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Developmental profiles of childhood attention-deficit/hyperactivity disorder and irritability: association with adolescent mental health, functional impairment, and suicidal outcomes

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Cédric Galéra, Massimiliano Orri, Francis Vergunst, Maria Melchior, Judith van Der Waerden, et al.. Developmental profiles of childhood attention-deficit/hyperactivity disorder and irritability: association with adolescent mental health, functional impairment, and suicidal outcomes. *Journal of Child Psychology and Psychiatry*, In press, 10.1111/jcpp.13270 . hal-02888482

HAL Id: hal-02888482

<https://hal.sorbonne-universite.fr/hal-02888482>

Submitted on 7 Jul 2020

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2 **Developmental Profiles of Childhood Attention Deficit/Hyperactivity Disorder (ADHD) and**
3 **Irritability: Association with Adolescent Mental Health, Functional Impairment and Suicidal**
4 **Outcomes**
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50 **Number of words:** 5439

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ACKNOWLEDGMENTS

Dr Orri reports receiving a postdoctoral research fellowship from the Canadian Institutes of Health Research (CIHR). Dr Vergunst is funded by a Fonds de Recherche du Québec Santé (FRQS) postdoctoral fellowship. Drs Boivin and Tremblay report holding a Canada Research Chair in Child Development funded by the CIHR. Dr Côté reports being a research fellow of the Fonds de Recherche du Québec. Dr Tremblay reports being funded by the Canadian Institute of Advanced Research. All other authors declare no competing interests. Dr Bouvard has received financial support for the organization of and attendance at scientific meetings and was also the principal investigator in clinical trials for the pharmaceutical industry.

CONTRIBUTORS

CG contributed to the literature search, data analysis, data interpretation, and writing. MO contributed to the data analysis, data interpretation and writing. FV contributed to the data interpretation and writing. MM contributed to the data interpretation and writing. OC contributed to the data analysis, data interpretation, and writing. MPB contributed to the data interpretation and writing. JYW contributed to the data interpretation and writing. MPB contributed to the data interpretation and writing. MB contributed to the study design, data collection, data interpretation and writing. RET contributed to the study design, data collection, data interpretation and writing. SMC contributed to the study design, data collection, data analysis, data interpretation and writing. SMC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

FUNDING/SUPPORT

The larger Québec Longitudinal Study of Child Development was supported by the Québec Government's Ministry of Health, Ministry of Education, and Ministry of Family Affairs, The Lucie and André Chagnon Foundation, the Robert-Sauvé Research Institute of Health and Safety at Work, and the Québec Statistics Institute. Additional funding was received from the Fonds de Recherche du Québec–Santé, the Fonds de Recherche du Québec–Société et Culture, Canada's Social Science and Humanities Research Council, the Canadian Institutes of Health Research, and the St. Justine Research Center.

ROLE OF THE FUNDER/SPONSOR

Québec Statistics Institute collected data. The sponsors had no role in the design and conduct of the study; management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

KEY POINTS

What's known: The high frequency of irritability in ADHD makes the combination of ADHD and irritability a phenotype particularly likely to be associated with greater severity in terms of psychiatric outcomes. However, there is a lack of large longitudinal studies from the general population describing the long-term covariations of ADHD and irritability during childhood and quantifying the associations with a wide range of psychiatric, functional impairment and suicidal outcomes during adolescence.

What's new: This study describes for the first time the developmental course of ADHD and irritability symptoms over 6 years, providing a graphical representation of the developmental heterogeneity. It shows that children with the combined ADHD/irritability phenotype are more likely to show externalizing, internalizing, functional impairment and suicidal outcomes during adolescence than children with moderately high ADHD or with moderately high irritability or low ADHD and irritability.

What's clinically relevant: Childhood irritability in ADHD is stable over time and the combined phenotype is a meaningful predictor of a broad array of clinical difficulties during adolescence. Clinicians should systematically track irritability when assessing ADHD and treat this dimension specifically with the aim of improving long-term outcomes.

ABSTRACT

Background: Irritability is frequently comorbid with ADHD. Although irritability alone has been linked to deleterious mental health and adaptive issues, the joint developmental course of ADHD and irritability symptoms during childhood as well as its association with later mental health and suicidal outcomes is not fully understood. We aimed to describe the developmental trajectories of childhood ADHD and irritability symptoms and to quantify their association with adolescent mental health and suicidal outcomes.

Methods: The Quebec Longitudinal Study of Child Development (QLSCD) included 1407 participants from the general population followed up from age 5 months to 17 years. We used a multi-trajectory approach to identify developmental trajectories of childhood (6-12 years) ADHD and irritability symptoms. Outcome measures were adolescent (13-17 years) mental health (psychiatric symptoms/functional impairment) and suicidal outcomes.

Results: We identified distinct developmental profiles: combined absent or very low ADHD and absent or very low irritability (940 [66.8%]; reference group), moderately high irritability and low ADHD (158 [11.2%]), moderately high ADHD and low irritability (198 [14.1%]) and combined high ADHD and high irritability (111 [7.9%]). Multivariate modeling showed that, compared to children in the reference group, those in the combined high ADHD and high irritability profile showed higher levels of ADHD continuity (d ranges=0.40-0.50), externalizing (d ranges=0.25-0.59), internalizing (d ranges=0.20-0.29), and functional impairments (d ranges=0.17-0.48) and suicidal behaviors (Odds Ratio (OR)=2.12, Confidence Interval (CI)=1.47-3.06) in adolescence.

Conclusions: The presence of persistently high levels of irritability along with ADHD symptoms during childhood significantly predict adolescent ADHD continuity, externalizing, internalizing and suicidal outcomes. Systematic consideration of irritability when assessing and treating ADHD may improve long-term mental health outcomes.

Keywords: ADHD, Irritability, Mental health problems, Suicide, Functional impairment.

INTRODUCTION

Attention Deficit/Hyperactivity Disorder (ADHD) is a common and impairing behavioral condition defined by developmentally inadequate levels of inattention and hyperactivity-impulsivity. Whether or not emotional symptoms should be included in the core ADHD features has been largely debated. Although this option was not chosen in the latest nosographic classification (DSM-5), the relevance of the emotional dimension of ADHD remains the focus of active scientific/clinical research. 25 to 45% of youths with ADHD display disproportionately high levels of emotional symptoms (Shaw, Stringaris, Nigg, & Leibenluft, 2014), which encompass a broad range of clinical features including emotional lability, impulsivity and dysregulation, and the concept of irritability (Faraone et al., 2019; Shaw et al., 2014; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016).

From the clinician's perspective, irritability represents the most relevant emotional symptom to address. First, irritability is related to frequent requests for help due to the significant burden for the youth and the family. Second, it is clearly defined in the DSM-5 (American Psychiatric Association, 2013), which clarifies its clinical features and makes inter-rater reliability more accurate. Notably, irritability is characterized by frequent temper outbursts typically occurring in response to frustration and can be verbal or behavioral (i.e. aggression against property, self, or others). It is an observable behavior during interactions between children and their peers, teachers, and parents (Althoff, Verhulst, Rettew, Hudziak, & van der Ende, 2010). Third, the combination of ADHD and irritability could mark a more severe entity, given its correlations with poorer outcomes and long-term impairments (Ambrosini, Bennett, & Elia, 2013; Anastopoulos et al., 2011; Biederman et al., 2012; Eyre et al., 2017, 2019; Faraone et al., 2019; Lee et al., 2018; Seymour, Chronis-Tuscano, Iwamoto, Kurdziel, & Macpherson, 2014; Surman et al., 2013; Wakschlag et al., 2015).

From the researcher's perspective, ADHD and irritability share neuropsychological, neural, genetic and environmental commonalities (Ambrosini et al., 2013). First, at a neuropsychological level, the association between irritability and ADHD may stem from a broad deficit in emotional self-regulation (Bunford, Evans, & Langberg, 2018; Faraone et al., 2019; Shaw et al., 2014). Second, additional altered neuropsychological mechanisms described in ADHD (e.g. metacognition/executive functioning/motivation) (Faraone et al., 2019; Shaw et al., 2014), may be at play to jeopardize emotional regulation. Third, at the neural level, neuroimaging research suggests the involvement of cortical (i.e. orbitofrontal/prefrontal) and subcortical (i.e.

1 amygdala/ventral striatum) structures/networks (Faraone et al., 2019; Pagliaccio et al., 2017; Shaw
2 et al., 2014) in both ADHD and irritability. Finally, shared environmental (e.g. coercive parenting)
3 and biological (e.g. genetic) risk factors may also explain the overlap between ADHD and
4 irritability (Barkley, 2015; Shaw et al., 2014).
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9 Prior research in this area has faced at least two kinds of limitation. First, the comorbid
10 ADHD/irritability phenotype has often been poorly defined and constructed. Varying definitions of
11 emotional symptoms and the lack of longitudinal appraisal hampered the ability to measure
12 adequately covariations in ADHD and irritability symptoms as a function of time. Second, few
13 studies have assessed the joint contribution of ADHD and irritability because they did not
14 discriminate between individuals presenting with one or both dimensions. Thus, while the
15 independent effect of ADHD and irritability has been examined, whether comorbid
16 ADHD/irritability during the elementary school years predicts adolescent mental health, especially
17 when compared to ADHD without irritability, has been insufficiently investigated. Yet
18 understanding the developmental psychopathological sequences is key to clinical comprehension
19 and to the effective implementation of screening/preventive measures (Brotman, Kircanski, &
20 Leibenluft, 2017; Shaw et al., 2014; Vidal-Ribas et al., 2016).
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29 The aim of the present study was to overcome previous limitations by (1) identifying longitudinal
30 profiles of ADHD and irritability symptoms during childhood, and (2) examining their associations
31 with subsequent mental health problems, functional impairment, and suicidal behaviors during
32 adolescence. We used a large birth cohort prospectively followed up for 17 years and applied multi-
33 trajectory modeling to capture the overlap between childhood ADHD and irritability.
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Participants and procedure

43 Data were drawn from the Quebec Longitudinal Study of Child Development (QLSCD), which was
44 approved by the Quebec Statistics Institute and the St. Justine Hospital Research Center ethics
45 committees. Participants were selected from the Quebec Birth Registry and stratified on birth
46 rate/living area. Families were included if the pregnancy lasted 24-42 weeks and the mother could
47 speak French or English. Data were collected by the Quebec Statistics Institute. Follow-up was
48 conducted yearly during childhood and biyearly during adolescence. From 5 months to 13 years,
49 trained interviewers collected data about parental, family, and child characteristics during home
50 interviews conducted with the person most knowledgeable about the child (the mother in 98% of
51 cases). Youths' behaviors were rated by teachers from 6 to 12 years and were self-reported from 13
52 to 17 years. Written informed consent was obtained from all the participants. The initial
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2 representative sample comprised 2120 infants born in the Canadian province of Quebec in
3 1997/1998. The information used to conduct the study relied on children's hyperactivity-
4 impulsivity/inattention and irritability symptoms (6 to 12 years) and subsequent mental health
5 problems (15 and 17 years), resulting in a sample of 1407 participants. The included and not
6 included samples were similar except for child's sex and socioeconomic status (**Table 1**).
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10 11 12 **Measures**

13 14 **Teacher Ratings of Childhood ADHD and Irritability Symptoms**

15 School teachers rated children on the Behavior Questionnaire at 6, 7, 8, 10, and 12 years. This
16 questionnaire, created for the Canadian National Longitudinal Study of Children and Youth
17 (*Statistics Canada. Longitudinal Survey of Children and Youth (NLSCY).*, 2009), includes items
18 from the Child Behavior Checklist(Achenbach, Edelbrock, & Howell, 1987), the Ontario Child
19 Health Study Scales (Offord, Boyle, & Racine, 1989), and the Preschool Behavior Questionnaire
20 (Tremblay, R. E., s. d.). ADHD symptoms (i.e. hyperactivity-impulsivity and inattention) were
21 evaluated using nine items ($\alpha=.84-.88$): "could not sit still, was restless or hyperactive," "couldn't
22 stop fidgeting," "was unable to wait when someone promised him/her something," "was impulsive,
23 acted without thinking," "had difficulty waiting his/her turn in games," "couldn't settle down to do
24 anything for more than a few moments," "was unable to concentrate, could not pay attention for
25 long," "was easily distracted, had trouble sticking to any activity," "was inattentive". Items were
26 rated using a 3-point Likert scale according to the frequency of the behavior during the past 6
27 months (0=never/1=sometimes/2=often). The child's behavior was assessed by a different teacher at
28 each wave, thus reducing rater bias. At all points, the ADHD score was built by calculating the
29 mean of the items. The score was standardized (range:0-10).
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32 Teachers evaluated irritability symptoms using four items ($\alpha=.94-.97$) (Orri et al., 2019; Orri,
33 Galera, et al., 2018): "had temper tantrums or hot temper", "reacted in an aggressive manner when
34 teased", "reacted in an aggressive manner when contradicted", "reacted in an aggressive manner
35 when something was taken away from him/her". At all points, the irritability score was built by
36 summing the first item (temper tantrum) with the mean of the other three items, as they assessed the
37 same behavior (reacting in an aggressive manner) in three different situations. The score was
38 standardized (range:0-10).
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42 43 44 **Adolescents' Mental Health and Suicidal Outcomes**

45 Adolescents filled in the Mental Health and Social Inadaptation Assessment for Adolescents (MIA)
46 which reflects the DSM-5 symptoms and shows good validity and reliability (Côté et al., 2017).
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2 The MIA included: 1) psychiatric symptoms (a) internalizing (social phobia/generalized
3 anxiety/depression), b) externalizing (oppositional defiant disorder/conduct
4 disorder/psychopathy/delinquency/contact with police/aggression), c) ADHD (hyperactivity-
5 impulsivity/inattention)), d) eating disorders and 2) functional impairment
6 (behavior/anxiety/depression/total). Mental health outcomes were assessed at ages 15 and 17 and
7 the final scores were averaged across these two data points.
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9 Suicidal outcomes included suicidal ideation and suicide attempt assessed at ages 13, 15, and 17
10 years. Adolescents were asked, “In the past 12 months, did you ever seriously think of attempting
11 suicide?” and if so, “How many times did you attempt suicide?”. The variable lifetime suicidality
12 (i.e. reporting ≥ 1 serious suicide ideation or attempt at 13, 15, or 17 years) was derived.
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20 21 **Data analysis**

22 **Estimating childhood ADHD and Irritability Profiles**

23 We estimated developmental trajectories of ADHD and irritability symptoms from 6 to 12 years
24 using multi-trajectory modeling (Nagin, Jones, Passos, & Tremblay, 2018). The multi-trajectory
25 modeling method is a person-oriented approach that allows groups of individuals who share similar
26 attributes to be identified. This application makes it possible to model the trajectories of multiple
27 dimensions jointly using semi-parametric mixture models, and to identify different profiles defined
28 by the joint development of symptoms across childhood. By identifying latent clusters of
29 individuals following similar trajectories across multiple dimensions, multi-trajectory modeling
30 allowed us to describe the overlap between ADHD and irritability symptoms. Parameters were
31 estimated using maximum likelihood estimation by a Newton-Raphson optimization algorithm and
32 censored-normal modeling. The selection of the best model in terms of number of groups and
33 polynomial order of the trajectories was based on interpretability and statistics including several fit
34 indices (log-likelihood/Bayesian information criterion/entropy/mean odds of correct classification).
35 The assignment of each participant to a specific profile was based on the highest posterior
36 probability.
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50 **Quantifying the Associations between Childhood ADHD and Irritability Profiles and** 51 **Adolescent Mental Health and Suicidal Outcomes**

52 In order to provide a broad picture regarding the possible mental health outcomes associated with
53 the ADHD and irritability profiles, we conducted a series of regression models. We used linear
54 regression models to estimate the associations of childhood ADHD and irritability profiles with
55 adolescent mental health problems, the reference being the profile with the lowest level of
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1 symptoms, and β representing the change in the mental health score (range:0-10) as a function of
2 the profile. We used logistic regression models to estimate the associations between childhood
3 profiles and suicidal outcomes (odds ratios (ORs) with their 95% confidence intervals (CI)). We
4 conducted all the analyses using inverse probability weighting to handle sample attrition (based on
5 key variables significantly associated with attrition). The objective of this analysis was to weight
6 observations, taking into account the fact that individuals with certain characteristics are more likely
7 to be missing at follow-up, thus compromising the generalizability of the results with respect to the
8 initial cohort sample. We applied the Benjamini-Hochberg procedure (Benjamini, 2010) to correct
9 for multiple testing. We computed Cohen's d as a measure of effect sizes. All the estimates were
10 standardized. **We systematically adjusted on child's sex, family socioeconomic status, maternal
11 age at childbirth, no intact family, maternal and paternal hostile-reactive parenting score,
12 maternal depression, maternal and paternal antisociality in adolescence.** We tested sex \times profile
13 interactions. We conducted further secondary analyses: 1) stratifying by sex, independently from
14 the significance of interaction, given the underpower of interaction testing in multivariate modeling
15 and the large sex differences in mental health/suicidal outcomes (Schrijvers, Bollen, & Sabbe, 2012;
16 Zahn-Waxler, Klimes-Dougan, & Slattery, 2000); 2) comparing profiles with one another to explore
17 whether the distinct profiles differed. Finally, we conducted sensitivity analyses without inverse
18 probability weights.

34 RESULTS

35 Estimating Childhood ADHD and Irritability Profiles

36 The study included 1407 children followed up to 17 years of age (742 (52.7%) females and 665
37 (47.3%) males). The model with five profiles was chosen because it represented the best
38 compromise in terms of both statistics and interpretability, compared to the alternatives (**eTable 1**).
39 This model is shown in **Figure 1**: (A) no ADHD and no irritability (401 [28.5%]), (B) very low
40 ADHD and very low irritability (539 [38.3%]), (C) moderately high ADHD and low irritability (198
41 [14.1%]), (D) moderately high irritability and low ADHD (158 [11.2%]), and (E) combined high
42 ADHD and high irritability (111 [7.9%]). Fit indices of the model were good: log-likelihood=-
43 17,336.34; BIC=-17,424.77; entropy=0.79 (adequate if >0.70); mean odds of correct
44 classification=16.01 (adequate if >5.0). The combined profile displayed the highest levels of both
45 ADHD and irritability symptoms. Profiles 1 and 2 were merged to build a reference group showing
46 no/very low levels of both ADHD and irritability, thus likely to correspond to a clinically non-
47 problematic group (940 [66.8%]). Individual and family characteristics of each profile are presented
48 in **Table 2**. When compared to the reference group, children with high ADHD and high irritability
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2 were more likely to be male, to have low socioeconomic status, younger mothers, depressed
3 mothers, maternal and paternal adolescent antisociality, to come from non-intact families, and to be
4 exposed to hostile-reactive parenting (all $p < 0.01$). The distribution of adolescent mental health
5 problems and suicidal outcomes by childhood profile of ADHD and irritability by sex is presented
6 in **eTable 2**.
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10 11 12 **Quantifying the Associations between Childhood ADHD and Irritability Profiles and** 13 **Adolescent Mental Health and Suicidal Outcomes**

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15 **Table 3** reports the weighted associations between childhood profiles, adolescent psychiatric
16 symptoms, suicidal outcomes, and adolescent functional impairment in the whole sample. The
17 **combined high ADHD and high irritability profile** was consistently associated with higher risk
18 levels of adolescent psychiatric symptoms (i.e. internalizing, ADHD, externalizing), suicidal
19 outcomes, and functional impairments due to behavior, anxiety, depression, and total score
20 symptoms compared to the reference group. Effect sizes ranges were: $d = 0.20-0.29$ for internalizing
21 symptoms, $d = 0.40-0.50$ for ADHD symptoms, $d = 0.25-0.59$ for externalizing symptoms, $d = 0.17-$
22 0.48 for functional impairment. The increase in the odds of suicidal outcomes was more than two-
23 fold higher (when compared to the reference group). The **moderately high ADHD and low**
24 **irritability profile** was weakly associated with adolescent ADHD symptoms ($d = 0.10-0.32$)
25 externalizing symptoms ($d = 0.06-0.23$), suicidal outcomes ($OR = 1.50$), and functional impairment
26 ($d = 0.02-0.20$). The **moderately high irritability and low ADHD profile** was weakly associated
27 with the outcomes in terms of effect sizes and number of outcomes. It was associated with
28 adolescent ADHD symptoms ($d = 0.14-0.22$), externalizing symptoms ($d = -0.03-0.24$), and functional
29 impairment ($d = 0.11-0.25$).
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33 **eTable 3** displays the weighted associations between childhood profiles, adolescent psychiatric
34 symptoms, suicidal outcomes, and adolescent functional impairment stratified by sex. The
35 **combined high ADHD and high irritability profile** was consistently associated with higher risk
36 levels of adolescent psychiatric symptoms, suicidal outcomes, and functional impairments due to
37 anxiety, depression, and total score symptoms compared to the reference group, both in females and
38 in males. In females, effect sizes were large for delinquency and contact with police, and
39 aggression. The **moderately high ADHD and low irritability profile** was weakly associated with
40 adolescent ADHD symptoms (in males and females), externalizing symptoms (in males), and
41 suicidal outcomes (in males). The **moderately high irritability and low ADHD profile** was
42 associated with adolescent ADHD symptoms (in males), externalizing symptoms (in females), and
43 suicidality (in males) and total functional impairment (in females). In females, it was also associated
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2 with functional impairment due to behavior, anxiety, depression.

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4 **eTable 4** shows the associations between childhood profiles and adolescent outcomes using
5 different reference categories. The **combined high ADHD and high irritability profile** was
6 significantly associated with more severe psychiatric (internalizing, externalizing and ADHD)
7 symptoms and functional impairment, when compared to the two other groups (i.e. moderately high
8 ADHD and low irritability/moderately high irritability and low ADHD). We found significant
9 sex×profile interactions regarding social phobia, suicidality and the functional impairment scale for
10 depression. Results were robust to attrition in unweighted sensitivity analyses (**eTable 5**).
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19 DISCUSSION

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21 To our knowledge, this is the first investigation of the developmental pattern of ADHD and
22 irritability over a period of 6 years during childhood and its associations with mental health,
23 functional impairment and suicidal outcomes during adolescence. We identified different clusters of
24 symptom evolution (i.e. combined high ADHD/irritability, moderately high ADHD and low
25 irritability, moderately high irritability and low ADHD, and two clusters of no/very low levels of
26 ADHD/irritability) and showed that the children in the combined high ADHD/Irritability profile
27 presented a significantly severe phenotype. First, children in the combined phenotype presented
28 with a higher severity of concurrent ADHD symptoms compared to the level of ADHD symptoms
29 of all groups including the moderately high ADHD and low irritability profile, consistently with the
30 literature (Vidal-Ribas et al., 2016). Second, these children had a higher propensity than those in the
31 other profiles to exhibit enduring ADHD symptoms later on, confirming prior findings (Biederman
32 et al., 2012). Third, these children showed the worst adolescent outcomes including higher
33 psychiatric symptoms (externalizing, and internalizing), higher functional impairments, and suicidal
34 behaviors compared to the lowest level of ADHD and irritability. Underlying the clinical/predictive
35 importance of the combined phenotype, effect sizes for psychiatric symptoms and impairment were
36 often beyond the medium range, and the increase in the risk for suicidal behavior was more than
37 twofold. Other developmental profiles were related to impaired outcomes, but to a lesser extent.
38 Moderately high ADHD and low irritability in childhood was linked to externalizing symptoms and
39 suicidal behaviors, and functional impairment, in adolescence. The fact that irritability may add
40 internalizing problems to ADHD without irritability is consistent with evidence showing a specific
41 increase in irritability in the liability towards depression and anxiety. Moderately high irritability
42 and low ADHD was modestly related to psychiatric symptoms and functional impairment. Analyses
43 by sex suggested stronger associations in females than in males, although their exploratory nature
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2 calls for cautious interpretation. In females, the combined high ADHD/Irritability phenotype had
3 strong associations with aggression, delinquency and contact with police, thus identifying a small
4 but high-risk subgroup regarding long-term adverse outcomes.
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7 Neuropsychological and neural mechanisms as well as environmental/biological commonalities
8 may underpin the association between ADHD and irritability. Particularly, the broad deficit in
9 emotional self-regulation can lead to hampered response inhibition to evocative situations and
10 translates into excessive/inadequate behaviors when frustrated (Barkley, 2015; Faraone et al., 2019;
11 Shaw et al., 2014). This results in harmful consequences, especially by triggering hostile feelings in
12 peers/caretakers, thus generating bidirectional negative relationships with the social environment.
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14 Pathways from comorbid ADHD/irritability to mental health problems could rest on short- and
15 long-term environmental consequences. Impairments in adaptive, daily living and social skills,
16 propensity to fight, rejection from peers and adults, academic failure, lowered quality of life and
17 self-esteem (Anastopoulos et al., 2011; Bunford et al., 2018; Lee et al., 2018; Surman et al., 2013)
18 are risk factors for psychiatric problems. Beyond internalizing/externalizing problems, emotional
19 distress combined with the tendency to act impulsively makes individuals more prone to suicidal
20 ideation and attempted suicide (Benarous et al., 2018; Orri, Perret, Turecki, & Geoffroy, 2018). The
21 multi-finality of environmental/biological commonalities may also underlie the associations
22 between ADHD, irritability, internalizing and externalizing problems. Finally, whether the link
23 between the combined phenotype and a more severe clinical evolution during adolescence is due to
24 irritability in itself or to a more severe ADHD in childhood could not be disentangled by our study.
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26 Future investigations will be needed to better understand this point.
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38 **Strengths and limitations**

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40 The present study has several strengths. First, it used a large population-based sample followed
41 from childhood to adolescence. Second, it was methodologically innovative by allowing the
42 concurrent appraisal of irritability and ADHD symptoms over 6 years. However, the study has
43 limitations. First, the study sample is likely to represent a less at-risk sample compared to the initial
44 sample and the observed associations are potentially underestimated. Indeed, the study was subject
45 to significant attrition. Despite the use of inverse probability weighting in the main analyses, this
46 attrition may still have influenced the results, thus limiting the generalizability of the findings to the
47 general population. Second, it must be acknowledged that irritability is close to the older concept of
48 aggressive behavior. Although the two concepts are part of the same phenomenon, they do not
49 strictly tap the same construct. As defined in the DSM5, irritability incorporates temper tantrums
50 and reacting in an aggressive manner. On the other hand, aggressive behavior includes proactive
51 and hostile aggression with the intention of inflicting harm or damage, and not only reactive
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1 aggression. Third, behavioral assessments relied on symptom-based scales rather than clinical tools.
2 However, these instruments have shown satisfactory psychometric properties (Tremblay, R. E.,
3 s. d.), and the dimensional approach in a population-based sample may be more accurate when the
4 aim of the research is to quantify associations between psychopathological risk factors and
5 outcomes. Fourth, teachers assessed childhood behaviors. Changing raters' perspectives over time
6 could generate a bias of instability. In addition, the lack of parental evaluation prevented the
7 appraisal of behavior problems limited to the home setting (Stringaris, Vidal-Ribas, Brotman, &
8 Leibenluft, 2018). However, compared to parent reports or self-reports, teacher reports are sensitive
9 to the environment in which the children live (i.e. school setting), because teachers interact daily
10 over many years with numerous children of the same age. Thus, they are well placed to identify
11 departures from normality, particularly regarding externalizing symptoms (Kerr, Lunkenheimer, &
12 Olson, 2007; Saudino, Ronald, & Plomin, 2005). Fifth, parental reports were not available for
13 childhood irritability or for adolescent mental health outcomes. Further studies should consider
14 combinations of parental and teacher/youth reports. Sixth, the fact that adolescent data relied on
15 self-reports could be viewed as problematic, especially in youths with ADHD, who might have a
16 positive illusory bias in reporting their own functioning. Reassuringly, there is evidence that self-
17 rated measures of both internalizing and externalizing problems are relevant as children become
18 adolescents. Regarding externalizing symptoms, covert behaviors hidden from adults can be
19 accurately evaluated through adolescent self-reports (Augenstein et al., 2016; Schaugency,
20 McGee, Raja, Feehan, & Silva, 1994; Ustun et al., 2017). Regarding internalizing problems, the
21 improvement in introspection with age allows a better appraisal of emotions (Salbach-Andrae,
22 Klinkowski, Lenz, & Lehmkuhl, 2009; Swanson et al., 2014). Seventh, our study used a person-
23 oriented approach regarding ADHD/irritability. Future research should include a variable-oriented
24 approach to complement the present findings.

25 **Implications**

26 Whether irritability should be considered a core symptom of ADHD, a distinct but correlated
27 dimension or a distinct entity is not yet clear. Irritability is non-specific, since it is also encountered
28 in people without ADHD. Reciprocally, emotional symptoms are not constant in ADHD. In
29 addition, other constructs (e.g. emotional impulsivity, deficient emotional self-regulation) might
30 better tap the dysregulated emotionality of ADHD (Faraone et al., 2019; Surman et al., 2013). The
31 transnosographic nature of irritability raises the question of whether the combined
32 ADHD/phenotype reflects the role of other diagnostic comorbidities (e.g. oppositional defiant
33 disorder, disruptive mood dysregulation disorder, depressive disorders, and bipolar disorder
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(Faraone et al., 2019). Bipolar disorder is very rare during childhood and is unlikely to explain our results. In addition, a recent molecular study relying on polygenic risk scores showed that irritability was more likely associated with ADHD than with mood and anxiety disorders (Riglin et al., 2017). Our findings have clinical implications. First, they suggest that systematic assessment of irritability with specific tools should be undertaken when diagnosing/monitoring ADHD, due to the clinical cross-sectional and longitudinal relevance of irritability. Second, ADHD interventions should target irritability when present, although the most effective interventions remain to be determined. Interestingly, irritability in ADHD is partly improved by ADHD treatments. Psychological interventions, including cognitive-behavioral, metacognitive, mindfulness therapies and parent behavior management training have shown promising results (Waxmonsky et al., 2016). By helping youths to regulate stress and label emotions, and by supporting parents to interrupt negative family dynamics, these interventions may be clinically beneficial for comorbid children. Stimulant and non-stimulant medications are somewhat efficient in the short term to reduce emotional symptoms (Blader et al., 2016; Moukhtarian, Cooper, Vassos, Moran, & Asherson, 2017). However, whether decreasing childhood irritability improves adolescent mental health and suicidal outcomes remains to be shown in randomized controlled trials.

Conclusions

The present study suggests that, at the extreme of the dysregulation spectrum, the combination of childhood ADHD and irritability is associated with a more severe clinical evolution during adolescence, including higher ADHD continuity and a wider spectrum of subsequent mental health problems, with additional internalizing outcomes compared to ADHD without irritability. If replicated in other population samples and settings, the findings suggest that better consideration of irritability when assessing and treating ADHD would allow a more accurate appraisal of the clinical heterogeneity of ADHD and would likely improve mental health and suicidal outcomes. Addressing the transnosographic dimension of irritability when assessing ADHD is necessary to enhance our etiologic understanding and to develop more efficient interventions. Future research on the irritable dimension of ADHD should target early risk factors, explore age differences and test interventions.

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For Peer Review

Table 1. Comparison of participants vs. non-participants on key variables^a, n=2,120, ELDEQ, Canada, 1998-2015.

Characteristics	Participants (n=1,407)	Non-participants (n=713)	Effect Size ^b
Child			
Male, No. (%)	665 (47.26)	415 (58.20)	-0.11 ^c
Low birth weight (<2500g), No. (%)	44 (3.13)	27 (3.79)	-0.007
Family			
Socioeconomic status, mean (SD) ^d	0.04 (0.94)	-0.15 (1.01)	-0.20 ^c
Maternal age at child birth, mean (SD), y	29.33 (5.19)	29.24 (5.30)	-0.02
Paternal age at child birth, mean (SD), y	32.26 (5.49)	32.26 (5.94)	0.001
Family dysfunction score, mean (SD) ^e	1.71 (1.44)	1.70 (1.50)	-0.007
No intact family (single or blended), No. (%)	251 (17.84)	155 (21.74)	-0.04
Hostile-reactive parenting score, mean (SD) ^f			
Maternal	2.94 (0.96)	2.90 (1.10)	-0.05
Paternal	2.59 (1.03)	2.58 (1.10)	-0.005
Parental mental health, mean (SD)			
Maternal depression ^g	1.38 (1.32)	1.45 (1.38)	0.06
Maternal antisociality in adolescence ^h	0.21 (0.47)	0.23 (0.54)	0.05
Paternal depression ^g	1.00 (0.95)	1.00 (0.99)	0.005
Paternal antisociality in adolescence ^h	0.57 (0.82)	0.51 (0.75)	-0.08

^a All variables were measured when the child was 5 months of age, except 3.5 years for hostile-reactive parenting. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistics Institute

^b Calculated as Cohen's d effect size or success rate difference (very small: <0.20; small: 0.20-0.50; medium: 0.50-0.80; large: 0.80-1.20; very large: 1.20-2.0; huge: > 2.0). p values are based on unpaired t test or Mann-Whitney test for continuous variables and χ^2 test for categorical variables

^c p<0.001

^d 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)

^e Assessed with 7 items (e.g., do not get along well together) from McMaster Family Assessment administered to the mother. Scores range from 0 to 10, with higher scores indicating lower family functioning

^f Assessed with 8 items (e.g., "When he or she broke the rules or did things that he or she was not supposed to, how often did you use physical punishment?") administered to the parent. Scores range from 0 to 10, with higher scores indicating high hostile-reactive parenting

^g Assessed using a short version of the Center for Epidemiological Study Depression Scale. Scores range from 0 to 10, with higher scores indicating higher depressive symptoms

^h Assessed with binary questions on 5 different conduct problems based on the *DSM-IV* criteria for conduct disorder and antisocial personality disorder. Scores range from 0 to 5, with higher scores indicating more antisocial behaviors

Table 2. Characteristic of participants on key variables^a by childhood profile of ADHD^b and irritability, n=1,407, ELDEQ.

Characteristics	Reference group (n=940)	Moderately high irritability & low ADHD ^b (n=158)	Moderately high ADHD ^b & low irritability (n=198)	Combined high ADHD ^b & high irritability (n=111)	p-value ^c
Child					
Male, No. (%)	347 (36.91)	96 (60.76)	133 (67.17)	89 (80.18)	<0.001
Low birth weight (<2500g), No. (%)	30 (3.19)	6 (3.80)	6 (3.03)	2 (1.80)	0.32
Family					
Socioeconomic status, mean (SD) ^d	0.15 (0.94)	-0.07 (0.87)	-0.16 (0.92)	-0.37 (0.92)	<0.001
Maternal age at child birth, mean (SD), y	29.65 (5.12)	29.26 (5.20)	28.82 (5.25)	27.62 (5.28)	<0.001
Paternal age at child birth, mean (SD), y	32.31 (5.19)	32.40 (6.46)	32.33 (5.99)	31.47 (5.69)	0.53
Family dysfunction score, mean (SD) ^e	1.67 (1.43)	1.92 (1.53)	1.75 (1.46)	1.69 (1.36)	0.25
No intact family (single or blended), No. (%)	137 (14.57)	122 (72.22)	155 (78.28)	73 (65.77)	<0.001
Hostile-reactive parenting score, mean (SD) ^f					<0.001
Maternal	2.84 (0.94)	3.16 (0.99)	3.15 (0.99)	3.19 (0.86)	<0.001
Paternal	2.52 (1.00)	2.73 (1.08)	2.78 (1.11)	2.70 (0.93)	0.01
Parental mental health score, mean (SD)					
Maternal depression ^g	1.25 (1.21)	1.69 (1.65)	1.54 (1.36)	1.72 (1.45)	<0.001
Maternal antisociality in adolescence ^h	0.18 (0.43)	0.25 (0.55)	0.23 (0.49)	0.32 (0.58)	0.01
Paternal depression ^g	0.98 (0.93)	1.12 (1.07)	0.97 (0.82)	1.08 (1.10)	0.34
Paternal antisociality in adolescence ^h	0.53 (0.75)	0.78 (1.08)	0.60 (0.90)	0.64 (0.81)	0.01

Note: Profiles “No ADHD and no irritability” and “Low ADHD and very low irritability” were combined and used as the reference group with n=401 (28.50%) and n=539 (38.31%), respectively

^a Variables were measured when the child was 5 months of age, except 3.5 years for hostile-reactive parenting. Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistics Institute.

^b ADHD, Attention Deficit Hyperactivity Disorder

^c p-values are based on ANOVA test for continuous variables and χ^2 test for categorical variables.

^d 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).

^e Assessed with 7 items (e.g., do not get along well together) from McMaster Family Assessment administered to the mother. Scores range from 0 to 10, with higher scores indicating lower family functioning.

^f Assessed with 8 items (e.g., “When he or she broke the rules or did things that he or she was not supposed to, how often did you use physical punishment?”) administered to the parent. Scores range from 0 to 10, with higher scores indicating high hostile-reactive parenting.

^g Assessed using a short version of the Center for Epidemiological Study Depression Scale. Scores range from 0 to 10, with higher scores indicating higher depressive symptoms.

^h Assessed with binary questions on 5 different conduct problems based on the DSM-IV criteria for conduct disorder and antisocial personality disorder. Scores range from 0 to 5, with higher scores indicating more antisocial behaviors

Table 3. Weighted associations between childhood profiles of ADHD^a - Irritability and adolescent psychiatric symptoms, suicidal outcome, and functional impairment. ELDEQ, Multivariate statistics.

	Childhood profiles			p ^b
	Moderately high irritability & low ADHD ^a	Moderately high ADHD ^a & low irritability	Combined high ADHD ^a & high irritability	
	B or OR (95%CI) <i>Effect size^c</i>	B or OR (95%CI) <i>Effect size^c</i>	B or OR (95%CI) <i>Effect size^c</i>	
Total of internalizing symptoms	0.05 (-0.26, 0.36) <i>0.03</i>	-0.01 (-0.30, 0.27) <i>-0.01</i>	0.57 (0.18, 0.96) <i>0.29</i>	*
Social phobia	-0.19 (-0.55, 0.18) <i>-0.08</i>	-0.17 (-0.51, 0.18) <i>-0.07</i>	0.60 (0.14, 1.07) <i>0.25</i>	*
Generalized anxiety	0.19 (-0.13, 0.52) <i>0.10</i>	0.07 (-0.23, 0.37) <i>0.03</i>	0.57 (0.15, 0.98) <i>0.27</i>	*
Depression	0.12 (-0.23, 0.46) <i>0.06</i>	0.04 (-0.28, 0.36) <i>0.02</i>	0.45 (0.01, 0.88) <i>0.20</i>	
ADHD^a	0.34 (0.04, 0.64) <i>0.19</i>	0.43 (0.15, 0.71) <i>0.24</i>	0.96 (0.58, 1.34) <i>0.50</i>	***
Hyperactivity-Impulsivity	0.37 (0.09, 0.65) <i>0.22</i>	0.16 (-0.10, 0.42) <i>0.10</i>	0.72 (0.37, 1.08) <i>0.40</i>	***
Inattention	0.26 (-0.06, 0.58) <i>0.14</i>	0.63 (0.33, 0.93) <i>0.32</i>	1.03 (0.62, 1.44) <i>0.50</i>	***
Total of externalizing symptoms	0.24 (0.03, 0.46) <i>0.19</i>	0.28 (0.08, 0.48) <i>0.21</i>	0.82 (0.55, 1.09) <i>0.59</i>	***
Oppositional defiant disorder	0.37 (0.11, 0.64) <i>0.24</i>	0.19 (-0.05, 0.43) <i>0.12</i>	0.93 (0.60, 1.26) <i>0.55</i>	***
Conduct disorder	0.05 (-0.16, 0.27) <i>0.04</i>	0.22 (0.02, 0.41) <i>0.17</i>	0.55 (0.28, 0.82) <i>0.41</i>	***
Psychopathy	-0.07 (-0.34, 0.20) <i>-0.04</i>	0.24 (-0.01, 0.49) <i>0.15</i>	0.44 (0.10, 0.78) <i>0.25</i>	*
Delinquency & contact with police	-0.02 (-0.15, 0.11) <i>-0.03</i>	0.18 (0.06, 0.30) <i>0.23</i>	0.41 (0.24, 0.57) <i>0.49</i>	***
Aggression	0.13 (-0.02, 0.29) <i>0.14</i>	0.05 (-0.09, 0.2) <i>0.06</i>	0.46 (0.26, 0.66) <i>0.45</i>	***
Eating disorders	0.17 (-0.13, 0.46) <i>0.10</i>	0.05 (-0.22, 0.32) <i>0.03</i>	0.26 (-0.11, 0.63) <i>0.14</i>	
Suicidality^d	1.24 (0.91, 1.69) <i>0.12</i>	1.50 (1.13, 1.98) <i>0.22</i>	2.12 (1.47, 3.06) <i>0.41</i>	***

Total functional impairment	0.45 (0.14, 0.75) <i>0.25</i>	0.28 (-0.01, 0.56) <i>0.15</i>	0.92 (0.54, 1.31) <i>0.47</i>	***
Functional impairment scale for behavior	0.25 (0.04, 0.47) <i>0.20</i>	0.18 (-0.02, 0.38) <i>0.14</i>	0.67 (0.4, 0.94) <i>0.48</i>	***
Functional impairment scale for anxiety	0.46 (0.09, 0.82) <i>0.21</i>	0.44 (0.11, 0.78) <i>0.20</i>	0.98 (0.52, 1.44) <i>0.42</i>	***
Functional impairment scale for depression	0.52 (0.16, 0.88) <i>0.24</i>	0.22 (-0.11, 0.56) <i>0.10</i>	0.95 (0.49, 1.41) <i>0.41</i>	***
Functional impairment scale for eating disorders	0.15 (-0.08, 0.38) <i>0.11</i>	0.02 (-0.19, 0.24) <i>0.02</i>	0.25 (-0.04, 0.54) <i>0.17</i>	

Note: Profiles "No ADHD and no irritability" and "Very low ADHD and very low irritability" were combined and used as the reference group with n=401 (28.50%) and n=539 (38.31%), respectively. Ns vary between 1,372 and 1,407

Note 2: Adjusted for child's sex, family socioeconomic status, maternal age at child birth, no intact family, maternal and paternal hostile-reactive parenting score, maternal depression, maternal and paternal antisociality in adolescence.

^a ADHD, Attention Deficit Hyperactivity Disorder

^b Multiple testing corrected p-values using the Benjamini-Hochberg procedure (*: p-value<0.05, **: p-value<0.01, ***: p-value<0.001)

^c Standardized effect size based on Cohen's d statistic (very small: <0.20; small: 0.20-0.50; medium: 0.50-0.80; large: 0.80-1.20; very large: 1.20-2.0; huge: > 2.0) or success rate difference

^d Odds ratios were estimated using logistic regressions

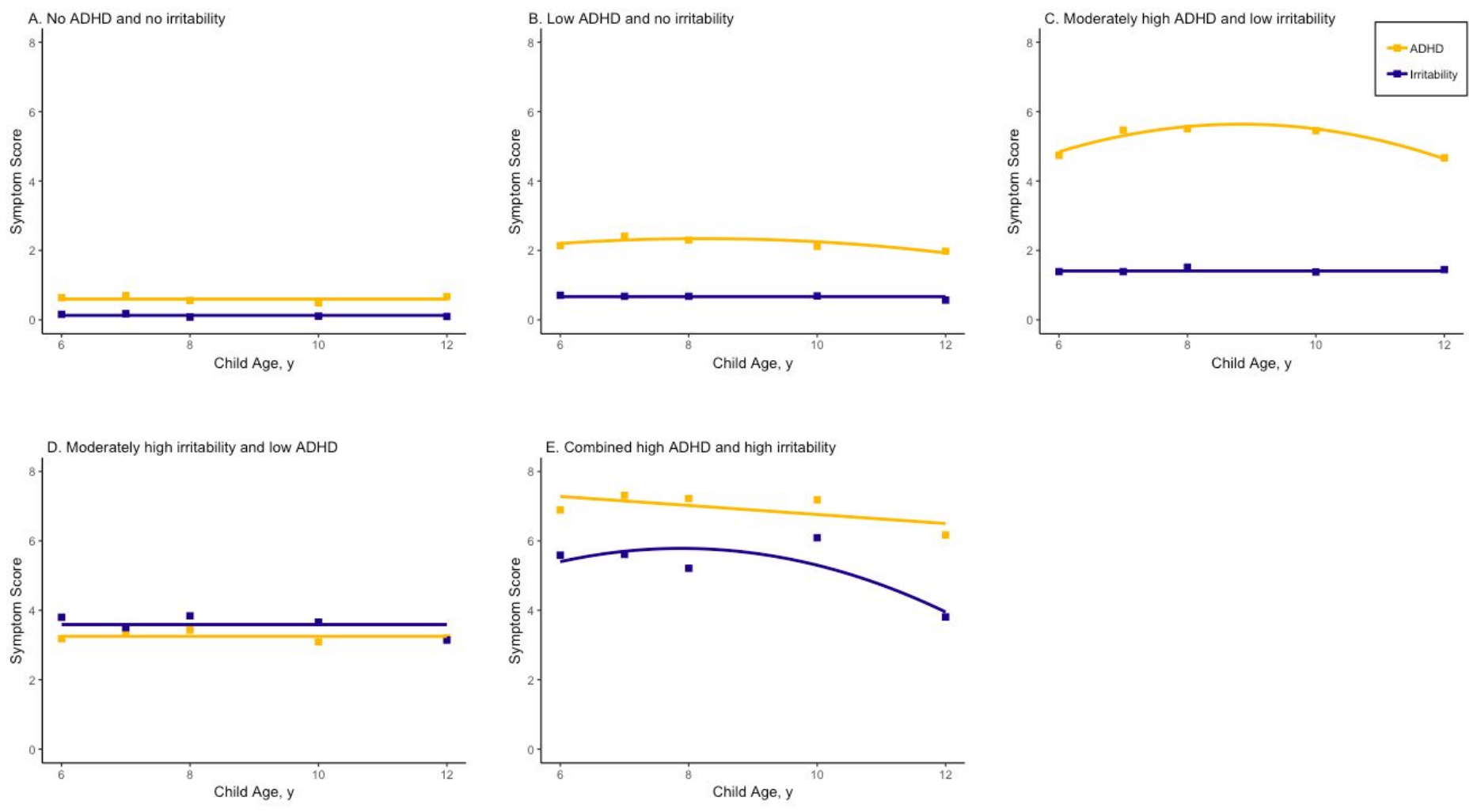


Figure 1. Multi-trajectories of childhood attention deficit hyperactivity disorder (ADHD) and irritability.

Each column represents a different profile in the multi-trajectory 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 represent observed value, and lines represent the fitted regression slopes

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eTable1. Multitrajectory modeling estimations

G	L	BIC	Entropy	Groups n (%)					
				1	2	3	4	5	6
4	-17420.15	-17490.16	82.28	408 (29.0)	565 (40.2)	331 (23.5)	103 (7.3)		
5	-17336.34	-17424.77	79.20	401 (28.5)	539 (38.3)	198 (14.1)	158 (11.2)	111 (7.9)	
6	-17269.34	-17390.93	75.63	383 (27.2)	429 (30.5)	210 (14.9)	160 (11.4)	142 (10.1)	83 (5.9)

Note: G, Number of Groups; L, Log likelihood; BIC, Bayesian Information Criterion
Selected model in bold

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eTable 2. Distribution of adolescent mental health problems^a and suicidal outcome^b by childhood profile of ADHD^c and irritability, ELDEQ.

Psychopathology scales ^a n (%)	Childhood profiles									
	Girls, n=742 (52.74)					Boys, n=665 (47.26)				
	Reference ^d	Moderately high irritability & low ADHD ^c	Moderately high ADHD ^c & low irritability	Combined high ADHD ^c & high irritability	<i>P</i> ^e	Reference ^d	Moderately high irritability & low ADHD ^c	Moderately high ADHD ^c & low irritability	Combined high ADHD ^c & high irritability	<i>P</i> ^e
	593 (79.92)	62 (8.36)	65 (8.76)	22 (2.96)		347 (52.18)	96 (14.44)	133 (20.00)	89 (13.38)	
Total of internalizing symptoms	4.39 (1.79)	4.43 (1.73)	4.08 (1.56)	5.32 (1.89)	0.06	2.73 (1.53)	2.90 (1.59)	3.03 (1.61)	3.28 (1.80)	0.03
Social phobia	3.13 (2.23)	2.72 (1.98)	2.42 (1.88)	4.07 (2.16)	0.01	1.78 (1.73)	1.90 (1.88)	2.14 (1.87)	2.40 (2.03)	0.03
Generalized anxiety	4.92 (1.83)	5.25 (1.86)	4.93 (1.68)	5.93 (1.98)	0.06	3.26 (1.73)	3.39 (1.79)	3.45 (1.72)	3.74 (1.93)	0.18
Depression	4.33 (1.98)	4.47 (2.15)	4.11 (1.70)	5.03 (2.28)	0.30	2.63 (1.75)	2.89 (1.80)	2.96 (1.91)	3.11 (1.95)	0.10
ADHD^c	3.25 (1.70)	3.73 (1.51)	3.77 (1.63)	4.15 (1.63)	0.006	2.91 (1.61)	3.33 (1.73)	3.43 (1.55)	4.07 (1.82)	<0.001
Hyperactivity- Impulsivity	2.58 (1.53)	3.08 (1.44)	2.82 (1.66)	3.47 (1.63)	0.006	2.42 (1.55)	2.86 (1.73)	2.68 (1.61)	3.31 (1.91)	<0.001
Inattention	3.38 (1.89)	3.75 (1.70)	4.10 (1.62)	4.15 (1.61)	0.008	2.92 (1.74)	3.24 (1.84)	3.60 (1.62)	4.16 (1.68)	<0.001
Total of externalizing symptoms	1.99 (1.13)	2.44 (1.24)	2.35 (1.24)	3.06 (1.89)	<0.001	1.92 (1.23)	2.20 (1.21)	2.31 (1.25)	2.86 (1.75)	<0.001
Oppositional defiant disorder	2.63 (1.48)	3.29 (1.57)	3.01 (1.46)	3.81 (1.55)	<0.001	2.55 (1.47)	2.93 (1.47)	2.83 (1.42)	3.64 (1.74)	<0.001
Conduct disorder	0.94 (1.12)	1.28 (1.27)	1.21 (1.18)	1.74 (2.18)	0.005	0.92 (1.12)	0.93 (0.93)	1.25 (1.39)	1.55 (1.77)	<0.001
Psychopathy	3.16 (1.37)	2.96 (1.50)	3.40 (1.45)	4.00 (1.62)	0.02	3.91 (1.66)	4.11 (1.62)	4.31 (1.70)	4.42 (1.74)	0.03
Delinquency & contact with police	0.14 (0.50)	0.11 (0.29)	0.28 (0.74)	0.86 (2.32)	<0.001	0.23 (0.59)	0.32 (0.78)	0.54 (1.28)	0.66 (1.33)	<0.001
Aggression	0.73 (0.69)	0.93 (0.73)	0.88 (1.08)	1.56 (1.87)	<0.001	0.92 (0.91)	1.15 (1.02)	1.01 (1.05)	1.38 (1.60)	0.006
Eating disorders	2.23 (1.82)	2.49 (1.89)	2.29 (1.66)	3.47 (1.67)	0.02	1.21 (1.24)	1.50 (1.33)	1.42 (1.52)	1.33 (1.15)	0.19
Total functional impairment	2.03 (1.80)	2.88 (2.11)	2.34 (1.78)	3.62 (2.61)	<0.001	1.07 (1.32)	1.28 (1.24)	1.40 (1.46)	1.83 (1.93)	<0.001
Functional impairment scale for anxiety	2.39 (2.16)	3.16 (2.05)	2.96 (2.20)	4.05 (3.09)	0.001	1.27 (1.58)	1.46 (1.52)	1.67 (1.96)	2.05 (2.10)	0.003
Functional impairment scale for depression	2.55 (2.12)	3.50 (2.27)	2.77 (2.18)	4.48 (3.19)	<0.001	1.22 (1.66)	1.42 (1.56)	1.49 (1.58)	1.88 (2.13)	0.02
Functional impairment scale for eating disorders	0.81 (1.47)	1.24 (1.92)	0.79 (1.59)	1.43 (1.79)	0.07	0.28 (0.81)	0.34 (0.71)	0.42 (0.87)	0.48 (1.01)	0.18

				JCPP							
	Functional impairment scale for behavior	0.51 (1.07)	0.99 (1.61)	0.77 (1.13)	1.21 (1.81)	0.002	0.51 (1.10)	0.72 (1.06)	0.73 (1.20)	1.25 (2.00)	<0.001
1	Suicidality^b	89 (15.00)	11 (17.74)	10 (15.38)	8 (36.36)	0.07	14 (4.03)	8 (8.33)	17 (12.78)	9 (10.11)	0.01

Note. Ns vary between 1,372 and 1,407.

^a The table reports the descriptive statistics for all the MIA scales, subscales and dimensions (mean / standard deviation). All scores were rescaled to be expressed on a scale from 0 to 10

^b Suicidality outcome was measured at ages 13, 15, and 17 years (n / %)

^c ADHD, Attention Deficit Hyperactivity Disorder

^d Profiles “No ADHD and no irritability” and “Very low ADHD and very low irritability” were combined and used as the reference group with n=401 (28.50%) and n=539 (38.31%), respectively

^e p values are based on ANOVA tests for continuous variables and x² test for categorical variables (multiple testing corrected p-values using the Benjamini-Hochberg procedure)

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eTable 3. Weighted associations between childhood profiles of ADHD^a - Irritability^{JCPP} and adolescent psychiatric symptoms, suicidal outcome, and functional impairment stratified by sex, ELDEQ, multivariate statistics.

	Childhood profiles							
	Girls				Boys			
	Moderately high irritability & low ADHD ^a	Moderately high ADHD ^a & low irritability	Combined high ADHD ^a & high irritability	p ^b	Moderately high irritability only & low ADHD ^a	Moderately high ADHD ^a & low irritability	Combined high ADHD ^a & high irritability	p ^b
	B or OR (95%CI) <i>Effect size^c</i>	B or OR (95%CI) <i>Effect size^c</i>	B or OR (95%CI) <i>Effect size^c</i>		B or OR (95%CI) <i>Effect size^c</i>	B or OR (95%CI) <i>Effect size^c</i>	B or OR (95%CI) <i>Effect size^c</i>	
Total of internalizing symptoms	0.01 (-0.48, 0.49) <i>0.003</i>	-0.36 (-0.85, 0.12) <i>-0.19</i>	0.87 (0.03, 1.72) <i>0.44</i>		0.12 (-0.25, 0.49) <i>0.07</i>	0.25 (-0.07, 0.58) <i>0.15</i>	0.52 (0.13, 0.92) <i>0.31</i>	*
Social phobia	-0.37 (-0.97, 0.23) <i>-0.16</i>	-0.70 (-1.30, -0.11) <i>-0.30</i>	0.93 (-0.11, 1.97) <i>0.38</i>	*	0.08 (-0.35, 0.50) <i>0.04</i>	0.28 (-0.09, 0.66) <i>0.15</i>	0.63 (0.18, 1.08) <i>0.33</i>	*
Generalized anxiety	0.27 (-0.24, 0.78) <i>0.14</i>	-0.07 (-0.57, 0.43) <i>-0.04</i>	0.92 (0.04, 1.80) <i>0.45</i>		0.11 (-0.3, 0.52) <i>0.06</i>	0.15 (-0.21, 0.52) <i>0.08</i>	0.45 (0.01, 0.89) <i>0.24</i>	
Depression	0.07 (-0.48, 0.61) <i>0.03</i>	-0.31 (-0.85, 0.23) <i>-0.15</i>	0.62 (-0.32, 1.57) <i>0.28</i>		0.18 (-0.25, 0.60) <i>0.10</i>	0.30 (-0.08, 0.68) <i>0.16</i>	0.42 (-0.03, 0.88) <i>0.22</i>	
ADHD^a	0.34 (-0.11, 0.80) <i>0.20</i>	0.38 (-0.08, 0.83) <i>0.21</i>	0.64 (-0.15, 1.43) <i>0.34</i>		0.35 (-0.03, 0.74) <i>0.21</i>	0.47 (0.13, 0.81) <i>0.27</i>	1.07 (0.66, 1.48) <i>0.61</i>	***
Hyperactivity-Impulsivity	0.36 (-0.05, 0.78) <i>0.23</i>	0.09 (-0.32, 0.50) <i>0.05</i>	0.61 (-0.11, 1.33) <i>0.36</i>		0.39 (0.01, 0.77) <i>0.23</i>	0.22 (-0.12, 0.56) <i>0.13</i>	0.77 (0.36, 1.17) <i>0.44</i>	***
Inattention	0.27 (-0.24, 0.77) <i>0.14</i>	0.60 (0.10, 1.10) <i>0.31</i>	0.55 (-0.33, 1.43) <i>0.27</i>		0.26 (-0.14, 0.66) <i>0.15</i>	0.63 (0.28, 0.99) <i>0.36</i>	1.20 (0.77, 1.63) <i>0.66</i>	***
Total of externalizing symptoms	0.32 (0.01, 0.63) <i>0.26</i>	0.21 (-0.10, 0.52) <i>0.18</i>	0.83 (0.29, 1.38) <i>0.65</i>	**	0.16 (-0.14, 0.46) <i>0.12</i>	0.31 (0.04, 0.58) <i>0.23</i>	0.81 (0.49, 1.13) <i>0.59</i>	***
Oppositional defiant disorder	0.48 (0.08, 0.88) <i>0.32</i>	0.20 (-0.20, 0.59) <i>0.13</i>	0.83 (0.14, 1.51) <i>0.51</i>	*	0.24 (-0.10, 0.59) <i>0.16</i>	0.16 (-0.15, 0.46) <i>0.10</i>	0.91 (0.55, 1.28) <i>0.58</i>	***
Conduct disorder	0.23 (-0.09, 0.55) <i>0.19</i>	0.14 (-0.17, 0.46) <i>0.12</i>	0.65 (0.10, 1.20) <i>0.50</i>		-0.13 (-0.41, 0.16) <i>-0.10</i>	0.25 (0.01, 0.50) <i>0.20</i>	0.51 (0.20, 0.81) <i>0.39</i>	**

				JCPP					
1	Psychopathy	-0.27 (-0.65, 0.11) -0.19	0.17 (-0.20, 0.55) 0.12	0.69 (0.03, 1.35) 0.45		0.14 (-0.25, 0.52) 0.08	0.32 (-0.02, 0.66) 0.19	0.41 (-0.01, 0.82) 0.23	
2	Delinquency & contact with police	-0.08 (-0.24, 0.08) -0.13	0.06 (-0.10, 0.22) 0.09	0.63 (0.35, 0.90) 0.96	**	0.03 (-0.17, 0.24) 0.04	0.28 (0.09, 0.46) 0.30	0.37 (0.15, 0.59) 0.39	***
5	Aggression	0.12 (-0.09, 0.33) 0.15	0.08 (-0.12, 0.29) 0.10	0.69 (0.33, 1.05) 0.82	**	0.12 (-0.12, 0.36) 0.11	0.03 (-0.18, 0.25) 0.03	0.40 (0.14, 0.66) 0.36	*
9	Eating disorders	0.07 (-0.43, 0.57) 0.04	-0.13 (-0.62, 0.37) -0.07	1.01 (0.14, 1.87) 0.50		0.22 (-0.09, 0.52) 0.16	0.17 (-0.10, 0.44) 0.13	0.07 (-0.25, 0.39) 0.05	
12	Suicidity ^d	1.06 (0.72, 1.57) 0.03	0.89 (0.60, 1.33) -0.06	2.39 (1.40, 4.10) 0.48	*	1.80 (1.01, 3.20) 0.32	3.35 (2.11, 5.33) 0.67	2.42 (1.38, 4.24) 0.49	***
16	Total functional impairment scale	0.72 (0.21, 1.22) 0.37	0.15 (-0.35, 0.65) 0.08	1.41 (0.54, 2.28) 0.69	**	0.12 (-0.21, 0.46) 0.08	0.28 (-0.01, 0.58) 0.19	0.73 (0.37, 1.09) 0.48	***
19	Functional impairment scale for behavior	0.39 (0.07, 0.70) 0.32	0.20 (-0.12, 0.51) 0.16	0.53 (-0.01, 1.08) 0.42	*	0.12 (-0.18, 0.41) 0.09	0.17 (-0.09, 0.43) 0.13	0.70 (0.39, 1.02) 0.52	***
23	Functional impairment scale for anxiety	0.72 (0.12, 1.32) 0.32	0.46 (-0.13, 1.06) 0.20	1.49 (0.45, 2.52) 0.61	**	0.12 (-0.29, 0.52) 0.07	0.35 (-0.01, 0.71) 0.19	0.75 (0.32, 1.18) 0.41	**
26	Functional impairment scale for depression	0.83 (0.24, 1.43) 0.37	0.03 (-0.56, 0.62) 0.01	1.73 (0.71, 2.76) 0.72	**	0.13 (-0.26, 0.53) 0.08	0.24 (-0.11, 0.59) 0.14	0.66 (0.24, 1.08) 0.36	*
29	Functional impairment scale for eating disorders	0.26 (-0.15, 0.68) 0.16	-0.15 (-0.56, 0.26) -0.09	0.57 (-0.15, 1.29) 0.34		0.02 (-0.17, 0.22) 0.03	0.11 (-0.06, 0.28) 0.13	0.15 (-0.05, 0.36) 0.17	

Note: Profiles "No ADHD and no irritability" and "Very low ADHD and very low irritability" were combined and used as the reference group with n=401 (28.50%) and n=539 (38.31%), respectively. Ns vary between 1,372 and 1,407

Note 2: Adjusted for child's sex, family socioeconomic status, maternal age at child birth, no intact family, maternal and paternal hostile-reactive parenting score, maternal depression, maternal and paternal antisociality in adolescence.

^a ADHD, Attention Deficit Hyperactivity Disorder

^b Multiple testing corrected p-values using the Benjamini-Hochberg procedure (*: p-value<0.05, **: p-value<0.01, ***: p-value<0.001)

^c Standardized effect size based on Cohen's d statistic (very small: <0.20; small: 0.20-0.50; medium: 0.50-0.80; large: 0.80-1.20; very large: 1.20-2.0; huge: > 2.0) or success rate difference

^d Odds ratios were estimated using logistic regressions

eTable 4. Weighted associations between childhood profiles of ADHD^a - Irritability^{JCPP} and adolescent psychiatric symptoms, suicidal outcome, and functional impairment (between profiles comparisons of the various ADHD - Irritability groups). ELDEQ, multivariate statistics.

	Childhood profiles		
	Combined high ADHD ^a & high irritability vs. Moderately high ADHD & low irritability	Combined high ADHD ^a & high irritability vs. Moderately high irritability & low ADHD	Moderately high ADHD ^a & low irritability vs. Moderately high irritability & low ADHD
	B or OR (95%CI) <i>Effect size^b</i>	B or OR (95%CI) <i>Effect size^b</i>	B or OR (95%CI) <i>Effect size^b</i>
Total of internalizing symptoms	0.58 (0.14, 1.02) 0.31	0.52 (0.07, 0.97) 0.28	-0.06 (-0.44, 0.31) -0.03
Social phobia	0.77 (0.24, 1.3) 0.34	0.79 (0.24, 1.34) 0.35	0.02 (-0.43, 0.47) 0.01
Generalized anxiety	0.50 (0.03, 0.96) 0.25	0.37 (-0.11, 0.85) 0.19	-0.12 (-0.52, 0.27) -0.07
Depression	0.40 (-0.09, 0.9) 0.19	0.33 (-0.18, 0.84) 0.16	-0.07 (-0.5, 0.35) -0.04
ADHD	0.53 (0.11, 0.95) 0.29	0.62 (0.18, 1.06) 0.34	0.09 (-0.28, 0.45) 0.05
Hyperactivity-Impulsivity	0.56 (0.16, 0.96) 0.33	0.36 (-0.06, 0.77) 0.21	-0.20 (-0.55, 0.14) -0.12
Inattention	0.41 (-0.05, 0.87) 0.21	0.77 (0.3, 1.25) 0.39	0.37 (-0.03, 0.76) 0.19
Total of externalizing symptoms	0.54 (0.24, 0.85) 0.41	0.58 (0.26, 0.9) 0.44	0.03 (-0.23, 0.3) 0.03
Oppositional defiant disorder	0.74 (0.37, 1.12) 0.46	0.56 (0.17, 0.95) 0.35	-0.18 (-0.51, 0.14) -0.12
Conduct disorder	0.34 (0.03, 0.64) 0.26	0.50 (0.18, 0.82) 0.39	0.16 (-0.1, 0.42) 0.13

1	Psychopathy	0.20 (-0.19, 0.58) 0.12	0.51 (0.11, 0.91) 0.31	0.31 (-0.02, 0.64) 0.20
2	Delinquency & 3 contact with police	0.23 (0.04, 0.41) 0.28	0.43 (0.23, 0.62) 0.54	0.20 (0.04, 0.36) 0.27
5	Aggression	0.41 (0.18, 0.64) 0.42	0.33 (0.09, 0.56) 0.34	-0.08 (-0.28, 0.11) -0.09
9	Eating disorders	0.21 (-0.21, 0.63) 0.12	0.09 (-0.34, 0.53) 0.05	-0.12 (-0.48, 0.24) -0.07
12	Suicidity ^d	1.42 (0.94, 2.13) 0.19	1.71 (1.11, 2.65) 0.30	1.21 (0.83, 1.76) 0.11
16	Total functional impairment	0.65 (0.21, 1.08) 0.34	0.48 (0.02, 0.93) 0.26	-0.17 (-0.54, 0.21) -0.09
19	Functional impairment 20 scale for behavior	0.48 (0.18, 0.79) 0.37	0.41 (0.1, 0.73) 0.32	-0.07 (-0.33, 0.19) -0.06
23	Functional impairment 24 scale for anxiety	0.54 (0.02, 1.05) 0.24	0.52 (-0.02, 1.06) 0.24	-0.01 (-0.46, 0.43) -0.01
26	Functional impairment 27 scale for depression	0.73 (0.21, 1.24) 0.33	0.43 (-0.1, 0.96) 0.20	-0.30 (-0.74, 0.15) -0.14
29	Functional impairment 30 scale for eating disorders	0.23 (-0.11, 0.56) 0.16	0.10 (-0.24, 0.44) 0.07	-0.12 (-0.41, 0.16) -0.09

33 Note: Profiles “No ADHD and no irritability” and “Very low ADHD and very low irritability” were combined and used as the reference group with n=401 (28.50%) and
34 n=539 (38.31%), respectively. Ns vary between 1,372 and 1,407

35 Note 2: Adjusted for child’s sex, family socioeconomic status, maternal age at child birth, no intact family, maternal and paternal hostile-reactive parenting score,
36 maternal depression, maternal and paternal antisociality in adolescence.

37 ^a ADHD, Attention Deficit Hyperactivity Disorder

38 ^b Multiple testing corrected p-values using the Benjamini-Hochberg procedure (*: p-value<0.05, **: p-value<0.01, ***: p-value<0.001)

39 ^c Standardized effect size based on Cohen’s d statistic (very small: <0.20; small: 0.20-0.50; medium: 0.50-0.80; large: 0.80-1.20; very large: 1.20-2.0; huge: > 2.0) or
40 success rate difference

41 ^d Odds ratios were estimated using logistic regressions

eTable 5. Associations (unweighted) between childhood profiles of ADHD^a - Irritability and adolescent psychiatric symptoms and suicidal outcome, ELDEQ, Multivariate statistics.

	Childhood profiles											
	All				Girls				Boys			
	Moderately high irritability & low ADHD ^a	Moderately high ADHD ^a & low irritability	Combined high ADHD ^a & high irritability	p ^b	Moderately high irritability & low ADHD ^a	Moderately high ADHD ^a & low irritability	Combined high ADHD ^a & high irritability	p ^b	Moderately high irritability & low ADHD ^a	Moderately high ADHD ^a & low irritability	Combined high ADHD ^a & high irritability	p ^b
	β or OR (95%CI) Effect size ^c	β or OR (95%CI) Effect size ^c	β or OR (95%CI) Effect size ^c		β or OR (95%CI) Effect size ^c	β or OR (95%CI) Effect size ^c	β or OR (95%CI) Effect size ^c		β or OR (95%CI) Effect size ^c	β or OR (95%CI) Effect size ^c	β or OR (95%CI) Effect size ^c	
Total of internalizing symptoms	0.06 (-0.24, 0.35) 0.03	0.04 (-0.23, 0.31) 0.02	0.56 (0.21, 0.92) 0.31	*	0.02 (-0.46, 0.51) 0.01	-0.37 (-0.84, 0.10) -0.20	0.88 (0.10, 1.67) 0.48		0.11 (-0.26, 0.48) 0.07	0.27 (-0.05, 0.60) 0.17	0.53 (0.14, 0.92) 0.32	*
Social phobia	-0.15 (-0.51, 0.20) -0.07	-0.06 (-0.39, 0.26) -0.03	0.61 (0.18, 1.04) 0.28	*	-0.36 (-0.95, 0.23) -0.16	-0.71 (-1.29, -0.13) -0.31	0.95 (-0.02, 1.92) 0.42	*	0.08 (-0.35, 0.50) 0.04	0.35 (-0.02, 0.73) 0.19	0.65 (0.20, 1.09) 0.34	*
Generalized anxiety	0.16 (-0.16, 0.47) 0.08	0.09 (-0.20, 0.38) 0.05	0.56 (0.19, 0.94) 0.29	*	0.29 (-0.2, 0.79) 0.15	-0.05 (-0.54, 0.43) -0.03	0.96 (0.14, 1.77) 0.50		0.06 (-0.36, 0.47) 0.03	0.15 (-0.21, 0.52) 0.08	0.46 (0.03, 0.89) 0.25	
Depression	0.15 (-0.19, 0.48) 0.07	0.07 (-0.24, 0.38) 0.03	0.43 (0.02, 0.83) 0.21		0.09 (-0.45, 0.62) 0.04	-0.34 (-0.86, 0.19) -0.16	0.59 (-0.29, 1.47) 0.29		0.21 (-0.21, 0.64) 0.11	0.29 (-0.08, 0.67) 0.16	0.43 (-0.02, 0.87) 0.22	
ADHD ^a	0.34 (0.05, 0.63) 0.20	0.41 (0.15, 0.68) 0.24	0.97 (0.62, 1.32) 0.55	***	0.34 (-0.11, 0.79) 0.20	0.35 (-0.10, 0.79) 0.20	0.66 (-0.08, 1.39) 0.38		0.36 (-0.03, 0.74) 0.21	0.45 (0.11, 0.79) 0.27	1.07 (0.66, 1.47) 0.62	***
Hyperactivity-Impulsivity	0.36 (0.08, 0.63) 0.22	0.15 (-0.11, 0.40) 0.09	0.74 (0.41, 1.07) 0.44	***	0.36 (-0.06, 0.77) 0.23	0.07 (-0.34, 0.47) 0.04	0.64 (-0.04, 1.32) 0.40		0.38 (0.00, 0.75) 0.23	0.20 (-0.14, 0.53) 0.12	0.77 (0.37, 1.17) 0.45	**
Inattention	0.27 (-0.05, 0.58) 0.14	0.61 (0.32, 0.90) 0.32	1.04 (0.66, 1.41) 0.54	***	0.26 (-0.24, 0.76) 0.14	0.57 (0.08, 1.05) 0.30	0.56 (-0.26, 1.37) 0.29		0.28 (-0.12, 0.68) 0.16	0.63 (0.27, 0.99) 0.35	1.18 (0.76, 1.60) 0.65	***

					JCPP								
1	Functional impairment scale for anxiety	0.40 (0.05, 0.75) 0.19	0.44 (0.12, 0.76) 0.21	0.94 (0.52, 1.36) 0.44	***	0.70 (0.11, 1.29) 0.31	0.43 (-0.15, 1.01) 0.19	1.50 (0.53, 2.47) 0.66	**	0.12 (-0.29, 0.52) 0.07	0.37 (0.02, 0.73) 0.21	0.75 (0.32, 1.17) 0.41	**
2													
3	Functional impairment scale for depression	0.46 (0.12, 0.81) 0.22	0.23 (-0.09, 0.55) 0.11	0.89 (0.47, 1.31) 0.42	***	0.83 (0.25, 1.42) 0.37	-0.02 (-0.59, 0.56) -0.01	1.69 (0.73, 2.65) 0.75	**	0.13 (-0.27, 0.53) 0.07	0.25 (-0.10, 0.61) 0.14	0.65 (0.23, 1.07) 0.36	*
4													
5	Functional impairment scale for eating disorders	0.17 (-0.05, 0.39) 0.13	0.05 (-0.15, 0.26) 0.04	0.25 (-0.02, 0.51) 0.18		0.36 (-0.06, 0.77) 0.22	-0.13 (-0.54, 0.27) -0.08	0.50 (-0.18, 1.18) 0.32		0.03 (-0.16, 0.23) 0.04	0.12 (-0.06, 0.29) 0.13	0.18 (-0.03, 0.38) 0.20	
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Note: Profiles “No ADHD and no irritability” and “Very low ADHD and very low irritability” were combined and used as the reference group with n=401 (28.50%) and n=539 (38.31%), respectively. Ns vary between 1,372 and 1,407

Note 2: Adjusted for child’s sex, family socioeconomic status, maternal age at child birth, no intact family, maternal and paternal hostile-reactive parenting score, maternal depression, maternal and paternal antisociality in adolescence.

- a ADHD, Attention Deficit Hyperactivity Disorder
- b Multiple testing corrected p-values using the Benjamini-Hochberg procedure (*: p-value<0.05, **: p-value<0.01, ***: p-value<0.001)
- c Standardized effect size based on Cohen’s d statistic (very small: <0.20; small: 0.20-0.50; medium: 0.50-0.80; large: 0.80-1.20; very large: 1.20-2.0; huge: > 2.0) or success rate difference
- d Odds ratios were estimated using logistic regressions

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