ORIGINAL ARTICLE

Early Risk Factors for Hyperactivity-Impulsivity and Inattention Trajectories From Age 17 Months to 8 Years

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Context: Attention-deficit/hyperactivity disorder is an etiologically heterogeneous neurodevelopmental condition with long-term negative outcomes. However, the early developmental course of hyperactivity-impulsivity and inattention symptoms and their association with previous environmental risk factors are still poorly understood

Objectives: To describe the developmental trajectories of hyperactivity-impulsivity and inattention symptoms and to identify their prenatal, perinatal, and postnatal risk factors.

Design: Birth cohort from the general population.

Setting: Quebec Longitudinal Study of Child Development.

Participants: The sample consisted of 2057 individuals, followed up from age 5 months to 8 years.

Main Outcome Measures: Prenatal, perinatal, and postnatal risk factors assessed at age 5 months were considered predictors of group membership in high hyperactivity-impulsivity and inattention trajectories from age 17 months to 8 years.

Results: The frequency of hyperactivity-impulsivity symptoms tended to slightly decrease with age, whereas the frequency of inattention symptoms substantially increased up to age 6 years. However, trajectories of hyperactivity-impulsivity and inattention symptoms were significantly associated with each other. Risk factors for high trajectories of both types of symptoms were premature birth (adjusted odds ratio [aOR], 1.93; 95% CI, 1.07-3.50), low birth weight (2.11; 1.12-3.98), prenatal tobacco exposure (1.41; 1.03-1.93), nonintact family (1.85; 1.26-2.70), young maternal age at birth of the target child (1.78; 1.17-2.69), paternal history of antisocial behavior (1.78; 1.28-2.47), and maternal depression (1.35; 1.18-1.54).

Conclusions: A large range of early risk factors, including prenatal, perinatal social, and parental psychopathology variables, act independently to heighten the likelihood of having persistently high levels of hyperactivity-impulsivity and inattention symptoms from infancy to middle childhood. Early interventions should be experimented with to provide effective tools for attention-deficit/hyperactivity disorder prevention.

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ATTENTION-DEFICIT/HYPERactivity disorder (ADHD) is a clinically significant condition with early childhood onset and persisting lifelong features. Etiologically, ADHD is believed to be a heterogeneous disorder within a developmental psychopathologic framework.[1,2] The large amount of research regarding the putative causes of ADHD clearly implicates genetic and environmental risk factors. Despite the high heritability of ADHD, recent molecular studies[3,4] suggest only small effects of multiple candidate genes contributing each to a relatively modest proportion of variance in ADHD expression. Conversely, environmental risk factors could play an influential role in the emergence of ADHD, particularly during the sensitive developmental periods of fetal and early life.[1,5] Consequently, a better identification of early environmental risk factors may afford better hindsight for mechanism understanding and potential interventions. This is all the more relevant because, to date, genetic studies have not provided immediate targets for intervention, and available therapeutic strategies have shown limited long-term efficacy.[6]

The most consistent research findings regarding the role of environmental factors in ADHD suggest prenatal, perinatal, and early postnatal factors. Smoking during pregnancy has been regularly linked to ADHD in offspring.[7,8] Other prenatal factors, such as alcohol, illegal drug, and psychotropic maternal consumptions, have

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Table 1. Sample Sociodemographic Characteristics[a]

Characteristic	Participants, %
Sex of the child	
Female	49.3
Male	50.7
Mother's immigration status	
Nonimmigrant	89.3
Immigrant	10.7
Maternal education	
High school diploma	82.2
No high school diploma	17.8
Family status	
Intact	81.1
Nonintact	18.9
Family annual income, Can$	
<30 000	29.0
30 000-60 000	40.9
>60 000	30.1

[a] Data are courtesy of the Quebec Institute of Statistics.

yielded more conflicting results.[8-10] Perinatal factors, such as low birth weight, preterm birth, and birth complications, have been studied but are difficult to untangle.[9,11-13] Studies[10,13-16] of postnatal social and relational factors have involved social adversity, hostile parenting, and parental psychopathology, whereas studies[9,17] of postnatal physical factors have suggested traumatic brain injury, lead exposure, food additives, and dietary deficiencies as putative causes.

This body of research regarding early environmental risk factors of ADHD has at least 5 important limitations. First, in most studies, the participants were elementary school children. This choice of participants prevented understanding the development of the disorder during the preschool years. Second, measures of risk factors were often retrospective and potentially affected by a memory bias. Third, the outcomes of most studies were the traditional ADHD taxonomic categories assessed at 1 point in time. This approach precluded understanding the dimensional and developmental nature of the disorder.[18] It is becoming clearer that hyperactivity-impulsivity and inattention may be more accurately conceptualized as 2 phenotypic dimensions varying with age rather than discrete categories with a clear age at onset.[1,5,19] The rare studies[20,21] of preschool developmental trajectories did not consider inattention. However, earlier developmental trajectories are necessary to assess chronic behavior problems rather than a 1-point diagnostic evaluation of older children. In addition, they have been shown to be associated with full disorder and later negative outcomes.[22,23] A fourth limitation is that many investigations relied either on clinical samples of males presenting with ADHD or on cohorts of at-risk individuals (ie, preterm or low-birth-weight newborns). This jeopardized the generalizability of the findings to community and female populations. Fifth, studies rarely simultaneously considered a large range of risk factors, which enhanced the possibility of residual confounding. Overall, despite their potential value, studies regarding the impact of a scope of environmental risk factors on early trajectories of hyperactivity-impulsivity and inattention symptoms are scarce in population-based samples.

The objective of the present study was to fill these gaps by examining the association between early environmental risk factors and early developmental trajectories of hyperactivity-impulsivity and inattention symptoms using a birth cohort representative of the general population. We first determined developmental trajectories of hyperactivity-impulsivity and inattention symptoms from age 17 months to 8 years using group-based trajectory modeling. We then created joint trajectories and assessed the effect of prenatal, perinatal, postnatal, and parental psychopathology risk factors on the joint trajectories of hyperactivity-impulsivity and inattention symptoms.

METHODS

PARTICIPANTS AND PROCEDURE

Data were drawn from the Quebec Longitudinal Study of Child Development, whose protocol was approved by the Quebec Institute of Statistics (Quebec City, Quebec, Canada) and the St-Justine Hospital Research Center (Montreal) ethics committees. Data were collected by trained interviewers through home interviews regularly conducted with the person most knowledgeable about the child (the mother in 98% of cases) to obtain information about child, parent, and family characteristics and behaviors. Written informed consent was obtained from all the participating families at each assessment. Assessments were conducted at the following ages: 5 months and 1½, 2½, 3½, 4½, 5, 6, and 8 years. The Quebec Longitudinal Study of Child Development sample was drawn from the Quebec Birth Registry using a stratified procedure based on living area and birth rate. Families were included if the pregnancy lasted 24 to 42 weeks and the mother could speak French or English. The initial sample comprised 2120 children evaluated at age 5 months and was representative of children born in the province of Quebec (Canada) in 1997 and 1998. The average response rate during the 8 years of data collection was 87.0% (range, 68%-100%). **Table 1** describes the sociodemographic characteristics of the sample used to build hyperactivity-impulsivity and inattention trajectories (N = 2057). No significant difference was noted between the 2 samples.

MEASURES

Outcome Variable: Hyperactivity-Impulsivity and Inattention Symptoms

Children's hyperactivity-impulsivity and inattention symptoms were reported through the Interviewer Computerized Questionnaire when the children were 1½, 2½, 3½, 4½, 5, 6, and 8 years of age. Ratings relied on the early childhood behavior scale from the Canadian National Longitudinal Study of Children and Youth.[24] This tool incorporates items from the Child Behavior Checklist,[25] the Ontario Child Health Study Scales,[26] and the Preschool Behavior Questionnaire.[27] This instrument has been shown to have good validity in early childhood and in predicting ADHD.[21,23] Five items were used to assess hyperactivity-impulsivity: "can't sit still, is restless or hyperactive," "fidgets," "is impulsive, acts without thinking," "has difficulty waiting for his or her turn in games," and "cannot settle down to do anything for more than a few moments."

Three items were used to assess inattention: "cannot concentrate, cannot pay attention for long," "is easily distracted, has trouble sticking to any activity," and "is inattentive." All items referred to the past 3 months and were coded on a frequency scale (never or not true=0, sometimes or somewhat true=1, and often or very true=2), which made it possible to build quantitative scores and then develop hyperactivity-impulsivity and inattention trajectories. Regarding the analysis of hyperactivity-impulsivity and inattention trajectories, 94.8% of the sample had at least 4 data points available.

Explanatory Variables

Child Characteristics. The sex of the child was coded as 1 for boys (50.7% of the sample) and as 0 for girls. Temperament was evaluated at age 5 months using 7 items (each item rated from 1 to 7) of the difficult temperament scale of the validated and widely used Infant Characteristics Questionnaire.[28] A higher score indicated a more difficult temperament. Informant total ratings were *z*-standardized. Methylphenidate hydrochloride (Ritalin; Novartis Pharmaceuticals, East Hanover, New Jersey) lifetime exposure corresponded to any methylphenidate taken between 72 and 96 months of age and was coded as 1 for any consumption (4.6% of the sample) and as 0 for no consumption.

Prenatal and Perinatal Factors. Information about the child's birth was obtained from hospital records: premature birth was coded as 1 if the child was born before the 37th week of gestation (5.0% of the sample) and as 0 if born at or after the 37th week. Low birth weight was coded as 1 if the newborn weighed 2500 g or less (3.5% of the sample) and as 0 if the newborn weighed more than 2500 g. When the child was 5 months old, the informant responded to questions concerning substance use (tobacco, alcohol, and illegal drugs) during pregnancy. Prenatal tobacco exposure was coded as 1 if the mother had smoked at least 1 cigarette per day while pregnant (25.0% of the sample) and as 0 if not. Prenatal alcohol exposure was coded 1 if the mother had drunk at least once per week during pregnancy (3.4% of the sample) and as 0 if not. Prenatal illegal drug exposure was coded as 1 if the mother had taken any illegal drug during pregnancy (1.4% of the sample) and as 0 if not.

Perinatal Social Factors. Family structure was coded as 1 if the family was nonintact (ie, children not living with both their biological parents; 18.9% of the sample) and as 0 if the family was intact (ie, children living with both their biological parents regardless of the type of conjugal relationship). Low maternal education corresponded to no high school diploma (coded as 1; 17.8% of the sample) vs a least a high school diploma (coded as 0). Maternal age at birth of the target child was coded as 1 if 21 years or younger (11.1% of the sample) and as 0 if older than 21 years. Insufficient household income was computed according to Statistics Canada's guidelines accounting for the family zone of residence, the number of people in the household, and the family income in the past year. Income was coded as 1 if insufficient (23.5% of the sample) and as 0 if sufficient.

Postnatal Family Factors. Family dysfunction at age 5 months was evaluated using the McMaster Family Assessment Device,[24] a scale containing 12 items measuring communication, showing and receiving affection, control of disruptive behavior, and problem resolution. Item codes are 0 (never), 1 (sometimes), and 2 (often). Informant total ratings were *z*-standardized. Mother-child interactions at child age 5 months were assessed using the responsiveness scale (eg, "responds verbally to child's vocalizations," "spontaneously praises the child at least twice," "tells child name of object or person during the visit") of the Home Observation for Measurement of the Environment–Infant Version.[29] Scores were dichotomized, with the lowest quartile being the at-risk group (27.1% of the sample, coded as 1) vs the remainder (coded as 0). The Parental Cognition and Conduct Toward the Infant Scale[30] was used to assess 4 dimensions of parenting when the child was 5 months old: coercive parenting, overprotection, self-efficacy, and parental impact. Dimension scores were *z*-standardized.

Parental Psychopathology. Maternal and paternal childhood/adolescent antisocial behaviors were assessed when the child was 5 months old. Parents were asked whether before finishing high school they had exhibited any of 5 different conduct problems referring to the *DSM-IV* criteria for conduct disorder and antisocial personality disorder.[31] If parents reported 2 or more antisocial items, the variable was coded as 1 (for mothers: 18.7% of the sample; for fathers: 17.3% of the sample) and as 0 otherwise. Maternal and paternal depressive symptoms (when the target child was aged 5 months) were assessed by using the abbreviated version (12 items) of the Center for Epidemiologic Studies Depression Scale.[32] Parents reported the frequency of depressive symptoms in the previous week. Each item was coded on a 4-point scale. Informant total ratings were *z*-standardized.

STATISTICAL ANALYSES

The analyses were performed in 3 steps. First, individual developmental trajectories of hyperactivity-impulsivity and inattention symptoms between 17 and 96 months of age were empirically identified. This identification was conducted through group-based trajectory modeling using semiparametric mixture models with censored-normal distributions.[33] Using the proc traj procedure of SAS,[34] we established the best models in terms of number of groups and polynomial order of the trajectories based on the Bayesian information criterion. To account for missing data and provide better estimates, subjects were included when at least 1 data point value was available. Second, a joint model of hyperactivity-impulsivity and inattention trajectories was estimated to allow examination of the 2 developmental patterns simultaneously. It provided joint probabilities (estimated percentages of children belonging simultaneously to hyperactivity-impulsivity and inattention trajectories) and 2 conditional probabilities (probability of a hyperactivity-impulsivity trajectory conditional on a given inattention trajectory and vice versa). Third, multivariate analyses (implemented in a logistic regression framework) were conducted to determine associations between risk factors and joint trajectory groups (high trajectory of hyperactivity-impulsivity and/or high trajectory of inattention vs others). To select the predictors included in the multivariate models, we estimated bivariate associations between risk factors and the outcome (bivariate logistic regression). Variables with $P<.25$ were subsequently entered into the initial multivariate models. Backward selection (variables deleted when $P\geq.05$) with control for confounding factors was then conducted. Statistical significance for all analyses was set at $P<.05$. To test the robustness of the findings, sensitivity analysis was performed using a multiple imputation model (number of imputations=5) under the missing at random nonresponse mechanism.[35] Fourth, interactions between sex and independent variables kept in the final model were tested.

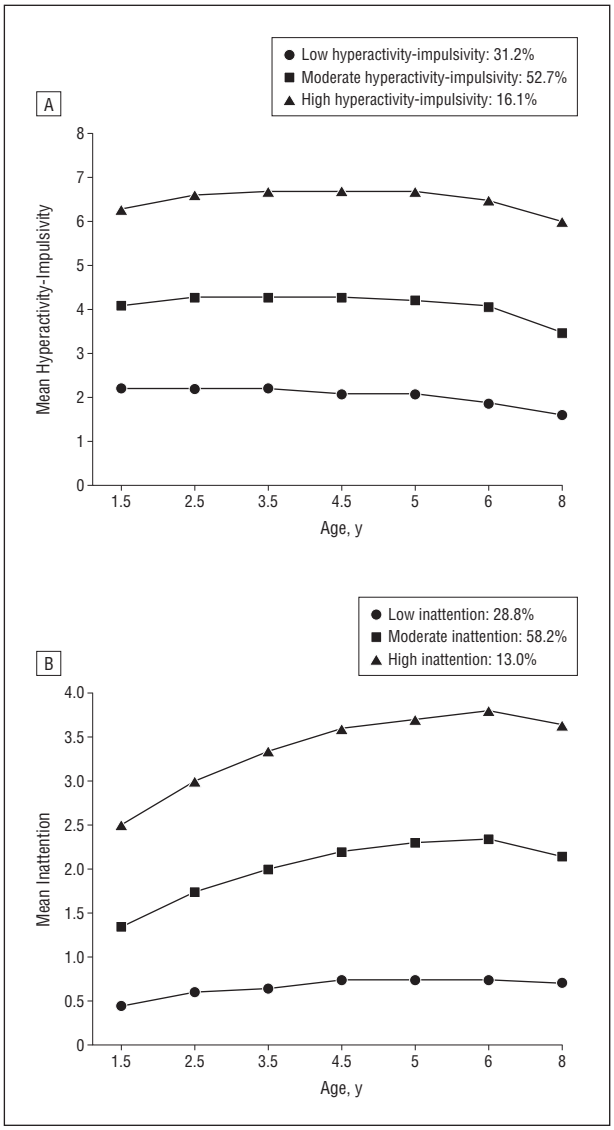

Figure. Developmental trajectories of hyperactivity-impulsivity (A) and inattention (B) from age 1.5 to 8 years.

RESULTS

JOINT DEVELOPMENTAL TRAJECTORIES OF HYPERACTIVITY-IMPULSIVITY AND INATTENTION

Modeling the data using a censored-normal distribution, we identified a 3-group model as the best fit for individual developmental trajectories of hyperactivity-impulsivity and a 3-group model as the best fit for individual developmental trajectories of inattention. All polynomial terms were quadratics. The **Figure** shows the joint trajectory model. The 3 hyperactivity-impulsivity trajectories were as follows: high (16.1%), moderate (52.7%), and low (31.2%). The 3 inattention trajectories were as follows: high (13.0%), moderate (58.2%), and low (28.8%). Hyperactivity-impulsivity symptom scores tended to slightly decrease with age, whereas inattention symptom scores substantially increased up to age 6 years and then declined. The first part of **Table 2** displays the probability of joint hyperactivity-impulsivity and inattention. In total, 12.3% of participants belonged to both the high hyperactivity-impulsivity group and the high inattention group; 3.7% had a high level of hyperactivity-impulsivity without high inattention; only 0.7% belonged to the high inattention group without being high for hyperactivity-impulsivity; and 83.3% did not belong to any high-level group. Almost no participants had high levels of symptoms of one type and low levels of another. The second part of Table 2 depicts the probabilities of inattention conditional on hyperactivity-impulsivity. Participants in the low hyperactivity-impulsivity group had a high probability ($P=.848$) of belonging to the low inattention group. Conversely, participants in the high hyperactivity-impulsivity group had a high probability ($P=.768$) of belonging to the high inattention group. The third part of Table 2 shows the probability of hyperactivity-impulsivity conditional on inattention. Participants in the low inattention group had a high probability ($P=.920$) of belonging to the low hyperactivity-impulsivity group. Conversely, participants in the high inattention group had a high probability ($P=.949$) of belonging to the high hyperactivity-impulsivity group.

Table 2. Joint and Conditional Probabilities of Hyperactivity-Impulsivity and Inattention[a]

Trajectory of Inattention	Trajectory of Hyperactivity-Impulsivity: Low	Moderate	High
Probability of Joint Hyperactivity-Impulsivity and Inattention[b]			
Low	.265	.022	.001
Moderate	.047	.499	.036
High	.000	.007	.123
Probability of Inattention Conditional on Hyperactivity-Impulsivity[c]			
Low	.848	.041	.007
Moderate	.152	.946	.225
High	.000	.013	.768
Probability of Hyperactivity-Impulsivity Conditional on Inattention[d]			
Low	.920	.075	.004
Moderate	.081	.857	.062
High	.000	.051	.949

[a] Data are courtesy of the Quebec Institute of Statistics.
[b] The sum of the cells is 1.
[c] Each column sums to 1.
[d] Each row sums to 1.

EARLY RISK FACTORS FOR HIGH HYPERACTIVITY-IMPULSIVITY AND/OR INATTENTION TRAJECTORIES

Owing to the large overlap between hyperactivity-impulsivity and inattention, we decided to consider together high levels on any dimension as the outcome measure. **Table 3** provides the results of multiple logistic regression models predicting trajectories of high levels of hyperactivity-impulsivity and/or inattention. Model 1 (n=1665) shows the results of multivariate models including all risk factors associated with the outcome with a $P<.25$. This model was significant (Wald $\chi^2=151.19$,

Table 3. Multiple Logistic Regression Models Predicting High Levels of Hyperactivity-Impulsivity and/or Inattention[a]

Independent Variable	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	
		Model 1	Model 2
Male	2.02 (1.58-2.58)	2.16 (1.59-2.90)	2.15 (1.60-2.87)
Lifetime methylphenidate use	6.17 (4.04-9.42)	6.11 (3.71-10.08)	6.61 (4.05-10.79)
Difficult temperament	1.17 (1.05-1.32)	1.15 (0.99-1.32)	1.18 (1.03-1.36)
Prenatal and perinatal factors			
Premature birth	1.74 (1.09-2.78)	1.97 (1.07-3.62)	1.93 (1.07-3.50)
Low birth weight	2.22 (1.31-3.74)	2.21 (1.17-4.20)	2.11 (1.12-3.98)
Prenatal tobacco exposure	1.84 (1.44-2.37)	1.37 (0.98-1.90)	1.41 (1.03-1.93)
Prenatal alcohol exposure	0.88 (0.44-1.73)		
Prenatal illegal drug exposure	1.67 (0.71-3.94)		
Perinatal social factors			
Nonintact family	1.86 (1.42-2.44)	1.73 (1.17-2.56)	1.85 (1.26-2.70)
Maternal age at birth	2.19 (1.59-3.01)	1.73 (1.10-2.73)	1.78 (1.17-2.69)
Insufficient income	1.88 (1.46-2.43)	1.16 (0.79-1.70)	
Maternal low education	1.75 (1.32-2.31)	1.00 (0.66-1.51)	
Postnatal family factors			
Family dysfunction	1.17 (1.05-1.31)	0.98 (0.83-1.16)	
Coercive parenting	1.17 (1.04-1.31)	1.08 (0.94-1.24)	
Overprotection	1.16 (1.03-1.32)	1.11 (0.95-1.29)	
Self-efficacy	0.92 (0.81-1.04)		
Parental impact	0.95 (0.89-1.02)		
Mother-child interaction	1.14 (0.87-1.50)		
Parental psychopathology			
Maternal history of antisocial behaviors	1.51 (1.14-2.16)	1.01 (0.70-1.45)	
Paternal history of antisocial behaviors	1.89 (1.39-2.56)	1.77 (1.26-2.50)	1.78 (1.28-2.47)
Maternal depression	1.34 (1.21-1.49)	1.27 (1.08-1.49)	1.35 (1.18-1.54)
Paternal depression	1.20 (1.07-1.35)	1.10 (0.96-1.27)	

Abbreviation: OR, odds ratio.
[a]Data are courtesy of the Quebec Institute of Statistics.

$P<.0001$), and the fit was good ($P=.51$). Model 2 (n=1721) displays results of the multivariate model with backward selection and step-by-step confounding control. This model was significant (Wald $\chi^2=154.52$, $P<.0001$), and the fit was good ($P=.20$). Insufficient income, low maternal education, maternal history of antisocial behaviors, paternal depression, family dysfunction, coercive parenting, and overprotection were significantly related to high hyperactivity-impulsivity and/or inattention in bivariate analyses but not in multivariate models. In the final model, premature birth, low birth weight, prenatal tobacco exposure, nonintact family, maternal age at birth younger than 21 years, paternal childhood/adolescent antisocial behaviors, maternal depression at child age 5 months, sex, methylphenidate lifetime exposure, and difficult temperament were significantly related to trajectories of high levels of hyperactivity-impulsivity and/or inattention. No significant statistical interaction was noted between the sex of the child and other significant risk factors. All the final predictive models were without multicollinearity (all condition index numbers <20). The sample with complete data used for multivariate analyses was largely similar to the initial sample regarding sociodemographic characteristics. However, there was a tendency for less advantaged families, nonintact families, and immigrant mothers ($P<.0001$ for all) to have missing values. The parameter estimates did not change with sensitivity analysis under the missing at random assumption. In addition, restricting the analyses of the hyperactivity-impulsivity and inattention trajectories by using individuals with at least 4 data points led to the same results. Further analyses to predict a high hyperactivity-impulsivity trajectory by adjusting for inattention provided similar results, and analyses predicting a high inattention trajectory by adjusting for hyperactivity-impulsivity led to comparable findings.

COMMENT

To our knowledge, this investigation is the first to focus on the development of joint trajectories of hyperactivity-impulsivity and inattention symptoms during the first 8 years of life. Compared with discrete category typing at 1 point in time, developmental trajectory analysis has the advantages of accounting for symptom intensity variations over age and of identifying clusters of individuals following similar typical and atypical courses of development. In addition, this study documented the contribution of a wide range of early risk factors. Results showed that a host of prenatal and early postnatal variables were independently associated with high levels of hyperactivity-impulsivity and inattention symptoms from infancy to the early school years. These findings rely on a population and sex-balanced longitudinal survey.

Regarding developmental trajectories, we found that 16.1% of children followed a high-declining hyperactivity-impulsivity trajectory, a decrease expected with age. Regarding inattention, 13.0% of children followed a high-ascending trajectory. To our knowledge, no study has

reported on early inattention trajectories. This ascending shape of the inattention trajectory may reflect either a specific developmental pattern or a measurement issue, attention being more easily detected with age. Joint analysis indicated that most children concurrently displayed both high levels of hyperactivity-impulsivity and inattention. This finding is of particular relevance because it sheds new light on the debate concerning changes to the *DSM-5*, that is, whether to keep the existing structure or replace it by considering a unique combined ADHD type (http://www.dsm5.org). The present data suggest that it is difficult to distinguish parent-reported hyperactivity-impulsivity from inattention up to age 8 years. However, the present study does not rule out the existence of an ADHD inattentive subtype. It is possible that the construct of early developmental trajectories taps into the ADHD combined subtype and that the ADHD inattentive subtype emerges later in life.

Regarding the prenatal and perinatal risk factors, we found an independent contribution of premature birth and low birth weight to the high hyperactivity-impulsivity and/or inattention trajectories. Previous literature linking attention problems and preterm and/or low birth weight arose from heterogeneous studies frequently using small and highly selected samples.[36,37] It has been shown that preterm and low-birth-weight newborns disproportionately have a reduction in gray matter and white matter injuries, anomalies associated with attention problems, executive dysfunction, and cognitive impairment.[38,39] Multiple biological and psychosocial factors could explain the relationship.[40] First, pregnancy and delivery complications may alter the brain and generate observed or more subtle cerebral damages. Second, immaturity, through biological programming or increased vulnerability to neuronal cell death, may produce neurologic sequelae and disruption in cortical development and brain connectivity.[38,41] Third, early life adversities associated with intensive care (ie, sensory stress, sleep deprivation, repetitive pain, and disturbance in parent-child interaction) may contribute to similar effects on the developing brain.[42] Fourth, prematurity is associated with more negative parent-child and family interactions at 4 months of age.[43] However, these last 2 variables do not explain the association in the present study. It has been suggested that being small for gestational age rather than prematurity or low birth weight may account for the risk of ADHD,[44] a hypothesis not tested in the present study.

The predictive association between maternal smoking during pregnancy and ADHD is consistent with previous research.[7,8] Some biological, nonheritable pathways could mediate the effect of prenatal tobacco exposure on later ADHD. Nicotine and other tobacco products, through damage and functional disturbance of the placenta, could generate chronic fetal hypoxia, resulting in observed intrauterine growth retardation and low birth weight.[45,46] Tobacco could also affect brain development in a more direct way, through deleterious effects on neurotransmission, neuronal differentiation, and migration.[47] Alternatively, this association may reflect a gene-environment correlation. A few genetically informed studies support the view that a common inherited genetic predisposition could link maternal smoking with ADHD in offspring.[48,49] Because results are contradictory,[50] more research is required to test this hypothesis more fully. Finally, a possible interaction between prenatal tobacco use and polymorphisms of *DAT1* and *DRD4* genotypes in increasing the risk of ADHD has been suggested.[51]

Prenatal alcohol and illegal drug exposure was not significantly linked to hyperactivity-impulsivity and/or inattention trajectories. This could be due to a real absence of association, particularly for alcohol, which has been inconsistently related to later ADHD, or to a lack of power, especially for illegal drug exposure.

Perinatal social variables also accounted for the risk of following the high hyperactivity-impulsivity and/or inattention trajectories. However, whereas young maternal age at birth of the target child and being from a nonintact family remained predictors in multivariate models, this was not the case for insufficient family income and low maternal education. Previous studies found connections between low socioeconomic status, low maternal education levels, and ADHD.[13,52] However, those studies did not consider a wide range of confounders. A possible explanation for the present results is that insufficient family income and having a mother without a high school diploma are more distal variables and may, thus, have been accounted for by more proximal risk factors in the causal chain, such as young maternal age and membership in a nonintact family. These latter factors could reflect parental conflict, parenting difficulties, violence exposure, neglect, or maltreatment. However, in the present study, the available family and parenting variables at child age 5 months were not conclusive in that regard in multivariate models.

Parental psychopathology increased the liability of following the high hyperactivity-impulsivity and/or inattention trajectories. Maternal depression and paternal history of antisocial behaviors were significant predictors and accounted for the prediction of paternal depression at child age 5 months and childhood/adolescent antisocial behaviors in mothers. These results are relevant because there is little research examining the heterotypic continuity between maternal postnatal depression, antisocial paternal behavior, and ADHD symptoms in offspring.[21,53] One possible interpretation is that this pattern of associations merely reflects the fact that parental mental health affected the ratings due to a shared source of variance with child behavior trajectories (ie, a measurement issue). An alternative interpretation is that there is a real association between parental psychopathology and ADHD symptoms. If so, the mechanisms underlying this intergenerational transmission could be complex and may involve a heritable common genetic liability and environmental processes through postnatal relational variables. Parenting at child age 5 months (family dysfunction, mother-child interaction, coercive parenting, and overprotection) was not significant in the adjusted models. This absence of association may be due to the interplay of other adjustment variables or may be related to weak measures of parenting variables in this study. Indeed, chronic or later parenting disturbances may have shown a greater contribution to ADHD trajectories. In addition, unmeasured factors, such as parental

ADHD, prenatal and postnatal anxiety, and depression could act as confounders.[15]

Finally, difficult temperament and being a boy were significantly associated with high trajectories of hyperactivity-impulsivity and/or inattention. Temperament could be implicated in the development of ADHD.[54] The link could be mediated through extreme approach tendencies or low effortful control and through some negative parenting resulting from ADHD symptoms.[20,21] As for the sex of the child, it is well documented that boys are more susceptible to neurodevelopmental disorders and other disruptive behaviors (among which is ADHD) from early childhood.[55]

Limitations should be considered when interpreting the present results. First, full-blown categorical ADHD was not assessed because we did not consider the impairment related to developmental trajectories. Clinical impairment will be more reliably assessed at a later age. Second, we relied on parental reports for assessing hyperactivity-impulsivity and inattention symptoms. Parental ratings remain the most accurate measure to investigate early trajectories. Teacher assessments of these individuals during the elementary school years will provide an opportunity to compare early parent assessments with teacher assessments during the school years. Third, because most risk factors were self-reported, mothers may have underreported their psychopathology and substance use during pregnancy, possibly leading to underestimation of these effects. Fourth, inherited genetic and epigenetic factors were not considered in the present study. This precluded examination of genetic × environment interactions and correlations. This is a point for future research because environmental effects may exert the strongest influence over individuals with a particular genetic vulnerability. Despite their small effect sizes, environmental risk factors may still be of major importance in vulnerable subgroups as genetic and environmental factors likely act together (additively and multiplicatively) to generate a neurobiological risk. This could be especially true during key stages of development, when fetal and social programming can produce long-term changes in gene expression and neurobiological pathways. Further investigations at a molecular level are needed to disentangle the epigenetic effects of prenatal and postnatal factors (silencing/activating genes of susceptibility or with protective effects).[1,5,56,57] Fifth, other potential confounders and effect modifiers, such as toxemia, antepartum hemorrhage, maternal hypothyroidism, antenatal stress, maternal depression during pregnancy, parental postnatal anxiety and ADHD status, prenatal and postnatal physical risk factors, breastfeeding, and medications other than methylphenidate (eg, other stimulants, nonstimulants, antihistaminics, antiepileptics, and antipsychotics), were not measured in this study. Sixth, the focus on very early risk factors limited the understanding of developmental pathways after 5 months of age. Nevertheless, later risk and protective factors (eg, other child internalizing and externalizing problems, family and relational difficulties, hostile-reactive parenting, traumas, and education) are likely to affect the developmental trajectories of ADHD symptoms and may represent potential targets to early interventions.

On the whole, these results support the hypothesis of the multifactorial etiology and heterogeneity of environmental causal processes implicated in ADHD. They extend this finding to a wide set of very early and independent risk factors in the prediction of early trajectories of hyperactivity-impulsivity and inattention symptoms. This is especially significant for the understanding of underlying mechanisms and for public health issues. Indeed, developmental trajectories connected to recognizable risk factors, some of which are modifiable, can be identified early on. Early development is a particular period of vulnerability but also plasticity, when influences on programming processes and on the developing brain are subject to modification.[1,5,56,57] This dynamic view suggests implementing alternative and complementary preventive tools in the management of ADHD. In addition to the promotion of adequate maternal habits during pregnancy, risk factors (including prenatal, perinatal, perinatal social, and parental psychopathology variables and difficult temperament of the child) could be evaluated early on to help in identifying high-risk children and families who may receive support. However, due to the weak predictive power of early risk indicators in multifactorial diseases and the ethical questions raised by primary intervention, some caution must be taken. Besides, the early risk factors identified are prone to multifinality. Indeed, they have been associated with other deleterious outcomes, including depression, anxiety, and disruptive behaviors.[58-60] Hence, experiments on early prevention would be welcome to determine whether and which among universal, selective, and indicated prevention programs would have the greatest effect on the early developmental trajectories of hyperactivity-impulsivity and inattention.

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