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Buschgens, Cathelijne J. M.; Swinkels, Sophie H. N.; Aken, Marcel A. G. van; Ormel, Johan; Verhulst, Frank C.; Buitelaar, Jan K.

Eur Child Adolesc Psychiatry (2009)
18:65–74 DOI 10.1007/s00787-008-0704-x

ORIGINAL CONTRIBUTION

Cathelijne J.M. Buschgens
Sophie H.N. Swinkels
Marcel A.G. van Aken
Johan Ormel
Frank C. Verhulst
Jan K. Buitelaar

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Accepted: 27 March 2008
Published online: 28 June 2008

C.J.M. Buschgens, MSc. (✉)
S.H.N. Swinkels, Ph.D.
J.K. Buitelaar, M.D., Ph.D.
Department of Psychiatry
Radboud University Nijmegen Medical Centre
PO Box 9101, HP 966
6500 HB Nijmegen, The Netherlands
E-Mail: c.buschgens@psy.umcn.nl

M.A.G. van Aken, Ph.D.
Department of Developmental Psychology
Utrecht University
Utrecht, The Netherlands

J. Ormel, Ph.D.
Department of Psychiatry
University Medical Centre Groningen
Groningen, The Netherlands

F.C. Verhulst, M.D., Ph.D.
Department of Child and Adolescent Psychiatry
Erasmus MC-Sophia
Rotterdam, The Netherlands

S.H.N. Swinkels, Ph.D.
J.K. Buitelaar, M.D., Ph.D.
Karakter Child and Adolescent Psychiatry University Centre
Nijmegen, The Netherlands

Abstract *Background* Accumulating evidence indicates that there is a rich and varied interplay between persons and their environments, which strongly suggests that this involves gene-environment correlations and interactions. We investigated whether familial risk (FR) to externalizing behaviors and prenatal and perinatal risk factors, separately or in interaction with each other, predicted externalizing behaviors. *Methods* The subjects were 10- to 12-year-old preadolescents who were taking part in TRAILS, a large prospective population-based cohort study (N = 2,230). Regression analyses were used to determine the relative contribution of FR and prenatal and perinatal risks to parent and teacher ratings of inattention, hyperactivity/impulsivity aggression, and delinquency. *Results* Regression models explained between 6 and 11% of the variance of externalizing behaviors. We found main effects of FR (vs. no FR), macrosomia (birth weight > 4,500 g), maternal prenatal smoking (MPS), pregnancy and delivery complications (PDCs), and gender that were rather consistent across rater and outcome measures. For some outcome measures, the effect of MPS and PDCs depended on the presence of FR. These included both positive and negative interaction effects. Correlations between FR and prenatal and perinatal risks were significant but rather low. *Conclusions* Both main effects and interaction effects of FR and prenatal and perinatal risks contributed to externalizing behaviors in preadolescents, but all effects were of small size. Further research including use of candidate gene polymorphisms is necessary to identify the underlying neurobiological mechanisms of these main and interaction effects.

Key words externalizing behavior – familial risk – prenatal and perinatal risks – gene-environment interaction

Introduction

Substantial achievements have been made in the fields of psychiatric genetics and psychology [41], where accumulating evidence indicate that 'there is a rich and varied interplay between persons and their environments, and every reason to suppose that this involves gene-environment correlations and interactions' [42, p. 358]. This means that 'indirect genetic causal effects may also occur as result of influences on individual differences in environmental risk exposure or susceptibility to risk environments' [41, p. 997]. In the present study, we investigated whether familial

risk to externalizing behaviors (FR) and prenatal and perinatal risk factors, separately or in interaction with each other, predicted externalizing behaviors (inattention, hyperactivity/impulsivity, aggressive and delinquent behaviors) in a large population sample of preadolescents.

Genetic influences

Numerous twin, adoption and family studies have clearly indicated that genetic influences, as they apply to individual differences in the liability to specific behaviors, are strong and pervasive but rarely determinative [41]. Different behavior genetic studies have focused on the genetic influences of specific disorders or domains, for instance, heritability estimates for attention deficit hyperactivity disorder (ADHD) are of 0.76 [15], of 0.55 for oppositional defiant disorder (ODD) and between 0.50–0.62 for conduct disorder (CD) [12, 17]. However, many risk factors, including genetic factors, are not disorder specific [23]. High levels of comorbidity among ADHD, ODD and CD are found [12], which is likely to be due to a substantial degree of shared genetic liability, either operating directly, or indirectly through gene-environment correlations or interactions [30]. After controlling for the overlap between internalizing and externalizing symptoms, familial risk (FR) to externalizing behaviors is specifically associated with externalizing but not with internalizing psychopathology in the offspring [35].

In line with earlier studies [13, 33, 35, 52], we used a proxy for familial risk, which was based on family history data. Since the heritability of externalizing disorders is relatively high, and the etiologic contribution of common environmental risk factors to externalizing disorders is relatively modest, we may assume that mostly genetic factor drive the FR measure. Note that this familial risk might be a consequence of both genetic and environmental factors [43].

Environmental influences

Research in behavioral genetics also demonstrates the importance of environmental influences (e.g. prenatal and perinatal risk factors) in the causation of externalizing behaviors. LBW (low birth weight, defined as <2,500 g) exerts effects on development, and is related to several externalizing problem behaviors (e.g. [10, 11, 32]). Compared with non-ADHD controls, ADHD cases were three times more likely to be born as LBW, even after controlling for potential confounders such as prenatal exposure to alcohol and cigarettes, parental ADHD, social class, and comorbid disruptive behavior disorders in parents and offspring [26]. In a twin study, the effect of LBW on child problem behavior remained after controlling for genetic or other environmental factors [51]. Though there has been a rise in the prevalence of large newborns over a few decades, and there is much evidence that fetal macrosomia (a birth weight of 4,500 g or more [3]) is associated with increased risk of complications both for the mother and the newborn [20], a direct causal relationship between large birth weight and external problem behavior is unknown.

Prenatal exposure to maternal smoking is associated with an increased risk of ADHD [28], ODD and CD [32] and broader categories of externalizing behavior [16]. Besides a dose-response relationship between maternal prenatal smoking (MPS) and externalizing behaviors [9, 25], the effects seem to be additional to the influence of additive genetic factors and nonshared environmental influences, and not attributable to shared rater effects, clinical referral bias, or covariation with antisocial behavior [46]. However, when studies control for genetic risk, the effect of MPS decreases substantially [24, 25] which suggests gene-environment correlation.

Risk factors associated with pregnancy and birth also affect externalizing behaviors. Prechtl and Touwen [37, 49]) introduced the 'obstetric optimality concept', by which each deviation from the optimal condition regarding prenatal and perinatal conditions of the mother, the fetus, and the placenta was summed. A more optimal obstetric situation was related to less externalizing behavior during childhood, but not to less internalizing behavior [5]. Other researchers found that maternal bleeding, smoking, family problems, and illicit drug use during pregnancy in particular were associated with ADHD [27]. Similar results were reported in a study of ADHD children, where neonatal complications were associated with higher total and externalizing scores on the Child Behavior Checklist (CBCL [1]) [6].

Gene environment correlations and interactions

Studies of environmental effects have universally shown that there are huge individual differences in response, with some individuals hardly and some severely affected [41]. Even though genetic and prenatal and perinatal environmental factors have been implicated in the etiology of externalizing behaviors, to the best of our knowledge, there have only been a small number of behavior and molecular genetic studies that have investigated the effect of both a genetic vulnerability and prenatal and perinatal risks [39, 47] and MPS [22, 31, 48]. We have defined FR at a phenotypic level, which was based on the family

history, and served as a proxy for genetic vulnerability [13, 33, 35, 52]. The availability of DNA analysis in the next future will allow us to refine our analyses by including genetic polymorphisms as risk factors.

We investigated the role of FR, prenatal and perinatal risk factors, and their correlation and interaction on the development of externalizing behaviors in a large community-based sample of preadolescents. To this end, we addressed the following hypotheses:

(1) Does FR increase the risk of externalizing behaviors?
(2) Do prenatal and perinatal risks, such as LBW, MPS, and pregnancy and delivery complications (PDCs), increase the risk of externalizing behaviors?
(3) Do FR and prenatal and perinatal risks correlate and interact to increase the risk of externalizing behaviors?

Methods

Sample

The subjects were participants of the tracking adolescents' individual lives survey (TRAILS), a prospective cohort study of Dutch preadolescents who will be measured biennially until they are at least 25 years old. The key objective of TRAILS is to chart and explain the development of mental health from preadolescence into adulthood, in terms of underlying vulnerability and environmental risk. Participants were 10-to-12 years old and lived in the three largest cities and some rural areas in the north of the Netherlands. A detailed description of the sampling procedure and methods is provided elsewhere [14].

Briefly, the present study involves the first assessment wave of TRAILS, which ran from March 2001 to July 2002 [13, 14, 33, 52]. Of all children approached for enrollment in the study (i.e., children selected by the municipalities and attending a school that was willing to participate; $N = 3{,}145$ children from 122 schools, with 90.4% of the schools responding), 6.7% were excluded because of incapability or language problems. Of the remaining 2,935 children, 76.0% were enrolled in the study, yielding a sample size of 2,230. Both the child and the parent consented to participate. The mean age of the children was 11.09 years (SD = 0.55); 50.8% were girls; 10.3% were children who had at least one parent born in a non-Western country; and 32.6% of children had parents with a low educational level (i.e., a lower track of secondary education was the highest level attained). Responders and nonresponders did not differ with respect to the prevalence rates of psychopathology and associations between sociodemographic variables and mental health outcomes [14].

Data collection

Well-trained interviewers visited one of the parents (preferably the mother, 95.6%) at home to administer an interview covering a wide range of topics, including the child's developmental history and somatic health, parental psychopathology, and care utilization. Besides the interview, the parent was also asked to fill out a written questionnaire. Children were evaluated at school, where they filled out questionnaires in groups, under the supervision of TRAILS assistants, and were assessed individually. Teachers were asked to fill out a brief questionnaire for each TRAILS child in their class. Measures that were used in the present study are described below.

Familial risk to externalizing behaviors (FR)

Five dimensions of lifetime parental psychopathology were assessed (depressive disorders, anxiety disorders, substance dependence, antisocial behavior, and psychosis), using the TRAILS family history interview (FHI), which was administered at the parent interview [35]. Each dimension was introduced with a vignette describing the main DSM-IV [4] characteristics of the psychopathology, followed by a series of questions to assess lifetime occurrence, professional treatment, and medication use. Both biological parents were assessed during the interview, using a single informant, typically the mother. For each spectrum, the parents were assigned to one of the categories 0 = (probably) never had an episode, 1 = (probably) yes, or 2 = (probably) yes *and* treatment and/or medication were provided. For antisocial behavior, the last category was: 2 = (probably) yes *and* picked up by the police. Prevalence rates in mother and fathers respectively were, for depression: 27 and 15%; for anxiety: 16 and 6%; for substance dependence: 3 and 7%; and for antisocial behaviour: 3 and 7%. The FHI rates were by and large comparable to the CIDI–DSM-IV lifetime rates obtained by direct interviewing in NEMESIS [8]; the exception being fathers' rates for anxiety disorder and substance dependence that were 40% too low [35, 52]. We did not focus on parental psychosis, depressive and anxiety disorders.

The construction of FR was based on the presence reported path coefficients regarding substance abuse and antisocial behavior by Kendler et al. [23], who preformed multivariate twin modeling to investigate the structure of genetic risk for common psychiatric

and substance use disorders. First, we combined the coefficients reported by Kendler et al. [23] for alcohol dependence and drug abuse/dependence to create the variable SAD (substance abuse/dependence), and likewise we created the variable ASB (antisocial behavior) by combining the coefficients for antisocial behavior and conduct disorder. Subsequently, FR scores were computed by filling in the following regression equation: FR to externalizing behaviors = SAD mother + SAD father + ASB mother + ASB father, FR ranged from 0 to 8 (skewness 3.78, kurtosis, 17.63). To enhance comparison with other TRAILS reports [33, 52] missing values (N = 67) were replaced by the sample mean (0.18). Two groups were created on the basis of the distribution of FR (Total N = 2,230); children with no FR (82.2%) and children with FR (17.8%). In the regression analyses these two groups were used as a dummy variable.

Prenatal and perinatal risks

Several prenatal and perinatal risks were assessed by means of the TRAILS Family History Interview, administered at the parent interview. Children who weighed less than 5 pounds (<2,500 g) were considered as low birth weight (LBW; 3.6%), and children weighing 9 pounds or more (≥4,500 g) as macrosomic (6.5%) (total N = 2,132). This cut-off is based on the ACOG definition of macrosomia [3].

MPS was estimated by asking the informant whether, and if so how much, the mother had smoked during pregnancy: 0 = not at all, 1 = a few times, less than 1 cigarette a day, 2 = 1–10 cigarettes a day, 3 = 11–20 cigarettes a day, 4 = 1–2 packets a day, and 5 = more than 2 packets a day. The categories were recoded into three groups: non-smokers (69.5%), mild smokers (≤10 cigarettes a day; 23.6%), and heavy smokers (>10 cigarettes a day; 6.9%); data were available for 2,168 mothers. In accordance with the literature [9, 25], the cut off between some and moderate/severe risk was set on 10 cigarettes a day.

An index of PDCs was composed by adding the score for the presence of pregnancy complications (i.e. physical, social or psychological problems during pregnancy), complicated deliveries (i.e. breech presentation, Caesarean section) and hospitalization of the mother (i.e. due to physical problems, postnatal depression) or child (i.e. lack of oxygen, blood transfusion, jaundice) [18, 27]. This PDC score ranged between 0 and 14 (m = 1.87, SD = 2.19). If no information was available for six or more items, cases were excluded from further analyses. Three groups were created on the basis of the distribution of PDCs and our aim to demarcate a top 10% with high PDCs (total N = 2,186): no complications (37.6%), between 1 and 4 complications (50.0%), and 5 or more complications (12.4%).

Externalizing behaviors

Externalizing behaviors were assessed with the child behavior checklist (CBCL), one of the most commonly used questionnaires in current child and adolescent psychiatric research [1, 53]. It contains a list of 112 behavioral and emotional problems which parents can rate as 0 = not true, 1 = somewhat or sometimes true, or 2 = very often true in the past 6 months. In addition to the CBCL, we administered the teacher's checklist of psychopathology (TCP). The TCP contains descriptions of problem behaviors corresponding to the syndromes scored with Achenbach's teacher report form [14]. Response options range from 0 (not applicable) to 4 (very clearly or frequently applicable). In this study we focused on the CBCL syndromes attention problems (α = 0.81), aggressive behavior (α = 0.89), and delinquent behavior (α = 0.68). Consistent with other reports [2], the agreement between parent-reported and teacher-reported problems was only moderate (r = 0.47 for inattention, r = 0.37 for impulsivity/hyperactivity, r = 0.32 for aggression and r = 0.27 for delinquency). We feel that the two informants perceive different aspects of problem behavior and that differences between informants are meaningful.

Statistical analysis

Two dummies were made for each of the predictors that consisted of three categories. For birth weight, the high and the low group were compared to the middle group (normal birth weight). This enables us to contrast both the macrosomic children and the LBW children separately to children with a normal birth weight. For the predictors MPS and PDCs, the first dummy included the contrast between the absence vs. the presence (regardless of the level) of the predictor. The second dummy included the contrast between the absence/mild presence vs. the extreme presence of the predictors, this contrast thus enabled us to examine whether a dose response effect was present.

To obtain comparable regression coefficients, z-scores were used for all dependent variables. Associations between variables were examined by means of Pearson correlations. Regression analyses were used to determine the relative contributions of FR, birth weight, MPS, PDCs, and gender to parents' and teachers' ratings of inattention, hyperactivity/impulsivity, aggression and delinquency. Interaction terms

between FR and prenatal and perinatal risks, and sex (as a covariate) were also entered into the regression models. No multicollinearity was present in our data (greatest VIF value was 4.59 for FR).

All analyses were performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 14.0).

Results

Bivariate correlation between predictors and externalizing behaviors

The (Pearson) bivariate correlations between the predictors and the dependent measures of externalizing behaviors are summarized in Table 1. Both FR and MPS were positively associated with all dependent measures as reported by parents and teachers. LBW was negatively correlated with parent-rated inattention and aggression. PDCs were positively correlated with inattention reported by parents and teachers, and with aggression and delinquency reported by parents. FR was positively correlated with MPS, and negatively with LBW. Thus person-environment correlations were present: children with a higher FR had been exposed to more prenatal and perinatal risks.

Multivariate models of inattention, hyperactivity and impulsivity

Multiple linear regression analysis showed that FR, prenatal and perinatal risks and gender together explained 8% of the variance in parent reported inattention (see Table 2). There was a main effect of FR (vs. no FR). Main effects were further found for MPS, PDCs (both at mild and severe levels), and gender, with boys having higher scores than girls. The main effects for FR, MPS and PDCs are shown in Fig. 1.

Table 1 Bivariate correlations between predictors and externalizing behaviors (standardized score)

Variable	FR	CBCL-inatt	TPC-inatt	TCP-HA/IMP	CBCL-aggr	TCP-aggr	CBCL-deli	TCP-deli
FR	–	0.15**	0.12**	0.12**	0.13**	0.14**	0.15**	0.13**
LBW & NBW	−0.05*	−0.08**	NS	NS	−0.06*	NS	NS	NS
HBW & NBW	NS	NS	NS	NS	NS	NS	NS	NS
MPS	0.20**	0.14**	0.16**	0.14**	0.10**	0.13**	0.14**	0.13**
PDCs	NS	0.13**	0.06**	NS	0.10**	NS	0.06**	NS

CBCL child behavior checklist, *TCP* teacher's checklist of psychopathology, *Inatt* inattention, *HA/IMP* hyperactivity/impulsivity, *Aggr* aggression, *Deli* Delinquency, *FR* familial risk (for externalizing behavior), *LBW* low birth weight (<2,500 g), *NBW* normal birth weight, *HBW* high birth weight/macrosomia (>4,500 g); *MPS* maternal prenatal smoking, *PDCs* pregnancy and delivery complications, *NS* not significant
*$P < 0.05$; **$P < 0.01$ (2-tailed)

Table 2 Multiple linear regression analyses, for each separate (standardized) dependent variable and informant

Variable	β						
	CBCL–inatt $R^2 = 0.08$	TPC-inatt $R^2 = 0.09$	TCP-HA/IMP $R^2 = 0.11$	CBCL-aggr $R^2 = 0.06$	TCP-aggr $R^2 = 0.10$	CBCL-deli $R^2 = 0\ .08$	TCP-deli $R^2 = 0.07$
Boys vs. girls	0.17**	0.20**	0.28**	0.13**	0.24**	0.19**	0.18**
FR vs. no FR	0.13**	NS	NS	0.14**	NS	0.15**	0.10*
LBW vs. NBW	NS	NS	NS	NS	NS	NS	NS
HBW vs. NBW	NS	0.07**	0.09**	0.06*	0.08**	NS	0.09**
MPS vs. MPS	0.12**	0.14**	0.10**	0.08**	0.10**	0.11**	0.07**
Severe MPS vs. no/ some MPS	NS	NS	0.06*	NS	0.07*	NS	0.10**
PDCs vs. no PDCs	0.06*	0.06*	NS	NS	NS	NS	NS
Severe PDCs vs. no/some PDCs	0.06*	NS	NS	0.07**	NS	0.05*	NS
FR vs. no FR * LBW vs. NBW	NS	NS	NS	NS	NS	NS	NS
FR vs. no FR * HBW vs. NBW	NS	NS	NS	NS	NS	NS	NS
FR vs. no FR * MPS vs. no MPS	NS	-0.11**	-0.08*	NS	NS	NS	NS
FR vs. no FR * severe MPS vs. no/some MPS	NS	0.09**	0.06*	NS	NS	NS	NS
FR vs. no FR * PDCs vs. no PDCs	NS	NS	NS	NS	NS	NS	NS
FR vs. no FR * severe PDCs vs. no/ some PDCs	NS	NS	NS	-0.07*	NS	NS	Ns

CBCL child behavior checklist, *TCP* teacher's checklist of psychopathology, *Inatt* Inattention, *HA/IMP* hyperactivity/impulsivity, *Aggr* aggression, *Deli* delinquency, *FR* familial risk for externalizing behavior, *LBW* low birth weight (<2,500 g), *NBW* normal birth weight, *HBW* high birth weight/macrosomia (>4,500 g), *MPS* maternal prenatal smoking, *PDCs* pregnancy and delivery complications, *NS* not significant
*$P < 0.05$, **$P < 0.01$ (two-tailed)

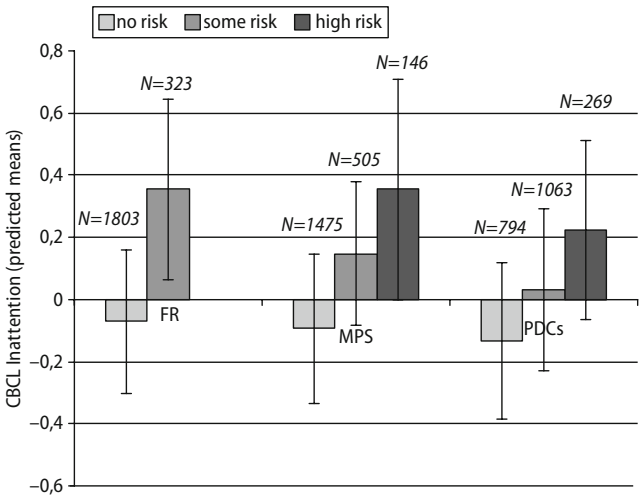

Fig. 1 Main effects of familial risk (FR), maternal prenatal smoking (MPS) and pregnancy and delivery complications (PDCs) as predictors for parent-reported inattention. The figure presents predicted values (and sd) from the multivariate model for the main effects of FR, MPS and PDCs. Group size and composition are different for each of these predictors. *Note:* FR consists of two groups: children with no FR and children with FR

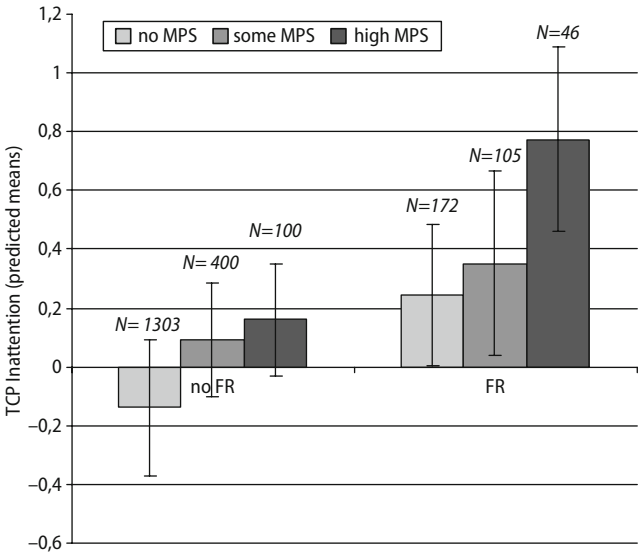

Fig. 2 The integration of two interaction effects between familial risk (FR) and maternal prenatal smoking (MPS) as predictors for teacher-reported inattention

Table 2 also shows that the model explained about 9–11% of teacher rated inattention and hyperactivity/impulsivity. Main effects were found for macrosomia, MPS (at both levels for hyperactivity/impulsivity), PDCs (vs. no PDCs, only for parent rated inattention) and male gender. No main effects of FR was found.

Four interactions effects were found for teachers' reported inattention and hyperactivity/ impulsivity. These interaction effects refer to FR and MPS at different levels. The first two were between FR (vs. no FR) and MPS (vs. no MPS) for teacher' reported inattention and hyperactivity/impulsivity. As shown in Table 2, this negative interaction effect indicates that the effect of MPS was stronger in children with no FR than in children with FR. The second two positive interaction effects were between FR (vs. no FR) and severe MPS (vs. no/some MPS) for teacher' reported inattention and hyperactivity/impulsivity, indicating that the effect of severe MPS was stronger for children with no FR than in children with FR. As illustrated in Fig. 2, these effects together reflect that MPS has initially at lower levels a stronger effect in the absence than in the presence of FR. However, at more severe levels of MPS this negative interaction is turned into a positive interaction and overruled.

Multivariate models of aggressive behavior

The models explained around 6% and 10% of the variance in aggressive behavior reported by parents and teachers, respectively. Main predictors of aggression, as measured with the CBCL, were FR, macrosomia, MPS (vs. no MPS), severe PDCs, and gender. Main predictors of teacher-rated aggression were macrosomia, MPS (both at mild and severe levels), and gender. One (negative) interaction effects was found for parent-rated aggression. This one concerns the effect between FR and severe PDCs: the effect of severe PDCs is stronger for children without FR than for children with FR.

Multivariate models of delinquent behavior

FR, prenatal and perinatal risks, and gender explained about 7 and 8% of the variance in delinquent behavior reported by parents and teachers. Several main effects but no significant interactions were found. Parent-rated delinquency was predicted by FR, MPS (vs. no MPS), severe PDCs, and gender. Main risk factors for teacher-reported delinquent behavior were FR, macrosomia, MPS (both at mild and severe levels), and gender.

Discussion

In line with two earlier papers based on the TRAILS dataset [13, 35, 52], we found FR to externalizing behaviors to be a main predictor of externalizing behaviors in preadolescents, as evidenced by significant bivariate correlations between FR and all seven dependent measures of externalizing behavior, and by a significant independent contribution to parent-rated inattention, aggression and delinquency and teacher-rated delinquency in the multivariate analyses.

Several prenatal and perinatal risk factors were found to be main predictors of externalizing behaviors, even after adjustment for other predictors in multivariate models. Although most studies have focused on LBW or even extreme LBW in relation to behavioral and psychiatric sequelae [10, 11], we were interested in both LBW and macrosomia. As expected, we found that, LBW was correlated with more parent-rated inattention and aggression. Since several studies suggest that LBW is also associated with internalizing problems [19] and depression [44], LBW does not seem to be a disorder-specific risk factor. In addition, the fact that LBW was not a risk factor of inattention may be due to other environmental factors that might moderate this relationships such as urban vs. suburban communities [11] and maternal warmth [50]. As a novel finding, macrosomia was a risk factor for one parent- and all teacher-reported externalizing behaviors. A possible explanation for this finding may be that macrosomia is related to adverse perinatal, neonatal and maternal outcomes (e.g. [7, 20, 29, 34]), and that these adversities are related to more problem behavior (e.g. [5, 6, 27]). Another possibility is that large babies are also more likely to have a large body size in childhood [36], and a large body size at age 3 was related to increased aggression at age 11 years [38]. Together these results indicate that the relationship between birth weight and externalizing problems is curvilinear, with both macrosomia and LBW contributing to higher levels of externalizing behaviors.

MPS was, as expected e.g. [16], also a main risk factor for all parent- and teacher-reported externalizing behaviors, even after adjusting for the effect of FR. MPS was associated with teacher-reported hyperactivity/impulsivity, aggression, and delinquency in a dose-dependent manner, with children who were prenatally exposed to more than 10 cigarettes a day showing more hyperactivity, aggression, and delinquency than children who were prenatally exposed to fewer cigarettes. This is also in line with other research e.g. [9, 25].

PDCs were directly related with the parent-reported inattention, aggression and delinquency and with teacher-reported inattention in multivariate analyses. These effects of PDCs, and especially a high level of PDCs, on all three parent-reported measures of externalizing behaviors survived in the multivariate analyses. Children with five or more PDCs were at more risk of some externalizing behaviors than children who had no or less PDCs. Boys showed more externalizing behaviors than girls.

Our study provided a unique opportunity to examine the evidence for the presence of person-environment correlations and interactions on behavioral problems. FR was significantly correlated with LBW, MPS, and the presence and severity of PDCs. For the interpretation of person-environment interaction, researchers will need to ensure that the environmental risk in question is not genetically mediated. When genes and environment are highly correlated, person-environment interactions may in fact represent gene-gene interactions, where the prenatal/perinatal risk, is in fact a marker for genetic risk [21]. Since we only found weak person-environment correlations, which indicate that there is some control of FR on the exposure to these prenatal and perinatal risk factors, we can be confident that our findings represent true person-environment interaction. In addition, we also found that prenatal and perinatal risks predicted externalizing behaviors, even when FR was controlled for; this suggests that some of these risks are truly environmental. Nevertheless, a number of recent twin studies have shown that the adverse effects of MPS on symptoms of conduct disorder [25, 45] or ADHD [24] decrease or even disappear when the analyses are controlled for genetic effects and also other confounders are taken into account. A possible explanation for this difference may be explained by the fact that the referred studies involve a twin design.

When examining person-environment interactions, we entered six interaction terms in seven multivariate analyses. Out of these 42 tests performed, 5 interactions terms were found to be significant at the $P = 0.05$ level. ($n = 42$, test proportion 0.05, $P > 0.05$ by binomial test). Although the number of significant interaction is at chance level, the four effects between FR and (severe) prenatal smoking are within the same domain, and are partially in line with molecular genetic studies that focussed on the effects of maternal prenatal smoking and a genetic vulnerability [22, 31, 48].

We like to note that we found both positive and negative interaction effects. The positive effects indicate that the influence of environmental risk factors is stronger in the presence of FR. This is in line with the stress-vulnerability model of psychopathology. In contrast, negative interaction effects entail that the influence of environmental factors is largest in the absence of FR. This model is less well-known and may be called the environment-permissiveness model. Possible explanations for this environment-permissiveness model are that strong environmental risk factors may overrule the more subtle influence of individual vulnerability factors and that the influence of genetic vulnerability factors is strongest in the absence rather than the presence of the environmental risk factor.

Differences and similarities in the results across parents and teacher reports of externalizing behaviors can generally be explained in several ways: risk factors

that seem to affect all types of externalizing behavior, independent of the rater (e.g. MPS, gender), risk factors which seems to affect behaviors in specific domains (e.g. FR, PDCs) and risk factors which seems to be 'disorder' specific (e.g. interaction effects between FR and MPS). Future studies should look into the mechanisms underlying these findings.

Limitations

This is the first study to combine the effects of FR and prenatal and perinatal risk factors in an epidemiological sample, without shared rater effects. However, our study had several potential limitations. Firstly, FR to externalizing behaviors was defined at a phenotypic level and was based on family history as a proxy for genetic vulnerability. With the caveat in mind that FR may reflect both genetic and environmental influences, the availability of DNA analysis in the next future will allow us to refine our analyses by including genetic polymorphisms as risk factors. Secondly, the use of family history interviews, as compared with direct interviews of relatives, may have led to underreporting of lifetime parental psychopathology, and thus underestimation of associations is possible [35]. However, except for father's rate for substance dependence, our prevalence rates were comparable to life time rates obtained by direct interviewing [8]. Thirdly, we investigated preadolescents and results may differ for other developmental periods. Future studies should examine whether the main and interaction effects found are also relevant to the prediction of externalizing problems in older children. Lastly, we obtained retrospective information on prenatal and perinatal risk factors. Underreporting cannot be excluded, although studies have shown that, after 4–9 years, the agreement between retrospective reports and information for medical records was generally 'very good', including birth weight, MPS and complications in pregnancy and labour [40].

Clinical implications

Because children who are genetically vulnerable to externalizing behaviors are at increased risk of showing more externalizing (problem) behavior, particular in conjunction with prenatal and perinatal risk factors, knowledge of a family history of alcohol and drug abuse/dependence and antisocial behavior may be used to help clinicians to prioritize cases. In addition, mothers, especially from genetically vulnerable families, who experience pregnancy and labour complications should be monitored as well; these risk should be limited as much as possible.

This study has mainly been descriptive in how FR and prenatal and perinatal risk factors are associated and interact with externalizing behaviors. The neurobiological mechanisms underlying the interactions between FR and environmental risks, such as low birth weight, macrosomia, MPS and PDCs, are largely unknown. Since both ends on the continuum of birth weight seem to be associated with more problem behavior, it is necessary to monitor the child's growth, and start from the prenatal period. Studies that focus on modelling of developmental trajectories, neuropsychological functions and brain activity/structure offer the opportunity to deepen our understanding of pathways to health and illness across childhood and adolescence and the relevant neurobiological mechanisms underneath, and may give more leads for prevention and intervention.

Acknowledgments This research is part of TRAILS, a multicenter cohort study involving the University of Groningen, the Erasmus Medical Center of Rotterdam, the Vrije University of Amsterdam, the Radboud University Nijmegen Medical Centre, and the Trimbos Institute and the University of Leiden, the Netherlands. TRAILS is financially supported by grants from the Netherlands Organization for Scientific Research (GB-MW 940-38-011, GB-MAG 480-01-006, ZonMw 100.001.001; NWO-175.010.2003.005) and the Department of Justice, and by the participating centers. C.J.M. Buschgens is supported by Radboud University Nijmegen Medical Centre.

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