23)
ADHD	4.90	6.33	5.06	5.26	5.09	4.98	4.87	6.51***	4.96	6.47**
	(3.41)	(3.44)	(3.47)	(2.90)	(3.46)	(3.30)	(3.34)	(3.75)	(3.44)	(3.07)
ODD	2.42	2.93	2.47	2.66	2.50	2.30	2.45	2.71	2.38	3.58***
	(2.30)	(2.45)	(2.34)	(2.17)	(2.37)	(1.97)	(2.33)	(2.27)	(2.30)	(2.38)
Conduct	2.11	2.41	2.18	1.71	2.17	2.03	2.12	2.36	2.04	3.40**
	(3.09)	(2.98)	(3.11)	(2.61)	(3.06)	(3.29)	(3.00)	(3.58)	(2.97)	(3.92)

*** p<.001, ** p<.01, * p<.05. ADHD: Attention deficit/hyperactivity disorders. ODD: Oppositional-defiant disorder.

Table 4. Standardized regression coefficients (SE) of the analyses including both the maternal and paternal psychiatric symptoms simultaneously (N=334 families). The child's psychiatric symptom score at follow-up was predicted by the child's psychiatric symptom score at baseline (T1), the parental psychiatric symptoms at baseline (β12s) and the parental psychiatric symptoms at follow-up (β22s).The child's psychiatric symptom score at baseline was also predicted by all parental psychiatric symptom scores at baseline (β11s).

	Child psychiatric problems outcome														
	Affective			Anxiety			ADHD			Oppositional-defiant			Conduct		
	β11	β12	β22	β11	β12	β22	β11	β12	β22	β11	β12	β22	β11	β12	β22
Child T1	.39* (.05)			.32* (.04)			.55* (.04)			.52* (.04)			.44* (.04)		
Mothers															
Depressive	.18	-.17	.10	.05	-.10	-.06	-.01	-.01	-.00	-.01	.01	.03	-.08	-.08	.02
	(.09)	(.08)	(.08)	(.07)	(.05)	(.06)	(.09)	(.07)	(.07)	(.06)	(.05)	(.05)	(.08)	(.06)	(.06)
Anxiety	.13	-.17	.29*	.25*	.01	.28*	-.12	-.04	.15	.08	-.17	.15	.12	-.01	.12
	(.12)	(.11)	(.11)	(.09)	(.08)	(.07)	(.12)	(.09)	(.09)	(.08)	(.06)	(.06)	(.10)	(.08)	(.07)
Avoidant	.05	.06	.07	.05	.06	.11	-.00	-.02	.01	-.03	-.04	-.01	-.08	-.04	.01
	(.11)	(.11)	(.12)	(.08)	(.07)	(.08)	(.11)	(.09)	(.10)	(.08)	(.06)	(.07)	(.10)	(.08)	(.09)
ADHD	-.03	.00	.11	-.11	-.05	.17*	.15	-.07	.19*	.06	-.07	.06	.06	-.07	.09
	(.07)	(.08)	(.07)	(.05)	(.05)	(.05)	(.07)	(.06)	(.06)	(.05)	(.05)	(.05)	(.06)	(.05)	(.05)
Antisocial	.15	-.10	.08	.15	-.07	.04	.06	-.06	.00	.09	-.04	.11	.11	-.03	.12
	(.10)	(.09)	(.11)	(.07)	(.06)	(.08)	(.10)	(.07)	(.09)	(.07)	(.05)	(.07)	(.08)	(.06)	(.08)
Fathers															
Depressive	-.08	.09	-.06	-.06	.01	.02	.05	.16	-.02	-.01	.08	-.01	.04	.10	-.03
	(.10)	(.09)	(.10)	(.07)	(.06)	(.07)	(.10)	(.07)	(.08)	(.07)	(.05)	(.06)	(.08)	(.06)	(.07)
Anxiety	.35*	-.15	.21	.15	-.08	.06	.04	-.19	-.00	.18	.02	-.03	.17	-.08	.03
	(.12)	(.11)	(.12)	(.09)	(.08)	(.08)	(.12)	(.09)	(.10)	(.08)	(.07)	(.07)	(.10)	(.08)	(.08)
Avoidant	-.03	-.12	.02	-.02	.01	-.06	-.24	-.08	-.05	-.16	-.11	.04	-.19	-.05	-.05
	(.11)	(.11)	(.13)	(.08)	(.07)	(.09)	(.11)	(.09)	(.10)	(.08)	(.06)	(.07)	(.09)	(.08)	(.09)
ADHD	.01	-.00	.01	.02	-.01	.06	.17	.06	.07	.04	.05	-.07	.01	-.02	.03
	(.08)	(.08)	(.09)	(.06)	(.05)	(.06)	(.07)	(.06)	(.07)	(.05)	(.04)	(.05)	(.06)	(.06)	(.06)
Antisocial	-.02	.10	-.07	-.08	.06	-.01	.05	-.00	.05	.10	-.12	.21*	.14	-.15	.24*
	(.09)	(.09)	(.09)	(.07)	(.06)	(.06)	(.09)	(.07)	(.07)	(.07)	(.05)	(.05)	(.08)	(.06)	(.06)

*p< 0.007. ADHD: Attention deficit/hyperactivity disorders.

Risk factors for the development and outcome of childhood psychopathology

SUMMARY AND DISCUSSION

Chapter 9

In this chapter I present a summary of the results of the studies described in this thesis followed by a discussion of the research and clinical implications.

Summary

In the first part of my thesis, several issues were addressed that looked at 1) designs in genetics with phenotypes obtained from different raters simultaneously, to obtain more reliable estimates of the influences of genetic and shared environmental factors on childhood psychopathology, 2) the differences between raters or informants in the assessment of childhood psychopathology and 3) the role of genetic and non-genetic factors on childhood psychopathology across ages and how such factors might explain stability over time.

Chapter 2 reports the results of a twin study estimating the role of genetic, shared environmental, and non-shared environmental factors on individual differences in affective, anxiety, somatic, attention deficit hyperactivity disorder (ADHD), oppositional-defiant disorder (ODD), conduct disorder (CD), and obsessive-compulsive (OCD) problems in 7-year-olds. Parents completed a checklist on their twin offspring and agreed to a large extent about the level of problem behaviors in their children (correlations between .6 and .75 for the different problem scales). The correlations between parental assessments did not depend on the child's gender. Differences between parents in the assessment of childhood psychopathology were also observed. Maternal ratings of childhood psychopathology were higher than the paternal ratings for all scales, regardless of the child's gender. Maternal and paternal ratings were analyzed simultaneously in a psychometric model, which decomposes the variances of the mother and father ratings into a part the parents agree upon (the common part) and into two uncorrelated parts reflecting the disagreement (the rater-specific parts). A psychometric model for data from multiple raters provides more reliable estimates of the influences of genes and the shared environment on childhood psychopathology than a model for data from a single rater by estimating the effect of genes on the common plus rater-specific part and the effect of the shared environment solely on the part of the variance the parents agree upon [97]. Genetic factors generally explained around 60% of the variance, except for childhood ADHD in which genes explained around 80% of the variance. For the phenotype which both parents agreed upon, shared environmental influences were significant for affective problems (13%), ODD (13%) and particularly high for CD (37%). Furthermore, as the rater-specific parts of parental ratings were also influenced by significant genetic influences and shared environmental influences, it could be

inferred that both parents assess unique aspects of their child's behavior, which are reliable, as indicated by heritability and maybe biased as indicated by the shared environmental influences.

Chapter 3 of this thesis introduced data from another group of raters, i.e., teachers, and aimed to answer two questions. First, do informant discrepancies depend on the gender or age of the child, or on the psychiatric symptoms assessed? Second, are mean differences in reports from men and women on childhood psychopathology found for parents as well as for teachers? We explored these question for internalizing and externalizing psychiatric symptom scores. Overall, significant mean differences in ratings of childhood psychopathology were observed between mothers and fathers. The paternal ratings for aggressive, attention, anxiety and emotional problems in 5 year-old children were higher than maternal ratings. The opposite was seen in 7, 10 and 12 year-old children, with the maternal scores exceeding paternal ratings for affective, anxiety, somatic, ADHD, ODD and CD problems. The differences between mothers and fathers were present for both boys and girls and for all behavioral domains. In contrast, female and male teacher ratings only differed for 12 year-old boys, with female teachers reporting more problems than male teachers. Gender of the informant thus only consistently influenced parental ratings and not teacher ratings.

Chapter 4 describes a longitudinal genetic analysis of conduct and adult antisocial personality problems. We explored how genetic and non-genetic factors influence individual differences over age and the persistence of the problems from childhood into adulthood. Mean symptom scores differed between males and females at all ages, with males having higher scores. However, the proportions of variance explained by the genetic and environmental factors did not differ between the sexes and the same factors seemed to be of importance in males and females. The effects of genetic and shared environmental factors on individual differences in conduct problems in 9-10 year-olds were similar, both explaining ~44% of the variance. In contrast, in adolescents and adults, the effect of the shared environment was absent and genetic and non-shared environmental effects accounted for 49% and 51% of the differences in adolescents and 43% and 57% in adults. Stable genetic factors mostly explained the persistence of conduct problems into adult antisocial personality problems. The observed longitudinal correlations varied between .20 and .38 and the genetic correlations varied between .39 and .67.

The second part of this thesis addressed issues regarding parental psychopathology in families with children with psychopathology in clinical samples, namely 1) resemblance in spouses for psychopathology in the clinical sample compared to spousal resemblance in the general population, 2) the influence of comorbid disorders on associations between parents and offspring for psychopathology and 3) the comparison of maternal and paternal psychopathology prevalence rates and the associations with their children's psychopathology.

Chapter 5 reports on the spousal resemblance (resemblance between partners) in psychiatric symptoms of parents of children with psychopathology and the spousal resemblance in parents of children from the general population. We analyzed spousal correlations within and across symptoms of depression, anxiety, avoidant personality problems, ADHD, and antisocial personality problems. Almost all spousal correlations were significant within and across the internalizing and externalizing symptom domains in both samples. However, the spousal resemblance was significantly higher, sometimes almost twice as a high, in the parents of children with psychopathology. There was significant asymmetry with respect to gender in the clinical, but not in the population-based sample. Paternal ADHD correlated higher with maternal internalizing and externalizing symptom scores than maternal ADHD with paternal internalizing and externalizing symptom scores. Maternal antisocial personality problems correlated higher with paternal internalizing and externalizing symptom scores than vice versa. In addition, parents in the clinical sample had higher mean psychiatric symptom scores than parents in the population-based sample. Overall, these results showed that parents whose children are evaluated at a child and adolescent outpatient clinic were at an increased risk to suffer from a variety of psychiatric symptoms, and were at an increased risk to have a partner with, not necessarily equivalent, psychopathology.

Chapter 6 describes a study on prevalence rates of parental depressive, anxiety, ADHD, avoidant personality and antisocial personality symptom scores and the associations with psychopathology in their offspring. Around 10-15% of the parents had a (sub)clinical score on depressive and avoidant personality problems, around 10% on ADHD problems, and around 24% had a (sub)clinical score on any of the psychiatric symptom scales. These prevalence rates did not differ between mothers and fathers. Maternal anxiety was associated with all offspring problem scores and maternal ADHD problems were associated with offspring ADHD problems. Paternal anxiety was associated with offspring depression and anxiety and paternal ADHD with offspring ADHD and ODD. These associations did not differ

between boys and girls and were not due to spousal resemblance for psychopathology. We also included a large sample of fathers. The prevalence rates for maternal and paternal psychopathology were similar and the associations with offspring psychopathology were in the same order of magnitude for mothers and fathers.

In *Chapter 7* it was investigated whether there are child, parental, or family characteristics that are associated with an increased risk for psychopathology in parents whose child is evaluated in a psychiatric outpatient clinic. We examined whether relationship status of the parents, their education level, occupational status, age and gender and their offspring's age, psychiatric diagnosis, and the presence of comorbidity in the child predicted parental depressive, anxiety, ADHD, avoidant personality and antisocial personality problems. In this large sample of 1,805 mothers and 1,361 fathers from 1,866 children, 35.7% of mothers and 32.8% of fathers scored (sub)clinical for at least one symptom domain, mainly depressive, ADHD or, only in fathers, avoidant personality problems. The parental psychiatric symptoms were generally predicted by unemployment of the parent. Parental depressive and ADHD problems were further predicted by offspring depression and offspring ADHD respectively, in addition to not being together with the other parent. Moreover, parental avoidant personality symptoms were predicted by offspring pervasive developmental disorders. Overall, these findings suggest that parental psychiatric symptom scores are mainly associated with adverse circumstances of the family and with similar psychopathology in their child.

Chapter 8 presents a longitudinal analysis to study the effect of internalizing and externalizing parental psychiatric symptoms on the child's outcome of psychopathology. Parental and offspring psychiatric symptoms were first measured at the time the child was evaluated in a psychiatric outpatient clinic, i.e., baseline, and again at follow-up after a period of on average 1.7 years. Both the offspring's psychopathology as well as the parental psychiatric symptoms decreased over time. Children with parents scoring above threshold for any of the psychiatric symptoms at baseline scored higher at baseline. Although the relative improvement was not smaller in children of parents scoring above the (sub)clinical threshold than in children of parents scoring in the normal range, at follow-up, the children of parents with psychopathology still scored higher. These higher scores at follow-up were not explained by long-term effects of parental psychiatric symptom scores at baseline. Instead, the child's follow-up scores were for the largest part predicted by the child's symptom score at baseline, in addition to predictions of concurrently measured

parental psychiatric symptoms present at time of the follow-up. The magnitude of the parent-offspring associations for psychopathology were of a similar strength for mothers and fathers and remained present when controlling for spousal resemblance. Overall, the higher scores in children at follow-up with parents with psychopathology were explained by a higher severity at baseline in addition to an association with parental psychiatric symptoms at follow-up.

Discussion

In this thesis, I addressed some of the outstanding issues regarding the heritability and assessment of childhood psychopathology in data from twins registered with the Netherlands Twin Register (NTR) [83], and looked at questions regarding familial factors associated with childhood psychopathology and its outcome in data from families with a child with psychopathology evaluated at a psychiatric outpatient clinic.

A major strength of the large population-based twin sample was that it offered possibilities to explore informant effects, effects of genotype x gender and genotype x age interaction, and to estimate the influence of genetic, shared and non-shared environmental factors on childhood psychopathology. Population-based samples have the advantage to be representative for the population, but they include a relatively small proportion of individuals with (multiple) psychiatric disorders. The large clinical sample provided the possibility to examine familial factors associated with childhood psychopathology in families at the extreme end of the distribution, and to study the implications of familial clustering of psychopathology for psychiatric outpatient clinics treating children with psychiatric disorders. A clinical sample, though, includes fewer individuals and may lack the generalizability to the general population. Furthermore, parent-offspring associations in the clinical sample do not allow drawing conclusions about causal influences of the shared environment or genes. Overall, both the population-based and clinical sample were complementary in the quest for finding risk factors for the development and outcome of childhood psychopathology in this thesis.

In all studies I analyzed the DSM-oriented problem scales of the age-appropriate versions of questionnaires belonging to the Achenbach System of Empirically Based Assessment (ASEBA). The questionnaires were originally developed to asses behavioral and emotional problems across a series of empirically defined scales based on exploratory and confirmatory factor analysis [99,175]. In contrast, the items defining the DSM-oriented scales were selected when experienced

psychiatrists and psychologist knowledgeable about ages 6-18 or ages 18-59 judged the item to be highly consistent with the relevant DSM-IV diagnostic category [99,101,175]. While scores on the DSM-oriented scales are associated with the presence or absence of DSM diagnoses [99], they are not the same. On the other hand, the strength of using these questionnaires is that they were designed to measure similar constructs over ages, which makes them especially suitable for studying parent-offspring associations and longitudinal analyses. Moreover, since these scores are continuous measures, they contain more information on the variation in psychiatric symptoms.

Implications for future research and clinical implications

By analyzing maternal and paternal ratings simultaneously, I found that shared environmental influences, corrected for rater bias, were only significant in 7 year-olds for affective, ODD and CD. Contrary to our finding that OCD is not influenced by familial factors, van Grootheest et al. [9], in a multiple informant design, estimated an unbiased effect of the shared environment of 10% on OCD in 7 year-olds. However, the study in this thesis used a larger sample size and analyzed the data with a liability-threshold model, which leads to more accurate estimates of genetic, shared and non-shared environmental effects in skewed data [110]. As significant rater bias in the assessment of a variety of psychiatric symptoms has been reported in children at other ages as well [6-22], I tend to conclude that familial environmental influences reported by earlier studies [102,103] relying on a single parent might have overestimated the effect of the shared environment due to a bias in rating childhood psychopathology.

Our findings confirmed the large role of genetic factors on childhood psychopathology as well as on its stability over age. This underlines the need to identify the genetic variants associated with these phenotypes to shed light on the etiology. The successes to find genetic variants associated with psychiatric disorders like, for example, schizophrenia [263] and, recently, also ADHD (submitted) demonstrate that increasing the sample size is one of the fruitful strategies. Given the high correlations for the genetic factors influencing maternal and paternal ratings, it has been suggested that aggregating multiple raters in molecular genetic studies can also improve power [129]. These studies do need to take into account the systematic mean differences which were observed between maternal and paternal ratings. This can either be done by separate analyses of maternal and paternal ratings

followed by meta-analysis or by correcting for these differences in maternal and paternal scores before performing the genetic association analysis.

Our study on rater differences also raised some questions for further research. Paternal scores were higher than maternal scores of psychiatric symptoms as measured by the Devereux Child Behavior in 5 year-old children, while maternal scores exceeded the paternal scores of psychiatric symptoms in 7, 10 and 12 year-old children as measured by the Child Behavior Checklist (CBCL). An explanation for this contrast besides an effect of age of the child, might be the difference in measurement instrument. Paternal scores exceeded the maternal scores of childhood psychopathology in 4-5 year-olds on the Strength and Difficulties Questionnaire (SDQ) [138,149], however, mothers have also been found to rate the problems as measured by the empirical subscales of the CBCL in their 3 year-old children as more severe than fathers [16]. More insight into parental informant differences determined by the measurement instrument by administering the same set of instruments to parents of a large group of children will resolve these questions.

I furthermore established that gender of the informant could not explain parental informant discrepancies as gender of the informant only consistently influenced parental discrepancies and not the discrepancies between female and male teacher ratings of childhood psychopathology. The question then remains why fathers and mothers differ in their assessment. Does difference in time spent with a child play a role? That would mean that in families where fathers and mothers spent equal time with their children, differences would be smaller. Does it depend on the circumstances the rater is with the child? Teachers observe children in a standardized environment, whereas parents have broader opportunities to interact with their offspring in larger variety of environments. Possibly this may explain why mothers rate their boys' and girls' behavioral problems as more severe than fathers, and also why such differences are not seen for male and female teachers.

Until there is more knowledge on the reasons for the discrepancies between parents, when considering multiple ratings of the same child it is important to keep in mind that ratings from mothers and fathers differ in mean levels, but that there is no "better parent" to consult in the assessment of childhood psychopathology since the genetic epidemiological analyses showed that both parents provide valuable unique information on their child's behavior and both parents are slightly biased in their assessment.

Do the results of our longitudinal analysis on conduct problems imply that the shared environment is not important anymore after childhood? I found a particularly high influence of the shared environment on conduct problems in 7 year-olds (37%) and 10 year-olds (40%). However, the effects of familial factors on conduct problems disappeared in adolescence and on antisocial personality problems in adulthood. If the shared environment is only of temporary influence during childhood this could mean that interventions should focus on other factors. However, family-oriented interventions in which improvement in behavioral problems is achieved by involving parents and children, have been shown to be moderately effective in reducing levels of conduct problems, not only in childhood, but also in adolescence [264,265]. Therefore, I speculate that shared environmental factors that explain differences in conduct problems during childhood may include protective factors that lose their influence during adolescence due to a changed parental role, e.g., different parental monitoring [186]. This could explain the absence of the influence of familial factors on adolescent conduct problems, while at the same time treatment involving the familial environment may reduce adolescent conduct problems. Perhaps future research could shed a light on the impact of parental monitoring on conduct problems in children and adolescents, as this may provide insight into its protective ability and thus may be helpful in the quest for finding effective treatment for conduct and antisocial personality problems.

One of the consequences of the fact that psychiatric disorders can run in families is that family members of individuals assessed for psychopathology are also at an increased risk.

All studies in the second part of this thesis analyzed multiple internalizing and externalizing parental and offspring psychiatric symptoms simultaneously and were therefore able to provide insight into within as well as across symptom associations, while controlling for the frequent comorbidity of psychiatric disorders. Noteworthy is that when we took comorbidity of psychiatric disorders into account, many cross-sectional and longitudinal parent-offspring associations for psychiatric symptoms disappeared. In addition, when taking the concurrent parent-offspring associations into account, i.e. parent offspring psychopathology measured at the same time, we hardly found any longitudinal associations between parental psychopathology at baseline and offspring outcome at follow-up. All in all, findings of parent-offspring associations without controlling for comorbidity may be due to associations between psychiatric symptoms within the individual and findings of longitudinal parent-

offspring associations may be due to parental psychopathology present at time of the follow-up measurement.

The comparisons of paternal and maternal psychopathology prevalence rates and the associations with child psychopathology did not show large differences between mothers and fathers. Overall, the studies in this thesis clearly emphasize the need to also include fathers in both research studies on the aggregation of psychopathology in families as well as in screening and offering subsequent treatment in psychiatric outpatient clinics.

I found that 35.7% of mothers and 32.8% of fathers scored (sub)clinical for at least one symptom domain, mainly depressive symptoms, ADHD or, only in fathers, avoidant personality problems. Parents of a child with psychopathology also more often both experience, not necessarily equivalent, psychiatric symptoms than parents of a child without psychopathology. An increased risk for parental psychopathology was seen in parents who were unemployed or not together with the other biological parent. The longitudinal study showed that children with parents with psychopathology had a poorer prognosis, which was mainly explained by a higher severity at baseline in addition to the presence of parental psychiatric symptoms at follow-up. All these associations do not imply a direction of effect. Parents in the clinical sample could, for example, more often be both affected by psychopathology due to the stress experienced as a consequence of the child's symptoms. It is, however, also likely that it is due to the fact that children of parents who both suffer from psychopathology have a higher risk for psychiatric symptoms and, thus, to be referred to a psychiatric outpatient clinic.

To conclude, these findings indicate that there is a group of children seen in child and adolescent psychiatric outpatient clinics that is especially disadvantaged. Future studies should focus on how the treatment of children with more severe symptoms should be adapted to improve their prognosis. Given the association with parental psychopathology, an obvious question is whether treatment of parental psychiatric symptoms improves the treatment effectiveness and long-term outcomes in the child. This argues for bridging the gap between child psychiatry and adult psychiatry and establishing clinics that provide integrated care for the whole family.

Risk factors for the development and outcome of childhood psychopathology

NEDERLANDSE SAMENVATTING

Het komt regelmatig voor dat psychiatrische klachten clusteren in families. Met andere woorden, familieleden van patiënten met psychopathologie hebben vaak een hoger risico om ook psychiatrische klachten te hebben of ontwikkelen. Deze familiaire clustering wordt gedeeltelijk verklaard door de invloed van genetische factoren. Tweeling- en familiestudies hebben de invloed van genen op kinderpsychiatrische stoornissen geschat tussen de 40% voor o.a. depressiviteit en angst stoornissen en 80% voor o.a. aandachts- en tekortstoornis met hyperactiviteit (ADHD) of autisme. Voor psychiatrische klachten op de kinderleeftijd spelen omgevingsfactoren die door kinderen binnen een gezin worden gedeeld ook nog een rol. Deze verklaren tussen de 10 en 30% van de variatie voor de meeste psychiatrische stoornissen tijdens de kindertijd, behalve voor ADHD waar de gedeelde omgeving niet van invloed is en de erfelijkheid hoog. In de adolescentie en de volwassenheid verdwijnen deze effecten en zorgen alleen genetische factoren voor gelijkenissen tussen familieleden.

Hoewel er al veel tweeling- en familiestudies naar psychopathologie bij kinderen zijn gedaan, is een aantal zaken nog niet eerder onderzocht. Zo worden psychiatrische klachten bij kinderen doorgaans door derden gerapporteerd, bijvoorbeeld door de moeder, de vader of een lera(a)res. Als er slechts van één informant wordt uitgegaan kan de beoordeling van de klachten betreffende het kind beïnvloed worden door een beoordelaar-bias. Door de beoordelingen van moeder en vader tegelijkertijd te analyseren kan de invloed van genen en omgeving op verschillende psychiatrische klachten bij kinderen betrouwbaarder worden geschat. Vervolgens is er bekend dat er verschillen zijn tussen vaders en moeders in hoe ze hun kinderen beoordelen. In hoeverre de verschillen tussen vaders en moeders in de beoordeling van psychiatrische klachten bij een kind samenhangen met het geslacht, de leeftijd of de psychiatrische klachten van het kind en of deze verschillen in de beoordeling ook gezien worden tussen vrouwelijke of mannelijke leerkrachten is een open vraag. Voorts kunnen de schattingen van genetische en omgevingsinvloeden afhangen van de leeftijd van het kind. Voor normoverschrijdende gedragsproblemen in de kindertijd en adolescentie en antisociale persoonlijkheidsproblemen in de volwassenheid, is nog weinig onderzoek gedaan naar genetische en omgevingsinvloeden op de verschillende leeftijden. Evenmin naar de factoren die het voortbestaan van deze normoverschrijdende problematiek van kindertijd tot de volwassenheid beïnvloeden.

Over de oorzaken van familiaire clustering van psychiatrische klachten binnen gezinnen waarvan een kind is aangemeld bij een polikliniek kinder- en

jeugdpsychiatrie is veel minder bekend dan over grote populaties. Wel weten we dat psychiatrische stoornissen in de familie van kinderen met een psychiatrische aandoening een risicofactor vormen voor het aanhouden van symptomen. Er is nog weinig bekend over de eventuele overeenkomsten van de psychiatrische klachten tussen vaders en moeders in deze gezinnen en of dit verschilt van de overeenkomsten tussen vaders en moeders in de algemene populatie. Nog minder is bekend over het voorkomen van meerdere psychiatrische stoornissen in families, terwijl familiaire clustering vaak niet beperkt is tot slechts één stoornis omdat psychiatrische klachten vaak samen voortkomen, zogeheten comorbiditeit. Tevens richtte het merendeel van eerdere studies zich op zgn. internaliserende klachten (emotionele en psychosomatische klachten waar het individu zelf last van heeft) bij moeders en dan met name op depressiviteit. Er is nog nauwelijks onderzoek gedaan naar andere externaliserende (zoals ADHD of antisociale problematiek waar de omgeving voornamelijk last van heeft) psychiatrische klachten of naar psychopathologie bij de vaders van kinderen met psychiatrische problemen.

De hoofddoelen van dit proefschrift waren, met in achtneming van bovenvermelde informatie, om de invloed van genen en de invloed van de omgeving op verschillende psychiatrische klachten bij kinderen te onderzoeken en de familiaire clustering van psychiatrische klachten in families met een kind dat werd aangemeld bij een polikliniek kinder- en jeugdpsychiatrie. De studies in dit proefschrift maken hiervoor gebruik van de data van families met tweelingen die geregistreerd zijn bij het Nederlands Tweelingen Register (NTR) alsook van data van families met een kind met psychopathologie die zijn aangemeld bij verschillende kinder- en jeugdpsychiatrische klinieken in Nederland. Een uitgebreide beschrijving van de tweede dataverzameling wordt gegeven in de *Appendix,* de NTR dataverzamelingen zijn uitgebreid gedocumenteerd op o.a. de NTR website.

Deel I: De erfelijkheid van psychopathologie bij kinderen en het effect van de beoordelaar

Hoofdstuk 2 van dit proefschrift beschrijft een tweelingstudie waarin de invloed van genen, de gedeelde omgeving en de unieke omgeving op individuele verschillen in psychische klachten bij zevenjarigen wordt onderzocht. Het gaat om depressieve, angst-, somatische, ADHD-, oppositioneel en opstandige (ODD), normoverschrijdende gedrags- en obsessieve compulsieve (OCD) problemen. Zowel de moeder als de vader rapporteerden over de klachten van hun tweeling en waren het grotendeels met elkaar eens; de correlaties varieerden tussen de .6 en .75 voor

de verschillende probleemschalen. Het maakte hierbij niet uit of het kind een jongen of een meisje was. Moeders rapporteerden gemiddeld wel meer klachten over hun kind dan vaders. Dit gold voor iedere probleemschaal en voor jongens en meisjes. Genetische factoren verklaarden rond de 60% van de individuele verschillen tussen kinderen bij de psychiatrische klachten verklaarden, met uitzondering van ADHD waarbij 80% van de variatie door genen werd verklaard. Schattingen van de invloed van de gedeelde omgeving varieerden van 13% voor depressieve en ODD tot 37% voor normoverschrijdende gedragsproblematiek bij zevenjarige kinderen. Genetische factoren waren ook van invloed waren op het deel van de klachten van het kind die alleen door moeder of vader werden gerapporteerd. Zowel de moeder als de vader rapporteren dus unieke waardevolle informatie over de psychische klachten bij hun kinderen. Het is waarschijnlijk dat ze ook beiden enige bias in hun beoordeling hadden omdat, hetgeen ook de gedeelde omgeving van invloed was op het deel van de klachten in het kind die alleen door moeder of vader werden gerapporteerd. Deze resultaten suggereren dat er geen 'beste' ouder is om te raadplegen bij de beoordeling van psychopathologie bij een kind, beide voegen waardevolle unieke informatie toe. Omdat we bij zoveel gezinnen de gegevens van vader en moeder konden analyseren, vonden we, in tegenstelling tot eerdere studies, slechts een gering of soms totaal geen effect meer van de gedeelde omgeving. Deze studie laat onder andere zien dat in tweelingstudies waarbij sprake is van één beoordelaar het effect van de gedeelde omgeving op psychopathologie bij kinderen kan worden overschat.

In *hoofdstuk 3* zijn naast beoordelingen van moeders en vaders, ook de beoordelingen van vrouwelijke en mannelijke leraren van de psychische klachten bij 5, 7, 10 en 12-jarige kinderen onderzocht. Het doel van deze studie was om na te gaan of de verschillen tussen beoordelaars afhankelijk zijn van het geslacht van het kind, de leeftijd van het kind of de psychiatrische probleemschaal. Ook werd getest of de systematische verschillen in de beoordeling van psychiatrische klachten bij kinderen die gezien werden tussen moeders en vaders in hoofdstuk 2, ook werden gezien tussen vrouwelijke en mannelijke leerkrachten. In deze studie werden opnieuw significante verschillen gezien tussen de beoordelingen van ouders psychiatrische klachten van hun kinderen. Dit gold voor alle probleem schalen, voor zowel jongens als meisjes op alle leeftijden. Op 5 jarige leeftijd rapporteerden vaders meer problemen op het gebied van agressieve-, aandacht,- angst- en emotionele klachten dan moeders. Op de andere leeftijden waren de scores van moeders gemiddeld hoger dan van vaders voor depressieve, angst-, somatische, ADHD-, ODD- en normoverschrijdende gedragsproblemen. Deze verschillen werden niet

gezien tussen vrouwelijke en mannelijke leerkrachten, met uitzondering van de beoordeling van klachten bij 12 jarige jongens. Hier scoorden de vrouwelijke leerkrachten hoger dan de mannelijke. Het geslacht van de beoordelaar speelt dus alleen consistent een rol bij ouders bij hun beoordeling van psychiatrische klachten van hun kinderen. Bij leerkrachten is dat niet het geval. Het is van belang dat in onderzoek rekening wordt gehouden met deze systematische verschillen tussen moeders en vaders in de beoordeling van psychopathologie bij hun kind. Dit geldt eveneens voor hulpverleners in kinder- en jeugdpsychiatrische klinieken die van de beoordeling van ouders gebruik maken. Nader onderzoek is gewenst om de factoren te definiëren die een rol spelen bij het feit dat moeders en vaders systematisch verschillen in hun beoordeling terwijl vrouwelijke en mannelijke leraren dat niet doen. Zo kunnen tijdsduur of de omstandigheden waarin de beoordelaar en kind met elkaar doorbrengen een rol van betekenis spelen. Leerkrachten zien jongens en meisjes in eenzelfde omgeving.

Hoofdstuk 4 beschrijft een longitudinale genetische analyse van normoverschrijdende gedragsproblematiek in de kindertijd en adolescentie en antisociale persoonlijkheidsproblemen in de volwassenheid. Er is onderzocht hoe genen, de gedeelde en unieke omgeving de individuele verschillen op de verschillende leeftijden beïnvloeden alsook de stabiliteit van de problemen van de kindertijd tot de volwassenheid. Mannen vertoonden significant meer normoverschrijdende gedragsproblemen dan vrouwen op alle leeftijden. Echter, de bijdrage van genetische en omgevingsfactoren aan het ontstaan van individuele verschillen was niet significant anders voor mannen en vrouwen en ook dezelfde genen leken een rol te spelen voor mannen en vrouwen. Het effect van genen en de gedeelde omgeving op de individuele verschillen in normoverschrijdende gedragsproblemen bij negen- en tienjarige kinderen was gelijk, beide verklaarden 44% van de variatie. In de adolescentie en volwassenheid daarentegen verdween het effect van de gedeelde omgeving en verklaarden alleen nog genetische en unieke omgevingsfactoren de verschillen in normoverschrijdend gedrag en antisociale persoonlijkheidsproblemen tussen mensen. De correlatie tussen gedragsproblemen in de kindertijd en adolescentie was .18, tussen de adolescentie en de volwassenheid .30 en tussen de kindertijd en adolescentie .22. Deze correlaties werden verklaard door stabiele genetische factoren. De genetische correlaties varieerden tussen de .39 en .67. Deze belangrijke rol van genetische factoren zowel normoverschrijdende gedragsproblematiek als in de verschillende psychiatrische klachten in kinderen zoals bestudeerd in hoofdstuk 2 benadrukt dat het belangrijk is om te blijven zoeken naar genetische varianten die verantwoordelijk zijn voor psychische klachten om

duidelijkheid te krijgen in de etiologie van deze klachten. De huidige trend in genetisch onderzoek laat zien dat hoe meer participanten geïncludeerd worden, hoe groter de kans op resultaat is.

Deel II: De familiaire clustering van psychiatrische klachten in een klinisch sample

In *hoofdstuk 5* worden de overeenkomsten in psychiatrische klachten tussen vaders en moeders van kinderen met psychiatrische stoornissen onderzocht en getest of deze verschillen van de overeenkomsten tussen vaders en moeders in de algemene populatie. Er werden correlaties berekend tussen scores van vaders en moeders voor depressieve, angst-, ontwijkende persoonlijkheids-, ADHD- en antisociale persoonlijkheidsproblemen. Alle correlaties waren significant groter dan nul, zowel in de gezinnen met een kind met een psychische stoornis als in de gezinnen uit de algemene populatie. De correlaties van de ouders met een kind met psychopathologie waren echter hoger, soms bijna twee keer zo hoog dan de correlaties van ouders in de algemene populatie. Verder was er een asymmetrie met betrekking tot het geslacht van de ouder in de klinische groep, maar niet in de algemene populatie. ADHD bij vaders correleerde namelijk hoger met alle psychiatrische problemen bij moeders dan ADHD bij moeders met de psychiatrische klachten bij vaders. Verder correleerde antisociale persoonlijkheidsproblemen bij moeders hoger met alle psychiatrische klachten bij vaders dan andersom. Tenslotte hadden ouders met een kind met psychopathologie significant meer psychiatrische klachten dan ouders in de algemene populatie. Deze resultaten laten zien dat ouders van wie een kind bij een kinder- en jeugdpsychiatrische kliniek aangemeld wordt, een verhoogd risico hebben om zelf psychiatrische klachten te ervaren. Deze ouders hebben ook een verhoogde kans op een partner met, niet perse dezelfde, psychiatrische klachten.

De studie in *hoofdstuk 6* toont de prevalenties, d.w.z. het aantal gevallen per honderd, van ouders met depressieve, angst-, ontwijkende persoonlijkheids-, ADHD- en antisociale persoonlijkheidsproblemen en de associaties van de ouderlijke klachten met de psychopathologie bij het kind. Ongeveer 10-15% van de ouders had een (sub)klinisch verhoogde score voor depressiviteit en ontwijkende persoonlijkheidsproblemen, ongeveer 10% had ADHD problemen en ongeveer 24% had een (sub)klinisch verhoogde score op minimaal één van de psychiatrische probleemschalen. Deze prevalenties verschilden niet tussen de moeder en de vader. De analyse van de ouder-kind associaties liet zien dat angstklachten bij de moeder samenhingen met alle internaliserende en externaliserende klachten bij het kind en

ADHD klachten bij de moeder met ADHD klachten bij het kind. Angstklachten bij de vader hielden verband met depressieve en angstklachten bij het kind en ADHD klachten bij de vader hingen samen met ADHD en oppositionele en opstandige problemen bij het kind. De associaties tussen ouders en kinderen verschilden niet tussen jongens of meisjes en werden niet verklaard door de overeenkomsten in psychiatrische klachten tussen de ouders zoals gevonden in hoofdstuk 5. Deze studie maakt duidelijk dat de prevalenties voor psychiatrische klachten bij ouders en de associaties van de ouderlijke klachten met de psychopathologie bij het kind niet verschillen tussen moeder en vader. Het is daarom belangrijk om ook vaders te betrekken in onderzoekstudies en zowel moeders als vaders te screenen op psychiatrische klachten wanneer een kind is aangemeld bij een polikliniek kinder- en jeugdpsychiatrie.

In *hoofdstuk 7* is onderzocht of er voorspellers zijn van ouderlijke psychopathologie in gezinnen waarvan een kind is aangemeld bij een polikliniek kinder- en jeugdpsychiatrie. Er werd hierbij gekeken naar kenmerken van de ouder, het kind en van de familiesituatie nl. naar de relatie status van de ouder, het opleidingsniveau van de ouder, de werkstatus van de ouder, de leeftijd van de ouder, het geslacht van de ouder, de leeftijd van het kind, de psychiatrische stoornis van het kind en co morbiditeit in het kind. In een multivariaat model werd getest of deze variabelen depressieve, angst-, ADHD-, ontwijkende persoonlijkheids- of antisociale persoonlijkheidsproblemen bij de ouder(s) konden voorspellen. Van de 1,805 moeders en 1,361 vaders van 1,866 kinderen met een psychiatrische stoornis diagnose bleken 35.7% van de moeders en 32.8% van de vaders (sub)klinisch verhoogd te scoren op tenminste één van de psychiatrische probleemschalen, voornamelijk voor depressieve of ADHD problemen en bij vaders ook voor vermijdende persoonlijkheidsproblemen. Deze verhoogde scores werden over het algemeen voorspeld door de werkstatus van de ouders. Depressieve en ADHD problemen werden voorspeld door depressiviteit en ADHD bij het kind alsook of de biologische ouders een relatie hadden of niet. Verder werden ontwijkende persoonlijkheidsproblemen bij de ouder voorspeld door autisme bij het kind. Deze resultaten duiden erop dat psychiatrische klachten bij ouders voornamelijk samen hangen met familie omstandigheden, namelijk met het wel of niet hebben van een baan en een relatie met de andere biologische ouder. Daarnaast hangen ouderlijke klachten deels samen met soortgelijke psychopathologie in hun kind. Deze resultaten wijzen er dus op dat er een groep kinderen is met een 'dubbel nadeel'. Zij hebben één of twee ouders met psychiatrische klachten en leven in familie omstandigheden

die nadelig kunnen zijn, zoals met een ouder zonder baan of ouders die niet meer samen zijn.

Hoofdstuk 8 is een longitudinale studie naar de effecten van internaliserende en externaliserende psychiatrische klachten bij ouders op de uitkomst van latere psychopathologie bij het kind. De psychiatrische klachten bij ouder en kind werden voor de eerste keer gemeten op het moment dat het kind aangemeld werd bij de kinder- en jeugdpsychiatrische kliniek, de zogenaamde baseline meting. De klachten zijn tijdens de vervolgmeting, gemiddeld 1.7 jaar later, opnieuw gemeten. Zowel bij het kind als bij de ouder waren de klachten verminderd. Ook bij kinderen met ouders met psychopathologie verbeterden de klachten, maar ze scoorden bij de vervolgmeting nog steeds hoger dan de kinderen van ouders zonder psychopathologie. De belangrijkste voorspeller van de score bij de vervolgmeting was de score van het kind bij de eerste meting. Verder waren de psychiatrische klachten van de ouders bij de vervolgmeting geassocieerd met de uitkomst bij het kind. De scores van ouders bij de baseline meting waren niet voorspellend voor de scores van het kind bij de vervolgmeting. Dit betekent dat de hogere scores van kinderen met ouders met psychopathologie voornamelijk verklaard werden door de hogere scores op het moment van aanmelding bij de psychiatrische kliniek en door het verband met de psychiatrische klachten bij de ouder ten tijde van de vervolgmeting. De ouder-kind associaties waren weer hetzelfde voor de moeder en de vader en konden niet verklaard worden door overeenkomsten in psychiatrische klachten tussen de ouders. De resultaten van dit onderzoek laten zien dat kinderen van ouders met psychiatrische klachten een slechtere uitkomst hebben wat betreft psychopathologie. Het is daarom belangrijk om de ouders te screenen op het moment dat een kind aangemeld wordt bij de kinder- en jeugdpsychiatrische kliniek en indien nodig een behandeling aan deze ouder(s) aan te bieden. Toekomstige studies moeten uitwijzen of de behandeling van de psychiatrische klachten bij de ouder(s) gunstig kan zijn voor de behandeling en uitkomst van psychpathologie bij het kind.

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APPENDICES

Appendix I: Data collection procedures, response rates and measurement instruments

In the second part of this thesis (i.e. chapter five to eight) data were analyzed that were collected in families with a child with psychopathology at the time the child was evaluated at a child and adolescent psychiatric outpatient clinic (first assessment) and one to five years later (second assessment). These data were gathered in four child and adolescent psychiatric outpatient clinics: 1) GGZ inGeest, department of child and adolescent psychiatry, 2) de Bascule, academic hospital for child and adolescent psychiatry, 3) the Erasmus University Medical Center-Sophia Children's Hospital, department of child and adolescent psychiatry/psychology, and 4) UvA Minds, the Academic Treatment Center for Parent and Child at the University of Amsterdam. All clinics mainly treated children with ADHD, conduct behavioral disorders, autism spectrum disorders, anxiety and/or depressive disorders.

Part of this data collection was funded by the Netherlands Foundation for Mental Health (20096398), and the Netherlands Organization for Health Research and Development Grant: "Genetic influences on stability and change in psychopathology from childhood to young adulthood" (ZonMW 912-10-020). This includes the data collection for the first assessment at GGZ inGeest and the Bascule, and for the second assessment at GGZ inGeest and Erasmus MC. This appendix describes these data collection procedures, final response rates and the administered measurement instruments.

The data collections at the first assessment at Erasmus MC and at the first and second assessment at UvA Minds were independent from these data collections. Given the large similarities in the data collection procedures and instruments used across studies (see chapters five to eight) it was decided to simultaneously analyze the data.

Data collection

First assessment

A pilot study was conducted between April 2010 and May 2012 to optimize procedures for data collecting of psychopathology in parents of children evaluated at two child and adolescent psychiatric outpatient clinics in Amsterdam: the department of child and adolescent psychiatry of GGZ inGeest and at two different branches of de Bascule (i.e., the emotional disorders, and autism spectrum disorders). With the

invitation for the first appointment at the clinic, parents received information on this study and were asked to participate by completing a survey assessing their own psychopathology, in addition to the survey they completed on their children's psychopathology as part of the usual clinical practice. Families were excluded when Dutch language was not sufficient to fill in the survey. Non-responders were reminded by letter or telephone call by research assistants. The family-response rate was 18.5%. Surveys were completed by both parents in 110 families, by mothers in 66 families and by fathers of 15 families. The pilot data indicated that 37.3% (n=66) of the mothers and 31% (n=39) of the fathers had a score in the (sub)clinical range for any of the disorders assessed. Further diagnostic assessment was offered and an interview by phone was completed for 43 mothers and 20 fathers (the Composite International Diagnostic Interview, see 'assessment of psychopathology' below).

Given the high rates of parents with psychopathology as observed in the pilot study, screening of parental symptoms was implemented as a standard procedure in the first assessment of the child at the department of child and adolescent psychiatry at GGZ inGeest. In case of (sub)clinical scores, parents were offered further diagnostic assessment and treatment. Families were excluded when Dutch language was not sufficient to fill in the survey (42 out of 751 families, 5.6%). From May 2012 until December 2016 the family response rate was 72.11%, (surveys from 511 out of 709 different families). Of the 511 families, 36.5% (n=176) of the mothers and 22.5% (n=67) of the fathers had a score in the (sub)clinical range on any of the disorders assessed. Additional assessment was completed for 96 mothers and 50 fathers, which revealed a clinical diagnosis (either current or in remission) in 64 mothers and 33 fathers. The article of van Veen et al. [266] on the feasibility of the implementation of screening parents of new registered children for psychopathology and offering parents further psychiatric assessment and if necessary treatment, reported that eventually 14.3% of the parents who completed the survey at the first assessment made use of the offer to get treatment. Data from 117 surveys of 86 different families were excluded for the analyses described in this thesis as they refused consent for the use of the collected data for research purposes. In 9 families, a survey was excluded for one parent, while the survey of the other parent was included. Data were available for research purposes from both parents of 222 families, from mothers of 183 families and from fathers of 29 families.

Second assessment: Follow-up

Families that completed the first set of surveys were approached approximately between one and five years later to complete the same survey assessing their child's and their own psychiatric symptoms. From April 2014 until October 2016, at intervals, a total of 320 families from GGZ inGeest sample were approached. In 70.31% of the total families, the child was 12 years or older and therefore received a self-report survey assessing their psychiatric symptoms. Non-responders were reminded by letter and twice by telephone call. The family response rate was 34.06% (surveys from 109 different families were received). Data were available from both parents of 39 families, from mothers of 61 families and from fathers of 8 families. Data from children older than 12 were available for 49 families.

From April 2015 until October 2016, a total of 382 families from the Rotterdam sample were approached. In 78.5% of the total families, the child was 12 years or older and received a self-report survey assessing their own psychiatric symptoms. Non-responders were reminded by letter and twice by telephone call. The family response rate was 31.4% (surveys from 121 different families were received). Data were available from both parents of 46 families, from mothers of 57 families and from fathers of 13 families. Self-reports from children were available for 51 families.

Collection of biological material

Families that participated in the pilot study or before August 2014 in GGZ inGeest were also asked to participate in the collection of biological material sometime after the first assessment, either by letter or telephone call. From August 2014 until December 2016, families that visited GGZ inGeest were asked to collect buccal swaps, in addition to completing the surveys at the time of the first assessment. The buccal swabs [267] were collected for DNA isolation. Families were provided with 4 sets of buccal swabs per family member and a return envelope. The family response rate of the pilot study was 55.5% (53.32% of these families willing to participate actually returned the buccal swab samples). The family response rate at GGZ inGeest at the first assessment was 38.9% (with 60.2% of those families returning the buccal swab samples) and for the follow-up 22.1% (with 67.6% of those families returning the buccal swab samples). In total, DNA samples were returned by 173 children, 187 mothers and 137 fathers.

Assessment of psychopathology

Behavioral and emotional problems in parents and children were measured with the age-appropriate versions of the questionnaires belonging to the Achenbach System of Empirically Based Assessment (ASEBA), i.e., the Child Behavior Checklist (CBCL), the Youth Self-Report (YSR) [99] and the Adult-Self-Report (ASR) [175]. All three questionnaires measure comparable problems over ages and include the following DSM-oriented syndrome scales; depressive, anxiety, somatic, attention deficit/hyperactivity, oppositional defiant and conduct problems. In addition, the ASR offers the avoidant and antisocial personality problem scales.

Demographical information on age, sex, nationality, educational attainment, work and family composition was obtained in a separate questionnaire (Appendix II).

From May 2012 until August 2013 participants were offered the option to choose between a paper and an online version of the survey. From August 2013 until August 2014 the survey was only offered on paper due to the transition to a new online survey program. From August 2014 until December 2016, parents were provided with personal log-in details to complete the survey online, with the option to receive a paper version of the survey. Overall, about a two third of all surveys were filled in online, while the remaining third were completed in paper form.

In GGZ inGeest, if parents scored in the (sub)clinical range for any of the empirical and DSM-oriented syndrome scales assessed by the ASR, further diagnostic assessment was offered. Additional diagnostic assessment in the parents consisted of the Composite International Diagnostic Interview (CIDI) [232] a fully standardized diagnostic interview administered by me, or another trained research assistant, by telephone. The following disorders were assessed: anxiety (social phobia, generalized anxiety, panic disorder and agoraphobia), mood (depression, dysthymia) and alcohol use (alcohol abuse and dependence). The Conners' Adult ADHD Ratings Scale (CAARS) [233] was added in the diagnostic interview as an additional module to assess attention deficit/hyperactivity in adults. The outcomes from the clinical interview were used as additional information to assess the treatment need of parents.

Appendix II: Questionnaire about demographical information

A. Biografische gegevens

1. Datum van vandaag : ……. - …….. - ……..
2. Geboortedatum van het aangemelde kind : ……. - …….. - ……..
3. Uw geboortedatum : ……. - …….. - ……..
4. Uw geboorteplaats : ……
5. De cijfers van uw postcode : ……
6. Uw geslacht : Man / Vrouw
7. Wilt u het geboorteland van uw ouders aangeven?
Geboorteland vader : ……
Geboorteland moeder : ……
8. Heeft u wel eens meegedaan aan onderzoek van het Nederlands Tweeling Register? : Ja / Nee

B. Gezinssituatie

9. Wat is uw relatie tot uw kind? Ik ben:
- o Biologische moeder
- o Biologische vader
- o Stiefmoeder
- o Stiefvader
- o Pleegmoeder
- o Pleegvader
- o Adoptiemoeder
- o Adoptievader
- o Anders, namelijk ……

Vragen 10 en 11 zijn bestemd voor de *biologische ouder*.
Indien u niet de biologische ouder van het kind bent, kunt u deze vragen overslaan.

10. Woont u samen met de andere biologische ouder van het kind? Ja/nee

11. Indien u niet meer samenwoont met de andere biologische ouder van het kind, hoe oud was het kind toen u uit elkaar ging? …… jaar en/of …… maanden

12. Wat beschrijft uw gezinssituatie met het kind het beste?
- o Gezin met biologische vader en biologische moeder
- o Gezin met biologische vader en nieuwe partner
- o Gezin met biologische moeder en nieuwe partner
- o Eén-oudergezin na scheiding, kind woont grotendeel bij moeder
- o Eén-oudergezin na scheiding, kind woont grotendeels bij vader
- o Co-ouderschap na scheiding, kind woont afwisselend bij beide biologische ouders
- o Eén-oudergezin
- o Pleeggezin
- o Adoptiegezin
- o Anders, namelijk ……

12. Hoe oud was het kind toen de bij vraag 12 aangegeven gezinssituatie ontstond?
- o Vanaf de geboorte
- o Anders, namelijk vanaf de leeftijd van ……jaar en/of …… maanden

14. Woont het kind
- o Voltijds in uw gezin
- o Deels in uw gezin, namelijk gemiddeld …… dagen per maand
- o Niet in uw gezin

15. Indien het kind deels of helemaal niet bij u woont, is dit
- o Bij de andere biologische ouder
- o In een pleeggezin
- o In een gezinsvervangend tehuis
- o Anders, namelijk……

16. Heeft het kind broers en zussen? Ja / Nee

Zo ja, geef a.u.b. de kolommen de aantallen weer.
Ook wanneer deze kinderen (deels) in uw gezin wonen.

Aantal		*Aantal*	
……	Zussen met dezelfde vader en moeder	……	wonen in mijn gezin
……	Broers met dezelfde vader en moeder	……	wonen in mijn gezin
……	Halfzussen met dezelfde vader	……	wonen in mijn gezin
……	Halfbroers met dezelfde vader	……	wonen in mijn gezin
……	Halfbroers met dezelfde moeder	……	wonen in mijn gezin
……	Niet-biologisch verwante zussen	……	wonen in mijn gezin
……	Niet-biologisch verwante broers	……	wonen in mijn gezin
……	Halfzussen met dezelfde moeder	……	wonen in mijn gezin
……	Andere kinderen	……	wonen in mijn gezin

17. Indien er broer(s) en / of zus(sen) niet in uw gezin wonen, verblijven zij
- o Bij de andere biologische ouder
- o In een pleeggezin
- o In een gezinsvervangend tehuis
- o Anders, namelijk ……

18. Zijn er verder nog bijzonderheden ten aanzien van uw gezinssituatie waarvan u denkt dat deze belangrijk kunnen zijn? Ja / Nee
Zo ja, licht a.u.b. toe ……

C. Opleiding en werk

19. Wat is uw *hoogst* gevolgde opleiding?

- o Lagere school, basisschool
- o Lager beroepsonderwijs (bijv. LTS), VMBO (leerweg beroepsonderwijs)
- o Mulo, MAVO, VMBO (theoretische leerweg)
- o HAVO of VWO (hbs, athenaeum, gymnasium)
- o 1-jarig MBO (middelbaar beroepsonderwijs)
- o 2 tot 4-jarig MBO (middelbaar beroepsonderwijs)
- o HBO (hoger beroepsonderwijs)
- o Universiteit of post-HBO onderweg
- o Post-doctoraal / tweede fase opleiding of promotie (doctorsgraad)

20. Is deze opleiding met een diploma afgerond?

- o Nee, niet met een diploma afgerond
- o Ja, wel met een diploma afgerond

21. Wat is uw huidige werksituatie?

- o Betaald werk ……. uren per week
- o Vrijwilligerswerk ……. uren per week
- o Scholier / student
- o Huisvrouw / huisman
- o Werkeloos, sinds ……

D. Gezondheid en medicijngebruik

22. Hoe is in het algemeen uw gezondheid?

- o Slecht
- o Matig
- o Redelijk
- o Goed
- o Uitstekend

23. Gebruikt u medicijnen? Ja/nee

Zo ja, welke?

……
……
……

24. Bent u ooit onder behandeling geweest voor psychische klachten? Ja/nee

Zo ja, kunt u aangeven welke diagnose is gesteld of welke klachten u had?

……
……
……

Risk factors for the development and outcome of childhood psychopathology

LIST OF PUBLICATIONS

2017 **Wesseldijk LW**, Bartels M, Vink JM, van Beijsterveldt CEM, Ligthart L, Boomsma DI, Middeldorp CM (2017). *Genetic and environmental influences on conduct and antisocial personality problems in childhood, adolescence, and adulthood.* European Child & Adolescent Psychiatry.

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2016 **Wesseldijk, LW,** Fedko IO, Bartels M, Nivard MG, van Beijsterveldt CEM, Boomsma DI, Middeldorp CM (2016). *Psychopathology in 7-Year-Old Children: Differences in Maternal and Paternal Ratings and the Genetic Epidemiology*. American Journal of Medical Genetics Part B: Neuropsychiatric Disorders.

2016 **Wesseldijk LW**, Dieleman GC, Lindauer RJL, Bartels M, Willemsen G, Hudziak JJ, Boomsma DI, Middeldorp CM (2016). *Spousal resemblance in psychopathology: A comparison of parents of children with and without psychopathology.* European Psychiatry.

2016 van Veen SC, Batelaan NM, **Wesseldijk LW**, Rozeboom J, Middeldorp CM (2016). *Psychopathology in families: an integral approach via the family outpatient clinic.* Tijdschrift voor Psychiatrie.

2015 Middeldorp CM, **Wesseldijk LW**, Hudziak JJ, Verhulst FC, Lindauer RJ, Dieleman GC (2016). *Parents of children with psychopathology: psychiatric problems and the association with their child's problems.* European Child and Adolescent Psychiatry.

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