Orri, M., Galéra, C., Turecki, G., Boivin, M., Tremblay, R. E., Geoffroy, M.-C., and Côté, S. M.
Pathways of Association Between Childhood Irritability and Adolescent Suicidality.
Journal of the American Academy of Child & Adolescent Psychiatry 58(1), 99-107. 2019

Pathways of association between childhood irritability and adolescent suicidality

Massimiliano Orri, PhD, Cedric Galera, MD, PhD, Gustavo Turecki, MD, PhD, Michel Boivin, PhD, Richard E. Tremblay, PhD, Marie-Claude Geoffroy, PhD, * Sylvana M. Côté, PhD.*

* Shared senior authorship

Affiliations:

McGill Group for Suicide Studies, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Montreal, Québec, Canada (Drs Orri, Turecki, Geoffroy); Bordeaux Population Health Research Centre, INSERM U1219, University of Bordeaux, Bordeaux, France (Drs Orri and Côté); University of Bordeaux, Department of Child and Adolescent Psychiatry, Charles Perrens Hospital, Bordeaux, France (Dr Galera); School of Psychology, Laval University, Québec city, Québec, Canada (Dr Boivin); Institute of Genetic, Neurobiological, and Social Foundations of Child Development at Tomsk State University, Tomsk, Russian Federation (Dr Boivin); School of Public Health, Physiotherapy and Sports Science, University College Dublin, Dublin, Ireland (Dr Tremblay); Department of Pediatrics, University of Montréal, Montreal, Québec, Canada (Dr Tremblay); Department of Psychology, University of Montréal, Montreal, Québec, Canada (Dr Tremblay); Department of Social and Preventive Medicine, University of Montreal, Montreal, Québec, Canada (Dr Côté)

Corresponding author: Marie-Claude Geoffroy, PhD. McGill Group for Suicide Studies, Douglas Mental Health University Institute, Department of Psychiatry, McGill University, Frank B. Common Pavilion, 6875 Lasalle Blvd, Montreal, Quebec, H4H 1R, Canada (marie-claude.geoffroy@mcgill.ca)

Acknowledgments. The authors report no competing interests. The Quebec Longitudinal Study of Child Development (QLSCD) was supported by funding from the Québec Government's Ministry of Health, Ministry of Education, Ministry of Family Affairs, The Lucie and André Chagnon Foundation, the Robert-Sauvé Research Institute of Health and Security at Work, and the Québec Statistics Institute (ISQ).

Additional funding was received by the Fonds de Recherche du Québec - Santé (FRQS), the Fonds de Recherche du Québec - Societé et Culture (FRQSC), the Social Science and Humanities Research Council of Canada, the Canadian Institutes of Health Research, the St-Justine Research Centre. Dr Orri holds a postdoctoral fellowship awarded by the Canadian Institutes of Health Research (CIHR). Dr Geoffroy (junior) and Dr Côté (senior) are research fellows of the FRQS. Dr Boivin holds a Canada Research Chair in Child Development funded by CIHR. Dr Turecki holds a Canada Research Chair (Tier 1) funded by CIHR, and a National Alliance for Research on Schizophrenia and Depression Distinguished Investigator Award. Funders had no role in study design, data analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. Drs Côté and Geoffroy share senior authorships.

Keywords. Childhood irritability, suicidal ideation, suicide attempt, pathways, longitudinal

Abstract

Objective. Childhood irritability predicts suicidal ideation/attempt (suicidality), but it is unclear whether irritability is an independent and direct risk factor for suicidality, or a marker of intermediate mental health symptoms associated with suicidality. We aimed to (1) identify developmental patterns of childhood irritability; (2) test whether childhood irritability is directly associated with suicidality, or whether it is indirectly associated via intermediate mental health symptoms.

Method. N=1,393 participants from the Quebec Longitudinal Study of Child Development (QLSCD) were followed from birth to 17 years. Teachers assessed irritability yearly (6 to 12 years) and children self-reported intermediate mental health symptoms (depression, anxiety, disruptiveness, hyperactivity-impulsivity; 13 years), and suicidality (15 and 17 years).

Results. We identified 4 irritability trajectories: low (74.7%), rising (13.0%), declining (7.4%), persistent (5.0%). Children following a rising irritability trajectory (versus low trajectory) were at higher suicidality risk. A large proportion of this association was direct (OR=2.11, 95%CI=1.30-3.43) and a small proportion was indirect, via depressive symptoms (accounting for 23% of the association; OR=1.17, 95%CI=1.03-1.34). Children on a persistent irritability trajectory (versus low trajectory) were at higher risk of suicidality and this association was uniquely indirect, via depressive symptoms (accounting for 73% of the association; OR=1.51, 95%CI=1.16-1.97). The declining trajectory was not related to suicidality; no association via anxiety, disruptiveness and hyperactivity-impulsivity was found.

Conclusions. Rising irritability across childhood represents a direct risk for suicidality. Persistent irritability appears to be a distal marker of suicidality, acting via more proximal depressive symptoms.

Introduction

Suicide is one of the leading cause of death among adolescents worldwide, with a suicide rate of ~10 per 100,000 adolescents in the Unites States.[1] Suicidal ideation and attempts (suicidality) are main predictors of suicide, and have their highest prevalence during adolescence.[2] Several studies indicate that adolescents' suicidal ideations and attempts are associated with a range of negative outcomes later in life, including suicide mortality, ill-health, and low educational attainment and employment.[2–6] Prevention of early suicidal manifestations is therefore among the highest public health priorities.

Childhood irritability is gaining considerable attention as a risk factor involved in the development of suicidality. Irritability is defined as increased proneness to anger, and typically occurs in response to frustration.[7,8] It encompasses both mood (irritable, grouchy) and behavioral manifestations (aggression against property, self, or others).[9] Irritability is found in both internalizing and externalizing psychopathology –it is present in 15 *DSM-5* syndromes, including depression, anxiety, oppositional defiant disorder (ODD), and attention-deficit/hyperactive disorder (ADHD).[9] Chronic severe irritability is also the main feature of disruptive mood dysregulation disorder (DMDD), a newly introduced *DSM-5* diagnosis,[9] as well as a candidate transdiagnostic marker in the National Institute of Health's research domain criteria project.[7,8]

The association between irritability and suicidality has been investigated in 3 longitudinal population-based studies, all reporting positive associations between high levels of irritability and later suicidal ideation, plan, and attempts.[10–12] However, it is unclear whether childhood irritability is independently associated with higher suicidal risk later in life, or whether it is an early marker of mental health problems which, in turn, increase the suicidal risk. Indeed, irritability was found to predict a range of internalizing and externalizing disorders in adolescence and adulthood.[13–18] For instance, meta-analyses indicate that children with high levels of irritability were almost twice as much at risk of suffering from depression and anxiety than children low on irritability.[8] Highly irritable children were also at risk for later ODD and ADHD.[8,19–21] These syndromes are known for their associations with suicidal ideation/attempts.[22]

Clarifying whether childhood irritability is an independent predictor of later suicidality, or an early marker of future mental health problems associated with suicidality would allow to (i) identify early

pathways in childhood that lead to later suicidality, on which interventions may efficaciously focus, (ii) gain knowledge on the etiology of suicidality, and (iii) find potential early targets for suicide prevention focusing on early transdiagnostic symptoms.

Using data from a 17-year population-based cohort, our first aim was to identify the developmental trajectories of irritability during childhood (6-12 years) and test whether children on these trajectories have different suicidal risk. Our second aim was to disentangle the association between childhood irritability trajectories and suicidality in adolescence (15-17 years), by testing the intermediate role of 4 mental health problems (13 years), associated with both irritability and suicidality: depression, anxiety, disruptiveness, and hyperactivity-impulsivity symptoms.[13,22]

Methods

Subjects

Participants were drawn from the Québec Longitudinal Study of Child Development (QLSCD), a birth cohort including 2,120 infants born in 1997/98 in Québec, Canada, followed-up until 17 years of age. The protocol was approved by the Quebec Statistics Institute and the St-Justine Hospital Research Center (Montreal) ethics committees. Participants were selected from birth registers following a random procedure based on living areas and birth rates. Families were included if pregnancy lasted 24-42 weeks and if the mother could speak French or English. Analyses were based on 1,393 participants (**Table 1**) with available data on variables of interest (i.e., childhood irritability trajectory exposure and at least one suicidality self-report during adolescence). Distribution of sociodemographic characteristics at baseline were comparable for both included and excluded participants, except for 2 characteristics: boys and participants from low socioeconomic status families (SES) were underrepresented in included participants. Inverse probability weighting, in which weights represent the probability to be included in the sample estimated from baseline sex and SES, were therefore used in all analyses.[23]

Measures

Childhood irritability. Teachers assessed irritability at ages 6, 7, 8, 10, and 12 years using items from the Social Behavior Questionnaire (teacher-form), a validated scale[24] used in the Canadian National

Longitudinal Study of Children and Youth,[25] incorporating items from the Child Behavior Checklist,[26] the Ontario Child Health Study Scales,[27] and the Preschool Behavior Questionnaire.[28] Based on a prior publication[12] 4 items were used to asses irritability (0=never/1=sometimes/2=often): "had temper tantrums/hot temper", "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". As in our prior publication,[12] the irritability score (range 0-10) at each age was calculated as follows: we first averaged the 3 items measuring reactive aggression (as they measure the same behavior in different contexts), and then summed the single item measuring temper tantrum. Thus, the 2 components of irritability – reactive aggression and temper tantrum – had equal weight in the final score. The internal consistency was high from 6 to 12 years (α=0.85-0.91) (see **Table S1**, available online).

Intermediate mental health symptoms at age 13 years. Intermediate mental health symptoms were assessed with the Social Behavior Questionnaire (teenager-form) administered to the participants at age 13 years.[24] Depressive symptoms were assessed with 4 items: "I am unhappy/sad", "I am not as happy as other children", "I have trouble enjoying myself", and "I cry a lot" (α=0.83). Anxiety symptoms were assessed with 3 items: "I am too fearful/anxious", "I was worried", and "I am nervous, high-strung or tense" (α=0.88). Disruptiveness was assessed with 9 items measuring aggression and oppositionality (i.e., hurtful/headstrong behaviors), e.g.: "I get into many fights", "I physically attack people", "I am defiant or refused to comply with adults' requests/rules" (α=0.89). Hyperactive-impulsive symptoms were assessed with 4 items: "I can't sit still, I am restless", "I cannot stop fidgeting", "difficulty waiting my turn in games/group activities", and "I am impulsive, I act without thinking" (α=0.77) (see **Table S2**, available online).

Adolescent suicidality at 15 and 17 years. Adolescents were asked "in the past twelve months, did you ever seriously think of attempting suicide" and "how many times did you attempt suicide" (0 versus ≥1) at 15 and/or 17 years.[29,30] The variable suicidality (i.e., reporting ≥1 serious suicide ideation or attempt at 15 or 17 years) was then derived.

Adjustment variables. Our models were a-priori adjusted for: child sex, parental SES when participants were aged 0-6 years (i.e., aggregate of five items regarding parental education, parental

occupation, and annual gross income, range -3=low to 3=high, zero-centered),[31] known to be associated with suicidality in the QLSCD. Additionally, models were adjusted for baseline (6 years) mental health including: depressive (α=0.88), anxious (α=0.87), disruptiveness (α=0.95), and hyperactive-impulsivity (α=0.91) symptoms assessed via the Social Behavior Questionnaire (teacher-form). Items were identical than those used to measure self-report mental health symptoms at 13 years.

Analysis

Trajectories of childhood irritability. Developmental trajectories of childhood irritability (6-12 years) were identified using Latent Growth Curve Analysis in M*plus* version 7.4.[32] Models with 1 to 6 classes were estimated, each including intercept and slope parameters. The model minimizing the Bayesian Information Criterion was chosen as the best fitting, and the bootstrapped likelihood ratio test was used as an additional selection criterion. Once the best model was selected, participants were classified into the trajectory having the highest posterior probability of class membership. Entropy >0.70 was used as indication of the quality of the classification operated by the model.

Pathways of associations between childhood irritability trajectories and suicidality. Path analysis was used to estimate the direct and indirect associations of irritability trajectories with suicidality. The direct association was defined as the association between the exposure (irritability trajectory) and the outcome (suicidality) adjusted for the effect of the intermediate mental health symptoms. The indirect association was defined as the association between the exposure and the outcome *via* the intermediate mental health symptoms. It was calculated by the product of the 2 coefficients estimating (i) the association between the exposure and the intermediate mental health symptoms, and (ii) the association between the intermediate mental health symptoms and suicidality. We estimated the reduction of the effect of the exposure on the outcomes attributable to the intermediate mental health symptoms by computing the proportion of the total association (direct+indirect association, i.e. the unadjusted association) accounted by the indirect mental health symptoms (proportion mediated=indirect association/total association). This quantity indicates the effect size of the indirect association.

As recommended in path analysis,[33] we tested for differences in the direct and indirect associations between boys and girls by comparing the fit of 2 models: the first, most parsimonious, having the paths

constrained to be equal for boys and girls; the second having the paths freely estimated for each sex. As we found no evidence of superiority of the latter model (Chi-square[12 DF]=12.47, p=0.409), the final model was estimated for both sexes combined.

Path analysis was performed with M*plus* using the robust (Huber-White, handling non-normal distributions) maximum likelihood estimator with logit link. Associations were estimated via logistic regression and expressed as odds ratios. Missing data were handled using Full Information Maximum Likelihood.

Complementary analysis. We used suicidal ideation (excluding attempters) and suicide attempt as separate outcomes to see if the patterns differed between these two outcomes. Additionally, we re-estimated our model using intermediate mental health symptoms measured at 15 years (instead of 13 years) with the Mental Health and Social Inadaptation Assessments for Adolescents[29] to assess the consistency of our findings.

Results

Trajectories of childhood irritability

Four developmental trajectories were identified (**Figure 1**): low (N=1,040, 74.7%), showing low levels of irritability at all time points; persistent (N=69, 5.0%), showing high stable levels of irritability at all time points; rising (N=181, 13.0%), initially showing low levels of irritability and progressively increasing; declining (N=103, 7.4%), initially showing high levels of irritability, comparable to the persistent trajectory, then declining until reaching the level of the low stable trajectory.

Association between childhood irritability trajectories and intermediate mental health symptoms

At age 13 years, children in the rising and persistent irritability trajectories scored higher on depression (rising: B=0.11, SE=0.04, p=0.009; persistent: B=0.29, SE=0.08, p=0.000), anxiety (persistent only: B=0.28, SE=0.09, p=0.000), disruptiveness (rising: B=0.35, SE=0.14, p=0.014; persistent: B=0.78, SE=0.25, p=0.002), and hyperactivity-impulsivity (rising: B=0.50, SE=0.21, p=0.020; persistent: B=1.40, SE=0.36, p=0.000) symptoms scales compared to children in the low trajectory in adjusted analyses.

Children in the declining trajectory did not have higher scores on any intermediate mental health symptom compared to children in the low trajectory.

Association between intermediate mental health symptoms and suicidality

At 15 and17 years, 144 (10.3%) adolescents reported suicidal ideation and/or suicide attempt (**Table 2**). We found that high depressive (OR=4.24, 95%CI=2.49-7.22) and disruptive symptoms (OR=1.20, 95%CI=1.01-1.44) increased the likelihood of later suicidality independently from the other intermediate mental health symptoms, irritability, sex, SES, and baseline mental health symptoms. However, no independent associations were found for anxiety (OR=0.72, 95%CI=0.46-1.12) and hyperactive-impulsive symptoms (OR=0.99, 95%CI=0.87-1.11).

Pathways of association between childhood irritability trajectories and suicidality

Path analysis decomposed the association between childhood irritability trajectories and adolescent's suicidality outcomes in direct associations (uniquely due to the trajectory, beyond the effect of the intermediate mental health symptoms) and indirect associations (due to the intermediate mental health symptoms).

Children in the rising trajectory, compared to those in the low trajectory, were significantly more at risk for suicidality (total association: OR=2.64, 95%CI=1.59-4.38; **Table 3**). This risk was mainly explained by the direct association of the rising trajectory on suicidality (OR=2.11, 95%CI=1.30-3.43), suggesting that the heightened suicidal risk was independent from the depressive, anxious, disruptive, and hyperactive-impulsive symptomatology (i.e., the intermediate mental health symptoms) at 13 years, as well as from baseline covariates. However, we also found evidence for an indirect association between the rising irritability trajectory and suicidality through depressive symptoms at 13 years. Specifically, children in the rising trajectory had an increased risk for suicidality attributable to the increasing in depressive symptoms (OR=1.17, 95%CI=1.03-1.34). No indirect effects through anxiety, disruptiveness, and hyperactive-impulsive symptoms were found. The indirect pathways explained 22.8% of the association between the rising trajectory and suicidality.

Children in the persistent trajectory, compared to those in the low trajectory, showed a significant higher risk for suicidality in adolescence uniquely attributable to increased depressive symptoms at 13 years

(OR=1.46, 95%CI=1.18-1.80, i.e., the indirect association of irritability on suicidality via depressive symptoms). As for the rising trajectory, we did not find any indirect association via anxiety, disruptive, and hyperactive-impulsive symptoms. For the persistent trajectory, 73.4% of the association was accounted by the indirect pathways.

Finally, we did not find any evidence of increased suicidality risk (neither though direct or indirect associations) for children in the declining trajectory, compared to those belonging to the low trajectory.

Complementary analysis

Associations for suicidal ideation and attempt (as separate outcomes) were virtually identical than those for suicidality, and estimating our models using the intermediate mental health outcomes at 15 years showed consistent results (see **Table S3** and **Table S4**, available online).

Discussion

Using a prospective birth cohort from the Canadian province of Québec, the objectives of this study were (i) to characterize the developmental trajectories of irritability during middle childhood and test whether children in these trajectories had different rates of suicidality (ideation and attempt) in adolescence, and (ii) to test the intermediate role of mental health symptoms in the association between childhood irritability trajectories and adolescent suicidality.

We identified four trajectories of irritability based on teacher ratings from kindergarten to the end of elementary school: low, rising, declining, and persistent. While the majority of children consistently exhibited low levels of irritability (75%), about 12% exhibited high levels in kindergarten (i.e., persistent and declining trajectories). For more than a half of these children (7% of the sample), irritability decreased across the course of childhood, while for the others (5%), irritability remained high until the beginning of adolescence. We also identified a fourth group exhibiting initial low levels which subsequently increased up to the end of elementary school (13%). To our knowledge, this study is the first to describe the developmental trajectories of irritability from middle childhood to the beginning of adolescence. Only two previous studies described the developmental trajectories of irritability among adolescent/young adults aged 12 to 20 years through self-reports,[34] and among children aged 3 to 9 years through maternal reports.[35] Our

findings with teacher reports are consistent with both studies, which described both stable and varying irritability trajectories.[34,35] We found that, among children showing early high irritability (persistent and declining trajectories), persistently irritable children showed heightened risk of depressive symptoms at 13 years, which associated with a heightened risk for suicidality at 15-17 years. Children in the declining trajectory did not show high risk for suicidality or other mental health symptoms. Among children with low irritability in kindergarten (rising and low trajectories), 75% continued to follow a low irritability trajectory, while 15% exhibited increasing levels of irritability and became at high risk for suicidality.

The pathways explaining the link between irritability and suicidality differed between children following these 2 at-risk trajectories (persistent and rising). For children with persistent irritability, the suicidality risk largely operated via depressive symptomatology in early adolescence (74% of the association). For children with rising irritability, the suicidality risk was mostly direct and independent from mental health status at 13 years. Indeed, only a small proportion of the association between rising irritability and suicidality (23% of the association) came about via depressive symptomatology at 13 years. These different pathways linking irritability and suicidality suggest that the etiology of suicidality for children following a persistent or a rising trajectory differs. For children with persistent irritability, the continuity between irritability symptoms and later depressive symptoms may indicate emotional regulation deficits underlying both irritability and depressive symptoms.[36,37] Therefore, irritability may be an early marker of depression for these children. The concept of disruptive mood dysregulation disorder, a mood disorder characterized by irritability during childhood and associated with later depression, may encompass these emotional deficits. On the other hand, for children with rising levels of irritability, the relative low explanatory power of the mental health symptoms in early adolescence suggests that irritability increased the risk for suicidality over and beyond depressive and other common mental health symptoms in adolescence.

These findings are consistent with previous population-based[10,11] and clinical studies[38] showing positive associations between irritability and suicidal behaviors. Additionally, we showed that the most important intermediate pathway between irritability and suicidality is depressive symptoms. This is consistent with evidence linking persistent irritability with later depressive symptoms,[8] and a previous study

reporting that the joint presence of irritability and depressive/anxious mood predicts later suicidal ideation and attempt.[12] Consistently with the literature, we also found associations between irritability and externalizing symptoms (disruptiveness and hyperactivity-impulsivity),[8,13,19–21] but these associations did not translate into increased suicidal risk. Our findings are also consistent with studies showing that impulsive-aggressive traits (usually measured in adolescence/young adulthood) are risk factors for suicidality,[39,40] suggesting that childhood irritability may be an early marker of impulsive-aggression. The overlap between these concepts, which is an ongoing research topic,[41] merits further investigation from a developmental perspective.

Although our findings need replication, they have important implications for targeted prevention of suicidality. Indeed, our results suggest that preventing the emergence of depressive symptoms in elementary school children with persistent irritability could prevent suicidality; however, prevention of depressive symptoms would be of more limited efficacy for children on a rising trajectory of irritability compared to those on a persistent trajectory. The relatively low explanatory power of the mental health symptoms for children on the rising irritability trajectory may also indicate that other intermediate factors are at play. In particular, future studies should investigate the role of psychosocial factors such as family adversities or peer victimization, which were associated with irritability and suicidal behaviors in previous studies.[30,35,42] Such studies may also suggest possible targets for psychosocial interventions.

Finally, our analyses identified a group of children with high levels of irritability in kindergarten and first grade who were not at risk for suicidality. Indeed, half of the children showing high irritability in kindergarten (6 years) were no longer irritable at age 12 years and were not at high risk for suicidality or other mental health symptoms in adolescence. Thus, preventive interventions during kindergarten and early elementary school grades need to attend to this important difference. Studies identifying early markers that can differentiate between these two groups of children are needed. Detailed assessment of associated mental health symptoms and psychosocial factors may help distinguish between children that will follow a persistent irritability pattern from those that will follow a declining pattern, with the aim of personalizing irritability management. This group of children is also important as it shows a resilience pathway that should be better understood in future studies.

Strengths and limitations

This study relied on a large population sample followed from birth to 17 years with repeated assessment of irritability, hence allowing the use of sophisticated longitudinal methods. Although previous studies assessed irritability using either mother-reports[34] or self-reports,[34,35] our irritability measures relied on teacher-reports, thus on behaviors exhibited in the school context. Kindergarten and early elementary school teachers are often an untapped resource for identifying and helping at-risk children. Our study also tests, for the first time, the intermediate mental health pathways of the association between irritability and suicidality, thus disentangling the role played by irritability itself and the role played by proximal adolescent mental health symptoms associated with both irritability and suicidality. However, limitations should be acknowledged. First, due to attrition (e.g., emigration, lost to follow-up, refusal), analyses included about 70% of the initial representative sample. Although we used inverse probability weighting accounting for the probability to be missing at follow up, and little sociodemographic differences were found between included and excluded participants, caution should be used in generalizing our findings to the larger population of Québec. Second, at the 15 and 17-year assessments we measured recall of the past 12-month for suicidality. This means that we potentially missed cases that occurred during the 16th year, thus underestimating our associations. Third, the irritability items reflect the *DSM* definition, and provide an assessment which is psychometrically sound,[12] but comparisons between our findings and other studies should take into account differences in how the irritability construct was measured. Finally, we did not measure important constructs such as personality traits (e.g., neuroticism), which may play a role in the association between irritability and suicidality.[11]

Conclusions

This population-based study highlighted different pathways linking childhood irritability and adolescent suicidality. Significant associations between irritability and suicidality were found solely for children following a rising trajectory of irritability during childhood. Indirect associations through proximal depressive symptoms were found for both children following a rising and a persistent irritability trajectory. However, while those indirect associations largely explained the association between the persistent trajectory of irritability and suicidality, they only marginally accounted for the association between the

rising trajectory and suicidality. Monitoring developmental patterns of irritability during kindergarten and early elementary school through teacher assessments is important because they represent clear targets for suicide risk identification and for preventive interventions.

References

1. CDCMMWR. QuickStats: Suicide Rates for Teens Aged 15–19 Years, by Sex — United States, 1975–2015. *MMWR Morb Mortal Wkly Rep*. 2017;66. doi:10.15585/mmwr.mm6630a6

2. Nock MK, Green JG, Hwang I, et al. Prevalence, Correlates, and Treatment of Lifetime Suicidal Behavior Among Adolescents: Results From the National Comorbidity Survey Replication Adolescent Supplement. *JAMA Psychiatry*. 2013;70(3):300-310. doi:10.1001/2013.jamapsychiatry.55

3. Goldman-Mellor SJ, Caspi A, Harrington H, et al. Suicide attempt in young people: a signal for long-term health care and social needs. *JAMA Psychiatry*. 2014;71(2):119-127. doi:10.1001/jamapsychiatry.2013.2803

4. Hawton K, O'Connor RC. Self-harm in adolescence and future mental health. *The Lancet*. 2012;379(9812):198-199. doi:10.1016/S0140-6736(11)61260-9

5. Bostwick JM, Pabbati C, Geske JR, McKean AJ. Suicide Attempt as a Risk Factor for Completed Suicide: Even More Lethal Than We Knew. *Am J Psychiatry*. 2016;173(11):1094-1100. doi:10.1176/appi.ajp.2016.15070854

6. Reinherz HZ, Tanner JL, Berger SR, Beardslee WR, Fitzmaurice GM. Adolescent suicidal ideation as predictive of psychopathology, suicidal behavior, and compromised functioning at age 30. *Am J Psychiatry*. 2006;163(7):1226-1232. doi:10.1176/appi.ajp.163.7.1226

7. Leibenluft E. Irritability in children: what we know and what we need to learn. *World Psychiatry*. 2017;16(1):100-101. doi:10.1002/wps.20397

8. Vidal-Ribas P, Brotman MA, Valdivieso I, Leibenluft E, Stringaris A. The Status of Irritability in Psychiatry: A Conceptual and Quantitative Review. *J Am Acad Child Adolesc Psychiatry*. 2016;55(7):556-570. doi:10.1016/j.jaac.2016.04.014

9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (5th Ed.)*. Washington, DC, US: Author; 2013.

10. Conner KR, Meldrum S, Wieczorek WF, Duberstein PR, Welte JW. The Association of Irritability and Impulsivity with Suicidal Ideation Among 15- to 20-year-old Males. *Suicide Life Threat Behav*. 2004;34(4):363-373. doi:10.1521/suli.34.4.363.53745

11. Pickles A, Aglan A, Collishaw S, Messer J, Rutter M, Maughan B. Predictors of suicidality across the life span: the Isle of Wight study. *Psychol Med*. 2010;40(9):1453-1466. doi:10.1017/S0033291709991905

12. Orri M, Galera C, Turecki G, et al. Association of Childhood Irritability and Depressive/Anxious Mood Profiles With Adolescent Suicidal Ideation and Attempts. *JAMA Psychiatry*. March 2018. doi:10.1001/jamapsychiatry.2018.0174

13. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. *Am J Psychiatry*. 2009;166(9):1048-1054. doi:10.1176/appi.ajp.2009.08121849

14. Savage J, Verhulst B, Copeland W, Althoff RR, Lichtenstein P, Roberson-Nay R. A genetically informed study of the longitudinal relation between irritability and anxious/depressed symptoms. *J Am Acad Child Adolesc Psychiatry*. 2015;54(5):377-384. doi:10.1016/j.jaac.2015.02.010

15. Burke JD, Hipwell AE, Loeber R. Dimensions of oppositional defiant disorder as predictors of depression and conduct disorder in preadolescent girls. *J Am Acad Child Adolesc Psychiatry*. 2010;49(5):484-492.

16. Stringaris A, Zavos H, Leibenluft E, Maughan B, Eley TC. Adolescent irritability: phenotypic associations and genetic links with depressed mood. *Am J Psychiatry*. 2012;169(1):47-54. doi:10.1176/appi.ajp.2011.10101549

17. Whelan YM, Stringaris A, Maughan B, Barker ED. Developmental continuity of oppositional defiant disorder subdimensions at ages 8, 10, and 13 years and their distinct psychiatric outcomes at age 16 years. *J Am Acad Child Adolesc Psychiatry*. 2013;52(9):961-969. doi:10.1016/j.jaac.2013.06.013

18. Whelan YM, Leibenluft E, Stringaris A, Barker ED. Pathways from maternal depressive symptoms to adolescent depressive symptoms: the unique contribution of irritability symptoms. *J Child Psychol Psychiatry*. 2015;56(10):1092-1100. doi:10.1111/jcpp.12395

19. Shaw P, Stringaris A, Nigg J, Leibenluft E. Emotion dysregulation in attention deficit hyperactivity disorder. *Am J Psychiatry*. 2014;171(3):276-293. doi:10.1176/appi.ajp.2013.13070966

20. Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic Versus Episodic Irritability in Youth: ACommunity-Based, Longitudinal Study of Clinical and Diagnostic Associations. *J Child Adolesc Psychopharmacol*. 2006;16(4):456-466. doi:10.1089/cap.2006.16.456

21. Dougherty LR, Smith VC, Bufferd SJ, Kessel EM, Carlson GA, Klein DN. Disruptive mood dysregulation disorder at the age of 6 years and clinical and functional outcomes 3 years later. *Psychol Med*. 2016;46(5):1103-1114. doi:10.1017/S0033291715002809

22. Franklin JC, Ribeiro JD, Fox KR, et al. Risk Factors for Suicidal Thoughts and Behaviors: A Meta-Analysis of 50 Years of Research. *Psychol Bull*. November 2016. doi:10.1037/bul0000084

23. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Stat Methods Med Res*. 2013;22(3):278-295. doi:10.1177/0962280210395740

24. Murray AL, Eisner M, Ribeaud D. Can the Social Behavior Questionnaire Help Meet the Need for Dimensional, Transdiagnostic Measures of Childhood and Adolescent Psychopathology? *Eur J Psychol Assess*. December 2017:1-6. doi:10.1027/1015-5759/a000442

25. Government of Canada SC. National Longitudinal Survey of Children and Youth (NLSCY). http://www23.statcan.gc.ca/imdb/p2SV.pl?Function=getSurvey&SDDS=4450. Published May 14, 2009. Accessed December 5, 2016.

26. Achenbach TM, Edelbrock C, Howell CT. Empirically based assessment of the behavioral/emotional problems of 2- and 3- year-old children. *J Abnorm Child Psychol*. 1987;15(4):629-650. doi:10.1007/BF00917246

27. Offord DR, Boyle MH, Racine Y. Ontario Child Health Study: correlates of disorder. *J Am Acad Child Adolesc Psychiatry*. 1989;28(6):856-860. doi:10.1097/00004583-198911000-00008

28. Behar LB. The Preschool Behavior Questionnaire. *J Abnorm Child Psychol*. 1977;5(3):265-275. doi:10.1007/BF00913697

29. Côté SM, Orri M, Brendgen M, et al. Psychometric properties of the Mental Health and Social Inadaptation Assessment for Adolescents (MIA) in a population-based sample. *Int J Methods Psychiatr Res*. 2017: doi:10.1002/mpr.1566

30. Geoffroy M-C, Boivin M, Arseneault L, et al. Associations Between Peer Victimization and Suicidal Ideation and Suicide Attempt During Adolescence: Results From a Prospective Population-Based Birth Cohort. *J Am Acad Child Adolesc Psychiatry*. 2016;55(2):99-105. doi:10.1016/j.jaac.2015.11.010

31. Willms D, Shields M. *A Measure of Socioeconomic Status for the National Longitudinal Study of Children*. Vol 9607. Fredericton, New Brunswick: Atlantic Center for Policy Research in Education, University of New Brunswick and Statistics Canada; 1996.

32. Muthén L, Muthén, B. *Mplus User's Guide. Seventh Edition.* Los Angeles, CA: Muthén & Muthén; 1998.

33. Kline RB. *Principles and Practice of Structural Equation Modeling, Third Edition*. Guilford Press; 2010.

34. Caprara GV, Paciello M, Gerbino M, Cugini C. Individual differences conducive to aggression and violence: trajectories and correlates of irritability and hostile rumination through adolescence. *Aggress Behav*. 2007;33(4):359-374. doi:10.1002/ab.20192

35. Wiggins JL, Mitchell C, Stringaris A, Leibenluft E. Developmental Trajectories of Irritability and Bidirectional Associations With Maternal Depression. *J Am Acad Child Adolesc Psychiatry*. 2014;53(11):1191-1205.e4. doi:10.1016/j.jaac.2014.08.005

36. Brotman MA, Kircanski K, Stringaris A, Pine DS, Leibenluft E. Irritability in Youths: A Translational Model. *Am J Psychiatry*. January 2017:appiajp201616070839. doi:10.1176/appi.ajp.2016.16070839

37. Platt B, Waters AM, Schulte-Koerne G, Engelmann L, Salemink E. A review of cognitive biases in youth depression: attention, interpretation and memory. *Cogn Emot*. 2017;31(3):462-483. doi:10.1080/02699931.2015.1127215

38. Frazier EA, Liu RT, Massing-Schaffer M, Hunt J, Wolff J, Spirito A. Adolescent but Not Parent Report of Irritability Is Related to Suicidal Ideation in Psychiatrically Hospitalized Adolescents. *Arch Suicide Res*. 2016;20(2):280-289. doi:10.1080/13811118.2015.1004497

39. McGirr A, Turecki G. The relationship of impulsive aggressiveness to suicidality and other depression-linked behaviors. *Curr Psychiatry Rep*. 2007;9(6):460-466.

40. McGirr A, Renaud J, Bureau A, Seguin M, Lesage A, Turecki G. Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. *Psychol Med*. 2008;38(3):407-417. doi:10.1017/S0033291707001419

41. Toohey MJ, DiGiuseppe R. Defining and measuring irritability: Construct clarification and differentiation. *Clin Psychol Rev*. 2017;53:93-108. doi:10.1016/j.cpr.2017.01.009

42. Björkenstam C, Kosidou K, Björkenstam E. Childhood adversity and risk of suicide: cohort study of 548 721 adolescents and young adults in Sweden. *BMJ*. 2017;357:j1334. doi:10.1136/bmj.j1334

Table 1. Socio-demographic characteristics at birth of the study sample

	N (%) of 1,393
Sex	
Male	737 (52.9)
Female	656 (47.1)
Maternal age (birth of the target child), y	
≤21	75 (5.4)
>21	1,318 (94.6)
Maternal education	
High school diploma or higher	1,163 (83.6)
No high school diploma	229 (16.5)
Family sufficient income	
Sufficient income	1,088 (79.0)
Insufficient income	290 (21.0)
Family status	
Intact family (married or common-law union)	1,144 (82.3)
Blended/single mother	246 (17.7)
Maternal depression	
Yes (≥2.67 CESD)	185 (13.3)
No (<2.67 CESD)	1,204 (86.7)

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistic Institute.

CESD=Centre for Epidemiological Study Depression scale

Table 2. Suicidality, suicidal ideation and suicide attempt rates in adolescence by childhood irritability trajectory (N=1393)

	Suicidality N (%)		**Ideation** N (%)		**Attempt** N (%)	
	No	Yes	No	Yes	No	Yes
Low (n=1,040, 74.7%)	942 (90.6)	98 (9.4)	1,305 (93.7)	88 (6.3)	998 (96.0)	42 (4.0)
Rising (n=181, 13.0%)	151 (83.4)	30 (16.6)	161 (89.0)	20 (11.1)	167 (92.3)	14 (7.7)
Declining (n=103, 7.4%)	94 (91.3)	9 (8.7)	97 (94.2)	6 (5.8)	100 (97.1)	3 (2.9)
Persistent (n=69, 5.0%)	62 (89.9)	7 (10.1)	65 (94.2)	4 (5.8)	66 (95.7)	3 (4.4)
Entire sample (1,393)	1,249 (89.7)	144 (10.3)	1,305 (93.7)	88 (6.3)	1,331 (95.6)	62 (4.5)

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistic Institute.

Table 3. Direct and indirect associations between childhood irritability trajectories and suicidality in adolescence

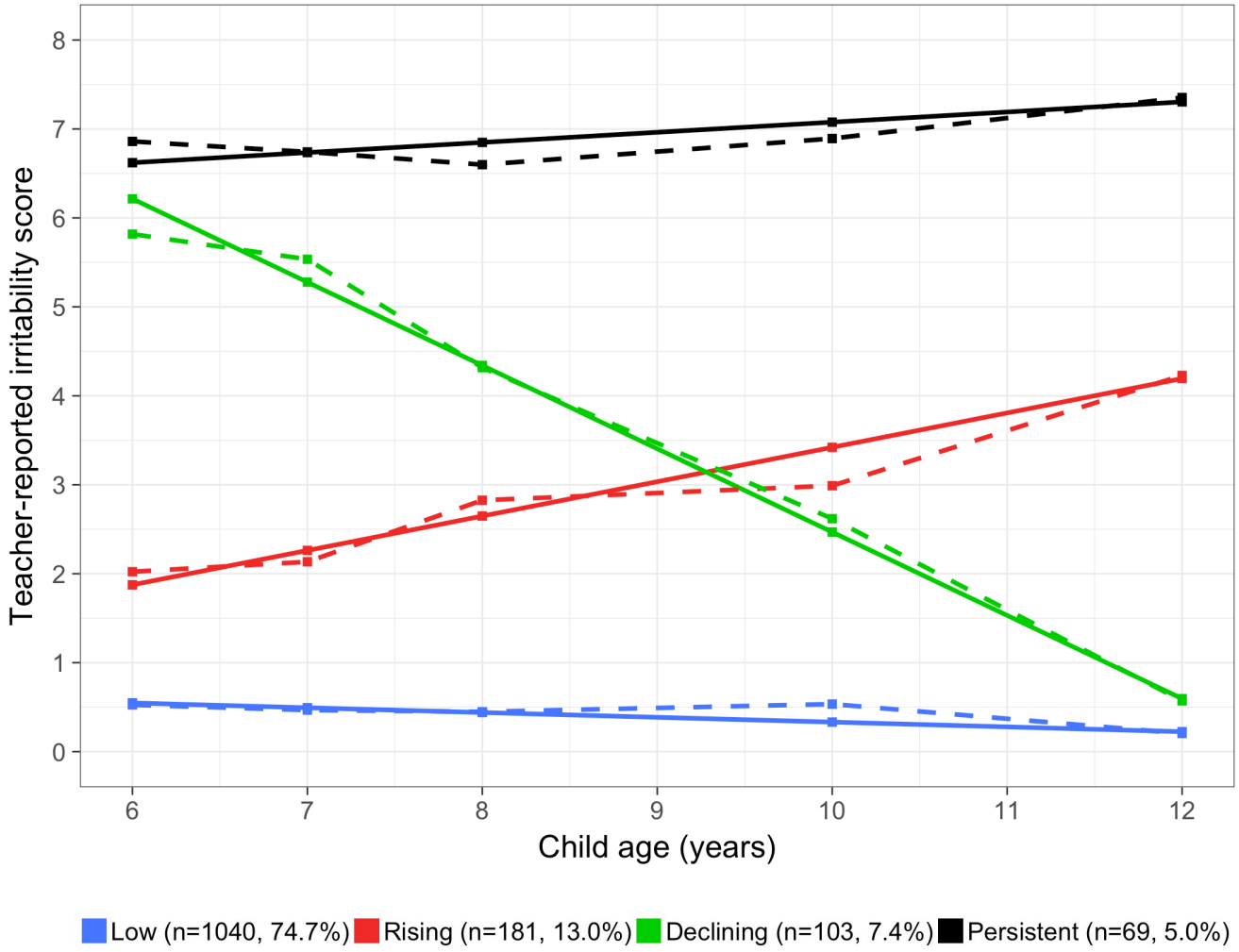
	Suicidality risk, OR (95%CI)		
	Rising	Declining	Persistent
Total association	**2.64 (1.59-4.38)**	0.93 (0.41-2.08)	1.83 (0.77-4.37)
Direct association	**2.11 (1.30-3.43)**	0.81 (0.36-1.84)	1.17 (0.48-2.90)
Indirect association			
via Depressive symptoms	**1.17 (1.03-1.34)**	1.13 (0.99-1.29)	**1.51 (1.16-1.97)**
via Anxiety symptoms	1.00 (0.97-1.04)	0.96 (0.91-1.02)	0.91 (0.80-1.04)
via Disruptiveness symptoms	1.07 (0.98-1.16)	1.05 (0.97-1.15)	1.16 (0.97-1.37)
via Hyperactivity-impulsivity symptoms	0.99 (0.93-1.06)	1.00 (0.95-1.04)	0.98 (0.82-1.16)

Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistic Institute.

Table reports the Odds Ratio (OR) and 95% Confidence Intervals (CI) for the total, direct, and indirect associations from the path analysis model. ORs refer to the increase risk of suicidality (any suicidal ideation and/or suicide attempt) of the rising, declining, and persistent irritability trajectories (compared to the low trajectory). The model is adjusted for child sex, SES, and baseline levels (6 years) of depressive, anxiety, disruptiveness, and hyperactivity-impulsivity symptoms.

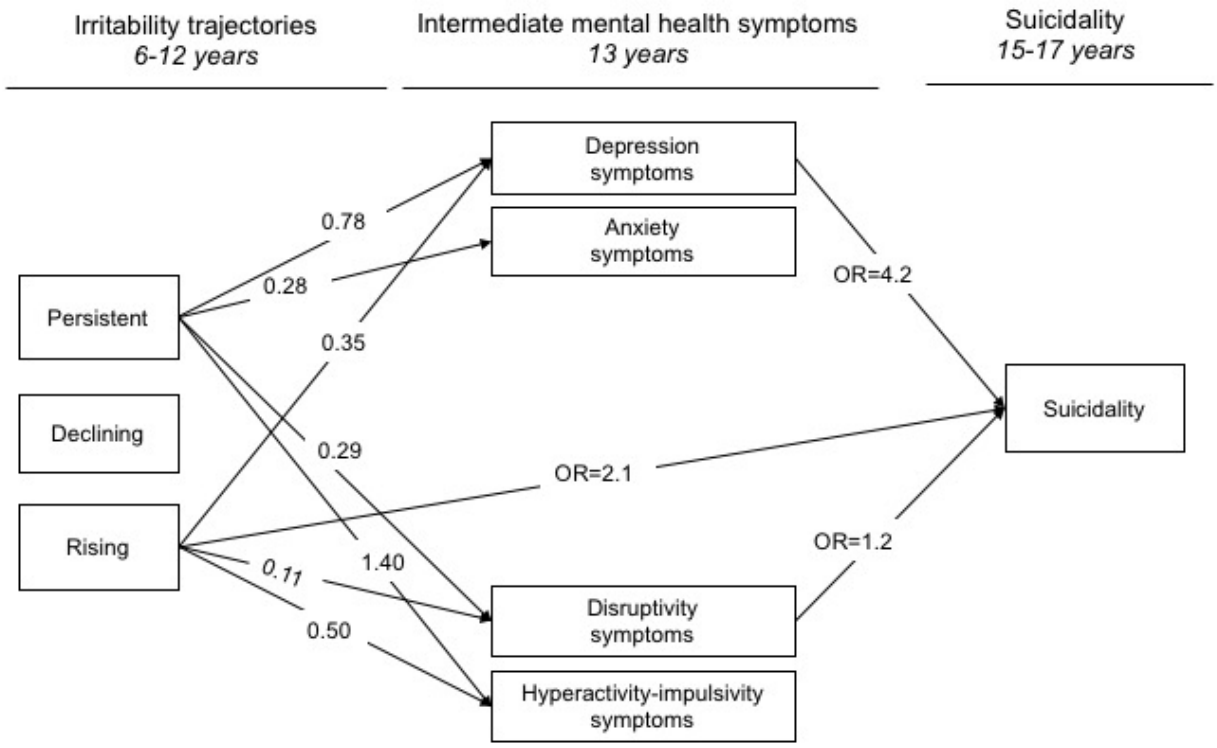
Total effect (i.e., the sum of direct and indirect effect) is the effect before adjustment/partialing for the indirect mechanisms. Direct and Indirect association = decomposition of the total association into the association due to the intermediate variables (indirect association) and the specific (partialed/controlled) association due to the predictor (direct association).

Figure 1. Developmental trajectories of childhood irritability from 6 to 12 years



Dotted lines represent the trajectories for the observed value, whether solid lines represent the trajectories as estimated by our model. Model fit information: Bayesian Information Criterion=21,776.811, Entropy (average posterior probability of class membership; range 0-1) = 0.890, Bootstrap Likelihood Ratio Test (BLRT) p-value=0.000 (for the BLRT, a significant p-value for a model with *N* classes indicates that the model is better than one having *N*-1 classes).

Figure 2. Path analysis model estimating the direct and indirect associations between irritability trajectories and suicidality



Arrows indicate the effect of one variable on another. The low trajectory is the reference category. The associations of the irritability trajectories and the mediator (i.e., continuous variables) are reported as linear regression coefficients, while the associations of both irritability trajectories with intermediate mental health symptoms with suicidality (i.e., binary variable) are reported as Odds Ratios. Non-significant arrows ($p<0.05$) are omitted for clarity. Models are adjusted for child sex, SES, and baseline levels of depressive, anxiety, disruptiveness, and hyperactivity-impulsivity symptoms. The model fit indices based on weighted least square mean and variance adjusted analysis are the following: Chi-square=11.21 (16 degrees of freedom), p=0.796; CFI=1.000; TLI=1.017; RMSEA=0.000, 90%CI=0.000-0.016.