

RUNNING HEAD: Comorbidity of Disruptive Behaviors from age 1½ to 5 years

Comorbid Development of Disruptive Behaviors from age 1½ to 5 years in a Population Birth-Cohort and Association with School Adjustment in First Grade

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Integrity of research and reporting

Informed consent has been appropriately obtained and Institutional Review Board of the University of Montreal provided ethical approval. Therefore this study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Conflict of interest

The authors declare that they have no conflict of interest.

Abstract

Comorbidity is frequent among disruptive behaviors (DB) and leads to mental health problems during adolescence and adulthood. However, the early developmental origins of this comorbidity have so far received little attention. This study investigated the developmental comorbidity of three DB categories during early childhood: hyperactivity-impulsivity, non-compliance, and physical aggression. Joint developmental trajectories of DB were identified based on annual mother interviews from age 1½ to 5 years, in a population-representative birth-cohort (N=2045). A significant proportion of children (13% to 21%, depending on the type of DB) consistently displayed high levels of hyperactivity-impulsivity, non-compliance, or physical aggression from age 1½ to 5 years. Developmental comorbidity was frequent, especially for boys: 10% of boys and 3.7% of girls were on a stable trajectory with high levels of symptoms for the three categories of DB. Significant associations were observed between preschool joint-trajectories of DB and indicators of DB and school adjustment assessed by teachers in first grade. Preschoolers who maintained high levels of hyperactivity-impulsivity, non-compliance, and physical aggression, displayed the highest number of DB symptoms in first grade for all categories according to their teacher. They were also among the most disadvantaged of their class for school adjustment indicators. Thus, DB manifestations and developmental comorbidity of DB are highly prevalent in infancy. Early childhood appears to be a critical period to prevent persistent and comorbid DB that leads to impairment at the very beginning of school attendance and to long-term serious health and social adjustment problems.

Keywords: Disruptive behaviors, trajectories, comorbidity, preschool years, school entry.

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Comorbid Development of Disruptive Behaviors from age 1½ to 5 years in a Population Birth-Cohort and Association with School Adjustment in First Grade

A number of studies examining developmental issues and comorbidity between disruptive behaviors (DB) embedded in diagnostic categories of Attention-Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), and Conduct Disorder (CD), have shown that children with a comorbid condition are more likely to experience later school difficulties, peer rejection, unemployment and social maladjustment than their peers with a single diagnosis (Odgers et al. 2007; Rutter, Kim-Cohen & Maughan, 2006; Waschbusch, 2002). These studies also showed that comorbid conditions can be observed in clinical and in population samples (Connor et al. 2003; Costello, Egger & Angold, 2005; Waschbusch, 2002). However, most of these investigations have focussed on school-aged children and adolescents. Thus, the developmental patterns of comorbidity across different types of DB are not known for preschool children from the general population. One reason for this lack of studies is that some of the DB symptoms outlined in DSM diagnostic categories do not apply to preschool children (Wakschlag, Tolan & Leventhal, 2010). Moreover, the concept of impairment that is part of the diagnostic process lacks concrete references for this early age, which makes it difficult to distinguish between normative and problem behaviors.

Despite these difficulties in applying diagnostic categories to young children, recent studies have reported preschool symptoms of ADHD, ODD, physical aggression, or combined DB, as well as their continuity in the elementary school years, supporting the idea of a preschool onset for these disorders (Bufferd, Dougherty, Carlson, Rose & Klein, 2012; Ezpeleta, Granero, De la Osa, Penelo & Domenech, 2012; Keenan et al. 2011; Lahey, Pelham, Loney, Lee & Willcut, 2005; Shaw, Lacourse & Nagin, 2005; Tremblay et al. 2004; Wichstrøm et al. 2012). There is also evidence that the comorbidity observed in school age children is already present in early

childhood (Bendiksen et al. 2014; Bufferd et al. 2012; Egger & Angold, 2006; Gadow & Nolan, 2002; Wichstrøm et al. 2012). Moreover, preschool DB symptoms related to ADHD, ODD and CD have been associated with adjustment problems in the first years of school attendance (Brennan et al. 2014; Campbell et al. 2006; Cherkasova et al. 2013; Lavigne et al. 2001; Leblanc et al. 2008; Shaw, Bell & Gilliom, 2000). Although some studies did not observe this association or reported significant variations between DB in the preschool to early school period (Alatupa et al. 2001; Bunte et al. 2014), failure to account for the comorbidity between DB might partly explain the discrepant results. Indeed, some evidence suggests stability from the preschool to the school age period is especially pronounced in children with comorbid DB, notably ADHD/CD (Campbell, Shaw & Gilliom, 2000) and ADHD/ODD (Gadow & Nolan, 2002).

Building on the above findings, developmental theories of DB early starters postulate: 1) the onset of childhood DB in preschool years, 2) their relative stability up to elementary school and beyond, and 3) the greater risk for young children exhibiting more than one type of DB to experience a variety of negative outcomes later on (Campbell et al. 2000; Shaw, 2013; Tremblay, 2010). This developmental course is hypothesized to result from both genetic and environmental factors (e.g., poverty, family stress, maternal depression, inconsistent child-care) that operate jointly to sustain and aggravate the child's problem behaviors (Shaw et al. 2000; Shaw, 2013; Tremblay, 2010). However, most existing studies of DB during early childhood have either: 1) focused on children from the middle to late preschool years, 2) examined a single type of problem behavior, 3) used small, clinical or at-risk samples, or 4) relied on few assessments over time. Considering that previous studies support the idea of a preschool onset of comorbidity between DB, and the serious long-term consequences observed for children with a comorbid condition, a systematic investigation of the developmental course of DB comorbidity over the preschool years in the general population is needed.

Reports of gender differences are also inconsistent among studies investigating preschool DB. Some studies found a higher prevalence, severity or stability of DB in boys (Bendiksen et al. 2014; Keenan et al. 2011; Leblanc et al. 2008; Wichstrøm et al. 2012), whereas others observed only weak or no gender differences (Baillargeon, Keenan & Cao, 2012; Basten et al. 2015; Bufferd et al. 2012; Wichstrøm et al. 2012). In addition, sex differences did not always refer to the same DB in the different studies. Variations in age range across studies might explain some of the discrepancies, since consistent gender differences are hypothesised to emerge only around the age of 4 or 5 years (Keenan & Shaw, 1997). Differences in sample characteristics – the use of a clinical, at-risk or population-based sample - might also be a factor. Thus, gender differences in the developmental course of DB in preschool children warrant further investigation.

To address these issues, the first aim of the present study was to use a large population-based birth cohort to describe the developmental comorbidity of DB symptoms corresponding to ADHD (Hyperactivity-Impulsivity: H-I) and CD (Physical aggression: PA) diagnostic categories, and to Non-compliance (NC; see: Measures), an important aspect of DB associated with both ODD and CD. Specifically, based on five annual assessments from age 1½ to 5 years, we used a group-based method to identify subgroups of children with distinct developmental trajectories for each of the three DB categories and then analyzed their joint-course over the preschool period. Based on previous reports with preschool and older children, it was expected that a significant proportion of children would consistently display higher levels of DB symptoms, and that early comorbidity would be prevalent among these preschoolers. It was also expected that both girls and boys would be among the children with higher levels of DB, although boys should be represented in greater proportion. The second aim of this study was to examine the association between joint-trajectories of DB in preschool and children's DB and school adjustment in first grade. Comorbidity of DB over the course of the preschool years was expected to be associated

with poorer behavior and academic outcomes. Children displaying both high levels of H-I and PA, and especially those also displaying high NC, should be the most impaired in first grade. Finally, because the developmental course of DB is hypothesized to be partly influenced by individual factors inherent in the child, it was expected that the above associations would be observed even when controlling for environmental risk factors typically linked with DB, notably, parental and family characteristics, and socioeconomic status.

Methods

Participants

Study participants were a birth cohort of 2045 infants (50.3% boys) representative of the children born in the province of Quebec, Canada, in 1997-1998, and were part of an ongoing longitudinal study, the Québec Longitudinal Study of Child Development (QLSCD; Jetté and Des Groseillers, 2000a). The cohort was originally drawn from the Quebec Birth Registry using stratified sampling by living area and birth rate. Targeted families were first contacted through mail with an introduction letter and an information brochure presenting the objectives of the study and explaining the duration and procedure of the home interview, the financial compensation (\$20) and confidentiality agreement. Informed written consent was obtained separately for each assessment wave and ethical approval of all aspects of the study was provided by the University of Montreal's Institutional Review Board. Children and their families were assessed first at the age of 5 months and at yearly intervals thereafter. The assessments consisted of a face-to-face home interview with the most knowledgeable person about the child (the mother in 99% of cases) and lasted on average for 1 hour and 45 minutes. A variety of dimensions regarding the child, the parents and the family were assessed by a trained interviewer using a computerized questionnaire available in French and English. Preschool assessments at the ages of 1½, 2½, 3½, 4½, and 5 years were used in the present study. Attrition from time 1 to time 5 was

14.0%, with a response rate of 97.7%, 95.4%, 95.1% and 86.0%, respectively, from age 2½ to age 5. Participants who remained in the study were compared to those lost due to attrition in regard to demographic and socioeconomic family characteristics (i.e., mother's and father's age and education, and family SES), and parent ratings of children's H-I, NC, and PA at time 1. No significant differences emerged, except for a slightly higher SES of the remaining families compared to the families lost due to attrition; $F(df=1)=17.72, p<.001$, Cohen's $d=.19$. It should be noted, however, that this difference is considered to be extremely small and near zero (Cohen, 1977; Wolf, 1986). The demographic and socioeconomic characteristics of the participating families at the first time of assessment are presented in Table 1.

Measures

Disruptive Behaviors in the Preschool Years

As with most large scale epidemiological studies of young children, parents were used as reporting sources. Considering the difficulties in applying psychiatric diagnoses to very young children, measures focused on applicable and observable behaviours from age 1½ year onwards. Moreover, in order to compute developmental trajectories, items needed to be the same across all times of assessment. Consequently, the items selected were limited to behaviors that could be reasonably observed at age 1½ and up until age 5 years. For ADHD, previous studies have highlighted the unreliability of early measures of inattention (Curchack-Lichtin, Chacko & Halperin, 2014) and concluded that general hyperactivity-impulsivity symptoms are the best qualifier of ADHD for young children prior to school entry (Lahey et al. 2005). We therefore focused on hyperactivity and impulsivity symptoms for creating the *Hyperactivity-Impulsivity (H-I)* scale, using five items from previous studies (Leblanc et al. 2008): can't stand still, is agitated; fidgety; impulsive, acts without thinking; difficulty waiting for his/her turn; difficulty remaining quiet. For CD symptoms, it was important to avoid symptoms that rely on the

understanding of complex rules or language skills, which are not yet developed very well in young children (Keenan & Wakschlag, 2002). Therefore, and also given the obvious difficulty in assessing symptoms related to "Destruction of property" "Deceitfulness or theft" or "Serious violations of rules" in preschoolers, we focused on symptoms related to "Aggression against persons" – specifically, *Physical aggression (PA)* - for CD, based on the 3 following items: fights; physically attacks others; hits, bites or kicks. Regarding ODD, the other category of DB, the same rationale led us to exclude symptoms related to "Vindictiveness" subdimension. As for irritability, it is often considered a non-specific symptom of psychiatric disorder, and its manifestation in early childhood is associated with a wide range of psychiatric disorders and functional impairment both concurrently and prospectively (Dougherty et al. 2013; Stringaris, 2011). We therefore focused on behaviors relative to defiance/non-compliance, which at this early age are difficult to disentangle from behaviors reflecting the violation of rules usually linked to CD. Considering this, we adopted the term *Non-compliance (NC)*, common to both ODD/CD categories as a construct label. This construct refers to a child's defiance, non-adherence and non-compliance with an adult's requests or rules that occur along with a lack of guilt after misbehaving as well as to nonresponsiveness to external control (e.g., punishment). Similar constructs have alternatively been labeled opposition-defiance or disregard for rules in previous studies (Baillargeon, Keenan & Cao, 2012; Baillargeon, Morisset, Keenan et al. 2012; Baillargeon, Normand, Séguin et al. 2007; Petitclerc et al. 2009; 2011). The items describing NC category were: is rebellious/defiant or refuses to comply with adults' requests or rules; has no remorse after misconduct; doesn't change his/her behavior after being punished. These items were included in Canada's National Longitudinal Survey of Children and Youth (Statistics Canada, 1995), and originate from the Child Behavior Checklist/2–3 (Achenbach, 1992). The scale has shown good psychometric properties and stability between ages 17 and 41 months

(Baillargeon, Keenan & Cao, 2012), and between 29 and 74 months (Petitclerc et al. 2009), as well as a substantial genetic basis (Petitclerc et al. 2011). All DB items were rated on a 3-point scale: 0/*never*; 1/*sometimes*; and 2/*often*. Confirmatory factor analysis with all of the above items indicated that three factors corresponding to the three categories (i.e., H-I, NC, and PA) were extracted at each time, and that most items selected for a given category were loading primarily on the same factor, with average loadings of .642, .693, and .728 for H-I, NC, and PA, respectively, across the 5 times of assessment. These results lend additional support to both the selected items and the distinction between the DB scales. Scores for each item were summed to create the DB scales, resulting in a 10-point scale for H-I, and a 6-point scale for NC and PA.

Considering the ordinal nature and the low number of items (between 3 and 5) per scale, internal consistency was assessed using the Split-half adjusted reliability coefficient (Brown, 1996; Callender and Osburn, 1979). This method is appropriate for ordinal data when underlying normality is not assumed. It is also well suited when the sample size is large and the number of items in a scale is small (Ten Berge and Socan, 2004) and estimates the reliability of a test divided into two parts of unequal length (Feldt and Charter, 2003). The resulting coefficients computed from age 1½ to 5 years were .61, .73, .73, .73, .73 (Average: .71) for H-I, .65, .65, .73, .73, .74 (Average: .70) for PA, and .53, .60, .67, .68, .70 (Average: .64) for NC. Notably, as it is often the case with DB scales in preschool years, coefficients were lower at younger ages (e.g., Shaw et al. 2005). However, because the number of items in a scale is known to affect the size of reliability coefficients (Nunnally, 1978), and for comparison purposes, we used the Spearman-Brown formula (Brown, 1996) to estimate the reliability coefficients of the scales if they had been composed of the same number of items as the corresponding scales based on teacher ratings in first grade (see: next section), assuming new items were similar to the existing ones. After correction, the average reliability estimates were .85 for H-I, .84 for PA, and .81 for NC, which

were similar to the reliability estimates for the first grade scales with the same number of items (.89 for H-I, .81 for CD, and .89 for Opposition, respectively). This procedure underscored the impact of the low number of items on the reliability coefficients, and underlines the need for caution in the interpretation of their size.

Teacher's assessment of DB and school impairment in first grade

The principals of schools attended by QLSCD participants were contacted by mail to introduce the study and request authorization for teachers' participation. Following the principal's authorization a similar procedure was used with teachers, who were informed that a \$10 compensation would be offered for their time. Teacher ratings of children's DB and school adjustment were based on the Self-Administered Questionnaire for Teacher (SAQT; Lemelin & Boivin, 2007), completed at the end of first grade. The SAQT is a 163-item questionnaire based on the Early Development Instrument (EDI; Janus and Offord, 2007), which assesses teachers' perceptions of children's school readiness at the end of kindergarten. The SAQT was adapted to correspond to the level of development of first graders, by removing inappropriate items (e.g., referring to language and cognitive skills typically preceding school entry) and by adding others (e.g., referring to advanced skills and to academic performance) drawn from the National Longitudinal Study of Children and Youth (NLSCY; Statistics Canada, 1995). The DB scales used in the present study were hyperactivity-impulsivity, inattention, opposition, and conduct disorder (alphas=.89, .84, .89, and .81, respectively).

The items describing each category were as follows: *Hyperactivity-Impulsivity (H-I)*: couldn't stop fidgeting; could not sit still; couldn't settle down for more than a few moments; was restless-hyperactive; was impulsive, acted without thinking; was unable to wait when someone promised him/her something; had difficulty waiting for his/her turn. *Inattention*: cannot concentrate/pay attention for long; is easily distracted, has trouble sticking to any activity; is

inattentive. *Opposition (OP)*: had temper tantrums/hot temper; was defiant or refused to comply with adults' requests or rules; punishment didn't change his/her behaviour; reacted aggressively when teased; reacted aggressively when contradicted; reacted aggressively when something was taken away from him/her; when mad at someone said bad things behind the other's back.

Conduct Disorder (CD): scared other children to get what he/she wanted; hit, bit, or kicked other children; got into fights; physically attacked people; damaged or broke things belonging to others; committed acts of vandalism; told lies or cheated; stole things.

Teachers were also asked to rate the children on five school adjustment indicators.

Language and cognitive skills were based on the following items: the ability to use language effectively, to listen, to tell a story, to take part in imaginative play, to communicate his/her needs, to understand, and to articulate clearly. These 7 items, which were rated on a scale from 0 to 4 (very poor, poor, average, good, excellent), were summed to create a continuous scale ($\alpha=.92$). *School performance* was assessed using teacher ratings of children's performance in four categories (reading, writing, mathematics, and general academic skills). For each of these categories, teachers were asked to compare the child's performance to the average performance of his/her schoolmates on a 5-point Likert scale, where 1 indicated *Clearly under average*, 3 indicated *Average*, and 5 indicated *Clearly above average*. A total school performance score was used in the analyses by calculating the average of the four evaluations. The validity of this school performance score has been demonstrated by its high correlation with other types of school performance measures, such as report cards (Mattanah et al. 2005). *Attitude toward learning* was based on the following 5 items, rated as 0-*Never*, 1-*Rarely*, 2-*Sometimes*, 3-*Often*, 4-*Always*: Listens attentively, follows instructions, completes work on time, autonomous, and works neatly and carefully. These items were added up to a 20-point scale ($\alpha=.85$). *Implication in the classroom* was based on 6 items, which were also rated on the same 4-point scale and added up to

a 24-point scale ($\alpha=.90$): Challenges the teacher in a positive way, is creative, has problem-solving capacity, puts a lot of effort into work, participates in class, and asks questions when he/she does not understand. *Expectation for future education*: Teachers rated how far they expected the child would go in school using the following categories: 1-complete elementary school, 2-complete some high school, 3-graduate from high school or learn a trade, 4-college degree, or 5-university degree. Finally, a *Parent-teacher relationship* measure was based on two items describing the quality of the relationship with the mother and the father, respectively. The response scale ranged from 0-Bad, 1-Not very good, 2-Neither good nor bad, 3-Good, to 4-Very good. The two items were summed into a single 8-point scale used as control variable in the analyses to account for the possible influence of teachers' knowledge of parents' characteristics on their child ratings.

Information from the teacher was available for 1313 children (64.7% of sample). The comparison of these children with children not assessed by teachers ($n=732$) on Time 1 (1½ year) and Time 5 (5 years) measures did not show any significant differences on mother-rated hyperactivity-impulsivity, non-compliance, or physical aggression. Additionally, there were no significant differences between families of the children assessed by teachers and families of children without teachers' assessment on household income, family status, number of siblings, and mother's and father's education and age group at the first time of assessment. Finally, no significant differences were observed for the proportion of children not assessed by teachers (ranging between 30% and 37%) in the different trajectory-groups.

Demographic and socioeconomic control variables

In order to identify the developmental risk specifically associated with the different comorbidity profiles, the following demographic and socioeconomic characteristics of the family generally associated with children's social adjustment problems (Shaw, 2013; Tremblay, 2010)

were included as covariates in the models: family income, family structure (intact, reconstituted, single-parent), number of children in the household, mother's and father's education (high school degree or not), and age group.

Data analysis

In the first series of analyses, the mother-reported measures of DB collected over the five assessment times were used to identify subgroups of children with distinct trajectories during preschool years, separately for each DB. To this end, we performed semi-parametric mixture modeling in SAS (Jones et al. 2001), which can accommodate unequally spaced measurements as well as missing data. Thus, participants with incomplete assessments across repeated measures can be included and all values available at each time are used for the trajectory estimation (Nagin, 1999, 2005). Trajectory models are described by the number of groups of subjects following a similar course, and the shapes (flat, linear or curvilinear) of these trajectories, using the Bayesian Information Criteria for model selection and optimization (BIC; Nagin, 1999; 2005). The BIC rewards parsimony for the number of groups included in a trajectory model. Moreover, for each participant, this statistical procedure provides: 1) the probability of belonging to each trajectory group, and 2) the assigned trajectory group based on the highest probability – as each individual is assigned to a single group. Mean group probabilities equal to or greater than .70 imply satisfactory model fit (Nagin, 2005).

In the next series of analyses, the best model identified for each DB was used: 1) to analyze joint DB trajectories, based on their joint and conditional probabilities (Nagin, 2005), in order to describe their co-occurrence over the age 1½ to 5 years developmental period, and 2) to examine the association between the joint trajectories and children's adjustment in first grade. A joint-trajectory factor was created by including joint trajectory-groups with at least one *High* trajectory (see: Results section), and a reference group composed of children who did not follow

a *High* trajectory for any DB (i.e., children who followed either a Low (L) or a Moderate (M) trajectory for all DB: 72% of the sample). This resulted in a 7-level independent factor: *High* H-I only, *High* NC only, *High* PA only, *High* H-I and NC, *High* NC and PA, *High* on all three DB categories, and the reference-group (L/M) without a *High* trajectory. Analyses consisted of a series of Univariate General Linear Models with the 7-level independent factor of joint-trajectories as main predictor and teacher-rated DB scales and school adjustment indicators as dependent variables. Analyses followed three steps: 1) single-predictor models were tested first, using joint-trajectories as unique predictor of each teacher-rated DB scale and school adjustment indicator; 2) next, demographic and socioeconomic characteristics of the family were included as control variables in the models; and 3) finally, post-hoc group mean comparisons were conducted examining each joint trajectory-group with at least one *High* trajectory against the reference group (L/M). To this end, we used the least significant difference (LSD) pairwise multiple comparison test with Holm-Bonferroni correction for the number of pairwise comparisons.

Results

Trajectories of Mother-Rated Disruptive Behaviors from Age 1½ to 5 Years

Three groups with distinct trajectories of H-I were identified (Figure 1): The first group (32% of the children) followed a consistently *Low* trajectory of H-I across the five assessment times; the second group (54%) followed a consistently *Moderate* trajectory of H-I at all times; the third group (14%) followed a *High* H-I trajectory, with a peak at 3½ years and a very slight decrease afterward. The average posterior probabilities of individuals belonging to their assigned trajectory-group were .89 for Low, .89 for Moderate, and .90 for the High-trajectory group, thus, well above the .70 threshold suggested by Nagin (2005) for satisfactory fit. Significant gender differences were also observed; $X^2(2df)=44.9, p<.001$. Boys were about two times more likely to be on a High-trajectory than girls (17.2% vs 9.6%, respectively), whereas girls were more likely

to be on a Low trajectory than boys, in a 3:2 ratio (37.2% vs 25.8%). Trajectories of NC followed similar patterns as those observed for H-I: Two groups with flat trajectories across the five times of assessment, one with consistently *Low* levels of NC (20.9% of the sample) and another with consistently *Moderate* levels of NC (58.6%). A third group (20.5 %) followed a *High* quadratic trajectory with a marked increase between 1½ and 3½ years and a very slight decrease thereafter. The average group posterior probabilities were respectively .79, .83, and .88, for the Low, Moderate and High trajectory-groups, indicating satisfactory fit. Significant gender differences were found; $X^2(2df)=7.93, p<.05$. However, these differences were much smaller than what had been observed for H-I: 18% of girls vs 22.9% of boys followed a High trajectory, whereas 22.1% of girls vs 19.8% of boys were on the Low trajectory. Finally, three groups with distinct trajectories of PA were identified: 31.5% of children consistently showed no or very *Low* PA throughout all assessment times; 52.5% exhibited consistently *Moderate* levels; and 16% followed a *High* trajectory. Both Moderate and High trajectories were quadratic in shape, with a considerable increase from age 1½ years to 3½ years and a decrease thereafter until age 5 years. The average group posterior probabilities for the three trajectory-groups were respectively .88, .84, and .83, indicating, here as well, a satisfactory fit to the data. Significant gender differences were also observed; $X^2(2df)=62.3, p<.001$. Boys were about two times more likely to be on a *High* PA trajectory than girls (21.1% vs 10.7%, respectively), whereas girls were more likely to be on a Low PA trajectory in a 3:2 ratio (38% vs 25.1% for boys).

Joint Trajectories from Age 1½ to 5 Years: Comorbidity between Disruptive Behaviours

Joint trajectory analysis of H-I, NC and PA resulted in 14 distinct trajectory-groups. Group composition and gender differences are shown in Table 2. Children following a joint *Moderate* trajectory for all DB scales represented the most prevalent profile, with a similar proportion of boys and girls (29.6% vs 26.9%, respectively). None of the joint trajectory-groups

included a *High* trajectory for one DB and a *Low* trajectory for another. Girls were more likely to follow joint trajectories composed of at least one Low trajectory: 51.9% of the girls were part of these groups against 35.7% for boys. In contrast, boys were more represented in joint trajectories composed of at least one High trajectory (34.8% of boys vs 21.3% of girls). Most of the children with at least one High trajectory of DB also followed high trajectories of other DB categories. The joint-trajectory group of children following a High trajectory for all DB was the most prevalent group including at least one High trajectory and represented 6.9% of the total sample, with nearly 3 times more boys (10.0%) than girls (3.7%). Developmental comorbidity involving high levels of DB appeared to be common among preschoolers: 14.4% were part of groups with 2 or 3 High trajectories, against 13.8% in groups including only one High trajectory. This propensity for comorbidity was more salient in boys (18.3% for multiple High trajectories vs 16.5% for a single High trajectory) than in girls (10.4% vs 10.9%, respectively). Among children classified on a High trajectory for PA, 61% of boys and 63.2% of girls followed a High trajectory for more than one DB. These proportions rose to 79.5% for boys and 75% for girls High for H-I, and to 80.5% and 69.1%, respectively, for those following a High trajectory of NC.

Teacher Rated DB and School Impairment at the End of 1st Grade

Results of the analyses examining joint DB trajectories in preschool as predictors of teacher-rated DB at the end of grade 1, with and without family demographic and socioeconomic characteristics as covariates, are shown in Table 3. Preschool joint DB trajectories were significantly linked to first grade symptoms of H-I ($F(df=6)=12.00, p<.001$), Inattention ($F(df=6)=3.60, p<.01$), Opposition ($F(df=6)=8.21, p<.001$), and CD ($F(df=6)=8.22, p<.001$), above and beyond family characteristics and the quality of the parent-teacher relationship. Among the covariates, mother's education was negatively associated with teacher-rated H-I ($F(df=1)=5.00, p<.05$) and Inattention ($F(df=1)=17.20, p<.001$), whilst family income was significantly

negatively linked with Inattention symptoms ($F(df=8)= 2.43, p<.05$). Finally, a higher quality of parent-teacher relationship was associated with lower levels of all four categories of teacher-rated DB in first grade ($p<.001$).

The results examining the predictive links of DB joint-trajectories in preschool with school adjustment in first grade, with and without family characteristics as covariates, are shown in Table 4. Joint-trajectories of early DB were associated with all but one indicator of school adjustment in single-predictor models without covariates, as the predictive effect for school performance was not statistically significant. These associations remained with the inclusion of family demographic and socioeconomic characteristics as covariates in the models, for language and cognitive skills ($F(df=6)=2.87, p<.01$), child's attitude toward learning ($F(df=6)=4.43, p<.001$), and child's implication in the classroom ($F(df=6)=2.51, p<.05$). Among the covariates, family income and mother's education were significantly associated with all five dimensions of school adjustment ($p<.01$). Additionally, father's education was positively associated with the child's language and cognitive skills ($F(df=6)=3.60, p<.01$), school performance ($F(df=6)=3.60, p<.01$) and teacher's expectation for future education ($F(df=6)=3.60, p<.01$). Mother's (higher) age was associated with higher school performance ($F(df=6)=3.60, p<.01$) and teacher's expectation for future education ($F(df=6)=3.60, p<.01$). Father's (higher) age was associated with higher school performance ($F(df=6)=3.60, p<.01$), and family structure (living in an intact family) was associated with the child's stronger implication in the classroom ($F(df=6)=3.60, p<.01$). Finally, the quality of parent-teacher relationship was positively associated with all five indicators of school adjustment in first grade ($p<.001$).

In post-hoc analyses (Table 5), joint trajectory-groups including at least one *High* trajectory were compared to the reference group, which included children who did not follow a High trajectory for any DB (L/M). As expected, children in the High-H-I/NC/PA (HHH) joint-

trajectory group showed significantly higher levels than their peers from the L/M group on all teacher-rated DB scales in grade 1. However, the other two joint-trajectory groups involving comorbidity of high levels of DB throughout preschool years (High-H-I/NC and High-NC/PA) were rated as being more adjusted by their first grade teacher: only High-H-I/NC children obtained higher ratings for H-I and Inattention in grade 1. Children in groups including a High trajectory of NC only or PA only in preschool were not rated by their teacher as being significantly higher than those in the reference group with respect to OP or CD in first grade, nor for any other DB. However, children in the joint-trajectory with High H-I only were rated higher than their L/M peers on all four DB in grade 1. Notably, children of all joint-trajectory groups including High H-I in preschool were rated significantly higher on H-I and Inattention in grade 1.

Regarding the associations between joint-trajectory groups and first grade school adjustment indicators, children in the High-H-I/NC/PA group were rated significantly lower than their peers from the L/M group in regard to their language and cognitive skills, attitude toward learning, and implication in the classroom. Children in the High-H-I/NC group obtained lower ratings in regard to their attitude toward learning, and those in the High-NC/PA group were lower in regard to language and cognitive skills. Among joint-trajectory groups including only one *High* single trajectory in preschool, High-H-I only children were rated lower than their L/M peers in regard to their attitude toward learning, whereas those in the High-PA only obtained lower ratings for language and cognitive skills. Interestingly, children of the High-NC only joint-trajectory did not differ from their L/M peers on school adjustment indicators. Thus, these two groups did not differ on any of the nine teacher-rated adjustment measures in first grade.

Discussion

Using a population birth-cohort, this study investigated the developmental comorbidity of three categories of disruptive behavior (DB) during early childhood - hyperactivity-impulsivity,

non-compliance, and physical aggression - and their association with DB and school adjustment in first grade. A trajectory of consistently Moderate levels was the modal category for all three DB categories, representing 54.0%, 58.6%, and 52.5% of the sample for H-I, NC and PA, respectively. This suggests that DB symptoms are fairly common in preschool children, and to some extent, a normative way of (mis)behaving rather than the expression of an adjustment problem (Keenan & Wakschlag, 2004). Importantly, a significant number of children (between 13% and 21% depending on the type of DB), showed persistently High levels of DB symptoms from ages 1½ to 5 years. Moreover, consistent with previous reports on the stability of DB from the preschool period onwards (Campbell et al. 2000; Shaw et al. 2005; Tremblay et al. 2004), there was no group of children that showed a unique escalating, declining or fluctuating profile across time. Findings also confirmed previous reports that boys are more likely to follow chronic trajectories of DB during the preschool years (NICHD Early Child Care Research Network, 2004; Tremblay et al. 2004). This preponderance of chronic problems for boys is consistent with results from older samples (Costello et al. 2005), although gender differences appear smaller during the preschool years. The increasing difference with age between boys and girls suggests that girls may be able to regulate their behavior at an earlier age than boys (Kochanska, Murray & Coy, 1997).

Studies of comorbidity usually compare diagnoses at a given point in time. We used a procedure that provided a longitudinal phenotype of comorbid development. The joint-trajectories procedure clearly showed that developmental comorbidity is highly prevalent in the preschool years. First, none of the children who followed a High trajectory for one DB were on a Low trajectory for another category. Thus, children who were frequently hyperactive-impulsive, or who frequently used PA from age 1½ to 5 years, were unlikely to show low frequencies of the other two types of DB during the same time period. These results are consistent with previous

reports of DB trajectories from both preschool and older samples (Nagin & Tremblay, 2001; Shaw et al. 2005). Second, children on one High trajectory were most likely to follow at least one other chronically high trajectory. Third, developmental comorbidity of High-PA/H-I always involved developmental comorbidity with High-NC. This was true for boys and girls. Importantly, the most prevalent group including at least one High trajectory was the joint-trajectory group composed of children following a High trajectory for all DB. As in most other cases of comorbid development, the prevalence of joint-High H-I, NC and PA was higher for boys than for girls. Gender differences for comorbidity were mostly due to the substantially lower proportion of girls on the chronic trajectories of H-I and PA.

As expected, significant associations were found between preschool joint-trajectories and teacher-rated indicators of DB and school adjustment at the end of first grade. Preschoolers who consistently displayed high levels of H-I, NC, and PA, from age 1½ to 5 years, obtained the highest ratings for all types of DB, and the lowest with respect to language and cognitive skills, attitude toward learning, and implication in the classroom, above and beyond the influence of family demographic and socioeconomic characteristics. Noteworthy, although the best-possible prediction of first grade measures was not the aim of the analyses, the proportion of variance ($R^2=.141-.152$) in teacher-rated DB explained by preschool trajectories and families' characteristics suggests that additional factors influenced the development of DB in first grade. Nonetheless, the effect size computed for the significant differences in Means between joint-trajectory groups and the reference L/M group (Table 5) indicated medium to large effects ($d=.65-1.11$) of the preschool comorbidity trajectories on teacher-rated DB. Among preschool DB, H-I stood out as the most important predictor of preschoolers' future adjustment in school. Children who followed a joint-trajectory including High H-I only displayed a profile very similar to their HHH peers in regard to teacher-rated DB, although they appeared better adapted

according to school adjustment indicators. Notably, children of this joint-trajectory group also consistently showed moderate levels of NC and PA throughout the preschool years. Children in all joint trajectory-groups including High H-I obtained high ratings of H-I and Inattention from their teacher in grade 1. This was not found for NC and PA, nor for the comorbid High-NC/PA group, which could mean that children learn to regulate NC and PA more readily than problems associated with H-I. The High-NC/PA and High-PA groups were given only one lower rating, for their language and cognitive skills in grade 1. It is thus possible that, besides their using PA, a developmental delay in acquiring these skills may have limited these children's ability to interact with others in conflict situations, but that these children have sufficiently developed such skills to reduce their level of PA by the end of first grade. Interestingly, children following a High-NC/Moderate-H-I+PA joint-trajectory over the preschool years did not differ from their peers who did not follow any High trajectory on teacher-rated outcomes in first grade. This finding suggests that High-NC and moderate levels of H-I and PA reported by the mother in preschool might be within the range of normative (mis)behavior (Keenan & Wakschlag, 2004).

Overall, these results are consistent with reports of homotypic and heterotypic continuity from the preschool to the elementary school years for H-I symptoms and ADHD (Bufferd et al. 2012; Leblanc et al. 2008). The results from this study are also consistent with previous reports that DB appear during the preschool years. Our findings emphasize the fact that comorbidities among DB already appear at this early age and remain stable beyond school entry for a substantial proportion of boys and girls, who are also at risk of school-related adjustment problems in first grade. This early manifestation and stability of DB comorbidity is consistent with evidence that ADHD/aggression comorbidity - linked to NC in our cohort - is significantly influenced by genetic factors (Hamshere et al. 2013). The likelihood of a strong genetic influence and the high level of maladjustment displayed at school entry by children with high preschool

comorbidity put them at considerable risk for later health, social, academic and work-related problems (Odgers et al. 2007; Rutter et al. 2006; Waschbusch, 2002). Together, these findings suggest that comorbidity of DB in early childhood warrants serious attention and intervention.

Strengths, Limitations and Conclusions

To our knowledge, this study is the first to describe the developmental comorbidity of DB symptoms linked with three categories of disorders, from the second year of life to school entry, in a large population cohort. As such, the present research substantially extends previous comorbidity studies that typically rely on a cross-sectional design. Another strength of the present study is the use of different reporting sources (mothers and teachers) in investigating the association between preschool DB trajectories and school adjustment in first grade. This strategy reduced the risk of inflated associations due to shared source variance. Nevertheless, our study is not without limitations. The limited number of items to assess DB during the preschool years did not fully cover the range of symptoms described in DSM. This limitation is inherent to the restricted behaviors with reliable clinical significance (Keenan & Wakschlag, 2002) observable from the second year of life, and to our method of analysis requiring the examination of the same behaviors across different time points. For the same reasons, our intended assessment of oppositional behavior in preschool was restricted to Non-compliance, which was confirmed as an independent factor in our confirmatory factor analysis, but relies on the subdimension of defiance/non-compliance of the ODD syndrome and on the notion of rules violation linked with CD. Given the early age of the children, and the nature of the behaviors examined, we believe that this measure was more in line with ODD than with the serious violation of rules described in CD symptomatology, more typical of older children. This perspective is also consistent with the view of ODD as a developmental precursor or a milder form of some aspects of CD (Lahey et al. 2000). However, the absence of items referring to the other subdimensions (i.e., irritability and

vindictiveness) of ODD, and the proximity with CD might have limited the associations of our NC measure with first grade outcomes. Additionally, restricting yearly measures to the same behaviors did not allow for the inclusion of age-specific items. Further research addressing developmental changes in relation to early DB comorbidity would benefit from including such information. Using observational or absolute measures of disruptive behaviors rather than subjective frequency ratings might also facilitate the observation of developmental variations. Regarding the source of information, relying on the mother as the single informant for preschool DB was not optimal. However, as in other similar large scale studies, an affordable alternative reporting source for such a large sample size was not available due to budgetary limitations (Egger & Angold, 2006; Keenan & Wakschlag, 2004; Shaw et al. 2005; Tremblay et al. 2004). Although analyses revealed no differences on most demographic, socioeconomic and behavior characteristics between children and families who remained in the trajectory-study and those who dropped out, and between those who were subsequently assessed or not by the teachers, attrition may have influence the results. The very small difference in SES observed in favor of remaining families may have resulted in more conservative findings if proportionally more vulnerable families and children were lost. This might have resulted in fewer children in the comorbidity groups, and weaker associations with teacher-rated measures in grade 1. Finally, the study was limited to a population of North-American children mostly raised in a French-speaking culture. Thus, replications are needed to examine to what extent the results are generalizable to other cultures.

Nonetheless, despite its limitations, our study contributes to filling an important gap in our understanding of the developmental comorbidity of DB. Our findings highlight the importance of providing early childhood services to preschool children whose frequent and

diverse DB symptoms persist over time, because they are at risk of significant impairment at school entry and possibly also of serious health and social adjustment problems in the long term.

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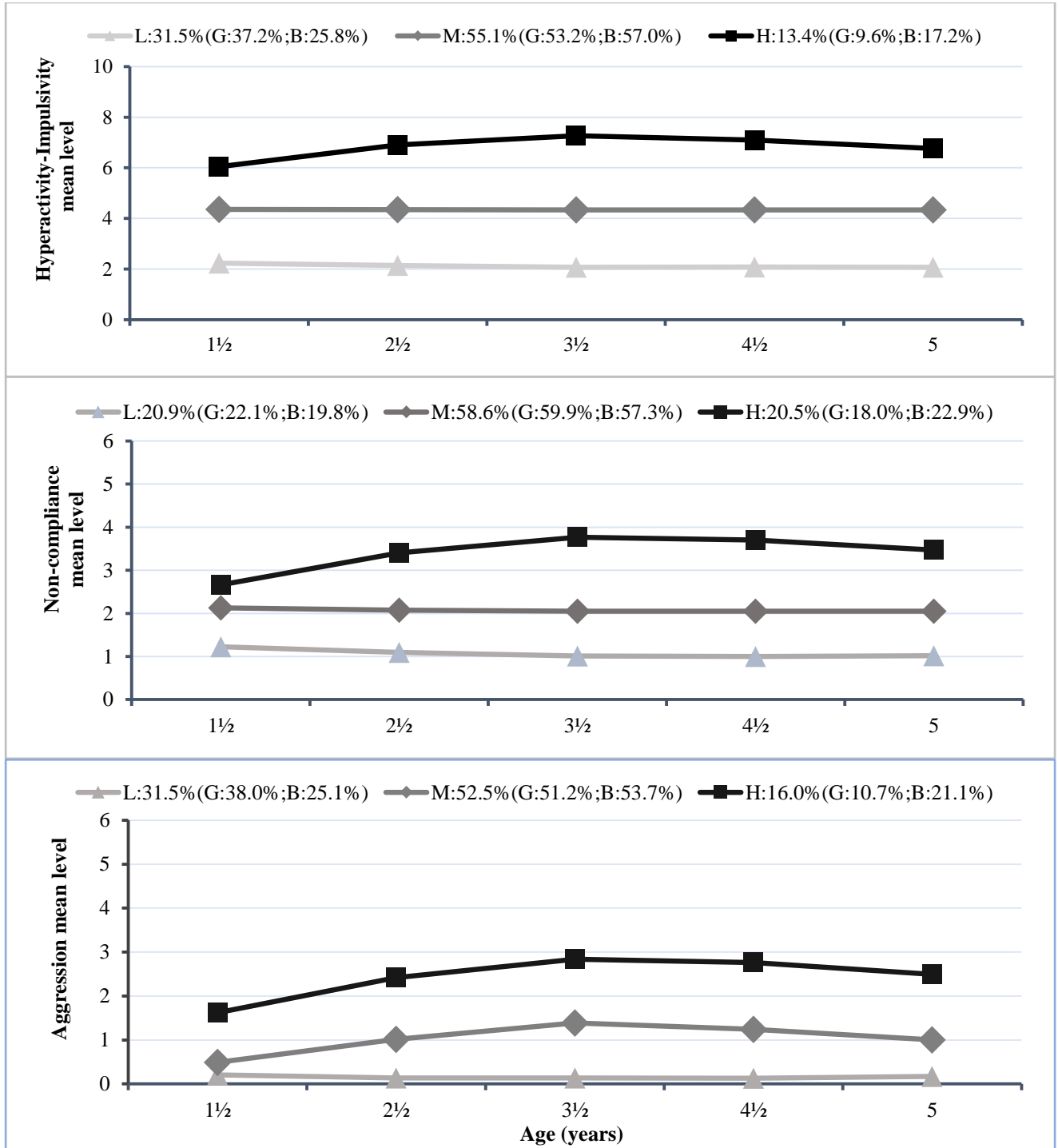
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Figure 1 Trajectories of Disruptive Behaviors in the Preschool Years



Trajectories: L = Low, M = Moderate, H = High. % for total sample (G: % for Girls; B: % for Boys).

Table 1
Socioeconomic Characteristics of the Families at the First Assessment Time¹

Families Socioeconomic Characteristics	%
<u>Household Income</u>	
- < \$30,000	32.8
- \$30,000 - \$59,000	39.6
- \$60,000 and +	27.6
<u>Family status</u>	
- Intact/two-parent family	80.0
- Non-Intact family	20.0
<u>Number of children in household</u>	
- No brother or sister	41.7
- 1 brother or sister	40.0
- 2 or more	18.3
<u>Education: Mother</u>	
- No high school diploma	17.9
- High school or Technical school diploma	22.1
- Post-secondary education	60.0
<u>Education: Father</u>	
- No high school diploma	17.6
- High school or Technical school diploma	24.2
- Post-secondary education	58.2
<u>Age Group of Mother</u>	
- < 20 years	3.3
- 20-39 years	94.3
- 40 years and +	2.4
<u>Age Group of Father</u>	
- < 20 years	0.5
- 20-39 years	91.0
- 40 years and +	8.5
<u>Race</u>	
- Caucasian	92.1
- Other	7.9

¹: Adapted from: Jetté and Des Groseillers (2000b).

Table 2

Joint Trajectories from Age 1½ to 5 years: Comorbidity Between Disruptive Behaviors

Preschool Joint Trajectories-groups			% Girls (N=1016)	% Boys (N=1029)	% Sample (N=2045)
<u>H-I</u>	<u>NC</u>	<u>PA</u>			
L	L	L	19.4***	12.1	15.7
L	L	M	9.5	7.1	8.3
L	M	L	1.3	0.8	1.0
M	L	L	1.7	1.9	1.8
M	M	L	11.4**	7.6	9.5
M	L	M	1.5	1.8	1.7
L	M	M	7.1*	4.4	5.7
M	M	M	26.9	29.6	28.3
<u>H</u>	M	M	2.5	4.0*	3.3
M	M	<u>H</u>	3.8	8.1***	6.0
M	<u>H</u>	M	4.6	4.4	4.5
<u>H</u>	<u>H</u>	M	3.7	5.7*	4.7
M	<u>H</u>	<u>H</u>	3.0	2.6	2.8
<u>H</u>	<u>H</u>	<u>H</u>	3.7	10.0***	6.9

PA: Physical Aggression; H-I: Hyperactivity-Impulsivity; NC: Non-compliance. L = Low, M = Moderate, H = High. The p levels indicate significant differences between boys and girls at:

*: $p < .05$ **: $p < .01$ ***: $p < .001$.

Table 3 Prediction of Teacher-Rated DB' Symptoms in 1st Grade From Preschool Joint-Trajectories of DB, Family Socioeconomic and Demographic Characteristics and the Parents-Teacher Relationship

Prediction and control variables	Hyperactivity-Impulsivity				Inattention				Opposition				Conduct Disorder			
	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>
Preschool trajectories ¹	1011.95	6	20.77	<.001	236.341	6	10.01	<.001	746.49	6	15.66	<.001	304.345	6	12.31	<.001
Family income	95.16	8	1.67	.101	69.01	8	2.43	.013	22.50	8	0.48	.847	56.41	8	1.91	.055
Family structure	0.48	1	0.07	.796	2.07	1	0.59	.444	9.35	1	1.41	.236	1.56	1	0.42	.516
Number of children in household	45.41	3	2.13	.095	7.45	3	0.70	.552	22.98	3	1.15	.327	13.00	3	1.18	.318
Mother's education	35.55	1	5.00	.026	60.95	1	17.20	<.001	22.37	1	3.36	.067	0.49	1	0.13	.715
Father's education	1.53	1	0.22	.642	0.65	1	0.18	.667	15.15	1	2.28	.132	3.82	1	1.04	.309
Mother's age group	36.17	6	0.85	.533	29.59	6	1.39	.215	25.77	6	0.65	.694	33.34	6	1.51	.172
Father's age group	15.75	6	0.37	.899	18.51	6	0.87	.516	43.90	6	1.10	.361	32.25	6	1.46	.189
Parents-Teacher relationship	305.73	7	6.14	<.001	198.49	7	8.00	<.001	251.97	7	5.41	<.001	111.05	7	4.31	<.001
Preschool trajectories	512.16	6	12.00	<.001	76.56	6	3.60	.002	327.43	6	8.21	<.001	181.67	6	8.22	<.001
Model	1172.61 <u>R²: .152</u>	39	4.23	<.001	590.97 <u>R²: .141</u>	39	4.28	<.001	878.1 <u>R²: .143</u>	39	3.47	<.001	528.52 <u>R²: .143</u>	39	3.68	<.001

¹: Single predictor model.

Table 4 Prediction of Teacher-Rated School Adjustment in 1st Grade From Preschool Joint-Trajectories of DB, Family Socioeconomic and Demographic Characteristics and the Parents-Teacher Relationship

Prediction and control variables	Language and cognitive skills				School performance				Attitude toward learning				Implication in classroom				Teacher's expectation for future education			
	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>	<u>Sum of squares</u>	<u>df</u>	<u>F</u>	<u>Sig.</u>
- Preschool trajectories ¹	910.61	6	5.75	<.001	16.05	6	1.979	.066	254.43	6	11.45	<.001	130.20	6	7.05	<.001	46.82	6	7.10	<.001
Family income	687.31	8	4.16	<.001	33.01	8	3.70	<.001	77.93	8	3.02	.002	105.16	8	5.02	<.001	36.39	8	7.18	<.001
Family structure	55.44	1	2.69	.102	0.14	1	0.00	1.00	0.08	1	0.03	.874	10.77	1	4.11	.043	0.20	1	0.28	.597
Number of children in household	101.92	3	1.65	.177	2.35	3	0.70	.551	1.84	3	0.19	.903	2.63	3	0.34	.800	0.65	3	0.30	.826
Mother's education	469.22	1	22.74	<.001	26.92	1	24.13	<.001	34.74	1	10.76	.001	23.38	1	8.93	.003	29.90	1	41.30	<.001
Father's education	375.60	1	18.20	<.001	15.877	1	14.24	<.001	1.57	1	0.49	.486	4.82	1	1.84	.175	10.22	1	14.53	<.001
Mother's age group	130.10	6	1.05	.391	15.21	6	2.27	.035	29.81	6	1.54	.162	19.02	6	1.21	.299	11.57	6	2.66	.015
Father's age group	82.05	6	0.66	.680	14.38	6	2.15	.046	14.53	6	0.75	.609	11.94	6	0.76	.602	2.43	6	0.56	.763
Parents-Teacher relationship	2514.26	7	17.41	<.001	66.36	7	8.50	<.001	271.95	7	12.03	<.001	328.92	7	17.94	<.001	65.94	7	13.01	<.001
Preschool trajectories	355.13	6	2.87	.009	3.11	6	0.47	.835	85.89	6	4.43	<.001	39.48	6	2.51	.020	5.83	6	1.34	.236
Model	6669.01	39	8.29	<.001	277.27	39	6.37	<.001	694.40	39	5.51	<.001	662.13	39	6.48	<.001	285.14	39	10.36	<.001
	<u>R²</u> : .254				<u>R²</u> : .201				<u>R²</u> : .172				<u>R²</u> : .197				<u>R²</u> : .349			

¹: Single predictor model.

Table 5 Teacher-Rated DB and School Adjustment in 1st Grade for Children Following Different Joint-Trajectories of DB during the Preschool Years

Preschool joint trajectories of DB			DB categories ¹								School adjustment ²									
			Hyperactivity-Impulsivity		Inattention		Opposition		Conduct Disorder		Language and cognitive skills		School performance		Attitude toward learning		Implication in classroom		Teacher's expectation for future education	
H-I	NC	PA	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
L/M	L/M	L/M	1.89	2.65	2.05	1.98	1.58	2.52	0.90	1.86	22.01	5.01	2.60	1.16	7.71	1.91	6.84	1.73	4.34	0.99
H	M	M	4.40 ^{***}	3.94	3.34 [*]	1.83	3.97 ^{***}	5.01	2.70 ^{***}	3.46	19.46 ⁺	5.62	2.18	1.23	6.70 [*]	1.70	6.11 ⁺	1.64	3.50	1.39
M	M	H	2.74	2.94	2.24	1.97	2.27	2.70	1.25	1.69	20.73 [*]	5.66	2.40	1.14	7.33	2.05	6.33	1.87	4.07	1.12
M	H	M	2.43	2.61	2.62	1.94	2.48	3.67	1.21	1.83	20.49	5.16	2.47	1.06	7.13	1.81	6.23	1.65	4.19	1.08
H	H	M	4.04 ^{***}	3.68	2.86 [*]	2.18	2.49	2.99	1.54	2.74	21.20	5.54	2.40	1.32	6.62 ^{***}	2.34	6.28	2.17	4.07	1.25
M	H	H	2.41	2.91	2.38	1.97	2.83	3.77	1.64	2.47	19.58 ^{***}	5.41	2.47	1.21	7.26	1.88	6.22 ⁺	1.92	3.77	1.42
H	H	H	4.89 ^{***}	3.54	3.38 ^{***}	2.01	4.46 ^{***}	3.36	2.66 ^{***}	2.69	19.71 [*]	5.31	2.31	1.17	6.32 ^{***}	1.83	5.93 ^{***}	1.65	3.70	1.11

H-I: Hyperactivity-Impulsivity; NC: Non-compliance; PA: Physical Aggression. L = Low. M = Moderate. H = High. Significance levels refer to the comparison of means against L/M category in complete model with covariates. Holm-Bonferroni correction for multiple pair comparisons was used.

¹: Effect size range for significant mean comparisons of DB: $d = .65 - 1.11$. ²: Effect size range for significant mean comparisons of School adjustment: $d = .25 - .73$.

*: $p < .05$ ***: $p < .001$ +: original $p < .05$, and $p < .10$ with Holm-Bonferroni correction.