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# Facteurs de risque environnementaux précoces et trajectoires développementales d'irritabilité et du trouble du déficit de l'attention avec ou sans hyperactivité

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**Facteurs de risque environnementaux précoces et  
trajectoires développementales d'irritabilité et du trouble  
du déficit de l'attention avec ou sans hyperactivité**

Sous la direction de : Cédric GALERA

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Monsieur le Professeur Manuel BOUVARD, président de jury

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## **Index des abréviations**

95%CI : 95% Confidence Intervalle

ADHD: Attention Deficit Hyperactivity Disorder

aOR: adjusted Odds Ratio

BIC : Bayesian Inclusion Criterion

CES-D : Center for Epidemiologic Studies-Depression Scale

DMDD : Disruptive Mood Dysregulation Disorder

ELDEQ : Étude longitudinale du développement des enfants du Québec

GBTM: Group Based Trajectories Modeling

NIMH: National Institute of Mental Health

NLSCY: National Longitudinal Survey of Children and Youth

OR: Odds Ratio

PACOTIS: Parental Cognitions and Conduct Toward the Infant Scale

PMK: Person Most Knowledgeable

QLSCD: Quebec Longitudinal Survey of Child Development

RDoC : Research Domain Criteria

TDAH : Trouble du déficit de l'attention hyperactivité

TDDE : Trouble Disruptif avec dysrégulation émotionnelle

## A. Introduction générale

L'irritabilité est un symptôme transnosographique partagé par plusieurs troubles psychiatriques et entraîne fréquemment la sollicitation de soins pédopsychiatriques (1). Devant l'importance de ce symptôme, le DSM-5 a récemment intégré un nouveau diagnostic : le trouble disruptif avec dysrégulation émotionnelle (TDDE) dont l'irritabilité chronique est le symptôme central. L'irritabilité peut être défini comme un abaissement du seuil d'expression de la colère en réponse à une frustration. Elle est fréquemment associée à une augmentation de l'agressivité verbale et/ou physique (2).

L'irritabilité est fréquemment associée au trouble du déficit de l'attention hyperactivité (TDAH). Le TDAH est le trouble neurodéveloppemental le plus fréquent et concerne environ 5% des enfants dans le monde (3). Cliniquement il se définit par la présence de symptômes d'inattention associés ou non à des symptômes d'hyperactivité et d'impulsivité. Les enfants souffrant de TDAH rencontrent des difficultés dans la sphère familiale, sociale et scolaire qui peuvent être en partie liées à leurs difficultés de régulation émotionnelle et à la présence d'une irritabilité chronique (4–6). Environ un patient sur cinq souffrant de TDAH a pour comorbidité une TDDE, ce qui se traduit par une faible maîtrise de soi, une symptomatologie TDAH plus sévère, des difficultés relationnelles avec ses pairs, et davantage de troubles externalisés comorbides par rapport aux patients présentant un TDAH isolé (7,8). Il n'existe pas de consensus concernant la place de l'irritabilité dans le TDAH, à savoir s'il s'agit d'un sous-type de TDAH ou d'une comorbidité (9). Plusieurs études ont pu mettre en lumière l'existence d'un sous-groupe de TDAH considéré comme « irritable » stable dans le temps. Ce sous-groupe ayant un pronostic clinique plus sombre présente un risque augmenté de troubles externalisés et internalisés au cours de l'adolescence (10–12).

Devant la difficulté de mettre en évidence les mécanismes sous-jacents du développement des pathologies psychiatriques en utilisant les classifications nosographiques, le National Institute of Mental Health (NIMH) propose l'utilisation d'une approche dimensionnelle à travers les Research Domain Criteria (RDoC) (13). D'un point de vue dimensionnel, les patients souffrant de TDAH et ceux présentant des symptômes d'irritabilité partagent un système de récompense altéré (14). Par ailleurs, un contrôle attentionnel permettant de se détourner des affects négatifs est nécessaire pour contrôler ses émotions et s'autoréguler (15,16).

Le TDAH et l'irritabilité ont des facteurs de vulnérabilité génétique communs qui s'expriment selon l'exposition à certains facteurs environnementaux (6,17–20). Connaître les facteurs de risques environnementaux spécifiques associés avec les profils

développementaux d'irritabilité et de TDAH permettraient la mise en place de campagnes de prévention en santé publique et une prise en charge précoce des enfants considérés comme étant à risque.

Les études s'intéressant aux facteurs de risques précoces du TDAH et de l'irritabilité présentent plusieurs limites : 1) l'irritabilité n'est pas définie de façon consensuelle, 2) les symptômes sont évalués de façon transversale, 3) les variations symptomatologiques de l'irritabilité et le TDAH sont étudiés séparément, 4) la nature transversale des études ne permet pas de vérifier que la présence des facteurs de risque précède l'apparition des symptômes.

Cette étude a pour objectif de s'intéresser aux facteurs de risques environnementaux précoces associés avec les profils développementaux des symptômes du TDAH et de l'irritabilité chez les enfants entre l'âge de 6 et 12 ans à partir des données d'une cohorte : étude longitudinale du développement des enfants du Québec (ELDEQ).

ELDEQ est une cohorte de naissance québécoise. Les enfants et leur famille ont été recrutés à l'âge de 5 mois. Pour participer à cette étude, les enfants devaient être nés entre 24 et 42 semaines de grossesse et avoir une mère parlant soit français soit anglais. L'échantillon considéré dans cette étude comportait 1 588 enfants et leur famille. Les données ont été récoltées par l'institut de statistique du Québec de façon annuelle jusqu'à l'âge de 8 ans puis tous les 2 ans lors d'un entretien standardisé au domicile parental. La cohorte a été approuvée par le comité éthique de santé du Québec. Un consentement écrit a été obtenu des parents ainsi que des enfants lorsqu'ils ont atteint l'âge 10 ans (21).

Les facteurs de risques considérés dans cette étude sont les suivants : le sexe de l'enfant, l'âge maternel à la naissance de l'enfant, le statut migratoire de la mère de l'enfant, la composition familiale ainsi que le niveau socio-économique familial entre l'âge de 5 mois et de 5 ans de l'enfant ainsi que les différentes pratiques parentales. Ces dernières regroupaient : le sentiment d'auto-efficacité parentale (soit la croyance en sa capacité de s'occuper de son enfant), l'impact parental perçu (soit la croyance que son comportement en tant que parent joue un rôle sur le développement de l'enfant), les pratiques parentales hostiles, les pratiques parentales positives, les pratiques parentales conséquentes (soit la propension du parent à réagir de façon identique lorsqu'il rencontre un comportement donné chez son enfant), la surprotection parentale ainsi que les interactions mère-enfant. Les antécédents de comportement antisocial pendant l'adolescence chez la mère et le père ainsi que la



symptomatologie dépressive paternelle aux 5 mois de l'enfant et les trajectoires de la symptomatologie dépressive chez la mère ont également été explorés. Les trajectoires des variables longitudinales ont été estimées à l'aide du Group Based Trajectories Modeling (22).

La symptomatologie TDAH et d'irritabilité a été évaluée par un enseignant différent chaque année entre l'âge de 6 et 12 ans à travers un auto-questionnaire standardisé. Les trajectoires conjointes de ces deux symptômes ont été estimées à l'aide de modélisation de trajectoires multiples (23).

Différents modèles de régression multinomiale ont été estimés entre les différentes trajectoires développementales et les différents facteurs de risque. Les analyses ont été réalisées en tenant compte d'un potentiel biais d'attrition en réalisant une pondération par probabilité inversée.

Les 1 588 sujets inclus dans cette étude diffèrent de la population non incluse. On retrouve une sous-représentation de garçons, de parents immigrés et de familles présentant un statut socio-économique bas par rapport aux sujets perdus de vue.

Quatre groupes de trajectoires développementales de symptomatologie de TDAH et d'irritabilité ont été modélisés ; un groupe considéré comme physiologique (regroupant les trajectoires symptomatologiques de pas de TDAH/pas d'irritabilité et de TDAH faible/pas d'irritabilité) comprenant 1 057 enfants (soit 66,6% de la population), et trois groupes pathologiques (symptomatologie d'irritabilité modérée (n= 180, 11,3%), de TDAH élevée (n=220, 13,9%) et de TDAH élevée/irritabilité élevée (n=131, 8,2%).

Les enfants classés dans la trajectoire combinée TDAH élevée/irritabilité élevée étaient plus souvent des garçons, apparaissent davantage à des familles monoparentales ou recomposées, avaient des mères plus jeunes à leur naissance et étaient issus de familles de niveau socio-économique plus faible que tous les autres profils développementaux ( $p < 0,001$ ).

Les facteurs de risques communs aux 3 profils pathologiques par rapport au profil physiologique sont le sexe masculin et un statut socioéconomique bas. La présence de pratiques parentales hostiles et l'absence de pratiques parentales conséquentes augmentent le risque d'appartenir au profil d'irritabilité modérée et au profil de TDAH élevé/irritabilité élevée. Le profil combiné et le profil TDAH haut sont associés aux familles monoparentales ou

recomposées. L'impact parental perçu et avoir une mère immigrée sont des facteurs protecteurs spécifiques du profil TDAH élevée/irritabilité tandis que la présence d'antécédents maternels de comportements antisociaux au cours de l'adolescence est un facteur de risque de ce profil. L'annexe 1 montre les facteurs de risques associés de façon statistiquement significative à au moins un des profils pathologiques.

Cette étude met en évidence 3 trajectoires développementales pathologiques des symptomatologies TDAH et irritabilité chez les enfants entre 6 et 12 ans. Seule la trajectoire combinée présente des facteurs de risques qui lui sont propres (l'impact parental perçu, avoir une mère immigrée, avoir une mère avec des antécédents de comportement antisociaux au cours de l'adolescence). Tous les facteurs de risques associés soit au profil TDAH haut, soit au profil irritabilité modérée sont également liés au profil combiné. La force d'association est toujours plus importante avec ce dernier profil qu'avec les autres profils.

Cette étude présente plusieurs limites. Pour commencer, il y a un risque de biais de sélection lié au fort taux d'attrition, entraînant une sous-représentation des enfants à risque de développer des pathologies psychiatriques. Ceci a été pris en compte lors des analyses statistiques, cependant les associations ont pu être sous-estimées. Ensuite, les questionnaires se sont concentrés sur la composante phasique de l'irritabilité, n'explorant pas la composante tonique. Cependant il a été montré que ces deux composants peuvent être interchangeables dans la population générale (24). Par ailleurs, la symptomatologie psychiatrique a été évaluée par des enseignants. Ceci a pu entraîner un biais de mesure, n'ayant pas accès à la symptomatologie présentée dans un contexte familial. Toutefois, les enseignants semblent aussi compétents que les parents pour évaluer les symptômes liés aux troubles externalisés (25,26).

La collecte prospective et conjointe des symptômes de TDAH et d'irritabilité ainsi que des facteurs de risques environnementaux est une des forces de cette étude. Une des innovations de cette étude est la modélisation conjointe des trajectoires développementales d'irritabilité et de TDAH. Pour finir, l'approche dimensionnelle de la symptomatologie TDAH et d'irritabilité pour chercher des facteurs de risque est recommandée par le NIMH dans le cadre des RDoC (15,16).

La présence de facteurs de risques partagés par plusieurs profils pathologiques de TDAH et d'irritabilité est en faveur de la poursuite des recherches selon les modalités RDoC. D'autant

plus, si l'irritabilité et la symptomatologie TDAH sont conceptualisés comme étant une continuité entre des processus physiologiques et pathologiques.

D'un point de vue de la santé publique, trouver des facteurs de risques spécifiques à plusieurs dimensions permettrait de mettre en place des campagnes de prévention particulièrement efficaces. En effet, en agissant sur un facteur de risque, plusieurs pathologies psychiatriques pourraient être prévenues.

D'un point de vue individuel, reconnaître l'hétérogénéité de la symptomatologie TDAH et d'irritabilité pourrait donner lieu à la mise en place de traitements personnalisés (27). Le repérage précoce des enfants à risque de présenter une trajectoire combinée permettrait une vigilance accrue du corps médical afin de proposer une prise en charge précoce si nécessaire. D'autant plus que ce profil prédit l'apparition de troubles externalisés et internalisés (12,28). Il paraît donc indispensable de rechercher systématiquement des symptômes d'irritabilité lors de l'évaluation d'un patient souffrant de TDAH.

Le lien causal entre les comportements parentaux précoces et le développement de trajectoires pathologiques de TDAH et d'irritabilité doit être confirmé. Cependant, il paraît pertinent de tenir compte des pratiques parentales dans le cadre de la prise en charge des jeunes enfants. Si cette association devait être confirmée dans de futures études, cela pourrait mener à des campagnes de prévention afin d'améliorer les pratiques parentales dans la population générale et ainsi prévenir la survenue de troubles psychiatriques chez les jeunes enfants.

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## B. Article

# Early life environmental risk factors of developmental profiles of childhood attention-deficit hyperactivity disorder and irritability: the QLSCD cohort

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**Abbreviations:** 95% Confidence Intervals, ADHD: Attention Deficit Hyperactivity Disorder, aOR: adjusted Odds Ratio, BIC : Bayesian Inclusion Criterion, CES-D : Center for Epidemiologic Studies-Depression Scale, DMDD: Disruptive Mood Dysregulation Disorder, GBTM : Group Based Trajectories Modeling, NIMH : National Institute of Mental Health, NLSCY : National Longitudinal Survey of Children and Youth, OR : Odds Ratio, PACOTIS : Parental Cognitions and Conduct Toward the Infant Scale, PMK :Person Most Knowledgeable, QLSCD : Quebec Longitudinal Survey of Child Development, RDoC : Research Domain Criteria

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## **ABSTRACT:**

**Introduction:** Irritability is a transnosographic symptom frequently related with attention deficit hyperactivity disorder (ADHD). Their combination predicts more severe symptoms and greater impairment in children. Therefore, it seems important to study their developmental variations jointly and to bring to light specific risk factors which can be modified through preventive public health campaigns. The aim of this study is to explore the association between early childhood environmental risk factors and irritability and ADHD developmental trajectories between the age of 6 and 12 years old from a population-based cohort.

**Methods:** Data was collected from the Quebec Longitudinal Study of Child Development (QLSCD) that followed 1588 children from 5 months to 12 years of age. Social factors, parenting behavior and parental psychopathology were considered as potential risk factor and were collected prospectively through home visits and standardized interviews. The child's behavior was rated by its schoolteacher yearly between the age of 6 and 12 years old. The irritability and ADHD trajectories were estimated through multitrajectory modeling. Multinomial regression analyses were carried out to estimate association between the different risk factors and developmental trajectories of ADHD and irritability.

**Results:** Four ADHD and irritability trajectories were estimated: one low ADHD/low irritability (n=1,057, 66.6%) which was considered as physiological and three pathological trajectories (moderate irritability (n= 180, 11.3%), high ADHD (n=220, 13.9%) and high irritability/high ADHD (n=131, 8.2%)). Compared to the reference group, the combined profile was associated with male gender (adjusted Odds Ratio (aOR) = 7.01, 95% Confidence Interval (95%CI)[4.67-10.54]), non-intact families (aOR = 2.11, 95%CI [1.38-3.22]), coercive parenting (aOR=1.57, 95%CI [1.02-2.42]), consistent parenting (aOR = 0.83, 95%CI [0.72-0.95]), parental impact (aOR = 0.90, 95%CI [0.80-1.00]) and maternal history of antisocial behavior in adolescence [aOR = 1.44, 95%CI [1.05-1.96]].

**Conclusion:** Several early childhood environmental factors were associated with the combined profile. Public health campaigns targeting parenting behaviors should be considered to prevent severe child psychopathology.

Keywords: ADHD, irritability, risk factors



## 1. Introduction

Irritability is a common clinical feature shared across a large range of psychiatric disorders. For example, irritability is a relevant symptom in mood and neurodevelopmental disorders in which it represents a disturbing and impairing externalized comorbid dimension. At the extreme of the irritable spectrum, it even constitutes a core symptom of disruptive mood dysregulation disorder (DMDD), as recently introduced in the DSM-5. Clinically, irritability is defined as a lowered threshold of experiencing anger when frustrated and is frequently associated to an increase in verbal and or physical aggressivity (1). Therefore, it is a common gateway to child psychiatric facilities. Of note, irritability is commonly related to attention-deficit hyperactivity disorder (ADHD) (2). ADHD is the most frequent neurodevelopmental disorder and concerns approximately 5% of children world-wide (3). Clinically it is defined as a discrepancy between the developmental age of the child and the occurrence of inattention and/or hyperactivity-impulsivity symptoms. ADHD is a chronic impairing disorder that impacts all the child's life aspects (from school, to family and social life) (4). Patients presenting with ADHD have emotional regulation difficulties and irritable mood (5). When DMDD is diagnosed in patients suffering from ADHD (about 21% of patients), they present poor self-control, more severe ADHD symptoms, higher rates of externalizing comorbidities and more peer relationship problems compared to ADHD alone. This comorbidity adds an important social burden (6,7). It is unclear whether irritability should be considered as a subtype of ADHD or as a comorbidity. However, it has been shown that high irritability in childhood increased the risk to be diagnosed with ADHD 7 years later (2). Studies have shown the existence of a stable subgroup of irritability profile in ADHD with an increase of a negative clinical outcome (8,9). When considering ADHD and irritability profiles in childhood, an ADHD-irritability profile has higher risks of externalizing and internalizing symptoms and bigger functional impairment when compared to the non-pathological profile, the irritability profile or the ADHD profile (10).

The National Institute of Mental Health (NIMH) considers that the nosographic classification of psychiatric disorders have yet to achieve to bring to light the complex mechanisms underlying the occurrence of psychiatric disorders. Therefore, they recommend to study them from a dimensional point of view through the Research Domain Criteria (RDoC) (11). From a RDoC perspective, ADHD patients as well as patients presenting irritability symptoms suffer from an impaired reward processing (12). Of note, attention control is necessary for emotional control and self-regulatory behaviors to be distracted from negative affect such as encountered in irritability (13,14). ADHD and irritability seem to have common psychopathology ground. The aggregation of these two entities seem to refer to a higher clinical severity with more negative outcomes.

This underscores the importance of distinguishing ADHD with irritability profiles from irritability alone and ADHD alone, since irritability can be found in other mental disorders (such as anxiety and depression) and that ADHD patients do not always present with irritability. ADHD and irritability may have common genetic vulnerabilities (5,15–17) that express themselves according to environmental factors. Acknowledging and identifying these specific risk factors could lead public health prevention campaigns.

Up to date, several early life environmental risk factors have been explored to explain the emergence of ADHD and irritability symptoms. For example, a cross sectional study found that single families, low socioeconomical status, impaired family functioning was associated with a higher risk of irritability in the general population for children aged between 9 and 17 years old (18). In a small sample of children aged between 7 and 18 years old, a correlation between DMDD symptoms and worse family functioning was found when comparing to ADHD and general population. This could have been the consequence of the presence of DMDD symptoms (19). These risk factors are not consistently found from one study to another (20). Male gender, parental hostile education, poorer quality of family activities and lack of parental warmth were considered as risk factors of ADHD with irritability symptoms compared to ADHD alone in a cross-sectional study (7). However, most studies present several limitations: 1) Irritability is not defined consistently from one study to another, limiting comparison between studies, 2) Comorbid irritability and ADHD aren't simultaneously compared to ADHD alone, irritability alone and to the general population, to highlight their common and specific risk factors, 3) Irritability and ADHD are assessed transversally, thus not allowing to consider their modulation through time, 4) Cross-sectional nature of most studies have hampered the study of the temporal precedence of the environmental risk factors.

The purpose of this study is to identify early childhood environmental risk factors, such as parenting behaviors and parental psychopathology, associated with developmental profiles of ADHD and irritability symptoms in children between the age of 6 and 12 years old from a population-based cohort; the Quebec Longitudinal Study of Child Development (QLSCD).

## 2. Methods

### 2.1. Participants and procedure

QLSCD is a population-based cohort which follows families whose child was born between October 1997 and July 1998 from the age of 5 months (21). A random stratified sample according to the living location and to the birth rate in each location was created with the Master birth register for the province of Quebec.

To participate in the study, the child had to be born between 24 and 42 weeks of pregnancy and the mother had to speak either English or French. Out of the 2940 families selected, 2120 families participated in the follow-up and 1588 were considered in this study which relies on the developmental trajectories of ADHD and irritability. Data was gathered by the Quebec Statistics Institute. Parental, familial and child characteristics were collected yearly until the age of 8 and every 2 years afterwards until the age of 12 by a trained interviewer during home visits with the person most knowledgeable of the child (the mother in 98% of the case).

The cohort was approved by the Health Quebec ethics committee. A written consent was obtained from the parents and from the child when he turned 10.

### 2.2. Measures

#### 2.2.1. *Early life environmental risk factors*

##### 2.2.1.1. Social factors

The social factors were gathered yearly during a home visit through a standardized interview between the age of 5 months and 5 years of the child. It included the maternal age at birth of the child, the immigration status of the mother (yes/no) and the family composition (intact or non-intact) and the family's socioeconomic status. The family was considered as non-intact if the parents of the child had separated at least once between his birth and his 5 years of age. The mean family socioeconomic status was obtained by the average over the 5 first years of the child of the socioeconomic score which is an aggregate of 5 items regarding annual gross income, parental educational level, and parental occupation at each wave. The score range went from -3 to 3 and was centered on 0, a high score indicated a high socioeconomic status.

### 2.2.1.2. Postnatal family factors

The parenting behaviors were assessed through the Parental Cognitions and Conduct Toward the Infant Scale (PACOTIS) which is a 28 items self-administrated questionnaire by the person most knowledgeable about the child (PMK) and rated each item according to what she thought, what she felt or what she did concerning her child, following an 11 point Likert scale (going from “not at all” to “exactly”) (22,23). The items of the questionnaire were regularly adjusted as the child grew older. It measured five different dimensions in parenting behaviors: self-efficacy, parental impact, coercive parenting, positive parenting, and overprotection. *Self-efficacy* referred to the perceived ability of the PMK to take care of his child. *Parental impact* referred to the belief of the PMK that his behavior with his child could play a role in his development. *Overprotection* was considered as the difficulty for the PMK to be separated from her child and to worry excessively on his well-being. Each of these dimensions were measured at the 5, 17 and 29-month interview. *Coercive parenting* was considered as negative parent-child interaction where a high score indicated that the PMK was prone to respond negatively and in a restrictive manner to the child, whereas a low score reflected a more rational relationship (the parent was more prone to calmly discuss problems with his child) and was measured at the 29, 41, 45-56-month and 5-year visit. *Positive parenting* reflected positive parent-child interaction. It was rated yearly from the 5-month visit to the 5-year visit. The dimension of *consistent parenting* was obtained during the home visit interview with the PMK. It was considered as the ability of the PMK to have the same response for the same child’s behavior. The 10 items of the questionnaire were originated from National Longitudinal Survey of Children and Youth (NLSCY) (24). The higher the score the more the rules established in the household were consistent. This dimension was evaluated yearly from the 29-month interview to the 5-year interview.

The *mother-child interaction* was the only dimension that was rated by the interviewer himself after the home visit and was considered as the level of verbalization of the PMK to her child during the interview by the means of the Home Observation for Measurement of the Environment revised edition (25) to which he was trained. It was measured at the 5, 17 and 29-month interview. The mean of each postnatal family factor at each wave was calculated and standardized to obtain a score between 0 and 10.

### 2.2.1.3. Parental psychopathology

*Maternal and paternal history of antisociality in adolescence* was collected by a self-administrated questionnaire at the 5-month visit. It was assessed via 5 binary questions based on DSM-4 criteria for conduct disorder and antisocial behavior before they had left high school such as “has often been in fights that they started”, “has stolen more than once”, “has been involved with youth protection or the police because of their misbehavior”, “has been expelled”(for fathers only) or “suspended from school”(for fathers only), “has skipped school more than twice in a year” (for mothers only), “has ran away from home overnight” (for mothers only). The score range went from 0 to 5, with higher scores indicating more antisocial behaviors (26).

*Maternal depression* was self-reported and evaluated by a 13-item abbreviated version of the Center for Epidemiologic Studies-Depression Scale (CES-D) (27) also used in the NLSCY (24). It was assessed at the 5, 17, 41-month and 5-year interview.

*Paternal depression* was assessed at the 5-month visit following the same method as the evaluation of maternal depression. The mean of each parental psychopathology variable at each wave was calculated and standardized to obtain a score between 0 and 10.

### 2.2.2. Teacher ratings of childhood ADHD and irritability symptoms

The ADHD and irritability symptoms were assessed through the behavior questionnaire by the different schoolteacher at the age of 6, 7, 8, 10 and 12 years old. It is a self-administrated questionnaire created for the NLSCY that regroups items from the child behavior checklist (28), the Ontario child health study scales (29) and the preschool behavior questionnaire (30). *ADHD symptoms* were evaluated through 6 items of hyperactivity-impulsivity symptoms (“could not sit still, was restless or hyperactive”, “couldn’t stop fidgeting”, “was unable to wait when someone promised him/her something”, “was impulsive, acted without thinking”, “had difficulties waiting his/her turn in games”, “couldn’t settle down to do anything for more than a few moments”) and 3 items of inattention (“was unable to concentrate, could not pay attention for long”, “was easily distracted, had trouble sticking to any activity”, “was inattentive”). Teachers rated each item according to the frequency of the behavior over the 6 past months using a 3-point Likert scale (from 0 = “never” to 2 = “often”). Then, the mean was calculated and standardized so that the score range went from 0 to 10. *Irritability symptoms* were rated through the sum of the score of the item “had temper tantrums or hot temper” and the mean score of the 3 other items that all reflected aggressive behavior (“reacted in an aggressive

manner when teased”, “reacted in an aggressive manner when contradicted”, “reacted in an aggressive manner when something was taken away from him/her”) (10,31,32).

## 2.3. Data analysis

### 2.3.1. *Estimating early life risk factors*

The mean of the different waves of measures was calculated for the dimensions of consistent parenting, overprotection, and parental impact.

Trajectories of coercive parenting, positive parenting, self-efficacy, mother-child interaction and mother depression through early childhood (between the child’s 5 months and 5 years of age) were estimated using the Group Based Trajectories Modeling (GBTM) adapted to censored normal distribution data (33). It permitted to bring to light several latent groups in each of these variables. To choose the best fitted model, clinical and statistical interpretability (through the same fit indices as the multitrajectory modeling) were considered. When the best fitted model had more than one group, groups considered as non-pathological were merged to create a reference group (34). Each child was allocated to the group to which he had the highest posterior probability to belong to.

### 2.3.2. *Estimating childhood ADHD and irritability profiles*

Developmental trajectories of ADHD and irritability symptoms from age 6 to 12 years were estimated using multitrajectory modeling (10,35). It allows to determine latent clusters of individuals that present comparable attributes by modeling trajectories of several dimensions simultaneously using a semi-parametric mixture model. This allowed to take into consideration the joint development and the overlap of ADHD and irritability symptoms through childhood. The maximum likelihood estimation by a Newton-Raphson optimization algorithm and censored normal modeling were used to estimate the model’s parameters. Several fit indices (such as the log-likelihood, the Bayesian Information Criterion (BIC), the entropy and the mean odds of correct classification) and clinical interpretability enabled the choice of the number of groups and polynomial order of the trajectories. Each child was assigned to the profile that he had the highest posterior probability to belong to.

### *2.3.3. Quantifying the association between childhood ADHD and irritability profiles and early life risk factors*

A series of regression models were carried out to get an overall appreciation of the early life risk factors associated with the ADHD and irritability trajectories. Multinomial logistic regression models were conducted to estimate the association between different ADHD and irritability profiles and each risk factor through odd ratios (OR) and their 95% confidence intervals (95%CI). The profile with lowest symptoms was considered as the reference group. Missing data were considered as missing at random and were imputed using the multiple imputation chain equation (36). To deal with sample attrition, all analyses were conducted using inverse probability weighting to allow generalization of results to the initial cohort sample. As individuals with certain characteristics were more likely to be missing at follow-up, the inverse probability was calculated according to key variables significantly associated with attrition such as maternal and paternal immigration status, the sex of the child and the mean family socioeconomic status. Each analysis for each risk factor was systematically adjusted on the other risk factors. Finally, a sensitivity analysis was realized without inverse probability weight.

### 3. Results

#### 3.1. Participants

The study included 1,588 participants followed up to 12 years of age. The comparison of the sociodemographic characteristics between participants and non-participants are shown in Table 1. Male children were underrepresented in the study sample (48,49% male vs. 58,27% in non-participants). The study sample had also less immigrated mothers and fathers (respectively 8.5% and 9.13% of immigrants in the participant vs. 22.36% and 18.05% in the non-participants) and a higher mean family socioeconomic status (0.01 vs. -0.17).

**Table 1. Comparison of participants<sup>a</sup> vs. non-participants on sociodemographic characteristics<sup>b</sup>, n=2,120**

Characteristics	Participants n=1,588	Non- participants n=532	Effect- size <sup>c</sup>
Sex of the child, No. (%)			-0.22 <sup>d</sup>
Female	818 (51.51)	222 (41.73)	
Male	770 (48.49)	310 (58.27)	
Maternal immigration status, No. (%)			-0.63 <sup>d</sup>
Nonimmigrant	1453 (91.50)	412 (77.44)	
Immigrant	134 (8.50)	119 (22.36)	
Paternal immigration status, No. (%)			-0.47 <sup>d</sup>
Nonimmigrant	1330 (83.75)	376 (70.68)	
Immigrant	145 (9.13)	96 (18.05)	
Maternal age at childbirth, Mean (SD)	29.26 (5.25)	29.43 (5.16)	0.03
Paternal age at childbirth, Mean (SD)	32.21 (5.52)	32.42 (5.99)	0.04
Family status, No. (%)			0.02
Intact	1109 (69.84)	199 (37.41)	
No intact	336 (21.16)	58 (10.90)	
Mean family socioeconomic status from 5 months to 5 years <sup>e</sup> , Mean (SD)	0.01 (0.98)	-0.17 (0.97)	-0.19 <sup>d</sup>

<sup>a</sup> Correspond to the sample used to build ADHD (Attention Deficit Hyperactivity Disorder)-Irritability trajectories (n=1,588)

<sup>b</sup> Data are courtesy of the Quebec Institute of Statistics

<sup>c</sup> Calculated as success rate difference. P values are based on  $\chi^2$  test for categorical variables and ANOVA for continuous variables

<sup>d</sup>  $p < 0.001$

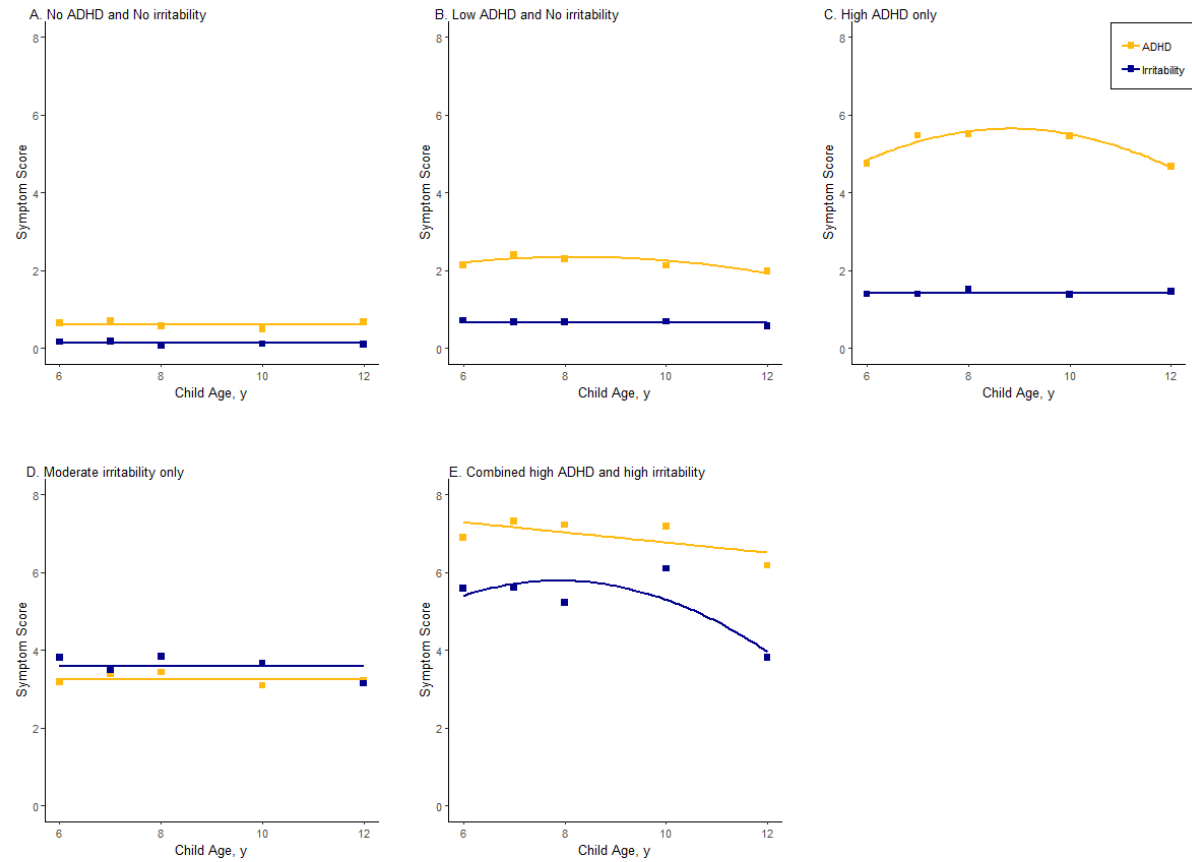
<sup>e</sup> Assessed with an aggregate of 5 items regarding parental educational level, parental occupation, and annual gross income (range, -3 to 3, centered at 0, with higher scores indicating higher socioeconomic status)



### 3.2. Estimating childhood ADHD and irritability profiles

The model with 5 profiles, shown in Figure 1, presented the best compromise between statistics and interpretability. The no ADHD/no irritability was merged with low ADHD/no irritability profile to form the reference group (n=1,057, 66.6% of the study sample) as they did not seem to be clinically problematic. The pathological profiles considered were a moderate irritability profile only (n= 180, 11.3%), a high ADHD profile only (n=220, 13.9%) and a high ADHD/high irritability profile (n=131, 8.2%). The fit indices of the model included a -17,339.73 log-likelihood, a - 17,424.47 BIC, an 0.80 entropy (classification is considered of good quality if > 0.70) and 16.01 mean odds of correct classification (meaning that the model chosen classifies 16.01 times better the participants than a classification by chance, it is considered as adequate if >5.0).

Table 2 shows the socio demographic characteristics of the participants according to their ADHD and irritability profile. The reference group had a higher rate of females, older mothers, a higher rate of intact families and a higher socioeconomic status than all the pathological profiles, whereas the high ADHD/high irritability profiles had higher rates of males and non-intact families, younger mothers at birth and a lower socioeconomic status than all the other profiles (p <0.001).



**Figure 1. Multi-trajectories of childhood attention deficit hyperactivity disorder and irritability, (ELDEQ cohort, n=1,588)**

Each column represents a different profile in the multitrajectory model and is defined by the trajectory of attention deficit hyperactivity disorder and irritability at 6, 7, 8, 10, and 12 years of age. Boxes represents observed value, and lines represent the fitted regression slopes. Fit indices of the model include log-likelihood, -17,339.73; Bayesian information criterion, -17,424.47; entropy, 0.80 (ie. quality of classification; adequate if >0.70); and mean odds of correct classification, 16.01 (ie. the model classifies the participants 16.01 times better than classification by chance; adequate if >5.0)

**Table 2. Sample sociodemographic characteristics by childhood profile of ADHD<sup>a</sup> and irritability, n=1,588**

<b>Characteristics</b>	<b>Reference group<sup>b</sup></b> <b>n= (1,057)</b>	<b>Moderate Irritability only</b> <b>n= (180)</b>	<b>High ADHD only</b> <b>n= (220)</b>	<b>High ADHD &amp; High Irritability</b> <b>n= (131)</b>	<b>p<sup>c</sup></b>
Sex of the child, No. (%)					<0.001
Female	653 (61.78)	68 (37.78)	71 (32.27)	26 (19.85)	
Male	404 (38.22)	112 (62.2)	149 (67.73)	105 (80.15)	
Maternal immigration status, No. (%)					0.42
Nonimmigrant	966 (91.39)	161 (89.44)	203 (92.27)	123 (93.89)	
Immigrant	91 (8.61)	19 (10.56)	17 (7.73)	7 (5.34)	
Paternal immigration status, No. (%)					0.84
Non-immigrant	899 (85.05)	146 (81.11)	178 (80.91)	107 (81.68)	
Immigrant	99 (9.37)	18 (10.0)	19 (8.64)	9 (6.87)	
Maternal age at childbirth, Mean (SD)	29.59 (5.19)	29.18 (5.29)	28.77 (5.36)	27.48 (5.13)	<0.001
Paternal age at childbirth, Mean (SD)	32.26 (5.21)	32.28 (6.33)	32.33 (6.10)	31.43 (5.86)	0.47
Family status, No. (%)					<0.001
Intact	787 (74.46)	114 (63.33)	141 (64.09)	67 (51.15)	
No intact	186 (17.60)	43 (23.89)	58 (26.36)	49 (37.40)	
Mean family socioeconomic status from 5 months to 5 years <sup>d</sup> , Mean (SD)	0.14 (1.00)	-0.12 (0.88)	-0.18 (0.91)	-0.45 (0.86)	<0.001

<sup>a</sup> ADHD, Attention Deficit Hyperactivity Disorder

<sup>b</sup> Profiles “No ADHD and No Irritability” and “Low ADHD and No Irritability” were combined and used as the reference group

<sup>c</sup> p values are based on  $\chi^2$  tests for categorical variables and ANOVA for continuous variables

<sup>d</sup> Assessed with an aggregate of 5 items regarding parental educational level, parental occupation, and annual gross income (range, -3 to 3, centered at 0, with higher scores indicating higher socioeconomic status)

### 3.3. Quantifying the association between childhood ADHD and irritability profiles and early life risk factors

The results of the weighted association between the different ADHD and irritability profiles with multiple imputed data are shown in Table 3. Male gender (adjusted OR (aOR): 2.70, 95%CI [2.02-3.60]) and coercive parenting (aOR: 1.57, 95%CI [1.07-2.29]) increased the risk to present a moderate irritability profile compared to the reference group. Whereas a high socioeconomic status (aOR: 0.82, 95%CI [0.68-0.99]) and consistent parenting were protective of belonging to this profile. The high ADHD profile was also related to the male gender (aOR: 3.52, 95%CI [2.67-4.64]) and the socioeconomic status (aOR: 0.78, 95%CI [0.66-0.93]). In addition, non-intact families increased the risk for the child to belong to this profile compared to the reference group (aOR: 1.53, 95%CI [1.10-2.14]). Consistent parenting (OR: 0.88, 95%CI [0.80-0.97]) and overprotection (OR: 1.10, 95%CI [1.04-1.17]) were associated with the high ADHD profile in the univariate analysis but were not maintained when the model was adjusted. Being male multiplied by 7 the risk to belong to the high ADHD/high irritability profile compared to the reference group (aOR: 7.01, 95%CI [4.67-10.54]). This profile was also associated with a non-intact family (aOR: 2.11, 95%CI [1.38-3.22]), coercive parenting (aOR: 1.57, 95%CI [1.02-2.42]), and maternal history of antisocial behavior during adolescence (aOR: 1.44, 95%CI [1.05-1.96]). Having an immigrant mother (aOR: 0.42, 95%CI [0.22-0.80]), a high family socioeconomic status (aOR: 0.59, 95%CI [0.46-0.75]), consistent parenting (aOR: 0.83, 95%CI [0.72-0.95]), parental impact (aOR: 0.90, 95%CI [0.80-1.00]) seemed to be protective factors against belonging to the high ADHD/high irritability profile. These results were mostly consistent with the non-weighted sensitivity analysis (Table 4). Main differences concerned the family socioeconomic status and the coercive parenting that were no longer associated with the moderate irritability profile, and coercive parenting and parental impact aren't associated with the high ADHD/high irritability profile.

**Table 3. Weighted multinomial regression models predicting levels of ADHD<sup>a</sup> and Irritability profiles, (ELDEQ cohort, n=1,588), results on multiple imputed data**

Independent Variables	Childhood profiles					
	Moderate Irritability		High ADHD <sup>a</sup> only		High ADHD <sup>a</sup> & Irritability	
	OR <sub>β</sub> <sup>b</sup> (95% CI)	OR <sub>α</sub> <sup>c</sup> (95% CI)	OR <sub>β</sub> <sup>b</sup> (95% CI)	OR <sub>α</sub> <sup>c</sup> (95% CI)	OR <sub>β</sub> <sup>b</sup> (95% CI)	OR <sub>α</sub> <sup>c</sup> (95% CI)
Male	2.67 (2.02, 3.55)	2.70 (2.02, 3.60)	3.35 (2.56, 4.39)	3.52 (2.67, 4.64)	6.45 (4.37, 9.53)	7.01 (4.67, 10.54)
<b>Social factors</b>						
No intact family	1.59 (1.13, 2.22)	1.32 (0.91, 1.91)	1.76 (1.31, 2.37)	1.53 (1.10, 2.14)	3.23 (2.27, 4.59)	2.11 (1.38, 3.22)
Maternal age at childbirth	0.99 (0.96, 1.01)	1.01 (0.98, 1.04)	0.97 (0.95, 1.00)	1.00 (0.97, 1.03)	0.93 (0.90, 0.96)	0.99 (0.95, 1.02)
Immigrant mother	1.30 (0.89, 1.90)	0.99 (0.64, 1.54)	0.87 (0.58, 1.29)	0.70 (0.44, 1.09)	0.64 (0.37, 1.12)	0.42 (0.22, 0.80)
Mean family socioeconomic status from 5 months to 5 years	0.76 (0.66, 0.88)	0.82 (0.68, 0.99)	0.73 (0.63, 0.83)	0.78 (0.66, 0.93)	0.51 (0.42, 0.61)	0.59 (0.46, 0.75)
<b>Postnatal family factors</b>						
Coercive parenting	2.14 (1.51, 3.02)	1.57 (1.07, 2.29)	1.25 (0.86, 1.80)	0.93 (0.62, 1.38)	2.45 (1.67, 3.59)	1.57 (1.02, 2.42)
Positive parenting	1.45 (1.05, 2.02)	1.31 (0.92, 1.87)	1.08 (0.78, 1.49)	1.07 (0.75, 1.52)	1.60 (1.11, 2.31)	1.52 (1.00, 2.31)
Consistent parenting	0.79 (0.71, 0.87)	0.85 (0.75, 0.95)	0.88 (0.80, 0.97)	0.96 (0.86, 1.07)	0.73 (0.65, 0.82)	0.83 (0.72, 0.95)
Overprotection	1.05 (0.98, 1.11)	0.98 (0.91, 1.05)	1.10 (1.04, 1.17)	1.07 (1.00, 1.15)	1.03 (0.96, 1.11)	0.91 (0.81, 1.00)
Self-efficacy	1.18 (0.89, 1.58)	1.04 (0.76, 1.42)	1.21 (0.92, 1.59)	1.26 (0.94, 1.69)	0.97 (0.69, 1.37)	0.81 (0.55, 1.20)
Parental impact	0.91 (0.84, 0.99)	1.02 (0.92, 1.12)	0.92 (0.85, 1.00)	0.99 (0.90, 1.09)	0.83 (0.76, 0.91)	0.90 (0.80, 1.00)
Mother-child interaction	1.16 (0.86, 1.57)	0.90 (0.65, 1.25)	1.24 (0.94, 1.63)	1.04 (0.77, 1.40)	1.08 (0.76, 1.53)	0.68 (0.46, 1.02)
<b>Parental psychopathology</b>						
Maternal history of antisocial behaviors	1.19 (0.89, 1.59)	1.01 (0.74, 1.37)	1.19 (0.92, 1.55)	1.08 (0.82, 1.42)	1.77 (1.36, 2.32)	1.44 (1.05, 1.96)
Paternal history of antisocial behaviors	1.22 (1.03, 1.45)	1.18 (0.98, 1.41)	1.08 (0.91, 1.27)	1.01 (0.85, 1.21)	1.21 (0.99, 1.48)	1.03 (0.81, 1.29)
Maternal depression	1.49 (1.08, 2.07)	1.12 (0.77, 1.63)	1.09 (0.79, 1.51)	0.88 (0.61, 1.26)	1.61 (1.12, 2.32)	1.05 (0.68, 1.63)
Paternal depression	1.06 (0.90, 1.25)	0.99 (0.83, 1.18)	1.01 (0.87, 1.17)	0.97 (0.83, 1.14)	1.12 (0.94, 1.34)	1.02 (0.83, 1.25)

<sup>a</sup> ADHD, Attention Deficit Hyperactivity Disorder

<sup>b</sup> OR<sub>β</sub><sup>b</sup>, crude Odds Ratios

<sup>c</sup> OR<sub>α</sub><sup>c</sup>, adjusted Odds Ratios

**Table 4. Multinomial regression models predicting levels of ADHD<sup>a</sup> and Irritability profiles, (ELDEQ cohort, n=1,588), results on multiple imputed data**

Independent Variables	Childhood profiles					
	Moderate Irritability		High ADHD <sup>a</sup> only		High ADHD <sup>a</sup> & Irritability	
	OR <sub>β</sub> <sup>b</sup> (95% CI)	OR <sub>α</sub> <sup>c</sup> (95% CI)	OR <sub>β</sub> <sup>b</sup> (95% CI)	OR <sub>α</sub> <sup>c</sup> (95% CI)	OR <sub>β</sub> <sup>b</sup> (95% CI)	OR <sub>α</sub> <sup>c</sup> (95% CI)
Male	2.66 (1.92, 3.69)	2.76 (1.98, 3.86)	3.39 (2.49, 4.62)	3.61 (2.63, 4.96)	6.53 (4.17, 10.21)	7.16 (4.49, 11.42)
<b>Social factors</b>						
Non intact family	1.60 (1.09, 2.34)	1.31 (0.86, 1.99)	1.77 (1.26, 2.48)	1.49 (1.02, 2.18)	3.13 (2.09, 4.68)	1.97 (1.22, 3.19)
Maternal age at childbirth	0.99 (0.96, 1.02)	1.01 (0.97, 1.04)	1.19 (0.43, 3.29)	1.00 (0.97, 1.03)	0.92 (0.89, 0.96)	0.98 (0.94, 1.03)
Immigrant mother	1.25 (0.74, 2.11)	1.01 (0.57, 1.82)	0.89 (0.52, 1.53)	0.74 (0.41, 1.34)	0.60 (0.27, 1.32)	0.40 (0.17, 0.98)
Mean family socioeconomic status from 5 months to 5 years	0.76 (0.64, 0.89)	0.80 (0.65, 1.00)	0.70 (0.60, 0.83)	0.76 (0.62, 0.93)	0.50 (0.41, 0.62)	0.59 (0.44, 0.78)
<b>Postnatal family factors</b>						
Coercive parenting	1.98 (1.30, 3.03)	1.43 (0.90, 2.25)	1.29 (0.84, 2.00)	0.92 (0.58, 1.48)	2.64 (1.69, 4.14)	1.59 (0.95, 2.65)
Positive parenting	1.47 (1.00, 2.15)	1.30 (0.86, 1.97)	1.10 (0.76, 1.61)	1.09 (0.72, 1.64)	1.61 (1.05, 2.47)	1.49 (0.91, 2.43)
Consistent parenting	0.80 (0.70, 0.90)	0.85 (0.74, 0.98)	0.87 (0.77, 0.97)	0.95 (0.83, 1.08)	0.72 (0.62, 0.82)	0.82 (0.69, 0.96)
Overprotection	1.04 (0.96, 1.12)	0.97 (0.89, 1.06)	1.11 (1.04, 1.19)	1.07 (0.99, 1.16)	1.04 (0.95, 1.13)	0.92 (0.82, 1.02)
Self-efficacy	1.27 (0.91, 1.78)	1.14 (0.79, 1.63)	1.26 (0.92, 1.72)	1.32 (0.94, 1.86)	1.04 (0.70, 1.55)	0.86 (0.54, 1.36)
Parental impact	0.91 (0.82, 1.01)	1.01 (0.90, 1.14)	0.91 (0.83, 1.00)	0.98 (0.88, 1.10)	0.81 (0.73, 0.90)	0.89 (0.78, 1.02)
Mother-child interaction	1.12 (0.79, 1.60)	0.88 (0.60, 1.28)	1.23 (0.89, 1.70)	1.00 (0.71, 1.42)	1.11 (0.73, 1.67)	0.69 (0.43, 1.10)
<b>Parental psychopathology</b>						
Maternal history of antisocial behaviors	1.18 (0.85, 1.65)	1.01 (0.71, 1.43)	1.21 (0.90, 1.64)	1.09 (0.79, 1.50)	1.83 (1.35, 2.49)	1.48 (1.04, 2.12)
Paternal history of antisocial behaviors	1.24 (1.03, 1.50)	1.19 (0.98, 1.46)	1.10 (0.91, 1.32)	1.03 (0.84, 1.25)	1.22 (0.98, 1.52)	1.04 (0.81, 1.34)
Maternal depression	1.48 (1.00, 2.20)	1.13 (0.73, 1.75)	1.12 (0.76, 1.65)	0.88 (0.57, 1.35)	1.73 (1.13, 2.67)	1.11 (0.67, 1.85)
Paternal depression	1.07 (0.90, 1.29)	0.99 (0.82, 1.21)	1.01 (0.86, 1.20)	0.97 (0.81, 1.16)	1.13 (0.93, 1.37)	1.01 (0.80, 1.26)

<sup>a</sup> ADHD, Attention Deficit Hyperactivity Disorder

<sup>b</sup> OR<sub>β</sub><sup>b</sup>, crude Odds Ratios

<sup>c</sup> OR<sub>α</sub><sup>c</sup>, adjusted Odds

## 4. Discussion

### 4.1. Main Findings

To our knowledge, this study is the first to highlight different early childhood risk factors of ADHD and irritability profiles between the age 6 and 12 in a population-based cohort. Three pathological profiles were identified (i.e., high ADHD, moderate irritability, and high ADHD/high irritability).

The male gender and a low socioeconomic status were pinpointed as common risk factors across all pathological profiles. These are well-known risk factors of developing externalizing symptoms (37).

Coercive parenting increased the risk to belong to either the moderate irritability or the high ADHD/high irritability profile whereas consistent parenting decreased the risk for both profiles. These results match previous findings. Children presenting with high ADHD symptoms also suffered from emotional dysregulation and reported inconsistent and ineffective parenting in their early school years (38). In addition, negative and ineffective discipline as well as a lack of positive interaction with the child was associated with irritability related mental disorders such as oppositional defiant disorder (39). Of note, parenting practices are a two-way street and are influenced by child disruptive behavior (40). The presence of irritability symptoms in children predicted less positive parenting (41) and maternal hostility was associated with ADHD symptoms (42).

The combined profile as well as the irritability profile were associated to maternal depression in early childhood when considering crude analysis and disappeared after adjusting on the other risk factors. These results are surprising since maternal depression is hypothesized as being a known risk factor for irritability and neurodevelopmental disorders in offspring (43–45). This could be due to either a lack of statistical power or to the measurement of depressive symptoms in mother. Indeed, we considered depressive maternal trajectories and not depressive episodes in specific time frames, therefore probably capturing subclinical depressive symptoms that were not severe enough to impact the child's development.

Interestingly, associations were equivalent or stronger between the above risk factors and the high ADHD/high irritability profile than with any other profile. Out of all the risk factors explored none were specific to the moderate irritability nor the high ADHD profile nor exclusively common to both.

Distinctive protective factors for the high ADHD/high irritability profile were detected such as parental impact and having an immigrant mother. Parents which believe that their behavior influences the development of their child are more prone to present positive parenting which is a known protective factor of externalizing problems (46). Of note, literature is unclear whether having an immigrant mother is associated with the development of ADHD and irritability. The protective factor we found could be the reflection of a confounding variable not taken into account or related to the assertion of irritable and ADHD symptoms. However, this last hypothesis seems rather unlikely given teachers rate equally symptoms of immigrant and non-immigrant children (47). The maternal history of antisocial behavior during adolescence was a distinctive risk factor to belong to the combined profile. Maternal antisocial behaviors (past and present) have been linked to externalizing disorders in offspring. It is hypothesized as being mediated through genetic factors as well as environmental factors such as negative parental behaviors or maternal depression (48–50).

Differences found between the main and the sensitivity analysis are mostly likely due to attrition and the under representation of at-risk families in the study sample. This was dealt with in the main analysis through a reverse weighted ponderation.

#### 4.2. Strengths and Limitations

These results should be interpreted considering the study limitations. First, there is a high attrition rate from the original cohort, and therefore an important risk of selection bias with an underrepresentation of children with high risks of developing psychiatric disorders. This limitation was statistically dealt with by using inverse weighted ponderation in the analysis. Nevertheless, associations might be underestimated, and the results might not be extrapolated to the general population. Second, the questionnaire only reflected the phasic component of irritability (referring to temper outbursts) and overlooked the tonic component (referring to a chronic grumpy mood). These two components are now necessary according to the DSM-5 to diagnose disruptive mood disorder, which defines severe chronic irritability (51). However it has been shown that the phasic and tonic components of irritability can be interchangeable in the general population (52). Third, the ADHD and irritability symptoms were rated by the child's teacher which informs on his behavior at school but not at home. This could have led to underestimate the occurrence of irritability symptoms in the population since it has been shown that irritability can be confined to only one setting (53). However, teachers seem to be as prone as parents to detect deviation from normal behaviors when considering externalized symptoms (54,55), probably because of their daily interaction with children of the same age. Moreover, irritability and ADHD symptoms were assessed by a different teacher at each wave



thus, reducing rater bias. In the future, studies should consider assessing symptoms through parent and teacher questionnaires to have a broad perspective of the child's behavior in different settings. Fourth, parenting behaviors were mostly rated through a self-administrated questionnaire by the PMK which was mostly the biological mother possibly introducing social desirability bias. Combined paternal, maternal but also external observer data could give a more precise overview of parental practices concerning the child.

A strength of this study is the concurrent prospective assertion of ADHD and irritability symptoms in children from the age of 6 to 12 years in a population-based cohort. Moreover, the prospective collection of data limited memory bias considering parental psychopathology and parenting behavior. A major innovation is the simultaneous modelling of ADHD and irritability symptoms. Finally, ADHD and irritability were assessed through symptom scales rather than clinical tools. Furthermore, a dimensional approach is particularly accurate to define ADHD (12) and irritability (14) symptoms and search for their risk factors as advised by the NIMH through the RDoC (56).

### 4.3. Implications

As shown in this study, several risk factors overlap two or three of ADHD and irritable profiles. This advocates for the use of dimensional constructs such as RDoC when exploring risk factors. Especially when considering irritability and ADHD symptoms as a continuum between pathological and physiological, differing in degree rather than in kind. The study of joint symptomatology could give insight into etiological mechanisms and common risk factors.

From a public health point of view, this could be particularly efficient in view of prevention campaign, as targeting one specific risk factor could prevent several pathologies. Campaigns concerning parenting practices and their impact on child development could therefore be profitable.

From an individual point of view, acknowledging heterogeneity in ADHD and irritability symptoms could lead to precise medicine and specific patient care (57). As some risk factors seem specific to the most severe profile, it could help practitioners to be particularly attentive to children bearing them and treat them early on if necessary. Therefore, irritability symptoms should systematically be explored when assessing ADHD symptoms. Especially since the co-occurrence of ADHD and irritability symptoms seems to represent a specific subgroup which predicts severe opposition and anxiety symptoms (58) as well as more severe impairment and

outcome (10). This subgroup could benefit from personalized treatment, combining for example a pharmacological treatment with psychosocial intervention (5,59).

## 5. Conclusion

This study suggests that the combined ADHD irritability profile accumulates its own risk factors with the two other pathological profiles' risk factors. Although a direct causal effect between early childhood parenting behaviors and ADHD and irritability profiles has yet to be proven, the association should be taken into consideration when treating young children. If this study's associations were confirmed through other research studies, campaigns aiming the improvement of parenting methods in general population could be an important leverage in preventing child psychopathology.

## 6. Declaration of interest

None

## 7. References

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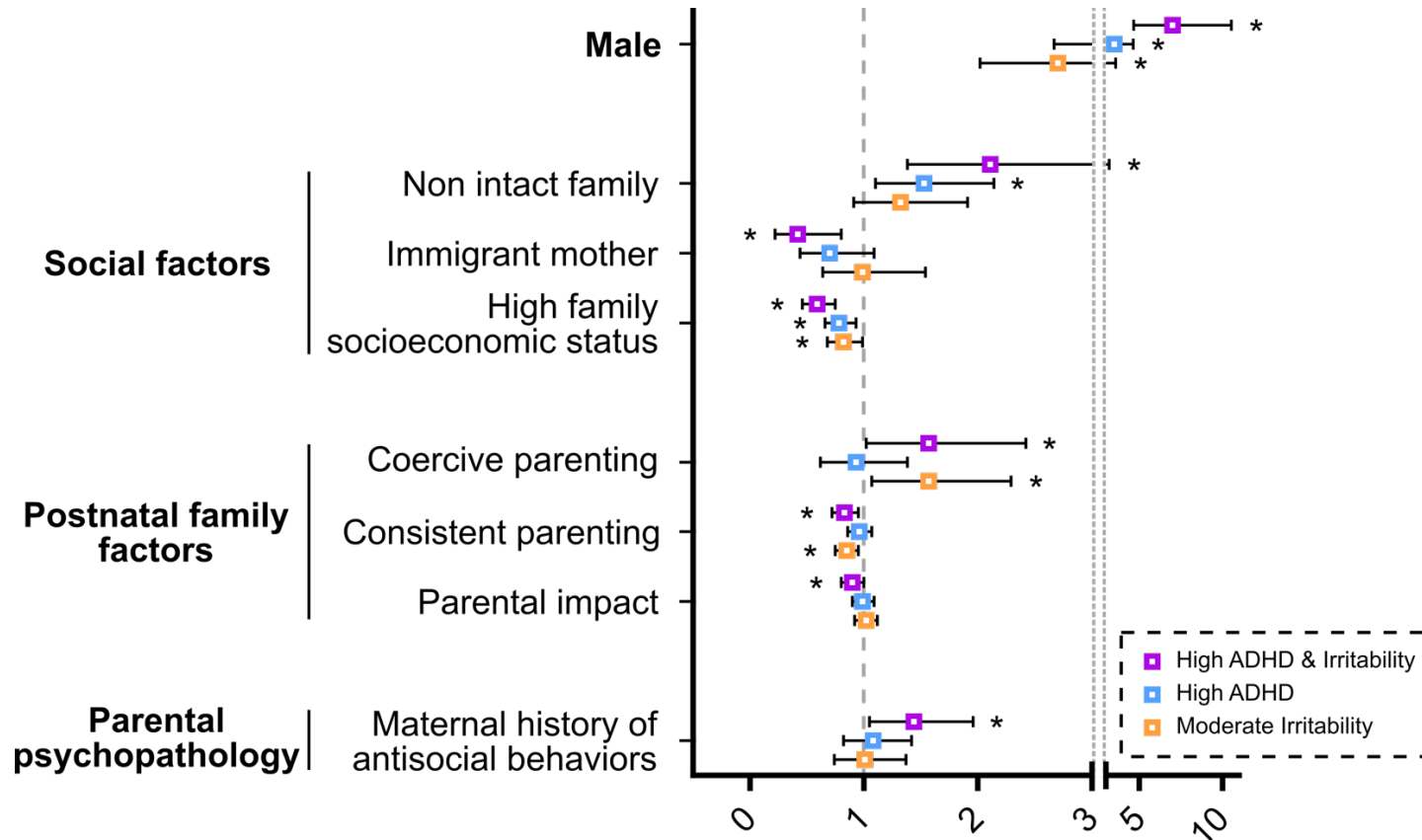
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# Annexe



**Figure. Forest plot representing associations between environmental risk factors and irritability and attention deficit hyperactivity disorder (ELDEQ cohort, n=1,588)**

Abbreviations: ADHD : Attention Deficit Hyperactivity Disorder

\* association statistiquement significative (p<0.05)

## LE SERMENT D'HIPPOCRATE

“Au moment d’être admis(e) à exercer la médecine, je promets et je jure d’être fidèle aux lois de l’honneur et de la probité.

Mon premier souci sera de rétablir, de préserver ou de promouvoir la santé dans tous ses éléments, physiques et mentaux, individuels et sociaux.

Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions. J’interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou leur dignité.

Même sous la contrainte, je ne ferai pas usage de mes connaissances contre les lois de l’humanité.

J’informerai les patients des décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n’exploiterai pas le pouvoir hérité des circonstances pour forcer les consciences.

Je donnerai mes soins à l’indigent et à quiconque me les demandera. Je ne me laisserai pas influencer par la soif du gain ou la recherche de la gloire.

Admis(e) dans l’intimité des personnes, je tairai les secrets qui me seront confiés.

Reçu(e) à l’intérieur des maisons, je respecterai les secrets des foyers et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances. Je ne prolongerai pas abusivement les agonies. Je ne provoquerai jamais la mort délibérément.

Je préserverai l’indépendance nécessaire à l’accomplissement de ma mission. Je n’entreprendrai rien qui dépasse mes compétences. Je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J’apporterai mon aide à mes confrères ainsi qu’à leurs familles dans l’adversité.

Que les hommes et mes confrères m’accordent leur estime si je suis fidèle à mes promesses ; que je sois déshonoré(e) et méprisé(e) si j’y manque.”

## Facteurs de risques environnementaux précoces et trajectoires développementales d'irritabilité et du trouble du déficit de l'attention avec ou sans hyperactivité

### Résumé :

**Introduction :** L'irritabilité est fréquemment associée au trouble du déficit de l'attention hyperactivité (TDAH). Leur comorbidité est liée à une symptomatologie plus sévère et à un plus grand retentissement fonctionnel. D'où l'importance d'étudier leurs variations développementales conjointement afin d'identifier des facteurs de risques spécifiques qui pourraient être la cible de campagnes de prévention. Cette étude explore l'association entre les facteurs de risques environnementaux précoces et le développement de trajectoires de TDAH et d'irritabilité à partir des données d'une cohorte.

**Méthodes :** Les données sont issues de la cohorte étude longitudinale du développement des enfants du Québec qui a suivi 1588 enfants de leurs 5 mois à leurs 12 ans. Les facteurs sociaux, les comportements parentaux, et la psychopathologie parentale ont été considérés comme des facteurs de risques potentiels. Le comportement de l'enfant était évalué annuellement par un enseignant entre ses 6 et ses 12 ans. Les trajectoires de TDAH et d'irritabilité ont été estimées par des modèles de trajectoires multiples. Des modèles de régression multinomiale ont été estimés.

**Résultats :** Quatre trajectoires ont été estimées : une physiologique (pas de TDAH/pas d'irritabilité) et trois pathologiques (irritabilité modérée, TDAH élevé, et TDAH élevé/irritabilité élevée). Par rapport au groupe de référence, le groupe combiné était associé au sexe masculin (Odds Ratio ajusté (ORa)=7.01, Intervalle de confiance 95% (IC95%)[4.67-10.54]), aux familles non-intactes (ORa=2.11, IC95%[1.38-3.22]), aux pratiques parentales hostiles (ORa=1.57, IC95%[1.02-2.42]), aux pratiques parentales conséquentes (ORa=0.83, IC95%[0.72-0.95]), à l'impact parental (ORa=0.90, IC95%[0.80-1.00]) et aux antécédents maternels de comportements antisociaux (ORa=1.44, IC95%[1.05-1.96]).

**Conclusion :** Des campagnes de prévention visant les comportements parentaux devraient être envisagées afin de prévenir les troubles pédopsychiatriques.

**Mots clés :** Irritabilité, TDAH, Facteurs de risque

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## Early life environmental risk factors of developmental profiles of childhood attention-deficit hyperactivity disorder and irritability

### Abstract:

**Introduction:** Irritability is frequently related with attention deficit hyperactivity disorder (ADHD). Their combination predicts more severe symptoms and greater impairment in children. Therefore, it seems important to study their developmental variations jointly and to highlight specific risk factors which can be modified through preventive public health campaigns. The aim of this study is to explore the association between early childhood environmental risk factors and irritability and ADHD developmental trajectories from a population-based cohort.

**Methods:** Data was collected from the Quebec Longitudinal Study of Child Development that followed 1588 children from 5 months to 12 years of age. Social factors, parenting behaviors and parental psychopathology were considered as potential risk factors. The child's behavior was rated by its schoolteacher yearly between the age of 6 and 12 years old. Developmental trajectories of ADHD and irritability were estimated through multitrajectory modeling. Multinomial regression analyses were carried out to estimate association between risk factors and developmental trajectories.

**Results:** Four trajectories were estimated: one low ADHD/low irritability which was considered as physiological and three pathological trajectories (moderate irritability, high ADHD, and high irritability/high ADHD). Compared to the reference group, the combined profile was associated with male gender (adjusted Odds Ratio (aOR) = 7.01, 95% Confidence Interval (95%CI)[4.67-10.54]), non-intact families (aOR = 2.11, 95%CI [1.38-3.22]), coercive parenting (aOR=1.57, 95%CI [1.02-2.42]), consistent parenting (aOR = 0.83, 95%CI [0.72-0.95]), parental impact (aOR = 0.90, 95%CI [0.80-1.00]) and maternal history of antisocial behavior in adolescence (aOR = 1.44, 95%CI [1.05-1.96]).

**Conclusion:** Public health campaigns targeting parenting behaviors should be considered to prevent severe child psychopathology.

**Keywords :** ADHD, Irritability, risk factors