SAPIENZA
UNIVERSITÀ DI ROMA

Externalizing symptoms and suicidal behaviour in adolescents; a 17 years population based longitudinal study

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Summary

Introduction

The present work summarizes background and main findings from two different research projects (Forte et al., 2019; Orri et al., 2018), based on data drown from the Quebec Longitudinal Study on Child Development (see Chapter 2), that Dr. Massimiliano Orri and I conducted from 2016, under the supervision of Prof. Sylvana M. Côté, director of the Research Group on Children Psychosocial Maladjustment at the University of Montreal.

Despite the recent research work, my interest and clinical activities on adolescent suicidality started in 2014, when I was working at the Suicide Prevention Center at Sapienza University, directed by Prof. Maurizio Pompili. There, I directly experienced, as a young clinician, the dramatic impact of young individuals suicide attempt on families, peers, as well as on professionals. Alonngside the burden and high costs of suicidal behavior in adolescents, in terms of mental health outcomes and loss of young lives, I noticed the paradox of the very few preventive instruments available for clinicians and professionals. Despite being a major public health concern among young people, suicidal behavior in adolescents receive a very little attention by public health policies and a small amount of funding, especially in Italy.

Moreover, as a clinician I often noticed that our intervention occurs too late in the history of young patients; in our clinical work, it is very common to deal with adolescent or young adults presenting suicidal behaviors, but patients are often asking for help many years before our intervention.

Therefore, the available literature suggests that there is still a lack of effective early suicide prevention strategies starting from elementary school. Nevertheless, such preventive initiatives should ideally start right after pregnancy (see chapter 1).

The aims of the present thesis are 1) to briefly summarize the present knowledge on the developmental aspects of suicidal behavior, in the light of a life history prospective 2) to summarize findings from two different research studies on the association between externalizing psychopathology among children and suicidal behavior in adolescents.

1. The developmental origins of suicidal behavior

1.1 Suicidal behavior in adolescents

Suicide is the second leading cause of death among 10–19 years old in Western countries (Turecki & Brent, 2016) and can be considered the major public health concern among adolescents. Therefore, a better knowledge of the mechanisms leading to suicidal behaviors (SB) in children and adolescents is of major interest and importance for the development of effective therapeutic interventions early in life.

The number of adolescent suicide had been increasing dramatically in the United States during recent decades. From 1950 to 1990, the suicide rate for adolescents 15 to 19 years old increased by 300%, but from 1990 to 2013, the rate in this age group decreased by 28% (Centers for Disease Control and Prevention (CDC), 2019). In 2013, there were 1748 suicides among people 15 to 19 years old. The right number of deaths from suicide may truly be higher, because some of these deceases may have been documented as "accidental." Adolescent boys 15 to 19 years old, compared to female, had a completed suicide rate that was 3 times greater (Shain, 2016). On the other hand the rate of suicide attempts was twice as high among girls than among boys, correlating to girls tending to choose less lethal methods. The ratio of attempted suicides to completed suicides among adolescents is estimated to be 50:1 to 100:1.5 (Shain, 2016).

In the last decades, the contributions of both social and individual factors to understanding suicide risk have been suggested (Pompili, 2018a). A number of models have been proposed, most emphasizing the interaction between predisposing and precipitating factors (see Figure 1). Suicide is considered to be etiologically heterogeneous, with significant variability in the strengths and patterns of association of risk factors across gender, age, culture, geographic location, and personal history (Pompili, 2018a; Turecki & Brent, 2016). Thus, models have been proposed to explain suicide risk in specific subgroups of

suicide, such as those exposed to early-life adversity (ELA) (Turecki & Brent, 2016).

In the vast majority of studies, the role of psychopathological factors in the emergence of SB is examined using a categorical approach. Therefore, the impact of each psychiatric disorder is studied separately. However, the limits of categorical models to predict the emergence of SB have been raised by several authors (Benarous et al., 2019; Brezo et al., 2007).

Over the last decades, the use of dimensional view of psychopathology, together with person centered approaches over and beyond medical categories (Pompili, 2018b), to model risk factors in suicide research has, therefore, been promoted (Turecki & Brent, 2016). In this view, suicide risk should be considered as a complex and multifactorial process, “generated over the course of several years via the developmental processes of the individual” (Pompili, 2018b).

1.2 Life course epidemiology

Life course epidemiology can be defined as the “study of long term effects on later health or disease risk of physical or social exposures during gestation, childhood, adolescence, young adulthood and later adult life*”* (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003b).

As stated by Kuh and colleagues (2003), the aim of life course epidemiology is to “elucidate biological, behavioral, and psychosocial processes that operate across an individual’s life course, or across generations, to influence the development of disease risk” (Kuh, Ben-Shlomo, Lynch, Hallqvist, & Power, 2003a). The interest for a life course approach in epidemiology came out from studies on the role of early life factors in cardiovascular and other chronic diseases, in particular the cohort studies used to explore the “fetal origins hypothesis” (D J P Barker, 1997; David J.P. Barker, 1995).

According to this hypothesis, environmental exposures such as under nutrition during critical periods of growth and development in utero may have long term effects on adult chronic disease risk by ‘‘programming the structure or function of organs, tissues, or body systems” (David J.P. Barker, 1995). This idea of ‘‘biological programming’’ could be considered as an alternative paradigm to

the adult lifestyle model of adult chronic disease that focuses on how adult behaviors (notably smoking, diet, exercise and alcohol consumption) affect the onset and progression of diseases in adulthood.
As noted by Kuh and colleagues, a life course approach does not deny the importance of conventional risk factors, such as smoking and hypertension, which were so successfully identified by the early post-war adult cohort studies, “rather its purpose is to study the contribution of early life factors jointly with these later life factors to identify risk and protective processes across the life course” (Kuh et al., 2003a).
Moreover, life course epidemiology attempts to integrate biological and social risk processes rather than postulate dichotomies between them and thus it overlap with social epidemiology, that branch of epidemiology that studies the role of social factors in the production of health and disease in populations. Therefore this model can have a special role in the study of the development of suicidal behavior and thus in studies on early intervention in psychiatry. More specifically, life course epidemiology studies how psychosocial exposures during childhood, adolescence, and early adult life influence adult disease risk and socioeconomic position, and consequently may account for mental disorders in adult as well as suicide mortality.

1.3 The developmental origins of suicidal behavior

There is a growing body of evidences supporting the developmental origins of many diseases (D J P Barker, 1997; David J.P. Barker, 1995; Wadhwa, Buss, Entringer, & Swanson, 2009). In mammals, early life adversities, including mother–pup interactions, shape the response of an individual to chronic stress or to stress-related diseases during adult life. While the prenatal factors that influence the development of physical adult diseases are clearly described (see Barker’s hypothesis), the nature of the increased vulnerability to mental disorders in response to a negative early-life environment has not been yet clarified. For example, Weaver et al. (2004) showed that the development of the HPA axis in the offspring is influenced by the extent of maternal care via epigenetic mechanisms based on DNA methylation and histone acetylation

(Weaver et al., 2004). Maternal behavior produces stable alterations of DNA methylation and chromatin structure, providing a mechanism for the long-term effects of maternal care on gene expression in the offspring. These epigenetic mechanisms suggested the fundamental role of maternal behavior on stress response in the offspring.

Epigenetic changes related to early-life adversities may also increase suicide risk by inducing significant changes in the stress-response systems and to the regulation of neurotropic factors (Turecki, Ernst, Jollant, Labonté, & Mechawar, 2012).

As noted by Turecky et al (2015), a large subgroup of individuals manifesting suicidal behaviors were exposed to early-life adversity, and these cases share a number of common characteristics. Suicidal behavior in this subgroup of individuals may result from a cascade of developmental processes, starting from various types of abuse and/or neglect experienced early in life.

To our knowledge, only a few studies aimed to better understand the importance of postnatal events such as exposure to maternal depression, as an early risk factor in the pathophysiology of suicidal behavior in adult life, and the role of early behavioral disturbances, such as externalizing behaviors.

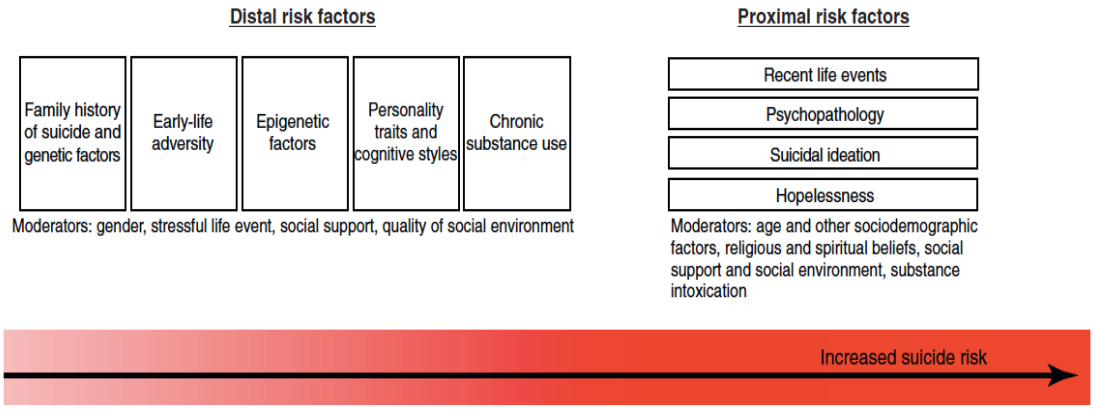


Fig.1 Exposure to early-life adversity increases epigenetic changes affecting the hippocampus, leading to hypothalamic–pituitary–adrenal (HPA) dysregulation and development of emotional, behavioral and cognitive phenotypes, which in turn increase risk for suicide (From Turecki et al, 2012)

Distal risk factors

Many studies showed that suicidal behavior runs in family (Turecki & Brent, 2016), indicating that distal factors can increase suicide risk. Family studies show that the risk of attempts is increased in the relatives of those who died by suicide, and vice versa. While psychopathology also aggregates in families, the transmission of SB appears to be mediated through the familial transmission of impulsive aggression (Brent, Bridge, Johnson, & Connolly, 1996). Despite several research focused on the heritability of SB, the identification of specific genes linked to suicide risk remains elusive, in spite of several candidate-gene and genome-wide association studies, which have mostly provided inconclusive results (Turecki, 2014). Future approaches in suicide research will gain from modeling the interactions between experience and genes (Turecki & Brent, 2016).

Developmental or mediating risk factors

Distal factors are likely to act through personality traits and cognitive styles that mediate their association with SB. Although depression and anxiety make strong contributions to SB across the lifespan, both retrospective and prospective studies find that interpersonal conflict, impulsive aggression, conduct disorder, antisocial behavior, and alcohol and substance abuse are more salient for SB in adolescents and young adults, while harm avoidance and mood disorders are increasingly present with increasing age (McGirr et al., 2008; Séguin, Beauchamp, Robert, DiMambro, & Turecki, 2014).

Proximal or precipitating risk factors

Proximal risk factors are temporally associated with SB and act as their precipitants. Beside past SA, psychopathology is the single most important predictor of suicide and strongly associates with other forms of SB. Retrospective, proxy-based interviews with informants, commonly referred to as psychological autopsies, indicate that approximately 90% of individuals who die by suicide had an identifiable psychiatric disorder prior to death. Major depressive episodes, either major among depressive or bipolar

disorder, account for at least half of suicide deaths (Holma et al., 2014). Among bipolar patients, mixed state episodes most strongly associate with SAs (Holma et al., 2014; Tondo, Pompili, Forte, & Baldessarini, 2016).

2. The association between childhood externalizing symptoms and suicidal behavior in adolescents: background and research hypothesis

2.1 ADHD and comorbid psychopathology

Most individuals exhibiting suicidal behavior also present with comorbid mental disorders. For instance, a strong association exists between the presence of psychopathology, mostly major depressive disorder (MDD) and Bipolar Disorders (BD), and suicide risk (Hawton & van Heeringen, 2009; Turecki et al., 2012). Comorbidity with substance disorders, such as alcohol and other drug dependence, is also frequently reported (Bronisch & Wittchen, 1994; Tondo et al., 1999).

Recent findings also highlight a link between attention-deficit/hyperactivity disorder (ADHD) and suicidal behavior (A. James, Lai, & Dahl, 2004; Stickley, Koyanagi, Ruchkin, & Kamio, 2016) and suggested that ADHD and SB share genetic and environmental risk factors (Ljung, Chen, Lichtenstein, & Larsson, 2014).

Indeed, ADHD is associated with an increased risk of both attempted and completed suicide (Ljung et al., 2014), and there is evidence that early life adversities and/or maternal depression, play a role in the development of suicidal behavior among those affected by ADHD (Chronis-Tuscano et al., 2010). Among subjects affected by ADHD, maternal depression was considered a very early predictor for suicide attempts. Specifically, among a cohort of 125 children who met DSM-IV criteria for ADHD, maternal depression and concurrent child emotional and behavior problems at 4 to 6 years of age were both predictive of depression and suicidal behavior (Chronis-Tuscano et al., 2010). However, further investigations are needed to clarify the role of ADHD in the link between maternal depression and youth suicidal behavior.

2.2 ADHD and suicidal behavior

Attention deficit hyperactivity disorder (ADHD) is a common disorder that affects children and adolescents with a prevalence of 5.29% (Polanczyk, de Lima, Horta, Biederman, & Rohde, 2007). Children and adolescent ADHD is related to several adult negative outcomes (Barbaresi et al., 2013; Nigg, 2013) such as completed suicide, attempt and ideation (Impey & Heun, 2012). Despite a few reports, there is still a lack of longitudinal investigation of the association between the course of ADHD symptoms and suicidal behavior in adolescents (Anthony James, 2012). Hyperactive and impulsive behaviors are highly associated with suicidal behaviors in clinical studies (Allely, 2014; Bangs et al., 2008; Lan et al., 2015; Ljung et al., 2014; Stickley et al., 2016; Swanson, Owens, & Hinshaw, 2014; Taylor, Boden, & Rucklidge, 2014), cross-sectional (Chronis-Tuscano et al., 2010; Hurtig, Taanila, Moilanen, Nordström, & Ebeling, 2012) and longitudinal population based studies (C Galéra, Bouvard, Encrenaz, Messiah, & Fombonne, 2008; Sourander et al., 2009).

To our knowledge, only two population-based studies investigated the association between ADHD and suicidal behaviors (Galéra, Bouvard, Encrenaz, Messiah, & Fombonne, 2008b; Sourander et al., 2009). Sourander and colleagues (Sourander et al., 2009) investigated early or middle childhood psychopathologic disorders and later completed suicides, but didn't focus specifically on the correlation between the development of hyperactivity/inattention and SB. Another population-based study found that the association between ADHD and suicidal behaviors held only for males (C Galéra et al., 2008; A. James et al., 2004; Sourander et al., 2009), but there seem to be not clear consensus yet regarding gender differences (Hurtig et al., 2012). Given the developmental origins of suicidal behavior (Turecki & Brent, 2016), we aimed at identifying the developmental aspects of hyperactivity/inattention symptoms and its correlation with suicidal behavior. Galera et al. found that the association between ADHD and SB held only for males (C Galéra et al., 2008), but there seem to be not clear consensus regarding sex differences since another study reported opposite results (Hurtig et al., 2012). Given the importance of individualized preventive

intervention taking into account sex differences in adolescent SB, it is relevant to clarify the extent to which sex differences play a role in SB of children showing hyperactive/inattentive symptoms.

2.3 Childhood irritability and suicidal behavior in adolescents

Irritability (defined as increased proneness to anger, relative to peers) (Leibenluft, 2017) is commonly reported among children seeking mental health evaluation (prevalence in the general population ~3%) (Althoff, Verhulst, Rettew, Hudziak, & Van Der Ende, 2010). This is especially true for children showing depressive symptoms, for which irritability is reported in one third of the cases (Stringaris, Maughan, Copeland, Costello, & Angold, 2013). Recent genetically informed studies corroborated the clinical findings showing that irritability has significant genetic overlap with depressive symptoms, supporting the hypothesis of two different phenotypes: one showing both depressive and irritability symptoms, one showing only depressive symptoms (Fava et al., 2010; J. Savage et al., 2015; Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012).

However, studies on the differences between these two phenotypes are still rare, especially among youths. A recent study reported that the phenotype showing both irritability and depression is more likely to show comorbid disruptive disorders than the phenotype showing only depressive symptoms, but they were similar with respect to other characteristics, such as anxiety comorbidity, developmental stage, and depression onset (Stringaris et al., 2013). Other cross-sectional studies among adults showed that irritable major depression was associated with early age of onset, lifetime persistence, comorbidity with anxiety, and impulse-control disorders (Fava et al., 2010; Perlis et al., 2009).

Despite this early evidence on the difference between these two phenotypes, the knowledge about how they predict later outcomes is very limited. The current literature mostly examined irritability and depression separately. Childhood depressive symptoms were consistently shown to be a risk factor for both depression and suicidality later in life (Brezo et al., 2008; Franklin et al., 2017; Sourander et al., 2009). Although several studies indicated that

childhood irritability predict internalizing disorders in adolescence (Whelan, Stringaris, Maughan, & Barker, 2013) and adulthood (Stringaris, Cohen, Pine, & Leibenluft, 2009), few prospective studies explored the association between irritability and suicidal behavior. These studies suggested that irritability during adolescence significantly increases the risk of suicidal behavior (ideation, plan, and attempt) later in life (Pickles et al., 2010) (. To our knowledge, only 1 study described the longitudinal association between the irritable depression and depression only phenotypes on adult depression, showing that these phenotypes tend to be stable (i.e., depressed individuals with irritability were more likely to continue to show irritable depression) (Stringaris et al., 2013). This study has however several limitations. First, it used a categorical definition of depression (DSM-based) and irritability. Dimensional evaluations, instead, has the advantage to investigate subclinical presentation of depressive symptoms, and are more suited to capture the depressive symptomatology in youth. This is especially the case in population samples and with behaviors, such as irritability, where the distinction between normal and pathological manifestations varies developmentally (Brotman, Kircanski, Stringaris, Pine, & Leibenluft, 2017). Additionally, dimensional measures are more suited to investigate the development of symptoms intensity across long periods. Second, the measure of irritability at 14 years on average does not encompass childhood, which is a key period for the development of irritability (Leibenluft, 2017). Finally, they used only 2 data collection time points with broad age groups (9-16 and 19-21 years), which do not allow the study of the developmental trajectories of those symptoms.

2.4 Research hypothesis and objectives of the studies

Using data from a large Canadian population based cohort, the objective of these studies were 1) to test the longitudinal association between longitudinal profiles of irritability and depressive symptoms during childhood, and suicidal behaviors and depressive symptoms during adolescence. Differently form previous studies (mostly relying of self-reports and/or mother-reports) we used repeated behavioral assessment performed by different teachers during the whole elementary school period (6-12 years). To maximize the potential of

these longitudinal data, we estimated, for the first time, the joint developmental trajectories of irritability and depressive symptoms. This approach also has the advantage of empirically derive distinct groups of individuals that share a common developmental pattern, thus providing new evidences on the evolution of the different profiles over time.

2) To clarify the predictive association between childhood symptoms of hyperactivity/impulsivity and inattention (ADHD symptoms) and suicidal ideation and attempt in adolescence. Especially, we investigated whether this association is different among girls and boys. We relied on longitudinal data from a population sample from Québec, Canada, using person-centered methods allowing us to identify children with atypically high irritability/depressive symptoms and ADHD symptoms over the course of childhood, and teacher-assessment of children behaviors.

3. The Québec Longitudinal Study of Child Development (QLSCD) – (1998-2019)

"Although the idea of early intervention as a preventive measure can be traced at least as far back as ancient Greece, the second half of the 20th century will certainly be recognized as the dawn of the field of social maladjustment prevention (Coie et al., 1993; Mrazek & Haggerty, 1994). Numerous programs have been developed for adolescents and teenagers to prevent school dropout, delinquency, drug addiction and suicide. Scientific evaluations of these programs have been far too few in number, but they tend to demonstrate that it is extremely difficult to help those most at risk in this age group (Rosenbaum & Hanson, 1998; Rutter, Giller & Hagell, 1998; Tremblay & Craig, 1995). It is becoming increasingly clear that the factors which lead to serious adaptation problems are in place long before adolescence. Hence the idea that the prevention of social adaptation problems should start at least during childhood, and preferably right from pregnancy (Olds et al., 1998; Tremblay, LeMarquand & Vitaro, 1999)."

Richard E. Tremblay, Ph.D., M.S.R.C.[1]

3.1 Phase I

The Québec Longitudinal Study of Child Development (QLSCD), principally funded by the Ministry of Health and Social Services, Québec, Canada, during its first phase, was mainly designed to advance the knowledge on child development. Its main objective has been to identify early childhood factors that might affect the social adjustment and academic performance of young subjects.

The first phase (1998) was conducted on a cohort of 2,120 Québec infants who were followed annually from 5 months to about 4 years of age. This representative sample included children (single births except highly premature) born to mothers residing in Québec in 1997-1998.

[1] Child psychologist and Professor of Pediatrics, Psychiatry, and Psychology at

Data collected enabled researchers to evaluate the influence of particular milieus (family, child care and the broader social environment) on various aspects of well-being. For instance, quite a few studies dealing with health, development (motor, social and cognitive), behavior, diet, sleep, the family and economic environment, use of childcare, etc., have already been performed.

This prospective longitudinal study allowed researchers to describe the changes over time for each measured variable concerning each individual. The researchers thus recorded the changes during the first three years of the children's lives. Profiles of children, parents and families as well as some developmental trajectories were drawn based on the data collected during the different stages (all questionnaires are available online http://www.jesuisjeserai.stat.gouv.qc.ca).

3.2 Phase 2 (2003-2010)

The relaunch of the QLSCD (2003-2010) was possible through funding by the Ministry of Health and Social Services, the Lucie and André Chagnon Foundation, the ministère de la Famille (Ministry of Family) and the Institut de la statistique du Québec (the Institut). The overall goal remained the enhancement of the actual knowledge of child development. However, analyses of the data in the second phase were focused on understanding the factors that contribute to academic success in primary school, while taking into account children's life experiences.

More than 1,500 children had been participating annually in the study, from kindergarten to second grade. During this period they also participated in two special data collections on psychomotor development and physical condition, in cooperation with Québec en forme (Québec in Shape). They have been visited every two years, namely in fourth and sixth grade. The visits were conducted in the spring, March to June, before their school year ends.

From the very beginning, the QLSCD used a variety of data collection instruments to gather information on the children and their families – computerized questionnaires, paper questionnaires, cognitive and psychometric activities . Since kindergarten, the children's teachers have also

been asked to respond to a questionnaire on various aspects of the participating children's development and adjustment to school (all questionnaires are available online http://www.jesuisjeserai.stat.gouv.qc.ca).

3.3 Phase 3 (2011-2015)

The third phase of the QLSCD included collections of data in 2011, 2013 and 2015. Aligning with the two previous phases, it aimed to follow young people throughout high school, from the age of 13 to 17. Informations collected during the third phase of the study made it possible to continue monitoring various aspects of social and school adjustment in youth. New realities that can arise during adolescence were examined, including work-school-play balance, romantic relationships, risky behavior (smoking, alcohol and drug use, gambling), school motivation and educational aspirations, bullying, school violence, and dropping out. The mental health status of the young respondents was still studied, as well as their families, friends, and school settings, particularly with regard to their role as protective factors.
In addition to the paper and computerized questionnaires administered to parents, online questionnaires were completed by the children (all questionnaires are available online http://www.jesuisjeserai.stat.gouv.qc.ca). Home visits also took place for each of the 3 collections.

3.4 Phase 4 (2016-2023)

The fourth phase of the QLSCD includes data collection rounds in 2017, 2018 and 2019, and two more are planned over the following years. Aligning with the three previous phases, Phase 4 aims to follow young people throughout their transition to adulthood, from the ages of 19 to 25.
The information collected during the fourth phase of the study has already been used to continue monitoring various aspects of social adjustment and well being in youth. Certain new realities that can arise in early adulthood will be examined, such as work, studies, relationships with parents and friends, romantic relationships, finances, lifestyle habits, career choices, and health and well-being. The young participants become now the only respondents.

Fig. 2 Different waves and data collection of the Quebec longitudinal study of child development: > 2000 births in 1997-1998

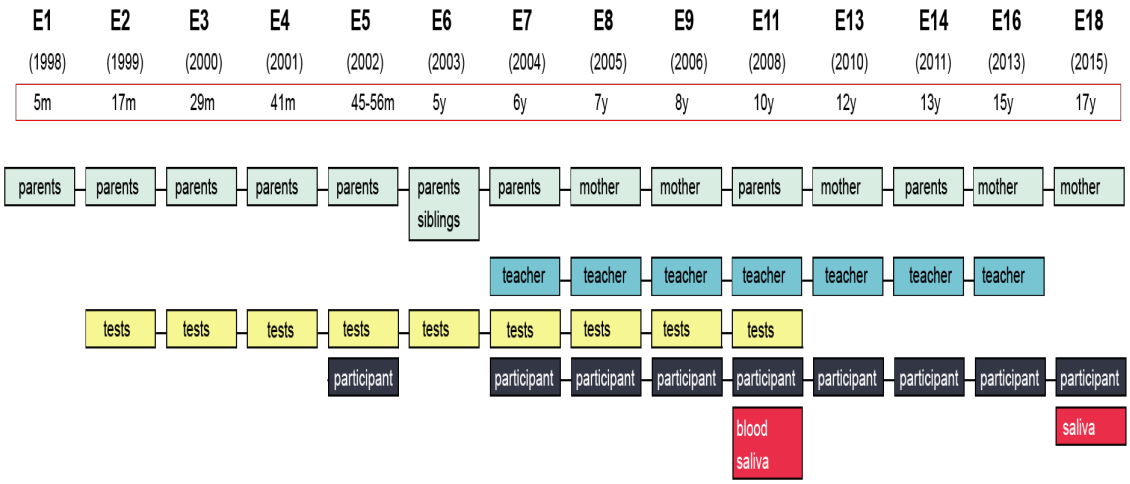


Fig. 3 Consent form for parents

Institut de la statistique Québec

I AM, I'LL BE
THE SURVEY ON THE FUTURE OF A GENERATION

Québec Longitudinal Study of Child Development
QLSCD (E18) – 2015 Round

Consent Form for the Parent

1. **I authorize the Institut de la statistique du Québec (Statistique Québec) to:**

   1.1. Have an interviewer from Statistique Québec, specially trained for the study, fill out a computerized questionnaire with me with the goal of collecting data on my teenager's development and environment;

   1.2. Obtain from the Ministère de l'Éducation, du Loisir et du Sport du Québec (MELS) my teenager's permanent code in order to give Statistique Québec access to information held by the MELS or by school boards;

   1.3. Send data collected on me, my teenager or the persons I represent, in an anonymous form (i.e., not revealing any name, address or telephone number) to affiliated researchers who will have committed to respecting Statistique Québec's standards regarding the security and confidentiality of information.

Fig. 3 Information sheet and consent form for the participation to the study

Information Sheet and Consent Form

(please read and keep this document)

Québec Longitudinal Study of Child Development

From Birth to Age 20 – 2018 Round on Mental Health

About the study

A special *I am, I'll be* data collection round entitled *From Birth to Age 20 – 2018 Round on Mental Health* will be carried out this winter among all study respondents. This special round is being funded in most part by the Centre hospitalier universitaire Sainte-Justine (CHU Sainte-Justine), with the support of a research grant from the Canadian Institutes of Health Research awarded to Sylvana Côté, doctor of psychology, researcher at the Université de Montréal and a member of the Research unit on children's psychosocial maladjustment of the CHU Sainte-Justine. The Institut de la statistique du Québec (Statistique Québec) is responsible for collecting the data and is also contributing to the funding. In addition to Sylvana Côté, the co-researchers for this round are Marco Battaglia, Ph.D., University of Toronto; Michel Boivin, Ph.D., Université Laval; Linda Booij, Ph.D., Concordia University; Jean-Philippe Gouin, Ph.D., Concordia University; Catherine Herba, Ph.D., Université du Québec à Montréal; Benoît Masse, Ph.D., Université de Montréal; Jennifer O'Loughlin, Ph.D., Université de Montréal; Richard E. Tremblay, Ph.D., Université de Montréal; Gustavo Turecki, Ph.D., McGill University; and Frank Vitaro, Ph.D., Université de Montréal.

Invitation to participate in this research project

The round *From Birth to Age 20 – 2018 Round on Mental Health* aims to collect data on the life experiences, values and psychological health of young people like you. These data will be compared with those collected in earlier rounds in order to gain a better understanding of the factors that contribute to the overall well-being of young adults in Québec.

About this round of the study

The mental health of young adults is a very important topic, as it contributes to academic achievement, successful integration into the labour market, and psychological well-being throughout life. Our objective is to better understand what promotes success, and at the same time, what can cause certain difficulties during the transition into adulthood, in the hopes of improving health and psychosocial support services that can help young people reach their full potential.

For all of these reasons, we are greatly interested in your positive experiences and in the challenges you are facing. We want to learn more about your daily concerns, your feelings, your behaviours and your values.

How the project will unfold

If you agree to participate in this round of the study, we will ask you to fill out a **30-minute online questionnaire**. To access your questionnaire, you simply need to go to the study homepage (www.iamillbe.stat.gouv.qc.ca/) and click on the button "Round 2018 Questionnaire" You will be asked to enter your identifier to access an electronic version of this information and consent form. Once you have agreed to participate, you will have access to the questions.

4. The association between childhood externalizing symptoms and suicidal behavior in adolescents: findings from the Quebec Longitudinal Study of Child Development

4.1 Association between Irritability/depressive symptoms and suicidal behavior in adolescence

4.1.1 Methods

Participants

Participants were drawn from the Quebec Longitudinal Study of Child Development (QLSCD), a representative sample of 2120 infants born in Québec, Canada, in 1997 and 1998 and followed up between 5 months and 17 years (14 data collections). The initial sample was selected from the Quebec Birth Registry using a stratified procedure based on living area and birth rate. Families were included if the pregnancy lasted 24 to 42 weeks and the mother could speak French or English. The final sample used to estimate the trajectories models comprised N=1630 participants (Table 1). From 5 months to 13 years, trained interview collected data about parental, family, and child characteristics during home interviews conducted with the person most knowledgeable about the child (the mother in 98% of cases). From 6 to 12 years, teachers also rated the children behavior, and from 13 to 17 years data were self-reported by the adolescents.

The protocol of the QLSCD was approved by the Quebec Institute of Statistics (Quebec City, Quebec, Canada) and the St-Justine Hospital Research Center (Montreal) ethics committees, and written informed consent was obtained from all the participants at each assessment.

4.1.2 Measures

Main outcomes. Outcome variables were measured using items from the Mental Health and Social Inadaptation Assessment for Adolescents (MIA), a self-report instrument designed for the assessment of mental health among population-based samples of adolescents using a dimensional approach and relying on the fifth edition of the Diagnostic and Statistical Manual of Mental

Disorders (DSM-5). The first outcome was lifetime suicidality, defined as having reported serious suicidal ideation or suicide attempts at least once at 13, 15, or 17 years. Suicidality was assessed using 2 questions: “in the past twelve months, did you ever seriously think of attempting suicide” (coded 0 if “no”/“don’t know”, 1 if “yes”), and “in the past twelve months, how many times did you attempt suicide,” (dichotomized as 0 versus ≥ 1).

The second outcome was depressive symptoms, measured at age 15 and 17 with 8 items corresponding to the DSM-5 symptoms for depression (e.g. “I lost interest in things I usually like”, “I felt sad and unhappy”, and “I felt I couldn't do anything well”; Cronbach’s alpha=0.90). Scores were averaged across 15 and 17 years, and the 80th percentile was used to define two groups showing high (coded 1) and low (coded 0) depressive symptoms.

Predictors. Teachers rated child behavior at 6, 7, 8, 10, and 12 years of age with items derived from the Canadian National Longitudinal Study of Children and Youth (Government of Canada, 2009), which incorporates items from the Child Behavior Checklist (Achenbach, Edelbrock, & Howell, 1987), the Ontario Child Health Study Scales (Boyle et al., 1993), and the Preschool Behavior Questionnaire (Tremblay, Desmarais-Gervais, Gagnon, & Charlebois, 1987). Items were rated using a 3-point Likert scale according to the frequency of the behavior in the past 6 months (0=never, 1=sometimes, 2=often). Each year, a different teacher assessed the child, as in Québec, during elementary school, a teacher teaches only at 1 level.

Depressive symptoms were evaluated using 5 items (Cronbach’s alpha range: .84-.88): “seemed to be unhappy or sad”, “was not as happy as other children”, “has no energy, was feeling tired”, “had trouble enjoying him/ herself”, and “cried a lot”. For each time point, the mean score was obtained.

The irritability symptoms scale was generated using 4 items (Cronbach’s alpha range: .94-.97): “had temper tantrums or 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”. Factor analysis was conducted in order to derive the items for the irritability scale, and verify the previously described (Stringaris et al., 2009; Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016; Whelan et al., 2013) dimensions of oppositionality. For each time point, the

irritability score was obtained by summing the first item (temper tantrum) with the mean of the other 3 items, as they evaluated the same behaviors (reacting in an aggressive manner) in 3 different situations. Both the depressive and irritability symptoms scores were rescaled to vary from 0 (low symptoms) to 10 (high symptoms).

Confounding. Confounding variables were selected from the literature (Bostwick, Pabbati, Geske, & McKean, 2016; Brezo et al., 2008, 2007; Nock et al., 2013; Sourander et al., 2009). The following variables were measured when the child was 5 months old: child sex (0=female, 1=male), age of the parents at the birth of the child, socioeconomic status of the family (i.e., aggregate of five items regarding parental education, parental occupation, and annual gross income, range -3 to 3) (Willms & Shields, 1996), family structure (1=nonintact family, i.e., blended or single-parent families; 0=intact family), family dysfunctioning (assessed with 8 items encompassing communication, problem resolution, and control of disruptive behaviors), low birth weight (<2500), parental depression, and parental antisocial behaviors in adolescence. Child verbal IQ (assessed with the Peabody Body Picture Vocabulary Test) was measured at 3.5 years old, and mother-reported hostile-reactive parenting (assessed with 4 items, e.g., corporal punishment, raising voice) was measured at 3.5, 4, and 5 years old and averaged.

Data analysis

First, we jointly estimated the developmental trajectories of irritability and depressive symptoms using Multi-trajectory modeling (Nagin, Jones, Passos, & Tremblay, 2016). This is a new application of Group-Based Trajectory Modeling (Nagin, 2005), which allows to jointly model the trajectories of multiple outcomes using semi-parametric mixture models (see also supplemental eMethod). The result of this analysis allowed describing different profiles defined by the joint development of irritability and depressive symptoms across childhood. Parameters were estimated using maximum likelihood estimation employing a Newton-Raphson optimization algorithm and censored-normal models. The selection of the best model in terms of number of groups and polynomial order of the trajectories was based on the

Bayesian Information Criterion. Then, each participant was assigned to the group having the highest posterior probability.

Second, we used binary logistic regressions to determine the predictive association between trajectory membership and our outcomes, controlling for confounders. In order to select the pertinent covariables, an initial pool of variables was chosen on the basis of the bivariate association between the examined confounding variables and our outcomes. The variables associated with $p<0.20$ were entered in the model, and a backward stepwise procedure deleted the variables having a $p\leq0.10$.

Data analyses were performed using Stata version 14, and the trajectories were estimated using the traj procedure.

Missing data and sensitivity analysis

Except for paternal depression (13.4%), all covariables had less the 10% of missing data. Attrition on the outcome variables was 12% for suicidality and 17% for depressive symptoms. In the main analysis multiple imputations by chained equation (n=50 datasets) (Van Buuren, Boshuizen, & Knook, 1999) were used to impute missing data on the covariables, without imputing missing data on our outcome variables. However, has this is a discussed topic (Johnson & Young, 2011), sensitivity analysis with imputed data on the outcomes were undertaken. The analyses were also repeated on completed cases only. Trajectories were estimated for all individual having at least one data point and assuming that data is missing at random. Sensitivity analyses were then undertaken restricting the analysis to the individuals having at least three data points. Concerning the first outcome (suicidality), sensitivity analyses were performed among individuals reporting suicidal ideation only, and those reporting suicidal attempts. Concerning the second outcome (high depressive symptoms), we performed sensitivity analysis on the continuous outcome (level of depressive symptoms) using multiple linear regression models.

Table 1. Socio-demographic characteristics of the sample

	Study sample (N=1630)	Representative sample (N=2120)	Effect size
Child characteristics			
Sex male, N (%)	790 (48.5)	1080 (50.9)	0.02
Low birth weight (<2500g), N (%)	56 (3.4)	71 (3.3)	0.00
Verbal IQ, 3.5 years	30.39 (14.63)	30 (14.53)	-0.16**
Difficult temperament	2.71 (1.60)	2.72 (1.62)	0.02
Parents and family characteristics			
Socioeconomic Status	0.04 (1.00)	-0.01 (1.00)	-0.21***
Low maternal education, N (%)	278 (17.1)	385 (18.2)	0.01
Low paternal education, N (%)	302 (18.5)	398 (18.8)	0.01
Maternal age at child birth	29.27 (5.23)	29.3 (5.23)	0.02
Paternal age at child birth	32.23 (5.52)	32.26 (5.64)	0.02
Family dysfunction	1.70 (1.44)	1.71 (1.46)	0.04
Family structure non-intact, N (%)	301 (18.5)	406 (19.2)	-0.01
Smoking during pregnancy, N (%)	417 (25.6)	533 (25.1)	-0.01
Maternal harsh parenting, 3.5 years	3.34 (1.32)	3.31 (1.33)	-0.12
Paternal harsh parenting, 3.5 years	2.72 (1.23)	2.72 (1.24)	0.00
Parental mental health			
Maternal depression	1.39 (1.33)	1.40 (1.34)	0.06
Maternal antisociality in adolescence	0.81 (0.92)	0.81 (0.94)	-0.01
Paternal depression	0.99 (0.94)	1.00 (0.96)	0.03
Paternal antisociality in adolescence	0.69 (0.95)	0.67 (0.95)	-0.10

The table shows the comparison between the study sample and the initial sample (representative of children born in Quebec in 1997-1998). Variables are measured when the child was 5 months of age and expressed as mean (standard deviation), if not otherwise specified. Effect sizes are Hedge's g for continuous variables and Phi for categorical variables. *P*-values are based on *t*-tests (continuous variables) or chi-square tests (categorical variables).
*p<0.05, **p<0.001, ***p<0.0001

4.1.3 Results

Joint developmental trajectories of irritability and depression

We identify a 5-group model as having the best fit, comprising of the following groups (Figure 1 and supplemental material): 1) very low symptoms (8.7%); 2) low symptoms (48.5%); 3) moderate irritability (25.8%); 4) high depression (5.3%); 5) high irritability & depression (11.7%). In further analysis we combined group 1 and 2 (low symptoms, 53.7%) because of their similarity. In the more parsimonious model, all polynomial were defined by the intercept parameters, except for irritability for the moderate irritability group, showing a decreasing slope, and both irritability and depressive symptoms for the high irritability group, both defined using quadratic polynomials. Statistically significant differences across groups were found for child sex (with more boys in the high irritability & depression and moderate irritability groups) and verbal intelligence at age 3.5 years (lowest values for the high depression group). The groups also significantly differed in terms of socio-economic status, family structure, and parental mental health (Table S1).

Prediction of suicidality and high depressive symptoms

In our sample, 182 (11.8%) participants showed serious suicidal ideation/attempt during adolescence. As 200 participants have missing data on the suicide variables, our analysis was restricted to those having complete data on the outcome variable (N=1430). Multiple logistic regression showed that only the moderate irritability (OR: 1.81, 95%CI: 1.23-2.66, p=0.002) and high irritability & depression (OR: 2.14, 95%CI: 1.28-3.60, p=0.004) groups significantly predicted suicidality at 13-17 years. The high depression group did not significantly predict later suicidality (OR: 1.52, 95%CI: 0.77-2.99, p=0.224).

Of the 1399 participants having data on the depressive symptoms variables, 290 were in the upper 20% of the distribution at 15-17 years. As for the suicidality outcome, multiple logistic regression showed that children in the moderate irritability and high irritability & depression groups were at higher risk of reporting high depressive symptoms in late adolescence (moderate irritability group, OR: 1.63, 95%CI: 1.16-2.29, p=0.005; high irritability &

depression group, OR: 2.19, 95%CI: 1.36-3.52, p=0.001; high depression group: OR: 1.42, 95%CI: 0.77-2.63, p=0.259).

Sensitivity analysis

Re-estimating our models using imputed data for the outcome variables, yielded to ORs virtually identical to the ones reported in the main analyses. This was also true for analyses in which the trajectories were re-estimated using children having at least 3 data points. Concerning the secondary outcomes (suicidal ideation only, suicidal attempt, continuous depressive symptoms score), analyses were consistent with the main outcomes. All sensitivity analyses are detailed in the supplemental material.

Table 2. Logistic regression models predicting suicidality at 13-17 years

	Model 1 (sex-adjusted)		**Model 2 (fully adjusted)**	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Multi-trajectory groups				
Moderate irritability	1.85 (1.27-2.71)	0.002	1.80 (1.23-2.64)	0.003
High depression	1.74 (0.89-3.38)	0.104	1.52 (0.77-2.99)	0.224
High irritability & depression	2.37 (1.42-3.94)	0.001	2.20 (1.31-3.70)	0.003
Sex male	0.33 (0.23-0.48)	0.000	0.34 (0.23-0.49)	0.000
Socioeconomic Status			0.77 (0.64-0.93)	0.006
Maternal age at child birth			1.02 (0.99-1.06)	0.168
Difficult temperament			0.91 (0.82-1.01)	0.074

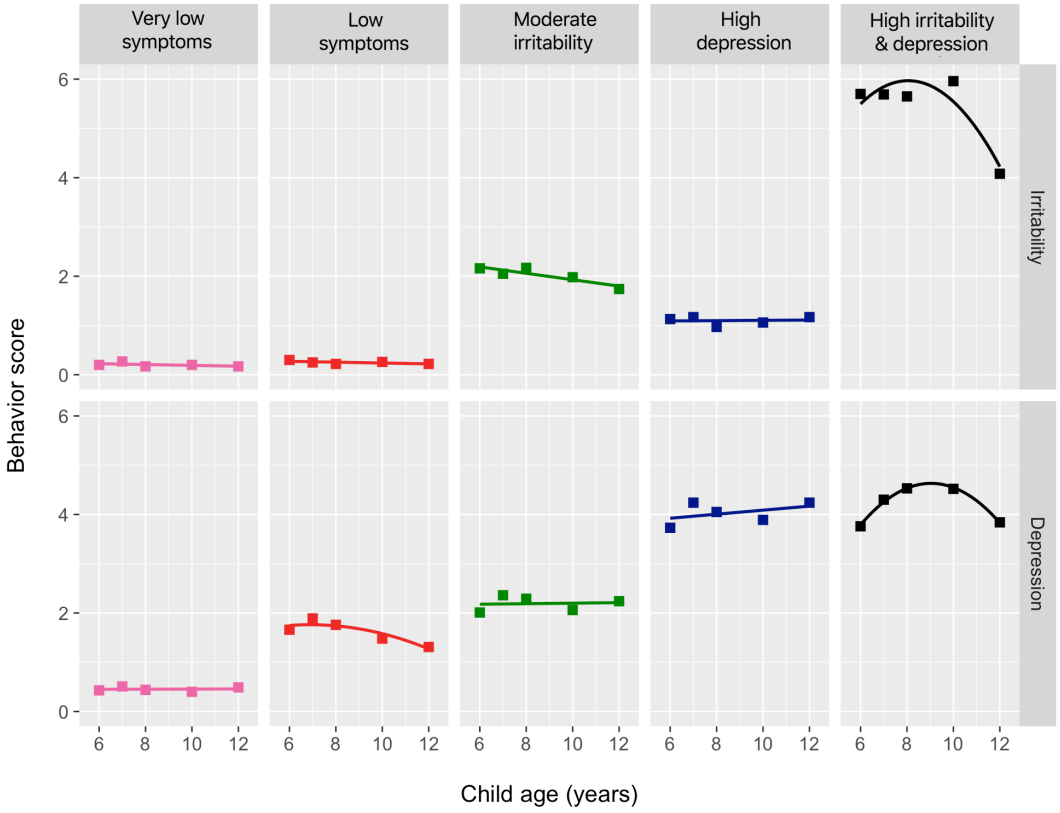
The table shows the adjusted odds ratios (OR) of the binary logistic regression model predicting suicidality at 13-17 years. The covariables in Model 2 were selected by a stepwise procedure. The low symptoms multi-trajectory group has been used as reference category.

Table 3. Logistic regression models predicting high depressive symptoms at 15-17 years

	Model 1 (sex-adjusted)		Model 2 (fully adjusted)	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Multi-trajectory groups				
Moderate irritability	1.63 (1.17-2.27)	0.004	1.63 (1.16-2.29)	0.005
High depression	1.34 (0.73-2.45)	0.341	1.42 (0.77-2.63)	0.259
High irritability & depression	2.18 (1.38-3.45)	0.001	2.19 (1.36-3.52)	0.001
Sex male	0.20 (0.14-0.27)	0.000	0.18 (0.13-0.26)	0.000
Paternal depression			1.16 (1.00-1.34)	0.056
Paternal age at child birth			1.03 (1.01-1.06)	0.031
Maternal smoking in pregnancy			1.42 (1.03-1.95)	0.032
Family structure intact			0.87 (0.60-1.26)	0.471

The table shows the adjusted odds ratios (OR) and 95% confidence intervals (CI) of the binary logistic regression model predicting high depressive symptoms at 15-17 years. The covariables in Model 2 were selected by a stepwise procedure. The low symptoms multi-trajectory group has been used as reference category.

Figure 4. Multi-trajectories of childhood irritability and depressive symptoms



Each column represents a different group in the multi-trajectory model, and is defined by the trajectory of irritability (upper panel) and depression (lower panel) of their member. Dots represent observed value, whether lines represent the fitted regression slope. The average posterior probability of group membership ranged from 0.70 to 0.83 across the 5 groups. The

odds of correct classification ranged from 3 to 38, suggesting that the model classifies the subjects in each group 3 to 38 times better then chance.

4.2 ADHD and suicidal behaviour in adolescence

4.2.1 Methods

Sample

Participants were drawn from the Quebec Longitudinal Study of Child Development (QLSCD), a representative sample of 2120 infants born in Québec, Canada, in 1997/98 and followed up between 5 months and 17 years. Random selection of the initial representative sample was made through the birth registry and following a procedure based on living area and birth rate. Mothers giving birth after 24 weeks of gestation and speaking French or English were eligible to participate in the study. Data were collected annually or bi-yearly from 1998 through 2015. We used teacher-reports of ADHD symptoms from 6 to 12 years, and self-report of suicidal ideation and attempt from 13 to 17 years. The final sample comprised of N=1407 participants for which data were available on SB (Table 4).

Table 4. Socio-demographic characteristics of the sample

	Attempt (N=80)	Ideation (N=89)	No attempt/ideation (N=1238)	*p*-value
Child characteristics				
Sex male, N (%)	19 (23.7)	29 (32.6)	617 (49.8)	0.000
Depressive/anxiety symptoms	2.4 (1.4)	2.1 (1.6)	2.1 (1.6)	0.255
ADHD medication use, N (%)	15 (18.7)	14 (15.7)	152 (12.2)	0.121
Opposition	3.8 (1.5)	3.5 (1.5)	3.6 (1.5)	0.363
Low birth weight (<2500g), N (%)	3 (3.7)	1 (1.1)	40 (3.2)	0.515
Parents and family characteristics				
Low Socioeconomic Status, N (%)	28 (35.9)	21 (23.6)	265 (21.5)	0.013
Maternal age at child birth	28.5 (5.5)	30.0 (5.3)	29.3 (5.1)	0.191
Paternal age at child birth	31.6 (5.5)	32.9 (4.7)	32.2 (5.5)	0.315
Family dysfunction	2.0 (1.5)	1.7 (1.4)	1.7 (1.4)	0.115
Family structure non-intact, N (%)	22 (37.5)	13 (14.6)	215 (17.4)	0.053
Smoking during pregnancy, N (%)	24 (30.7)	18 (20.2)	299 (24.2)	0.276
Parental mental health				
Maternal suicide attempt, N (%)	3 (3.8)	2 (2.2)	19 (1.5)	0.387
Maternal depression	1.6 (1.1)	1.4 (1.1)	1.4 (1.1)	0.207

The table provides basic socio-demographic characteristics of the sample. Descriptive statistics are mean (standard deviations) if not otherwise indicated. P-values are based on ANOVA (continuous variables) or Chi-squares (categorical variables).
Data were compiled from the final master file of the Québec Longitudinal Study of Child Development (1998-2015), Québec Government, Québec Statistic Institute.

Ethical Consideration

Ethical approval was given by the Quebec Statistics Institute and the St-Justine Hospital Research Centre. Written informed consent was obtained from all participants and their parents at each assessment. All adolescents and their parents were provided with a list of resources in case of needing help.

Measures

Outcome: Past-Year Suicidal Ideation and Suicide Attempt. Suicidal ideation was assessed at 13, 15, and 17 years using the question: “in the past 12 months, did you ever seriously think of attempting suicide” (yes coded 1, no coded 0; answering “don’t know” or refusal was coded as missing). If they answered affirmatively, they were asked: “in the past 12 months, how many times did you attempt suicide”, dichotomized as 0 versus ≥1. As in our previous publications (Orri et al., 2019, 2018) the following variables were derived: lifetime suicidal ideation (i.e., reporting ≥1 suicide ideation at 13 or 15 or 17 years but never suicide attempt) and lifetime suicide attempt (i.e., reporting ≥1 suicide attempt at 13 or 15 or 17 years).

Exposure

ADHD symptoms during childhood; ADHD symptoms were rated by schoolteachers when participants were 6, 7, 8, 10, and 12 years of age. Items were derived from the Behavior Questionnaire created for the Canadian National Longitudinal Study of Children and Youth, which incorporates items from the Child Behavior Checklist (Achenbach et al., 1987), the Ontario Child Health Study Scales (Boyle et al., 1993), and the Preschool Behavior Questionnaire (Tremblay et al., 1987). The following items were used and

summed-up to obtain the hyperactivity/inattention score at each year (range: 0 to 18; Cronbach's alpha range: 0.74-0.79), for hyperactivity-impulsivity: 1) could not sit still, was restless and hyperactive; 2) was impulsive, acted without thinking; 3) had difficulty waiting for his/her turn in games; 4) couldn't settle down to do anything for more than a few moments; For inattention: 1) was unable to concentrate, could not pay attention for long 2) was easily distracted, had trouble sticking to any activity 3) was inattentive. Each year, a different teacher rated the frequency of these behaviours in the past 6 months (0=never, 1=sometimes, 2=often).

Covariates

We used a parsimonious set of covariates for our multiple regression models, all measured before the exposure variable (i.e. age 6 years). Variables were selected on the basis of the literature (Galera et al., 2014; C Galéra et al., 2008; Hammerton, Zammit, Thapar, & Collishaw, 2015) and previous studies on the same sample (Cédric Galéra et al., 2011; Orri et al., 2018; Salla et al., 2016): maternal depressive symptoms, assessed using a short version of the Centre for Epidemiological Study Depression Scale (Poulin, Hand, & Boudreau, 2005); children depression-anxiety symptoms, assessed by teachers at age 6 and measured with 5 items (3 for anxiety, e.g., "was too fearful or anxious" and 2 for depression, e.g., "seemed to be unhappy or sad;"); family socioeconomic status (SES) at 5 months, an aggregate index of annual gross income, parental education level, and occupational prestige, based on Willms and Shields (range -3=low SES to 3=high SES, centered at zero) and dichotomized into low (i.e, 0-25th percentile) vs non-low (25th-75th percentile) (Willms & Shields, 1996). All questionnaires are available online (http://www.jesuisjeserai.stat.gouv.qc.ca).

Statistical Analyses

First, we estimated the developmental trajectories of ADHD symptoms among girls and boys, using Group based-trajectory modeling (Nagin, 2005). This approach is based on semiparametric mixture models, and allows us clustering children according to the similarities of their developmental pattern of ADHD symptoms from 6 to 12 years. Both the best number of trajectories

and the polynomial order of the trajectories (i.e., intercept only, linear or quadratic; determining the shape of the trajectory) were defined by comparing multiple models on the Bayesian Information Criterion.

Second, we used binary logistic regressions to test the predictive association between trajectory membership and suicidal ideation and attempt. We estimated unadjusted models as well as models adjusted for the influence of the selected covariates. Missing data on these covariates were handled using multiple imputations by chained equation: the models were estimated on 50 complete datasets, and the results were pooled. Data analysis was performed using Stata version 14, and the trajectories were estimated using the traj procedure.

4.2.2 Results

Prevalence of suicidal ideation and suicide attempt

At 13, 15, and 17 years respectively, 23 (1.9%), 43 (3.3%), and 51 (4.3%) adolescents reported suicidal ideation in the past year, while at those same ages respectively 28 (2.4%), 37 (2.8%), and 28 (2.4%) adolescents reported suicide attempt in the past year. In total, 29 boys (4.3%) and 60 girls (8.1%) reported suicidal ideation at least at one assessment (i.e, lifetime suicidal ideation), while 19 boys (2.8%) and 61 girls (8.2%) reported suicide attempt at least at 1 assessment (i.e., lifetime suicide attempt; Table 5).

Table 5. Prevalence of suicidal ideation and attempt by trajectory and sex

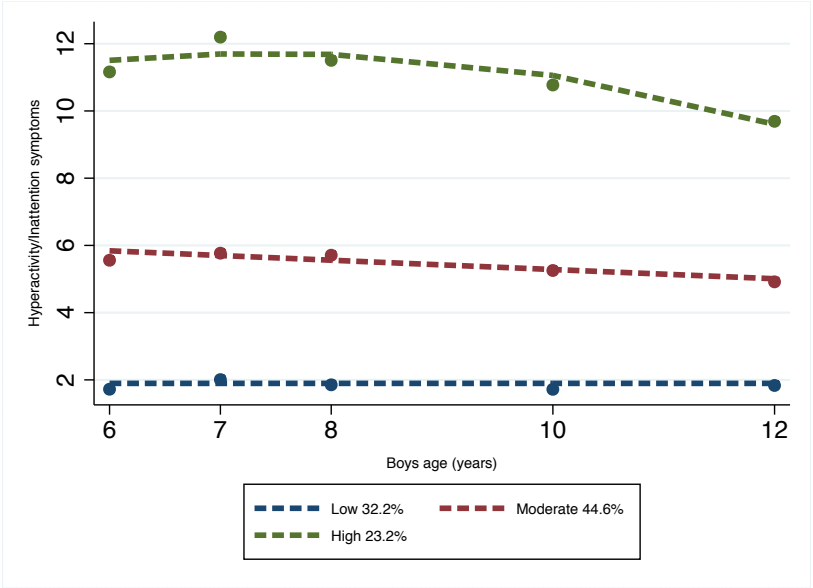
	Suicidal behavior Entire sample		**Suicidal behavior by trajectory**					
			Low trajectory		**Moderate trajectory**		**High trajectory**	
	Boys n=665	Girls n= 742	Boys n= 211	Girls n= 367	Boys n= 303	Girls = 312	Boys n= 151	Girls n= 63
Ideation	29 (4.3)	60(8.1)	3 (1.4)	30 (8.1)	18 (5.9)	23 (7.3)	8 (5.3)	7 (11.1)
Attempt	19 (2.8)	61(8.2)	4 (1.9)	19 (5.1)	8 (2.6)	31 (9.9)	7 (4.6)	11(17.4)

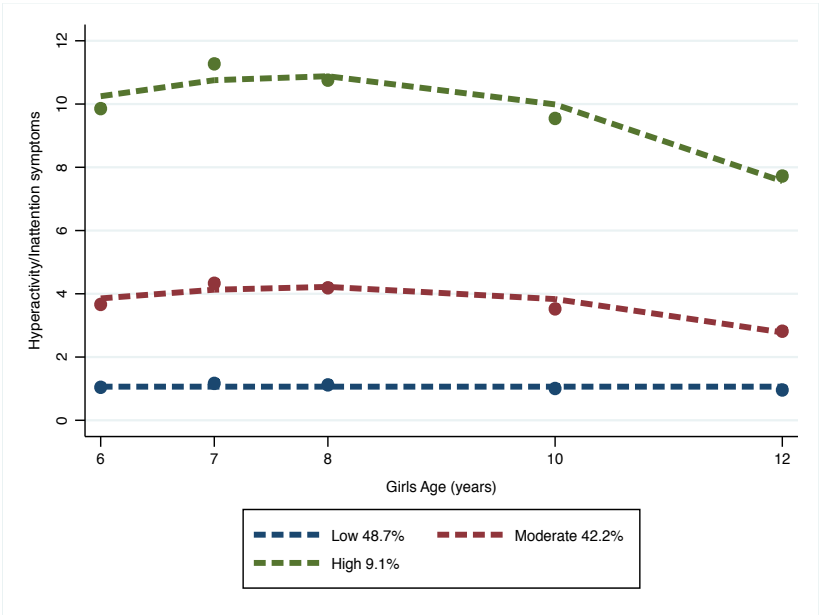
The table provides count (N) and percentage (%) of adolescents reporting suicide ideation and attempt at 13-17 years for each trajectory and by sex.

Developmental trajectories of ADHD symptoms

For both boys and girls, we identified a 3-group model as having the best fit (Figure 1): low trajectory (boys: 32.2%, girls: 48.7%), moderate trajectory (boys: 44.6%; girls: 42.2%), high trajectory (boys: 23.2%; girls: 9.1%). The trajectories showed similar developmental patterns for boys and girls. However, boys on the high trajectory had higher ADHD symptoms scores than girls on the high trajectory. Additionally, the proportion of children within each trajectory was different, with the high trajectory being larger for boys than for girls, and the low trajectory being larger for girls than for boys.

Figure 5. Trajectories of ADHD symptoms among boys and girls





Association between ADHD symptoms trajectories and suicidal ideation

Prevalence of suicidal ideation and attempt in each trajectory are shown in Table 5. For girls, the highest prevalence of suicidal ideation was found in the high trajectory (11.1%), while girls in the moderate and low trajectories had a slightly lower suicide ideation rate (7.3% and 8.1%, respectively). Logistic regression analyses (Table 6) showed that, girls in the low, moderate, and high trajectories were at similar risk of suicidal ideation (moderate vs. low, OR=0.9, 95%CI=0.5-1.5; high vs. low, OR=1.4, 95%CI=0.6-3.3), even after adjustment for the selected covariates (moderate vs. low, OR=1.0, 95%CI=0.5-1.7; high vs. low, OR=1.8, 95%CI=0.7-5.0).

Boys in the high and moderate trajectories had a similar suicidal ideation rate (5.3% and 5.9%, respectively), which was higher than that of boys in the low trajectory (1.4%). Consistently, logistic regression analysis showed that boys in the moderate and high trajectories had a 4-fold increased risk of suicide ideation compared to boys in the low trajectory (moderate, OR: 4.4, 95%CI: 1.3-15.1; high, OR=3.9, 95%CI=1.0-14.9). Odds ratios remained similar after adjustment for the selected covariables, although below the significance threshold for the high trajectory (moderate, OR: 4.2, 95%CI: 1.2-14.8; high, OR=3.6, 95%CI=0.8-15.1).

Association between ADHD symptoms trajectories and suicide attempt

There was a dose-response pattern indicating that the higher the ADHD symptoms, the higher the rate of suicide attempts (girls: 5.1%, 9.9%, 17,4%; boys: 1.9%, 2.6%, 4.6%, respectively for the low, moderate, and high trajectories; Table 5). Logistic regression (Table 6) showed that girls in both high (OR=3.9, 95%CI=1.7-8.6) and moderate trajectory (OR=2.0, 95%CI=1.1-3.6) had a higher crude risk for attempting suicide compared to girls in the low trajectory. However, those risks decreased and became non-significant after adjustment for the covariates (moderate, OR=1.6, 95%CI=0.8-3.0; high, OR=2.3, 95%CI=0.9-5.8).

A different pattern was observed for boys. Compared to boys in the low trajectory, boys in the moderate and high trajectories had, respectively, 1.4-fold (OR=1.4, 95%CI=0.4-4.7) and 2.5-fold (OR=2.5, 95%CI=0.7-8.7)

increased risk for suicide attempt. After accounting for the confounding role of the covariates, the risk became statistically significant for the boys in the high trajectory (OR: 4.5, 95%CI: 1.1-17.9), but not for the boys in the moderate trajectory (OR=1.8, 95%CI=0.5-6.3).

Table 6. Logistic regression models predicting suicidal ideation and suicide attempt at 13-17 years

	Suicidal ideation		**Suicide attempt**	
ADHD symptoms **trajectory**	**Unadjusted OR (95%CI)**	**Adjusted OR (95%CI)[a]**	**Unadjusted OR (95%CI)**	**Adjusted OR (95%CI) [a]**
Boys (665)				
Low ADHD symptoms	1 [reference]	1 [reference]	1 [reference]	1 [reference]
Moderate ADHD symptoms	4.4 (1.3-15.1)	4.2 (1.2-14.8)	1.4 (0.4-4.7)	1.8 (0.5-6.3)
High ADHD symptoms	3.9 (1.0-14.9)	3.6 (0.8-15.1)	2.5 (0.7-8.7)	4.5 (1.1-17.9)
Girls (742)				
Low ADHD symptoms	1 [reference]	1 [reference]	1 [reference]	1 [reference]
Moderate ADHD symptoms	0.9 (0.5-1.5)	1.0 (0.5-1.7)	2.0 (1.1-3.6)	1.6 (0.8-3.0)
High ADHD symptoms	1.4 (0.6-3.3)	1.8 (0.7-5.0)	3.9 (1.7-8.6)	2.3 (0.9-5.8)

[a] Odds ratios adjusted for child depressive symptoms, socioeconomic status, and maternal depression

5. Discussion and conclusions

5.1 Joint contribution of childhood irritability and depressive symptoms for the prediction of suicidality

To our knowledge, this is the first study aimed at clarifying the joint contribution of childhood irritability and depressive symptoms for the prediction of suicidality and depression in late adolescence. We investigated the predictive value of three phenotypes (low irritability, high depression, and high irritability & depression) that emerged from a multi-trajectory analysis of longitudinal assessments (6 to 12 years old) performed by teachers in a representative population cohort. The first contribution of this study is the use of an innovative person-centered approach that allowed describing the joint course of both irritability and depression. Previous studies using trajectory modeling only investigated the development of either depression or irritability (Caprara, Paciello, Gerbino, & Cugini, 2007; Côté et al., 2009; Dekker et al., 2007; Wiggins, Mitchell, Stringaris, & Leibenluft, 2014), or described the depression phenotypes (depression only versus irritable depression) on the basis of the cross-sectional presence of either one or both symptoms (Fava et al., 2010; Stringaris et al., 2013). Instead, the multi-trajectory approach allowed describing groups according to how those symptoms develop together throughout childhood. The difference is substantial, as the groups we described took into account the correlation of irritability and depressive symptoms, both within the same subject and over time. According to our analysis, developmental patterns of irritability and depressive symptoms appear to be stable, with no crossover among phenotypes. For instance, the high depression and high irritability & depression groups, which both have comparable level of depressive symptoms, showed very different scores of irritability at all time points. Stability of these phenotype has only been shown in one previous study among individual showing clinical depression (Stringaris et al., 2013), therefore our finding extend this previous research showing that those phenotypes are stable at the population level (i.e., considering sub-syndromic level of irritability and depression).

Our prediction analysis indicated that the 2 phenotypes that have been previously described (depression only, and irritable depression) are differently associated with later outcomes. Our high irritability & depression group showed statistically significant greater odds of showing both suicidality and high depressive symptoms in adolescence compared to the low symptoms group. The effects size of this associations is comparable to those reported in the literature for factors such as internalizing behaviors, previous suicide attempts, and childhood adversity (Franklin et al., 2017; Nock et al., 2013; Pickles et al., 2010). Little evidence was found for the high depression group, whose risk for later suicidality and depression was not statistically greater than the risk of the low symptoms group. Although the contrast test was not statistically significant (p=0.350), comparing the OR for these 2 groups we found that the high irritability & depression group has 70% more risk to show suicidality and 80% more risk of depression than the high depression group. The comparison of our findings with the existing literature is strongly limited by the lack of longitudinal studies in pediatric and population-bases samples. However, our findings agree with those from the STAR*D study (Perlis et al., 2009) and the National Comorbidity Survey Replication (Fava et al., 2010) (adult clinical samples), which reported more frequently history of suicide attempt, ideation, and thoughts of death among participants with irritable depression compared to those with non-irritable depression. Our findings are also in line with longitudinal studies indicating that individuals more at risk for suicidal behavior are those presenting both internalizing and externalizing symptoms (Brezo et al., 2008).

Of great interest is the moderate irritability group emerging from our multi-trajectory analysis, which is mainly characterized by moderate irritability slightly decreasing over time. Surprisingly, children presenting this sub-syndromic phenotype are at significantly higher risk of later suicidality and depression. Although previous longitudinal studies reported associations between irritability in childhood/adolescence and later depression (L.-É. Savage, Tarabulsy, Pearson, Collin-Vézina, & Gagné, 2019; Stringaris et al., 2009; Whelan et al., 2013), and suicidality (Kenneth R. Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004; Pickles et al., 2010), our findings strongly underline the importance of even moderate level of chronic irritability.

Moreover, it is possible that children presenting this pattern of symptoms are rarely seen by a mental health professional, and therefore the lack of associated symptoms (such as depressive symptoms) or the manifestation of irritability outside a clear behavioral syndrome (such as or dysregulation mood disorder) may result in less opportunity for the child to be diagnosed and treated. Additionally, the management of irritability symptoms appears to be difficult for child psychiatrists, and consensus about the best treatment is still unclear (Leibenluft, 2017; Vidal-Ribas et al., 2016). Those factors can result in overlooking of the importance of irritability in children.

Our findings have therefore important implications. From a preventive perspective, even moderate levels of irritability during childhood should be considered as an important risk factor, and targeted by early preventive interventions. This is even more important when high irritability and depressive symptoms are both present. From a clinical perspective, the longitudinal associations among irritability, depression, and suicidality, may have important research implications aimed at clarifying the role of antidepressants in the management of such at risk population (Hysinger et al., 2011; Jureidini et al., 2004). Psychotherapies aimed to develop better emotion regulation skills may be particularly useful, especially for moderate symptoms. For instance, cognitive behavior therapies may target both the behavioral dimensions and the cognitive impairments associated with both depression and irritability (Brotman et al., 2017). In the same way, transactional models describing the mutual influence between child behavior and parents reactions (Fanti, Panayiotou, & Fanti, 2013), suggested that parenting intervention could be useful to indirectly target child symptoms.

Strengths and limitations

This study was conducted in a large representative cohort of children followed from 5 months to 17 years, using innovative trajectory modeling techniques (modeling jointly depression and irritability), and behavioral assessment performed by different teachers interacting daily with the children and observing behaviors in a social setting (school). Despite these strengths, this study has limitations. The items used to assess irritability differ from those used in previous study, which can make comparisons difficult. However,

Cronbach's alpha and factor analysis shows that our measure had both good internal consistency and construct validity. Additionally, although the instrument used to measure depression had good psychometric properties and rely on DSM-5 symptoms, it is not a diagnostic tool.

5.2 Predictive association between childhood ADHD symptoms and suicide ideation and attempts in adolescence

The objectives of this population-based study were to test the predictive association between childhood ADHD symptoms and suicide ideation and attempts in adolescence, and to test whether the suicidal risk differed by sex. Our analyses showed that moderate to high levels of ADHD symptoms did not convey the same suicidal risk for boys and girls. We found that boys following moderate and high ADHD symptoms trajectories during the course of childhood (6-12 years) had a higher risk of suicidal ideation in adolescence (13-17 years), compared to boys following a low ADHD symptoms trajectory. In contrast, girls following a moderate or high ADHD symptoms trajectory did not have a heightened risk for suicidal ideation, compared to girls following a low ADHD symptoms trajectory. These associations were of similar magnitude after taking into account the confounding effects of childhood depressive symptoms, socioeconomic status, and maternal depression.

For suicide attempts, only boys following a high ADHD symptoms trajectory showed an increased (4.5 times higher) risk of suicide attempt compared to boys following a low trajectory. The risk of suicide attempts was not higher for girls on the high ADHD symptoms trajectory compared to girls on the low trajectory.

Our results are consistent with previous studies suggesting that ADHD symptoms might be considered early risk factors for suicide attempts during adolescence, especially among boys (C Galéra et al., 2008; Sourander et al., 2009). Our findings also extend prior knowledge in several ways. First, to our knowledge, this is the first population-based study to investigate the association between ADHD symptoms and SB using group-based trajectory

modeling. Given the developmental origins of suicidal behavior, it is important to identify the developmental aspects of ADHD symptoms and its longitudinal association with suicidal behavior using statistical techniques that account for population heterogeneity in the long term development of ADHD symptoms (Chronis-Tuscano et al., 2010; C Galéra et al., 2008; Sourander et al., 2009). Specifically, such techniques rely on a data driven approach that allows one to identify homogeneous group of children with typical and atypically high levels of symptoms without using arbitrary classifications. Second, previous studies were mainly based on cross-sectional designs and focused on clinical populations. Third, as previous studies mainly documented the association between ADHD symptoms and suicide mortality or serious attempts (i.e., requiring hospitalization) in boys (Sourander et al., 2009), our findings extend previous reports by showing that the association also holds for self-reported suicidal ideation and self-reported attempt. This is important because suicidal ideation precede suicide attempt in most cases. Only one previous population-based study found a positive association between childhood ADHD symptoms and SB among boys, although it was not based on a birth cohort (C Galéra et al., 2008; Sourander et al., 2009).

The underlying mechanisms of the sex difference in the association between ADHD symptoms and SB are still unclear, but they might be related to the type of ADHD symptoms that boys and girls experience. Boys with ADHD are more likely than girls with ADHD to display hyperactive-impulsive symptoms and less likely to experience inattentive symptoms (Nussbaum, 2012). Previous studies indicated that impulsivity is one of the pathway to suicidal behaviors, both in boys and girls (K R Conner, Duberstein, Conwell, Seidlitz, & Caine, 2001; Stewart et al., 2015; Swann et al., 2005), and a recent study also highlighted that different domains of impulsivity are connected to suicidal ideation and suicide attempt (respectively Pervasive Influence of Feelings and Feelings Trigger Action) (Auerbach, Stewart, & Johnson, 2017). Thus boys' higher levels of ADHD symptoms may explain why the association between hyperactivity-inattention and suicidal outcomes holds mainly for boys. Moreover, the same level of suicidal ideation may convert more easily into the acting out of suicide attempts in boys than in girls being facilitated by higher levels of hyperactivity-impulsivity, as previously suggested (Huang et al.,

2017; Orri et al., 2018; Wang et al., 2014). Previous studies distinguishing the role of impulsivity and inattention show that those symptoms have different long term effect on educational and mental health outcome (Pingault et al., 2011; Salla et al., 2016) but to our knowledge no study investigated suicidal outcomes. Therefore, studies distinguishing the role of inattention from that of hyperactive/impulsive symptoms in boys and girls are needed to clarify the origin of the sex difference that we observed. The lack of risk awareness which can be part of ADHD itself might also explain the finding that ADHD symptoms are risk factors for suicide attempt and ideation among boys, as these symptoms may confer to adolescents a higher risk of acting without considering the consequences of their acts. However, further studies are needed to clarify the underlying mechanisms of this association.

Our findings have clear clinical and preventive implications: boys presenting with moderate or high levels of ADHD symptoms throughout elementary school, might be considered more at risk for suicidal ideation and attempt later in life. These findings may guide clinicians to a more focused detection and prevention of SB in adolescents who manifested these symptoms throughout elementary school.

To our knowledge this is the first population-based study using trajectory modeling to clarify the association between ADHD symptoms during childhood and suicidal behavior during adolescence, with a focus on sex differences. Strengths of the study include: the use of a population-based sample followed-up from birth to 17 years; the yearly or bi-yearly assessments of hyperactivity/impulsivity and inattention by 5 different teachers providing independent assessments by adults with a good sense of normative behaviors in a group context (Tripp, Schaughency, & Clarke, 2006), and the assessment of suicidality at 3 time points during adolescence.

However, caution in interpreting the results is warranted in light of the following limitations. First, attrition (e.g., emigration, loss to follow-up, and refusal) is a limitation of all longitudinal cohort studies including this one. To limit the loss of data, we used multiple imputations to deal with missing on the covariates. Moreover, as the participants with the more severe mental health symptoms tended to drop out, our models are likely to provide conservative estimate of the association between ADHD symptoms and suicidality in the

population. Second, we focused on symptoms of hyperactivity/impulsivity and inattention, as the prevalence of ADHD diagnoses is low in population-based samples and we did not obtain clinical mental health evaluation during childhood.

This population-based study showed that boys with high and moderate levels of ADHD symptoms during childhood are at higher risk for later suicidal behavior. In particular, boys with moderate and high level of ADHD symptoms exhibited a higher risk for suicidal ideation, and a 4.5 times higher risk of suicide attempts in adolescence compared to those with low levels of ADHD symptoms. Interventions with pre-adolescent and adolescent boys showing ADHD symptoms should include a suicide prevention component. Population level suicide prevention for adolescents should particularly target boys with a history of ADHD problems.

5.3 Conclusions

The findings presented highlighted the importance of targeting early suicide preventive strategies at a population level, possibly starting from elementary school. First, the association between externalizing psychopatology and SB suggests that assessments of suicidality in adolescents with externalized disorders should be promoted in clinical and primary prevention settings as it is for internalizing disorders. Second, as effective treatment for externalizing psychopatology exists, the efficient assessment and treatment of irritability and ADHD in suicidal adolescents could facilitate recovery and favourable therapeutic outcomes.

Moreover, preventive strategies might be implemented and more specifically targeting externalizing psychopatology.

Also, our findings suggested that the presence of severe irritability in youth with other serious mental health problems (e.g., depressive disorders) might indicate increased vulnerability to SB and would deserve a special attention during routine clinical care.

However, further research are needed to clarify the underlying mechanism that could explain the association between externalizing psychopatology and

suicidal behavior; enviromental mediators, such as peer victimization and parenting, might have a role on this pathway and thus explain this association. Our findings also highlight the importance of a dimensional approach rather than categorial, on suicide prevention and thus elucidate more clearly which clinical dimensions deserve a closer attention in terms of preventive interventions.

Notably, our researches also encourage a life history prospective in approaching research on suicide prevention. Our finding suggest that early life psychopatological dimensions might confer a higher risk of suicide later in life, and thus support early preventive strategies starting from elementary school, involging teachers and parents as foundamental gatekeepers.

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