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**Association between irritability and suicide-related outcomes across the life-course. Systematic review of both  
community and clinical studies**

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## Abstract

**Background.** Irritability is gaining considerable attention as a risk factor for suicide-related outcomes (suicide mortality, attempt, and ideation). However, the evidence of this association is scant. We conducted a systematic review of the evidence regarding the associations between irritability and suicide-related outcomes across the life-course.

**Methods.** We conducted a systematic search on Medline and PsycINFO (up to 01/2018) for original articles published in English investigating the association between irritability and suicide-related outcomes. Two researchers independently screened the articles, assessed the quality of the evidence (New-Castle-Ottawa Scale) and extracted study characteristics.

**Results.** Thirty-eight studies were retrieved, most were of low/medium quality. Twelve assessed irritability in childhood/adolescence (6 in community samples, 6 in clinical samples) and 26 in adulthood (6 in community samples, 20 in clinical samples). In both childhood/adolescence and adult samples, most community-based studies reported a positive association between irritability and suicidal ideation and/or attempt, while clinical studies reported mixed findings. More specifically in clinical studies, the association of irritability with suicide-related outcomes (i) was not supported among adult depressed patients, (ii) findings were inconsistent in adult bipolar patients, (iii) for inpatients/outpatients with various psychiatric disorders/conditions, association was observed in adulthood but not in childhood/adolescence.

**Limitations.** Differences in methodology and definition/measurement of irritability limited the comparability of included studies.

**Conclusions.** Although irritability has been proposed as a promising transdiagnostic factor associated with suicide-related outcomes, the absence of consensus in the definition of irritability (vs anger or reactive/impulsive aggression), the poor methodological quality, and the lack of developmental considerations mitigate the conclusions.

**Keywords.** Irritability, suicide, suicide attempt, suicidal ideation, review.

## Introduction

With approximately 800 000 deaths yearly worldwide (1.4% of all deaths), suicide is among the leading causes of death, ranking second among 15–29 year olds (WHO, 2015). Many more people think or have attempted suicide, with lifetime prevalence of suicidal ideation and suicide attempt across 17 countries estimated at 9.2% and 2.7%, respectively (Nock et al., 2008).

One of the most important contributors of suicide-related outcomes is mental illness (Turecki & Brent, 2016). Nearly 90% of individuals who die by suicide have a comorbid mental disorder (Arsenault-Lapierre, Kim, & Turecki, 2004; Cavanagh, Carson, Sharpe, & Lawrie, 2003). However, mental disorders poorly predict suicide-related outcomes (Franklin et al., 2016) as most individuals with a mental health problems are not suicidal (Bolton, Gunnell, & Turecki, 2015). To improve our understanding of etiological factors associated with suicide-related outcomes, there has been an emerging interest in the identification of more specific or transdiagnostic risk factors (Glenn et al., 2018). Recently, irritability has attracted considerable attention in psychiatry. Irritability is a symptom present in 15 different *DSM-5* disorders (American Psychiatric Association, 2013), including both internalizing (e.g. Major Depressive Disorder), and externalizing disorders (e.g. Oppositional Defiant Disorder). It is also the defining feature of Disruptive Mood Dysregulation Disorder, a newly introduced mood disorder for children and adolescents (Roy, Lopes, & Klein, 2014). Most recently, irritability has also been considered by the National Institute of Health’s Research Domain Criteria project (RDoC) as a potential transdiagnostic phenotype (Brotman, Kircanski, & Leibenluft, 2017).

Irritability is an heterogeneous construct, difficult to define and measure (Avenevoli, Blader, & Leibenluft, 2015). One key issue is the proximity of irritability with related concepts such as anger and reactive/impulsive aggression (Toohey & DiGiuseppe, 2017). For example, anger and reactive/impulsive aggression are respectively a mood and a behavioral reaction that could be elicited by irritability. However, anger and aggression do not totally overlap with irritability: while anger and aggression (including impulsive aggression) usually manifest in response to a recognizable trigger, in the context of irritability they can both manifest without a trigger, or be of disproportionate intensity (Toohey & DiGiuseppe, 2017). Such overlap results in inconsistent measurement of irritability across studies, which failed to disentangle irritability from related concepts. A conceptual representation of the overlap between these constructs is presented in **Figure 1**, and a comprehensive discussion is available in Toohey & DiGiuseppe (2017). Several definitions of irritability have been proposed in the literature (Toohey & DiGiuseppe, 2017) and recently irritability has been defined as “a mood of partial physiological agitation characterized by an increased sensitivity to sensory stimuli and a non-cognitively mediated lowered threshold for responding with anger and/or aggression to typically less vexing stimuli; it is caused by factors that directly affect physiology and/or biology

such as hunger, lack of sleep, pain, and fatigue” (Toohey & DiGiuseppe, 2017) (page 105). This definition has the advantage to distinguish irritability from its related concept, i.e. anger, aggression. However, to date, there is no clear guideline for its measurement.

In light of the growing interest for irritability in psychiatry (see review: Vidal-Ribas, Brotman, Valdivieso, Leibenluft, & Stringaris, 2016), we aimed to provide a systematic review of up-to-date evidence on the associations between irritability and suicide mortality, suicide attempt, and suicidal ideation (suicide-related outcomes) and to discuss implications for future research.

## **Methods**

### **Search strategy and selection**

In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009), we systematically searched for all human studies that investigated the association between irritability and suicide mortality, and/or suicide attempt, and/or suicidal ideation (up to January 2018). We searched Medline (Pubmed) and PsycINFO (Ovid) for the following keywords: *irritab\* AND suicid\**. The reference list of all relevant articles was also scrutinized to identify supplementary studies not identified by our search algorithm. Two researchers (MO and LP) independently screened all retrieved articles, and articles were included if they met the following criteria: be an original peer-reviewed study published in English; investigate an association between irritability and suicide-related outcomes. We excluded studies assessing anger, aggression, impulsivity, impulsive-aggressive, and disruptive behaviors if irritability was not considered by the authors. We did not include studies on self-harm defined as the deliberate, self-inflicted destruction of body tissue without suicidal intent (Zetterqvist, 2015), but we did include those encompassing suicidal ideation and suicide attempt. Disagreements in the selection of studies were resolved throughout discussions among MO, LP and MCG.

### **Data extraction**

From each article we extracted the following information: name of the first author, study location (country), sample (community or clinical), number of participants, mean age of participants or age range, proportion of men, irritability assessments, suicide-related outcomes assessments, type of associations investigated (cross-sectional or longitudinal), covariates included in the adjusted model, estimates (e.g. odds ratio, B coefficient, and associated *p*-value) for the association between irritability (versus no irritability) or irritability scores and suicide-related outcomes. If the estimate was not reported, we interpreted the reported association based on *p*-value and authors’ narrative.

## Quality assessment

We assessed the quality of the included articles using the New Castle-Ottawa Quality Assessment Scale for cohort studies (Wells et al., 2012) and cross-sectional studies (adaptation in Herzog et al., 2013). This scale evaluates the following three domains: participant selection, comparability of groups, and ascertainment of the outcome. For each item within these three domains, a point is given if the criterion is fulfilled, for a total of 10 (cross-sectional studies) or 9 (cohort studies) points. Two researchers (MO and LP) independently rated the quality of the articles, and their agreement was quantified using the Intraclass Correlation Coefficient and interpreted as low if  $<0.40$ , fair if between 0.40 and 0.59, good if between 0.60 and 0.74, and excellent if  $>0.75$  (Cicchetti, 1994)

## Results

### Study selection and overview of studies

Our literature search retrieved 528 unique articles; from which 30 articles were retained after screening titles/abstracts, then full texts for inclusion/exclusion criteria, supplemented with 8 studies obtained from reference lists (**Figure 2**). In total, 38 articles were selected for this review, including more than 65,000 participants and median sample size of 322 participants ( $n$  range: 58-28,303). Twelve studies were based on community samples (median sample size of 1,350, range: 87-28,303) and 26 were based on clinical samples (median sample size of 254, range: 52-2,811). Most studies used data from either Europe ( $n=18$ , 47%) or North America ( $n=12$ , 32%).

Most studies ( $n=26$ , 68%) investigated association between irritability assessed during adulthood (age range 18-90 years old), and suicide-related outcomes, 20 were clinical and 6 community studies. Clinical studies included patients with major depression ( $n=4$ ), patients admitted to the emergency department for suicide attempt ( $n=5$ ), psychiatric inpatients or outpatients with any diagnosed mental disorders ( $n=4$ ) and inmates/forensic patients ( $n=1$ ). A third of the studies ( $n=12$ , 31%) examined associations of irritability assessed during childhood or adolescence (age range: 6-21 years old); 6 were based on clinical samples and 6 on community samples. Clinical studies included patients with major depression ( $n=3$ ), patients admitted to the emergency department for suicide attempt ( $n=1$ ), psychiatric inpatients or outpatients with any diagnosed mental disorders ( $n=1$ ) and inmates/forensic patients ( $n=1$ ). Thirty studies (79%) relied on cross-sectional observational studies, while the remaining 8 studies were based on longitudinal observational designs ( $n=7$ ) or randomized controlled trial ( $n=1$ ), with follow-up varying from three months (Kuba et al., 2011) to 43 years (Geoffroy, Gunnell, & Power, 2014).

*Measures of irritability.* More than half of the studies ( $n=21$ , 55%) used self-reported scales designed to assess irritability. All scales are described in **Table 1**. Thirteen of those 21 studies (38% of all studies; 12 among adult

samples), measured irritability using the Temperament Evaluation of Memphis, Pisa, Paris and San Diego-autoquestionnaire (TEMPS-A) (Akiskal, Akiskal, Haykal, Manning, & Connor, 2005), 5 studies (13% of all studies; 4 among adult samples) used the irritability subscale of the Buss & Durke Hostility scale (Buss & Durkee, 1957) or the Karolinska Scale of Personality (Schalling, Asberg, Edman, & Oreland, 1987, which uses the same items) as assessment instruments, 1 study used the Caprara Irritability Scale (Caprara et al., 1985), and 1 study used the Clinical scale for self-assessment of irritability (Snaith, Constantopoulos, Jardine, & McGuffin, 1978). Ten studies used either a single item ( $n=8$ ) or multiple items ( $n=2$ ) from other questionnaires (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961; Eysenck & Eysenck, 1964; Geller, Warner, Williams, & Zimmerman, 1998; Poznanski & Mokros, 1995; Rush et al., 2003; Tremblay, Desmarais-Gervais, Gagnon, & Charlebois, 1987; Young, Biggs, Ziegler, & Meyer, 1978). Finally, the remaining studies ( $n=6$ ) used clinical assessment of irritability (e.g. based on clinical judgment) without specific instruments, and in 2 cases the assessment of irritability was unspecified.

*Suicide-related outcomes:* Suicide-related outcomes were measured with self-reported items in 8 studies (24%, e.g. “in the past twelve months, did you ever seriously think of attempting suicide”), questionnaires (e.g. Beck Scale for Suicidal Ideation) (Beck, Steer, & Ranieri, 1988) ( $n=3$ ) or psychiatric assessment based on either a standardized tool (e.g., Columbia Classification Algorithm of Suicide Assessment) (Posner, Oquendo, Gould, Stanley, & Davies, 2007) ( $n=9$ ) or relying on clinical judgement ( $n=8$ ). Suicide attempt was assessed in 16 studies (47%), suicidal ideation in 12 studies (35%), and 10 studies (29%) relied on a broad category of suicidality without distinguishing between ideation and attempt (i.e., suicidality). Three studies assessed suicide mortality.

## **Quality assessment**

The result of the quality assessment is presented in **Table 2**. The agreement between the 2 raters was good (intraclass correlation coefficient = 0.71). Half of the studies scored 5 or less (out of 10 for cross-sectional studies and out of 9 for longitudinal studies), and only one study scored 8 or more. The minimum and maximum scores were 3 and 8, respectively.

## **Association between childhood irritability and suicide-related outcomes**

Twelve studies investigated associations of irritability measured in childhood or adolescence with concurrent (Bielas et al., 2016; Dalkilic et al., 2013; Frazier et al., 2016; Gabbay et al., 2015; Guerreiro, Sampaio, Rihmer, Gonda, & Figueira, 2013; Kosky, Silburn, & Zubrick, 1990) or later suicide mortality, suicide attempt, suicidal

ideation, and suicidality (Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004; Geoffroy et al., 2014; Kuba et al., 2011; Orri et al., 2018; Pickles et al., 2010; Vitiello et al., 2009) (**Table 3**).

### *Community-based samples*

Two cross-sectional and four longitudinal community-based studies investigated whether childhood/adolescence irritability was associated with suicidal-related outcomes.

Cross-sectional associations: Dalkilic et al. (2013) found a positive association between irritability and suicidal ideation that was independent from key covariates such as self-esteem, depression, and illicit drug/alcohol use in a large cross-sectional sample of Turkish high-school students ( $n > 30,000$ ). Conversely, Guerreiro et al. (2013) failed to report an association between irritable temperament (TEMPS-A) and suicidality after accounting for family typology, smoking status, alcohol and drug consumption (Adjusted odds ratio [AOR]=1.05,  $p=0.14$ ) in a cross-sectional sample of 12-20 years old public school students.

Longitudinal associations: In a longitudinal sample of adolescent males at risk for delinquency (aged 15-20 years at study baseline), Conner et al. (2004) found that higher irritability scores were predictive of severity of suicidal ideation 4 years later (AOR=1.15, 95%CI=1.03-1.28). Interestingly, this longitudinal association was independent from baseline characteristics known for their associations with irritability and suicidal ideation such as impulsivity, psychopathy, and alcohol dependency (Conner et al., 2004). In the Isle of Wight Longitudinal Cohort, Pickles et al. (2010) found that irritable adolescents (age range: 14-15 years; as assessed by 1 item of the Eysenck Personality Questionnaire: “Are you an irritable person”) were at increased risk for suicidality up to 3 decades later compared to less irritable adolescents (AOR=2.0, 95%CI=1.0-3.7), independently from their mental health status in adulthood (including major depression, substance disorders, and anxiety disorders) and a wide set of childhood covariables such as maltreatment. In the Quebec Longitudinal Study of Child Development, Orri et al. (2018) used group-based trajectory modeling to estimate the joint development of teacher-assessed irritability (defined as temper tantrum and reactive aggression) and depressive/anxious mood across middle childhood (6-12 years; see **Figure 3**). Children classified in the moderate irritability & low depressive/anxious mood, and high irritability & high depressive anxious mood trajectory profiles, were more likely to report higher suicidality risk (ideation/attempt) later in adolescence (13-17 years; AOR=1.51, 95%CI=1.02-2.25 for the former profile, and AOR=2.22, 95%CI=1.34-3.74 for the latter). Finally, in a large study with over 40 years follow-up, Geoffroy et al. (2014) reported no association between childhood irritability (rated by mothers with one item from the Reuter Behavior Scale) at age 7 and lifetime suicide mortality between 18-50 years, after adjusting for a range of covariates including childhood adversity and internalizing symptoms.

### *Clinical samples*

Six clinical studies based on samples of patients presenting with depression, psychiatric disorders, and suicidal ideation/attempt (four cross-sectional and two longitudinal) investigated whether childhood/adolescence irritability is associated with suicide-related outcomes.

Cross-sectional associations. Gabbay et al. (2015) found that irritability (assessed with two items from the clinician-reported Children's Depression Rating Scale [CDRS] and self-reported Beck Depression Inventory [BDI]) was associated with severity of suicidal ideation on the Beck Scale for Suicidal Ideation (non-irritable vs irritable:  $5.41 \pm 8.19$  vs  $10.35 \pm 11.18$ ,  $p=0.03$ ) among 91 clinically depressed adolescents (age range: 12-20 years). However, as the author investigated associations with several characteristics other than irritability, the association failed to reach significance after correction for multiple comparisons. In a sample of 322 psychiatric inpatients diagnosed with a mental disorder (age range: 12-18 years), Frazier et al. (2016) found a positive association between adolescent ratings of irritability (but not parental report) and suicidal ideation in multivariate analysis controlling for sex and mental health status (i.e., major depression, substance use, oppositional defiant disorder, conduct disorder, post-traumatic stress disorder;  $B=3.57$ ,  $SE=0.96$ ,  $p<0.001$ ). In a sample of adolescent males (age range: 13-19 years) detained in the Zurich Juvenile Detention Centre, Bielas et al. (2016) found that irritability (assessed with the Caprara Irritability Scale) was positively associated with suicidality ( $AOR=1.78$ ,  $95\%CI=1.07-2.99$ ) after controlling for adverse childhood experiences, age of incarceration, foreign nationality, and low socioeconomic status. Lastly, in a sample of patients presenting at the emergency department for suicidal ideation or suicide attempt, Kosky et al. (1990) found that irritability (clinical assessment) failed to discriminate between individuals reporting suicidal ideation and those reporting suicide attempt.

Longitudinal associations. The two clinical studies examining the longitudinal association of irritability in childhood or adolescence and suicide-related outcomes were conducted among individuals receiving antidepressant pharmacotherapy, with short follow-ups (3-9 months). In a sample of children and adolescents (age range: 6-24 years), Kuba et al. (2011) aimed to identify baseline risk factors (including irritability) associated with suicidality during antidepressant therapy. This study found that children/adolescents with irritability (clinical assessment) in the pretreatment period were at increased risk of suicidality assessed 3 months after the beginning of the antidepressant treatment. Vitiello et al. (2009) aimed to identify baseline risk factors (including irritability assessed with one item from the CDRS rating irritability from 1=rarely irritable to 6=constant experience of irritability) of suicidality among adolescents (age range: 12-17) diagnosed with major depressive disorders and enrolled in a randomized controlled

trial with 4 arms: fluoxetine, cognitive behavior therapy, combination of both, and placebo. After 9 months follow-up, no association between baseline irritability and suicidality were reported in either of the treatment arms.

Overall, the available community-based studies on children and adolescence suggested that irritability was associated with suicidal ideation and suicide attempt, but not suicide mortality. However, clinical studies reported mixed findings: two studies showed a significant association, two studies failed to show a significant association, and two studies showed a significant association only for adolescent-reported irritability (not parent-reported) or only before accounting for multiple testing.

### **Association between adult irritability and suicide-related outcome**

Twenty-six studies investigated the association between irritability measured in adulthood and suicidality, suicidal ideation, suicide attempt, and suicide mortality (Ardani et al., 2017; Azorin et al., 2010; Baldessarini et al., 2017; Baldessarini, Vázquez, & Tondo, 2016; Berk et al., 2017; Crook, Raskin, & Davis, 1975; Gagnon, Davidson, Cheifetz, Martineau, & Beauchamp, 2009; Guerreiro et al., 2013; Karam et al., 2015; Lester & Lindsley, 1988; Lester, 1968; Lester & Beck, 1975; Mitsui et al., 2017; Pawlak et al., 2013; Pedrelli et al., 2013; Pendse, Westrin, & Engström, 1999; Perlis et al., 2005; Pompili et al., 2008, 2016; Popovic et al., 2015; Rihmer et al., 2009; Skala et al., 2012; Stålenheim, 2001; Tanabe et al., 2016; Umamaheswari, Avasthi, & Grover, 2014; Westrin, Engstrom, Ekman, & Traskman-Bendz, 1998). With the exception of one longitudinal clinical study (Berk et al., 2017), all studies used a cross-sectional design (**Table 4**).

#### *Community samples*

Cross-sectional associations. Six cross-sectional studies were based on community samples (Karam et al., 2015; D. Lester & Lindsley, 1988; David Lester, 1968; Mitsui et al., 2017; Pedrelli et al., 2013; Skala et al., 2012), often including college students. Four studies, reported positive associations between irritability and suicidal attempt or ideation (Karam et al., 2015; David Lester, 1968; Mitsui et al., 2017; Skala et al., 2012). For example, Karam et al. (2015), using a large representative sample from Lebanon, found a 5-fold increased risk of suicide attempt among irritable individuals reporting any mental disorder, but not among individuals without mental disorders. Unlike previous studies, 2 studies failed to report an association between irritability (measured with 1 BDI items and with the TEMPS-A, respectively) and severity of suicidal ideation among college students presenting with depressive symptoms (Pedrelli et al. 2013) and history of suicide attempt in a sample of primary care patients (Rihmer et al., 2013). Finally, Lester & Lindsley (1988) found that suicidal ideators had higher scores of inward irritability (i.e., leading to internalized reactions; mean difference=1.21,  $p<0.025$ ) and outward irritability (i.e., leading to externalized

reactions; mean difference=1.45,  $p<0.005$ ) compared to non-suicidal individuals, while suicide attempters had higher scores on inward irritability only (mean difference=3.,  $p<0.01$ ) compared to non-suicidal individuals.

### *Clinical samples*

Twenty studies (1 longitudinal) based on individuals presenting with depression, psychiatric disorders, and suicidal ideation/attempt or died by suicide, investigated whether irritability was associated with suicide-related outcomes.

Cross-sectional associations. Four studies were based on individuals with depression. One study (Pendse et al. 1999) found that depressive suicide attempters scored higher on irritability compared to healthy controls ( $58.66\pm 12.9$  vs  $46.26\pm 7.7$ ,  $p=0.002$ ), but not compared with non-attempters with seasonal depression. The remaining 3 studies failed to report an association between irritability and suicide attempt (Azorin et al. 2010) and suicidal ideation (Perlis et al. 2005, Popovic et al. 2015) after accounting for confounding variables. Two studies included patients with bipolar disorder in their samples, and reported divergent results: Umamaheswari et al. (2014) found that inward, but not outward irritability, was associated with suicidal ideation among 140 bipolar patients, while Pawlak et al. (2013) did not find irritable mood to be associated with suicide attempt in a sample of patients suffering from either unipolar depression or bipolar disorder. In 5 studies, the association between adult irritability and suicide-related outcomes was investigated in inpatient samples suffering from various psychiatric diagnoses ( $n=4$ ) or forensic psychiatric patients ( $n=1$ ). All these studies reported an association between irritability and suicide attempt (Baldessarini et al. 2017, Baldessarini, Vázquez, & Tondo, 2016, (Stålenheim, 2001) and suicidality (Pompili et al. 2008). Five studies included individual presenting with suicidal attempt, 4 reporting that irritability was higher among individuals who attempted suicide (Rihmer et al. 2009, Tanabe et al. 2016, Westrin et al. 1998). Interestingly, one of these studies (Westrin et al. 1998) also reported that plasma-neuropeptide Y (a neurotransmitter involved in stress regulation) correlated positively with irritability in attempters and negatively in non-attempters ( $r$  attempters=0.44 vs  $r$  non-attempters=-0.30,  $p<0.01$ ). Unlike these previous studies, however, Lester & Beck (1975) failed to report association between irritability (derived from a factor analysis of the Beck Depression Inventory including irritability and somatic preoccupation) and severity of suicidal intent among a sample of suicide attempters. Finally, among the 2 studies investigating suicide mortality as an outcome, only one reported an association between irritability and suicide mortality (Gagnon et al. 2009). Gagnon et al. (2009) found that, among 14–25-year-old individual who died by suicide and their matched suicide attempters, irritability was more prevalent in individual who attempted suicide than individual who died by suicide (OR=0.16 95%CI=0.05-0.55) after accounting for several covariables. Conversely Pompili et al., (2016) failed to show

differences in irritable temperament (TEMPS-A) between individuals who died by suicide and mood disorder outpatients with or without history of suicide attempt.

Longitudinal associations. In a 2-year observational study of 239 outpatient with bipolar I or schizoaffective disorder, Berk et al. (2017) found higher levels of suicidality among irritable individuals (i.e., scoring  $\geq 2$  in the Young Mania Rating Scale, item 5; score range from 0=Absent to 8=Hostile, uncooperative; interview impossible) compared to non-irritable individuals (0.31 vs 0.18,  $p=0.004$ ) in multivariate analysis controlling for changes in mania symptoms between baseline and follow-up, depression, and physical and self-reported mental health symptoms.

Overall, studies based on community samples suggested a positive association between irritability and suicidal ideation, suicide attempt, and suicidality, although two of the seven studies failed to report significant associations (Ref). Studies based on clinical samples did not support an association between irritability and suicide-related outcomes among individual with depression, and reported mixed findings among individuals with bipolar disorder. However, studies suggested an association between irritability and suicide-related outcomes among samples of suicidal attempters, as well as among samples of inpatients/outpatients with various psychiatric disorders. Finally, although 1 study suggested that irritability discriminate between individuals who died by suicide and those surviving their suicide attempt (the latter having higher irritability scores), this was not the case in another study.

## Discussion

The objective of this systematic review was to summarize the available evidence on the association between irritability and suicide mortality, suicide attempt, and suicidal ideation. We found that most community-based studies reported a positive association between irritability and suicidal ideation and/or attempt in both childhood/adolescence and adult samples. However, studies on clinical samples reported mixed finding in both childhood/adolescent and adult samples. More specifically, in clinical studies, the association of irritability with suicide-related outcomes was (i) not supported among adult depressed patients samples, (ii) findings were inconsistent in adult bipolar patients samples, and (iii) for inpatients/outpatients with various psychiatric disorders/conditions (including suicide attempters) association was observed in adulthood but not in childhood/adolescence.

It is important to interpret these findings in light of the following considerations.

First, the definition and measure of irritability. The definition of irritability is still a topic of ongoing research debate (Brotman et al., 2017; Toohey & DiGiuseppe, 2017; Vidal-Ribas et al., 2016). The main challenge is to define irritability in relation to similar constructs such as anger, reactive/impulsive aggression, or frustration. These concepts have multiple overlaps, and some studies use them interchangeably, therefore adding to the confusion. Toohey and

DiGiuseppe (2017) proposed a definition that distinguishes irritability for its related concepts (refers to the full definition on the introduction section). However, the assessment of irritability according to this definition might be challenging, e.g., establishing whether the anger/aggressive response is non-cognitively mediated, or establishing whether the anger/aggressive response is of disproportional intensity. This is particularly true if irritability is assessed using self-reported questionnaires – the main source of information in psychiatry/psychology and epidemiology. Although some of the included studies assessed irritability with ad-hoc instruments, those instruments appear to be non-specific. For example, they use items referring to both anger and aggression (**Table 1**) to measure irritability. Therefore, the available evidence does not allow us to conclude that the positive association between irritability and suicide-related outcomes is specific to irritability or that it can or cannot be attributed to related constructs such as impulsive aggression ( McGirr et al., 2008; McGirr et al., 2009; McGirr & Turecki, 2007). In light of these observations, future studies should aim (i) to characterize the validity of irritability as a construct, differentiating it from related constructs such as anger or reactive/impulsive aggression, and (ii) to develop self-reported questionnaires that specifically assess irritability, and that can be used in large population-based and clinical studies.

Second, the role of irritability in the lifespan. Studies of irritability have focused on both childhood and adult populations. However, it is unclear to what extent irritability measured in childhood versus in adulthood refer to the same phenotype, i.e., whether they are measuring the same construct of irritability. Irritability is a commonly reported symptom during childhood, and 3% of the pediatric general population show chronic severe levels of irritability (Althoff, Verhulst, Rettew, Hudziak, & van der Ende, 2010). Irritability manifests during childhood with temper tantrums, grouchy mood, or reactive aggression. In clinical populations, irritability is exhibited in one-third of depressed children (Stringaris, Maughan, Copeland, Costello, & Angold, 2013) and is a core dimension of Oppositional Defiant Disorder (Stringaris & Goodman, 2009). Studies showed that the typical developmental trajectory of irritability across childhood follows a declining pattern over time (Copeland, Brotman, & Costello, 2015). This is probably due to children's improved self-control and social adjustment abilities over the course of maturation (Leibenluft, 2017). In adult studies, however, irritability is often defined as a temperamental/personality trait, i.e., stable over time and with strong biological bases (McCrae et al., 2000). To our knowledge, only one study investigated the stability over time of irritability including both childhood and young adulthood measures (follow-up 8 to 20 years of age) (Roberson-Nay et al., 2015). This study, conducted in a twin sample, showed that irritability is moderately correlated over time ( $r < 0.50$ ). Studies in adult samples, on the other hand, provide psychometric and neurobiological evidence for the biological foundation and time stability of irritability and anger-related traits (Kawamura et al., 2010; Montag & Reuter, 2014; Orri et al., 2017; Panksepp, 2006). However, no study extended

beyond the young adulthood period. As childhood studies measured age-specific irritability symptoms, while adult studies measured temperamental traits, comparisons across those 2 populations may be challenging. However, it is important to note that irritability differences between childhood and adult studies may be not contradictory. While irritability may be conceptualized as an underlying temperamental trait, the manifestation of irritability symptoms may have different functions in different developmental stages during the lifespan. Indeed, although irritability has a strong biological basis suggesting stability, it may also be a developmental adaptive response during a period in which full maturation is not achieved (Leibenluft, 2017). In sum, caution should be used when interpreting together studies measuring childhood irritability symptoms and adult irritability traits. In light of these observations, future studies should aim to clarify the relation between childhood/adolescent irritability and adult irritability (or irritable temperament), establishing whether these concepts are different expressions of a latent temperamental trait, or whether the apparent discordance is simply due to measurement and definition uncertainties.

Third, the evidence of the association between irritability and suicide-related outcomes is mined by the methodological characteristics of the retrieved studies. Indeed, most studies are cross-sectional from which it is difficult to establish whether irritability is a predictor of suicide-related outcomes or just a correlate. In addition, most studies assessed history of suicide attempt or suicidal ideation as outcomes, but not current or recent suicide attempt/ideation. Evidence of a predictive association between irritability and suicide-related outcomes is supported by 3 childhood/adolescence community-based studies with longitudinal follow-ups (Conner et al., 2004; Orri et al., in press; Pickles et al., 2010), but not by one study assessing suicide mortality (Geoffroy et al., 2014). In addition, the studies included in this review (especially those based on clinical samples) are most often based on convenience samples, and most of the times the control group is poorly defined. In light of these observations, future studies should use rigorous designs including longitudinal assessments and use of well-defined healthy control groups. Moreover, randomized studies aiming to reduce irritability should measure suicide-related outcomes, as this would help in establishing if the role of irritability is causal.

Fourth, suicidal ideation, suicide attempt, and suicidality are the outcomes most often considered by the included studies. As only three studies investigated suicide mortality as an outcome (Gagnon et al., 2009; Geoffroy et al., 2014; Pompili et al., 2016), strong evidence supporting the association between irritability and suicide mortality are lacking. Future studies should aim to fill this gap.

### **Strengths and limitations of the review**

This study provides the first systematic review of the association between irritability and suicide-related outcomes. We used broad inclusion criteria, no limited date range, and summarized evidence from both clinical and population-based samples in both childhood/adolescence and adult populations. However, the following limitations have to be considered. First, the review was limited to published articles in English, retrieved in Medline and PsycINFO, with no exploration of grey literature (e.g., theses, reports). Second, despite systematically conducted, our search strategy could have missed some published articles. Third, due to the heterogeneity of the retrieved articles, the comparability across studies was challenging, and only a narrative non-quantitative summary of the study results was possible.

## **Conclusions**

Irritability is a promising transdiagnostic symptom for psychopathology across the life-course. This review suggests that irritability could be also interesting for enhancing our understanding of suicidality. However, the current evidence is limited by the lack of systematic assessment of irritability across the studies (and the literature in general), the unclarified overlap between irritability and other emotional dysregulation dimensions (such as anger and reactive/impulsive aggression), and the reliance on poor quality cross-sectional studies.

**Conflict of interest:** The authors declare no conflict of interest.

**Author statement:** MO and LP conducted the search, the screening of the articles, and the evaluation of the quality, extracted study characteristics; disagreements were resolved in meetings with MCG. MO wrote the first draft of the paper. All authors interpreted the data, critically revised the manuscript for important intellectual contents, and approved the final version.

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## References

\*indicates studies included in the systematic review

- Akiskal, H. S., Akiskal, K. K., Haykal, R. F., Manning, J. S., & Connor, P. D. (2005). TEMPS-A: progress towards validation of a self-rated clinical version of the Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego Autoquestionnaire. *Journal of Affective Disorders*, 85(1-2), 3-16. <https://doi.org/10.1016/j.jad.2004.12.001>
- Althoff, R. R., Verhulst, F., Rettew, D. C., Hudziak, J. J., & van der Ende, J. (2010). Adult Outcomes of Childhood Dysregulation: A 14-year Follow-up Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 49(11), 1105-1116.e1. <https://doi.org/10.1016/j.jaac.2010.08.006>
- American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders (5th ed.)*. Washington, DC, US: Author.
- \*Ardani, A. R., Hosseini, F. F., Asadpour, Z., Hashemian, A. M., Dadpour, B., & Nahidi, M. (2017). Affective temperaments, as measured by TEMPS-A, among self-poisoning nonlethal suicide attempters. *Psychiatry Research*, 247:125-129. doi: 10.1016/j.psychres.2016.10.086
- Arsenault-Lapierre, G., Kim, C., & Turecki, G. (2004). Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry*, 4, 37. <https://doi.org/10.1186/1471-244X-4-37>
- Avenevoli, S., Blader, J. C., & Leibenluft, E. (2015). Irritability in Youth: An Update. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(11), 881-883. <https://doi.org/10.1016/j.jaac.2015.08.012>
- \*Azorin, J.-M., Kaladjian, A., Besnier, N., Adida, M., Hantouche, E., Lancrenon, S., & Akiskal, H. (2010). Suicidal behaviour in a French Cohort of major depressive patients: characteristics of attempters and nonattempters. *Journal of Affective Disorders*, 123(1-3), 87-94. <https://doi.org/10.1016/j.jad.2009.09.004>
- \*Baldessarini, R. J., Innamorati, M., Erbuto, D., Serafini, G., Fiorillo, A., Amore, M., ... Pompili, M. (2017). Differential associations of affective temperaments and diagnosis of major affective disorders with suicidal behavior. *Journal of Affective Disorders*, 210(Akiskal, H.S., Akiskal, K.K., Haykal, R.F., Manning, J.S., Connor, P.D. (2005). TEMPS-A: progress towards validation of a self-rated clinical version of the temperament evaluation of the Memphis, Pisa, Paris, and San Diego auto-questionnaire. *J. Affect Disord.*, 85, 3-16. <http://dx.doi.org/10.1016/j.jad.2004.12.001>), 19-21. <https://doi.org/10.1016/j.jad.2016.12.003>
- \*Baldessarini, R. J., Vázquez, G. H., & Tondo, L. (2016). Affective temperaments and suicidal ideation and behavior in mood and anxiety disorder patients. *Journal of Affective Disorders*, 198, 78-82. <https://doi.org/10.1016/j.jad.2016.03.002>

- Beck, A. T., Steer, R. A., & Ranieri, W. F. (1988). Scale for Suicide Ideation: psychometric properties of a self-report version. *Journal of Clinical Psychology, 44*(4), 499-505.
- Beck, A. T., Ward, C. H., Mendelson, M., Mock, J., & Erbaugh, J. (1961). An inventory for measuring depression. *Archives of General Psychiatry, 4*, 561-571.
- \*Berk, L., Hallam, K. T., Venugopal, K., Lewis, A. J., Austin, D. W., Kulkarni, J., ... Berk, M. (2017). Impact of irritability: A 2-year observational study of outpatients with bipolar I or schizoaffective disorder. *Bipolar Disorders, 19*(3), 184-197. <https://doi.org/10.1111/bdi.12486>
- \*Bielas, H., Barra, S., Skrivanek, C., Aebi, M., Steinhausen, H.-C., Bessler, C., & Plattner, B. (2016). The associations of cumulative adverse childhood experiences and irritability with mental disorders in detained male adolescent offenders. *Child and Adolescent Psychiatry and Mental Health, 10*, 34. <https://doi.org/10.1186/s13034-016-0122-7>
- Bolton, J. M., Gunnell, D., & Turecki, G. (2015). Suicide risk assessment and intervention in people with mental illness. *BMJ (Clinical Research Ed.), 351*, h4978.
- Brotman, M. A., Kircanski, K., & Leibenluft, E. (2017). Irritability in Children and Adolescents. *Annual Review of Clinical Psychology, 13*, 317-341. <https://doi.org/10.1146/annurev-clinpsy-032816-044941>
- Buss, A. H., & Durkee, A. (1957). An inventory for assessing different kinds of hostility. *Journal of Consulting Psychology, 21*(4), 343-349.
- Caprara, G. V., Cinnani, V., D'Imperio, G., Passerini, S., Renzi, P., & Travaglia, G. (1985). Indicators of impulsive aggression: Present status of research on irritability and emotional susceptibility scales. *Personality and Individual Differences, 6*(6), 665-674. [https://doi.org/10.1016/0191-8869\(85\)90077-7](https://doi.org/10.1016/0191-8869(85)90077-7)
- Cavanagh, J. T. O., Carson, A. J., Sharpe, M., & Lawrie, S. M. (2003). Psychological autopsy studies of suicide: a systematic review. *Psychological Medicine, 33*(3), 395-405.
- Cicchetti, D. V. (1994). Guidelines, criteria, and rules of thumb for evaluating normed and standardized assessment instruments in psychology. *Psychological Assessment, 6*(4), 284-290. <https://doi.org/10.1037/1040-3590.6.4.284>
- \*Conner, K. R., Meldrum, S., Wiczorek, W. F., Duberstein, P. R., & Welte, J. W. (2004). The Association of Irritability and Impulsivity with Suicidal Ideation Among 15- to 20-year-old Males. *Suicide and Life-Threatening Behavior, 34*(4), 363-373. <https://doi.org/10.1521/suli.34.4.363.53745>

- Copeland, W. E., Brotman, M. A., & Costello, E. J. (2015). Normative Irritability in Youth: Developmental Findings From the Great Smoky Mountains Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 54(8), 635-642. <https://doi.org/10.1016/j.jaac.2015.05.008>
- \*Crook, T., Raskin, A., & Davis, D. (1975). Factors associated with attempted suicide among hospitalized depressed patients. *Psychological Medicine*, 5(4), 381-388.
- \*Dalkilic, A., Yilmaz, H. B., Unlu, A., Evcin, U., Prajapati, P., & Pumariega, A. J. (2013). Risk factors for suicidal ideation among high school students in Istanbul. *Adolescent Psychiatry*, 3(1), 102-113. <https://doi.org/10.2174/2210676611303010018>
- Eysenck, S. B., & Eysenck, H. J. (1964). An improved short questionnaire for the measurement of extraversion and neuroticism. *Life Sciences (1962)*, 3, 1103-1109.
- Franklin, J. C., Ribeiro, J. D., Fox, K. R., Bentley, K. H., Kleiman, E. M., Huang, X., ... Nock, M. K. (2016). Risk Factors for Suicidal Thoughts and Behaviors: A Meta-Analysis of 50 Years of Research. *Psychological Bulletin*. <https://doi.org/10.1037/bul0000084>
- \*Frazier, E. A., Liu, R. T., Massing-Schaffer, M., Hunt, J., Wolff, J., & Spirito, A. (2016). Adolescent but Not Parent Report of Irritability Is Related to Suicidal Ideation in Psychiatrically Hospitalized Adolescents. *Archives of Suicide Research*, 20(2), 280-289. <https://doi.org/10.1080/13811118.2015.1004497>
- \*Gabbay, V., Johnson, A. R., Alonso, C. M., Evans, L. K., Babb, J. S., & Klein, R. G. (2015). Anhedonia, but not irritability, is associated with illness severity outcomes in adolescent major depression. *Journal of Child and Adolescent Psychopharmacology*, 25(3), 194-200. <https://doi.org/10.1089/cap.2014.0105>
- \*Gagnon, A., Davidson, S. I., Cheifetz, P. N., Martineau, M., & Beauchamp, G. (2009). Youth suicide: A psychological autopsy study of completers and controls. *Vulnerable Children and Youth Studies*, 4(1), 13-22. <https://doi.org/10.1080/17450120802270400>
- Geller, B., Warner, K., Williams, M., & Zimmerman, B. (1998). Prepubertal and young adolescent bipolarity versus ADHD: assessment and validity using the WASH-U-KSADS, CBCL and TRF. *Journal of Affective Disorders*, 51(2), 93-100.
- \*Geoffroy, M.-C., Gunnell, D., & Power, C. (2014). Prenatal and childhood antecedents of suicide: 50-year follow-up of the 1958 British Birth Cohort study. *Psychological Medicine*, 44(6), 1245-1256. <https://doi.org/10.1017/S003329171300189X>

- Glenn, C. R., Kleiman, E. M., Cha, C. B., Deming, C. A., Franklin, J. C., & Nock, M. K. (2018). Understanding suicide risk within the Research Domain Criteria (RDoC) framework: A meta-analytic review. *Depression and Anxiety*, 35(1), 65-88. <https://doi.org/10.1002/da.22686>
- \*Guerreiro, D. F., Sampaio, D., Rihmer, Z., Gonda, X., & Figueira, M. L. (2013). Affective temperaments and self-harm in adolescents: a cross-sectional study from a community sample. *Journal of Affective Disorders*, 151(3), 891-898. <https://doi.org/10.1016/j.jad.2013.07.034>
- Herzog, R., Álvarez-Pasquin, M. J., Díaz, C., Del Barrio, J. L., Estrada, J. M., & Gil, Á. (2013). Are healthcare workers' intentions to vaccinate related to their knowledge, beliefs and attitudes? A systematic review. *BMC Public Health*, 13, 154. <https://doi.org/10.1186/1471-2458-13-154>
- \*Karam, E. G., Itani, L., Fayyad, J., Hantouche, E., Karam, A., Mneimneh, Z., ... Rihmer, Z. (2015). Temperament and suicide: A national study. *Journal of Affective Disorders*, 184, 123-128. <https://doi.org/10.1016/j.jad.2015.05.047>
- Kawamura, Y., Akiyama, T., Shimada, T., Minato, T., Umekage, T., Noda, Y., ... Akiskal, H. S. (2010). Six-year stability of affective temperaments as measured by TEMPS-A. *Psychopathology*, 43(4), 240-247. <https://doi.org/10.1159/000313522>
- \*Kosky, R., Silburn, S., & Zubrick, S. R. (1990). Are children and adolescents who have suicidal thoughts different from those who attempt suicide? *The Journal of Nervous and Mental Disease*, 178(1), 38-43.
- \*Kuba, T., Yakushi, T., Fukuhara, H., Nakamoto, Y., Singeo, S. T., Tanaka, O., & Kondo, T. (2011). Suicide-related events among child and adolescent patients during short-term antidepressant therapy. *Psychiatry and Clinical Neurosciences*, 65(3), 239-245. <https://doi.org/10.1111/j.1440-1819.2011.02204.x>
- Leibenluft, E. (2017). Irritability in children: what we know and what we need to learn. *World Psychiatry*, 16(1), 100-101. <https://doi.org/10.1002/wps.20397>
- \*Lester, D., & Lindsley, L. K. (1988). Inward and outward irritability in the suicidally inclined. *The Journal of General Psychology*, 115(1), 37-39. <https://doi.org/10.1080/00221309.1988.9711086>
- \*Lester, D. (1968). Suicide as an aggressive act: A replication with a control for neuroticism. *Journal of General Psychology*, 79(1), 83-86. <https://doi.org/10.1080/00221309.1968.9710455>
- \*Lester, D., & Beck, A. T. (1975). Suicidal intent, medical lethality of the suicide attempt, and components of depression. *Journal of Clinical Psychology*, 31(1), 11-12. <https://doi.org/10.1002/1097-4679%28197501%2931:1%3C11::AID-JCLP2270310104%3E3.0.CO;2-Q>

- McCrae, R. R., Costa, P. T., Ostendorf, F., Angleitner, A., Hrebicková, M., Avia, M. D., ... Smith, P. B. (2000). Nature over nurture: temperament, personality, and life span development. *Journal of Personality and Social Psychology*, 78(1), 173-186.
- McGirr, A., Renaud, J., Bureau, A., Seguin, M., Lesage, A., & Turecki, G. (2008). Impulsive-aggressive behaviours and completed suicide across the life cycle: a predisposition for younger age of suicide. *Psychological Medicine*, 38(3), 407-417. <https://doi.org/10.1017/S0033291707001419>
- McGirr, A., Alda, M., Séguin, M., Cabot, S., Lesage, A., & Turecki, G. (2009). Familial Aggregation of Suicide Explained by Cluster B Traits: A Three-Group Family Study of Suicide Controlling for Major Depressive Disorder. *American Journal of Psychiatry*, 166(10), 1124-1134. <https://doi.org/10.1176/appi.ajp.2009.08111744>
- McGirr, Alexander, & Turecki, G. (2007). The relationship of impulsive aggressiveness to suicidality and other depression-linked behaviors. *Current Psychiatry Reports*, 9(6), 460-466.
- \*Mitsui, N., Nakai, Y., Inoue, T., Udo, N., Kitagawa, K., Wakatsuki, Y., ... Kusumi, I. (2017). Association between suicide-related ideations and affective temperaments in the Japanese general adult population. *PloS One*, 12(6), e0179952. <https://doi.org/10.1371/journal.pone.0179952>
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ (Clinical Research Ed.)*, 339, b2535.
- Montag, C., & Reuter, M. (2014). Disentangling the molecular genetic basis of personality: From monoamines to neuropeptides. *Neuroscience & Biobehavioral Reviews*, 43, 228-239. <https://doi.org/10.1016/j.neubiorev.2014.04.006>
- Nock, M. K., Borges, G., Bromet, E. J., Cha, C. B., Kessler, R. C., & Lee, S. (2008). Suicide and suicidal behavior. *Epidemiologic Reviews*, 30, 133-154. <https://doi.org/10.1093/epirev/mxn002>
- \*Orri, M, Galera, C., Turecki, G., Forte, A., Renaud, J., Boivin, M., ... Geoffroy, M.-C. (2018). Association between childhood irritability and depressive/anxious mood profiles and adolescent suicidal ideation and attempt. *JAMA Psychiatry*. Published online March 28, 2018. doi:10.1001/jamapsychiatry.2018.0174
- Orri, Massimiliano, Pingault, J.-B., Rouquette, A., Lalanne, C., Falissard, B., Herba, C., ... Berthoz, S. (2017). Identifying affective personality profiles: A latent profile analysis of the Affective Neuroscience Personality Scales. *Scientific Reports*, 7(1), 4548. <https://doi.org/10.1038/s41598-017-04738-x>
- Panksepp, J. (2006). Emotional endophenotypes in evolutionary psychiatry. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 30(5), 774-784. <https://doi.org/10.1016/j.pnpbp.2006.01.004>

- \*Pawlak, J., Dmitrzak-Weglarz, M., Skibinska, M., Szczepankiewicz, A., Leszczynska-Rodziewicz, A., Rajewska-Rager, A., ... Hauser, J. (2013). Suicide attempts and clinical risk factors in patients with bipolar and unipolar affective disorders. *General Hospital Psychiatry, 35*(4), 427-432.  
<https://doi.org/10.1016/j.genhosppsy.2013.03.014>
- \*Pedrelli, P., Nyer, M., Holt, D., Bakow, B. R., Fava, M., Baer, L., ... Farabaugh, A. (2013). Correlates of irritability in college students with depressive symptoms. *The Journal of Nervous and Mental Disease, 201*(11), 953-958.  
<https://doi.org/10.1097/NMD.0000000000000038>
- \*Pendse, B., Westrin, A., & Engström, G. (1999). Temperament traits in seasonal affective disorder, suicide attempters with non-seasonal major depression and healthy controls. *Journal of Affective Disorders, 54*(1-2), 55-65.
- \*Perlis, R. H., Fraguas, R., Fava, M., Trivedi, M. H., Luther, J. F., Wisniewski, S. R., & Rush, A. J. (2005). Prevalence and clinical correlates of irritability in major depressive disorder: a preliminary report from the Sequenced Treatment Alternatives to Relieve Depression study. *The Journal of Clinical Psychiatry, 66*(2), 159-166; quiz 147, 273-274.
- \*Pickles, A., Aglan, A., Collishaw, S., Messer, J., Rutter, M., & Maughan, B. (2010). Predictors of suicidality across the life span: the Isle of Wight study. *Psychological Medicine, 40*(9), 1453-1466.  
<https://doi.org/10.1017/S0033291709991905>
- \*Pompili, M., Innamorati, M., Milelli, M., Battuello, M., Erbuto, D., Lester, D., ... Girardi, P. (2016). Temperaments in completed suicides: Are they different from those in suicide attempters and controls? *Comprehensive Psychiatry, 65*, 98-102. <https://doi.org/10.1016/j.comppsy.2015.11.003>
- \*Pompili, M., Rihmer, Z., Akiskal, H. S., Innamorati, M., Iliceto, P., Akiskal, K. K., ... Girardi, P. (2008). Temperament and personality dimensions in suicidal and nonsuicidal psychiatric inpatients. *Psychopathology, 41*(5), 313-321.  
<https://doi.org/10.1159/000146069>
- \*Popovic, D., Vieta, E., Azorin, J.-M., Angst, J., Bowden, C. L., Mosolov, S., ... Perugi, G. (2015). Suicide attempts in major depressive episode: evidence from the BRIDGE-II-Mix study. *Bipolar Disorders, 17*(7), 795-803.  
<https://doi.org/10.1111/bdi.12338>
- Posner, K., Oquendo, M. A., Gould, M., Stanley, B., & Davies, M. (2007). Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. *The American journal of psychiatry, 164*(7), 1035-1043.  
<https://doi.org/10.1176/appi.ajp.164.7.1035>

- Poznanski, E., & Mokros, H. (1995). *Manual for the Children's Depression Rating scale*. Los Angeles, CA: Western Psychological Services.
- \*Rihmer, A., Rozsa, S., Rihmer, Z., Gonda, X., Akiskal, K. K., & Akiskal, H. S. (2009). Affective temperaments, as measured by TEMPS-A, among nonviolent suicide attempters. *Journal of Affective Disorders, 116*(1-2), 18-22. <https://doi.org/10.1016/j.jad.2008.10.024>
- \*Rihmer, Z., Gonda, X., Torzsa, P., Kalabay, L., Akiskal, H. S., & Eory, A. (2013). Affective temperament, history of suicide attempt and family history of suicide in general practice patients. *Journal of Affective Disorders, 149*(1), 350-354. <https://doi.org/10.1016/j.jad.2013.02.010>
- Roberson-Nay, R., Leibenluft, E., Brotman, M. A., Myers, J., Larsson, H., Lichtenstein, P., & Kendler, K. S. (2015). Longitudinal Stability of Genetic and Environmental Influences on Irritability: From Childhood to Young Adulthood. *The American Journal of Psychiatry, 172*(7), 657-664. <https://doi.org/10.1176/appi.ajp.2015.14040509>
- Roy, A. K., Lopes, V., & Klein, R. G. (2014). Disruptive mood dysregulation disorder: a new diagnostic approach to chronic irritability in youth. *The American Journal of Psychiatry, 171*(9), 918-924. <https://doi.org/10.1176/appi.ajp.2014.13101301>
- Rush, A. J., Trivedi, M. H., Ibrahim, H. M., Carmody, T. J., Arnow, B., Klein, D. N., ... Keller, M. B. (2003). The 16-Item Quick Inventory of Depressive Symptomatology (QIDS), clinician rating (QIDS-C), and self-report (QIDS-SR): a psychometric evaluation in patients with chronic major depression. *Biological Psychiatry, 54*(5), 573-583.
- Schalling, D., Asberg, M., Edman, G., & Oreland, L. (1987). Markers for vulnerability to psychopathology: temperament traits associated with platelet MAO activity. *Acta Psychiatrica Scandinavica, 76*(2), 172-182.
- \*Skala, K., Kapusta, N. D., Schlaff, G., Unseld, M., Erfurth, A., Lesch, O. M., ... Akiskal, H. S. (2012). Suicidal ideation and temperament: an investigation among college students. *Journal of Affective Disorders, 141*(2-3), 399-405. <https://doi.org/10.1016/j.jad.2012.03.010>
- Snaith, R. P., Constantopoulos, A. A., Jardine, M. Y., & McGuffin, P. (1978). A clinical scale for the self-assessment of irritability. *The British Journal of Psychiatry: The Journal of Mental Science, 132*, 164-171.
- \*Stålenheim, E. G. (2001). Relationships between attempted suicide, temperamental vulnerability, and violent criminality in a Swedish forensic psychiatric population. *European Psychiatry: The Journal of the Association of European Psychiatrists, 16*(7), 386-394.

- Stringaris, A., & Goodman, R. (2009). Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48(4), 404-412. <https://doi.org/10.1097/CHI.0b013e3181984f30>
- Stringaris, A., Maughan, B., Copeland, W. S., Costello, E. J., & Angold, A. (2013). Irritable mood as a symptom of depression in youth: prevalence, developmental, and clinical correlates in the Great Smoky Mountains Study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52(8), 831-840. <https://doi.org/10.1016/j.jaac.2013.05.017>
- \*Tanabe, S., Terao, T., Shiotsuki, I., Kanehisa, M., Ishii, K., Shigemitsu, O., ... Hoaki, N. (2016). Anxious temperament as a risk factor of suicide attempt. *Comprehensive Psychiatry*, 68, 72-77. <https://doi.org/10.1016/j.comppsy.2016.04.001>
- Toohey, M. J., & DiGiuseppe, R. (2017). Defining and measuring irritability: Construct clarification and differentiation. *Clinical Psychology Review*, 53, 93-108. <https://doi.org/10.1016/j.cpr.2017.01.009>
- Tremblay, R. E., Desmarais-Gervais, L., Gagnon, C., & Charlebois, P. (1987). The Preschool Behaviour Questionnaire: Stability of its Factor Structure Between Cultures, Sexes, Ages and Socioeconomic Classes. *International Journal of Behavioral Development*, 10(4), 467-484. <https://doi.org/10.1177/016502548701000406>
- Turecki, G., & Brent, D. A. (2016). Suicide and suicidal behaviour. *Lancet (London, England)*, 387(10024), 1227-1239. [https://doi.org/10.1016/S0140-6736\(15\)00234-2](https://doi.org/10.1016/S0140-6736(15)00234-2)
- \*Umamaheswari, V., Avasthi, A., & Grover, S. (2014). Risk factors for suicidal ideations in patients with bipolar disorder. *Bipolar Disorders*, 16(6), 642-651. <https://doi.org/10.1111/bdi.12179>
- Vidal-Ribas, P., Brotman, M. A., Valdivieso, I., Leibenluft, E., & Stringaris, A. (2016). The Status of Irritability in Psychiatry: A Conceptual and Quantitative Review. *Journal of the American Academy of Child & Adolescent Psychiatry*, 55(7), 556-570. <https://doi.org/10.1016/j.jaac.2016.04.014>
- \*Vitiello, B., Silva, S. G., Rohde, P., Kratochvil, C. J., Kennard, B. D., Reinecke, M. A., ... March, J. S. (2009). Suicidal events in the Treatment for Adolescents With Depression Study (TADS). *The Journal of Clinical Psychiatry*, 70(5), 741-747.
- Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., & Tugwell, P. (2012). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Consulté 17 février 2018, à l'adresse [http://www.ohri.ca/programs/clinical\\_epidemiology/oxford.asp](http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp)

\*Westrin, A., Engstrom, G., Ekman, R., & Traskman-Bendz, L. (1998). Correlations between plasma-neuropeptides and temperament dimensions differ between suicidal patients and healthy controls. *Journal of Affective Disorders*, 49(1), 45-54. <https://doi.org/10.1016/S0165-0327%2897%2900197-3>

WHO. (2015). WHO | Suicide data. Consulté 24 février 2018, à l'adresse [http://www.who.int/mental\\_health/prevention/suicide/suicideprevent/en/](http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/)

Young, R. C., Biggs, J. T., Ziegler, V. E., & Meyer, D. A. (1978). A rating scale for mania: reliability, validity and sensitivity. *The British Journal of Psychiatry: The Journal of Mental Science*, 133, 429-435.

Zetterqvist, M. (2015). The DSM-5 diagnosis of nonsuicidal self-injury disorder: a review of the empirical literature. *Child and Adolescent Psychiatry and Mental Health*, 9. <https://doi.org/10.1186/s13034-015-0062-7>

**Table 1. Definition of irritability and irritability measures**

<b>Instrument</b>	<b>Example of measures and their items</b>	<b>N of studies (Reference)</b>
<b>Ad-hoc questionnaires and scales</b>		
TEMPS-A (21 items) <sup>a</sup>	“People tell me I blow up out of nowhere”, “When angry, I snap at people I am a very skeptical person”, “I am known to swear a lot”, “I have been told that I become violent with just a few drinks”	13 (1 among children/adolescents) (Ardani et al., 2017; Azorin et al., 2010; Baldessarini et al., 2017, 2016; Guerreiro et al., 2013; Karam et al., 2015; Mitsui et al., 2017; Pompili et al., 2008, 2016; Rihmer et al., 2009; Rihmer et al., 2013; Skala et al., 2012; Tanabe et al., 2016)
Buss & Durke Hostility scale (11 items) or Karolinska Scale Personality (5 items) <sup>a, b</sup>	“I lose my temper easily but get over it quickly”, “I am always patient with others”, “If someone doesn’t treat me right, I don’t let it annoy me”	5 (1 among children/adolescents) (Crook et al., 1975; Lester, 1968; Pendse et al., 1999; Stålenheim, 2001; Westrin et al., 1998)
Caprara Irritability Scale (20 items) <sup>a</sup>	“It takes very little for things to bug me”, “I often feel like a powder keg ready to explode”, “When I am tired I easily lose control”	1 among children/adolescents (Bielas et al., 2016)
Clinical scale for self-assessment of irritability (8 items) <sup>a</sup>	Inward: “I feel like harming myself”, “I get angry with myself or call myself names”, and outward irritability; Outward: “I feel I might lose control and hit or hurt someone”, “I am patient with other people”	1 among adults (Lester & Lindsley, 1988)
<b>Items from other scales</b>		
Rutter Behavior Scale, (1 item) <sup>c</sup>	Irritable 0= “never”, 1= “sometimes”, 2= ‘frequently’	1 among children/adolescents (Geoffroy et al., 2014)
Behavior questionnaire, (4 items) <sup>d</sup>	“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”	1 among children/adolescents (Orri et al., 2018)
Eysenck Personality Questionnaire (1 item) <sup>a</sup>	Are you an irritable person	1 among children/adolescents (Pickles et al., 2010)
Kiddie Schedule for Affective Disorders and Schizophrenia – Mania Rating Scale (1 item) <sup>c, e</sup>	Felt more irritable than usual (0 to 6 scale)	1 among children/adolescents (Frazier et al., 2016)
Childhood Depression Rating Scale (1 item) <sup>e</sup>	Irritability rated from 1=“Rarely” to 6=“Constant experience of irritability”	2 among children/adolescents (Gabbay et al., 2015; Vitiello et al., 2009)
Beck Depression Inventory (1 item) <sup>a</sup>	0=“I am no more irritated now than I ever am”, 1=“I get annoyed or irritated more easily than I used to; 2=“I feel irritated all the time now”; 3=“I don’t get irritated at all by the things that used to irritate me”	2 (1 among children/adolescents) (Gabbay et al., 2015; Lester & Beck, 1975)
Inventory of Depressive Symptomatology - Clinician-rated (3 items) <sup>e</sup>	“Have you felt irritable in the past week?”, “Have you found yourself becoming more easily angered or irritated by others?”, “How much of the time in this past week?”	1 among adults (Perlis et al., 2005)
Young Mania Rating Scale (1 item) <sup>e</sup>	Clinician rate of irritability from 0=Absent to 8=Hostile, uncooperative; interview impossible	1 among adults (Berk et al., 2017)

<sup>a</sup> Self-report, <sup>b</sup> The 5 items from the Karolinska Scale of Personality originated from the Buss & Durke Hostility scale,

<sup>c</sup> Parent-report, <sup>d</sup> Teacher-report, <sup>e</sup> Clinician-report

**Table 2. Result of the quality assessment according to the New Castle-Ottawa Scale**

Studies	New Castle-Ottawa scale criteria			Score
	Selection	Comparability	Outcome	
<b>Cross-sectional</b>				
Ardani et al. 2017	4	0	3	8
Azorin et al. 2009	5	1	2	8
Baldessarini et al. 2016	4	0	1	6
Baldessarini et al. 2017	4	0	1	5
Crook et al. 1975	4	0	1	6
Dalkilik et al. 2013	4	2	1	7
Gagnon et al. 2009	0	2	3	5
Guerreiro et al. 2013	4	1	1	6
Bielas et al. 2016	4	1	2	8
Frazier et al. 2016	4	2	2	8
Gabbay et al. 2015	2	0	1	3
Kosky et al. 1990	2	0	1	4
Karam et al. 2011	5	1	2	8
Lester 1968	2	0	1	3
Lester & Lindsley 1987	4	0	1	4
Lester & Beck 1975	4	0	1	5
Mitsui et al. 2017	3	0	2	5
Pawlak et al. 2013	2	0	2	4
Pedrelli et al. 2013	2	0	2	4
Pendse et al. 1999	4	0	1	4
Perlis et al. 2005	4	2	2	8
Pompili et al. 2008	4	1	2	6
Pompili et al. 2016	3	0	2	6
Popovic et al. 2015	3	0	2	5
Rihmer et al. 2009	4	0	2	6
Rihmer et al. 2013	4	0	2	6
Skala et al. 2012	4	1	2	7
Stålenheim 2001	4	0	2	6
Tanabe et al. 2016	4	0	2	6
Umamaheswari et al. 2014	4	2	2	7
Westring et al. 1998	3	0	3	6
	4	1	2	6
<b>Longitudinal</b>				
Berk et al. 2014				
Conner et al. 2004	2	2	2	6
Geoffroy et al. 2013	4	2	3	8
Kuba et al. 2011	2	0	2	4
Orri et al. 2018	4	1	2	6
Pickles et al. 200	2	2	2	6
<b>Intraclass Correlation Coefficient</b>				
	0.68	0.94	0.66	0.71

For each criterion, we reported the mean score between the evaluation of the 2 independent raters.

**Table 3. Studies reporting the association between irritability assessed during childhood or adolescence and suicide-related outcomes (n=12)**

Study (Country)	Study type	Sample (age) <sup>a</sup>	Sample size (% male)	Suicide-related outcomes (assessment method)	Irritability measure (assessment method)	Results	Covariates
<i>Community samples (n=6)</i>							
Dalkilik et al. 2013 (Turkey)	Cross-sectional	Community sample (13-21 years)	28,303 (45.5% male)	Suicidal ideation (self-report; 1 item from the CESD)	Irritability or Anger scale (unspecified); self-report	Association between irritability and suicidal ideation in multivariate analysis ( $p=0.000$ )	Age, school type, immigration, family influence, parental education, school grade, self-esteem, anomie, faith, anxiety, depression, antisocial, time spent with peer, time spent with family, parental involvement, family substance abuse, peer influence, illicit drug/alcohol use
Guerreiro et al. 2013 (Portugal)	Cross-sectional	Community sample (12-20 years)	1,713 (44% male)	Suicidality (self-report; 2 questions complemented by a clinical assessment of responses)	TEMPS-A; self-report	Irritable temperament associated with suicidality in unadjusted (OR=1.078, $p=0.02$ ) but not in adjusted analysis (AOR=1.053, $p=0.14$ )	Family typology, smoking status, alcohol and drug consumption
Conner et al. 2004 (US)	Longitudinal (4 years follow-up)	Community sample of males at risk for delinquency (15-20 years)	625 (100% male)	Suicidal ideation (self-report; 1 item from the Brief Symptom Inventory)	Buss-Durkee Hostility Inventory; self-report	Association between irritability and suicidal ideation in multivariate analysis (AOR=1.15 [1.03-1.28])	Age, race, public assistance, guilt, suspiciousness, impulsivity, psychopathy, alcohol dependence
Geoffroy et al. 2013 (UK)	Longitudinal (43 years follow-up)	Community sample (7 years)	16,470 (unspecified)	Suicide mortality (ICD codes for suicide or undetermined death)	Rutter Behaviour Scale (1 item); mother-report	No association between irritability and suicide mortality	Low birth weight, smoking during pregnancy, birth order, maternal age at birth, dry during day after age 3 years, internalizing and externalizing behaviors, social class, emotional adverse experiences
Orri et al. 2018 (Canada)	Longitudinal (11 years follow-up)	Community sample (6-12 years)	1,430 (47.3% male)	Suicidality, ideation, attempt (self-report; 2 questions)	Childhood irritability (4 items assessing temper tantrums and reactive aggression from the Behavior	Children presenting with both high irritability and high depressive-anxious mood (AOR=2.22 [1.32-3.74]) and those with moderate irritability (AOR=1.51 [1.02-2.25]) were at increased suicidality risk.	Sex, socio-economic status

					Questionnaire; teacher-report)		
Pickles et al. 2009 (UK)	Longitudinal (31 years follow-up)	Community sample (14-15 years)	2,226 (50% male)	Suicidality (self-report)	1 item from the Eysenck Personality Questionnaire; self-report	Association between irritability and suicidal plan/attempt in multivariate analysis (AOR=1.9 [1.1-3.2])	Adverse family experience, childhood abuse, hard/harsh parenting, mother mental health, minor depression, anxiety, negative relation with parents, lonely, worry, major depression, generalized anxiety, other anxiety disorders, substance disorders
<b>Clinical samples (n=6)</b>							
Bielas et al. 2016 (Switzerland)	Cross- sectional	Inmate (13.8-19.5 years)	130 (100% male)	Suicidality (MINI- KID)	Caprara Irritability Scale; self-report	Association between irritability and suicidality in multivariate analysis (AOR=1.78 [1.07–2.99])	Adverse childhood experience, age of incarceration, foreign nationality, low socioeconomic status
Frazier et al. 2016 (US)	Cross- sectional	Psychiatric inpatients (12-18 years)	322 (40.4% male)	Suicidal ideation (Suicide Probability Scale)	1 item from the K-SADS-MRS; clinician-report from adolescents and parents report	Adolescent-rated, but not parent-rated, irritability was associated with severity of suicidal ideation in multivariate analysis (B=3.572, SE=0.958, $p<.001$ )	Sex, major depression, substance use, oppositional defiant disorder, conduct disorder, post-traumatic stress disorder
Gabbay et al. 2015 (US)	Cross- sectional	Patients with major depressive disorder (12-20 years)	90 (43.4% male)	Suicidality (Beck Scale for Suicidal Ideation)	Children's Depression Rating Scale and BDI; self-report	Irritability was not associated with severity of suicidal ideation in adolescents suffering from depression after accounting for multiple testing (5.41±8.19 vs 10.35±11.18, $p=0.03$ )	None
Kosky et al. 1990 (US)	Cross- sectional	Suicidal ideator/attempter form psychiatric outpatients with active suicidal ideation (12.9±2.9 years)	340 (51% male)	Suicidal ideation and attempt (collected during clinical interview)	Clinical assessment	No difference in irritability score between suicide attemptors and suicide ideators	None
Kuba et al. 2011 (Japan)	Longitudinal (3 months follow-up)	Individuals receiving antidepressant therapy (6-19 years)	70 (45.7% male)	Suicidality (clinical assessment)	Unspecified	Initial levels of irritability predict suicidality 3 months after the beginning of antidepressant treatment (87.5% vs 40.7%, $p<0.005$ )	None

Vitiello et al. 2009 (US)	Longitudinal (RCT; 9 months follow-up)	Patients with depression (12-17 years)	439 (46.0% male)	Suicidality (C-CASA)	1 item from the Children's Depression Rating Scale-Revised; clinician-report	Suicidality is not predicted by change in irritability during the trial	None
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*Abbreviations:* AOR=Adjusted Odds Ratio; C-CASA= Columbia Classification Algorithm of Suicide Assessment; K-SADS-MRS= Kiddie Schedule for Affective Disorders and Schizophrenia – Mania Rating Scale; MINI-KIDS=Mini-International Neuropsychiatric Interview for Children; OR=Odds Ratio; SE=Standard Error; TEMPS-A= Temperament Evaluation of Memphis, Pisa, Paris and San Diego autoquestionnaire

<sup>a</sup> Range or, if not available, mean ± SD. For longitudinal studies, the age at irritability assessment was reported.

**Table 4. Studies reporting the association between irritability assessed during adulthood and suicide-related outcomes (n=26)**

Study	Study type	Sample (age) <sup>a</sup>	Sample size (% male)	Suicide-related outcomes (assessment method)	Irritability measure	Results	Covariates
<i>Community samples (n=6)</i>							
Karam et al. 2011 (Lebanon)	Cross-sectional	Community sample (≥18 years)	1,320 (NA)	Suicide attempt (CIDI)	TEMPS-A; self-report	Irritable temperament associated with suicidal attempt but only in adults with any mental disorder (AOR=5.1 [1.2-22.2])	Sex, types of temperament (e.g. anxious, hyperthymic, cyclothymic, depressive), , major depression, social phobia, substance disorder, impulse disorder
Lester 1968 (US)	Cross-sectional	Community sample, college students (NA)	87 (NA)	Suicidality (Devries suicide potential scale)	Buss and Durkee hostility inventory; self-report	Irritability was positively associated with suicidality controlling for neuroticism (partial r=.30, p<0.005)	Neuroticism
Mitsui et al. 2017 (Japan)	Cross-sectional	Community sample (42.3±11.8 years)	638 (53.0% male)	Suicidal ideation (1 self-reported item from the PHQ-9)	TEMPS-A; self-report	Irritability was higher in depressed suicidal ideator than in healthy control (1.32±0.23 vs 1.10±0.13, p<0.001) and in depressed non-ideators (1.32±0.23 vs 1.19±0.16, p<0.001)	None
Pedrelli et al. 2013 (US)	Cross-sectional	Community sample, college students, with depressive symptoms (19.8±1.9 years)	288 (32.1% male)	Suicidal ideation (Suicide Behaviors Questionnaire Revised)	1 item form the BDI; self-report	No association between irritability and suicidal ideation	None
Skala et al. 2012 (Austria)	Cross-sectional	Community sample (college students) (18-25 years)	1,381 (37.7% male)	Suicidal ideation (1 self-reported question)	TEMPS-A; self-report	Irritable temperament associated with suicide ideation in multivariate analyses in the whole sample (AOR=1.06, p=0.001) and in male subsample (AOR=1.08 p=0.003), but not in female subsample	Smoking status, frequency of alcohol consumption, drug experience and educational status
Lester & Lindsley 1987 (Sweden)	Cross-sectional	Community sample (college students) (22.7±6.2 years)	242 (48.3% male)	Suicidal ideation and attempt (self-report)	Snaith et al. (1978) self-report scale	Suicidal ideators have higher scores of inward (Mean difference=1.21, t=2.23, p<0.025) and outward (Mean difference=1.45, t=3.02, p<0.005) irritability; suicide attempters have higher scores on inward irritability only (Mean difference=3.1, t=3.13, p<0.01)	None
<i>Clinical samples (n=20)</i>							

Ardani et al. 2017 (Iran)	Cross-sectional	Suicide attempters and matched healthy controls (21.1±4.5 years)	281 (19.6% male)	Suicide attempt (hospital admissions)	TEMPS-A; self-report	Higher levels of irritable temperament among female suicide attempters (not males) (27.0±19.1 vs 13.0±9.2, $p=0.018$ )	None
Azarin et al. 2009 (France)	Cross-sectional	Patients with major depressive disorder (46.23±12.58 years)	445 (28% male)	Suicide attempt (semi-structured interview)	TEMPS-A; self-report	Higher levels of irritable temperament among attempters only in univariate analysis (OR=1.81 [1.09-3.01])	Stepwise-selected variables: N of previous depressive episodes and, age at onset, multiple hospitalizations, cyclothymic temperament, rapid cycling
Baldessarini et al. 2016 (Italy)	Cross-sectional	Psychiatric inpatients (44.0±16.7 years)	2,561 (38.1% male)	Suicidal ideation or attempt (clinical assessment)	TEMPS-A; self-report	Higher levels of irritable temperament among suicide attempters (25.4±26.6 vs 18.8±21.2, $t=2.15$ , $p=0.03$ ) but not ideators (21.0±16.8 vs 16.8±19.9, $p=0.05$ )	None
Baldessarini et al. 2017 (Italy)	Cross-sectional	Psychiatric inpatients (39.4±12.9 years)	956 (45.5% male)	Suicidality (MINI)	TEMPS-A; self-report	Higher levels of irritable temperament among suicidal patients (8.68±4.24 vs 7.18±4.24, $t=5.41$ , $p<0.0001$ )	None
Crook et al. 1975 (US)	Cross-sectional	Psychiatric inpatients (16-60 years)	308 (NA)	Suicide attempt (clinical assessment)	Buss & Durke Hostility Inventory; self-report	Suicide attempters have higher irritability scores (2.44 vs 2.1, $F=4.54$ , $p=0.05$ )	None
Gagnon et al. 2009 (Canada)	Cross-sectional	Patients who attempted suicide or died by suicide (14-25years)	52 (57.7% male)	Suicide attempt and mortality and (coroners and/or school directors)	Unspecified	Irritability was more prevalent in individuals who attempted suicide than individuals who died by suicide in multivariate analysis (OR=0.16 [0.05–0.55])	Dissatisfaction with physical appearance, psychiatric disorder, functioning, mood responsiveness, obsessions, school suspension/expulsion, drug abuse, violation rules
Lester & Beck 1975 (US)	Cross-sectional	Suicide attempters (NA)	254 (44.0% male)	Suicidality (self-reported scale of seriousness of patient's suicidal intent and clinical assessment)	Beck Depression Inventory (irritability factor derived from factor analysis); self-report	The irritability factor was not associated with suicidal intent	None
Pawlak et al. 2013 (Poland)	Cross-sectional	Patients with bipolar or recurrent depressive disorder and healthy controls (18-84 years)	1,160 (39.7% male)	Suicide attempt (Operational Criteria Diagnostic Checklist)	Operational Criteria Diagnostic Checklist Questionnaire; clinician-report	No association between suicide attempts and irritable mood	None

Pendse et al. 1999 (Sweden)	Cross-sectional	Depressive patients (i) no seasonal subtype with suicide attempt, (ii) seasonal subtype without suicide attempt, (iii) healthy controls (matched) (18-62 years)	69 (15% male)	Suicide attempt	Karolinska Scales of Personality; self-report	Individuals with depression (not seasonal) who attempted suicide scored higher on irritability compared with controls (58.66±12.9 vs 46.26±7.7, $p=0.002$ ) but not compared with seasonal depressed non-attempters	None
Perlis et al. 2005 (US)	Cross-sectional	Patients with major depressive disorder (MDE) (40.4 years)	1,456 (37% male)	Suicide attempt (clinical interview)	1 item from the Inventory of Depressive Symptomatology ; clinician-rated	Association between irritability and history of suicide attempt in unadjusted (OR=1.52 [1.16-2.00]) but not adjusted analysis (AOR=1.12 [0.83-1.51])	Age at onset MDE, n of prior MDE, duration of current MDE, HAM-D, current alcohol, substance, GAD, CIRS symptoms, family typology, smoking status, alcohol and drug consumption, current/comorbid physical illness
Pompili et al. 2008 (Italy)	Cross-sectional	Psychiatric inpatients (41.6±13.9 years)	150 (33% male)	Suicidality (MINI)	TEMPS-A; self-report	Irritable temperament was associated with suicidal risk in multivariate analysis (AOR=1.12 (1.01–1.22))	Stepwise-selected variables: social introversion, hyperthymic temperament
Pompili et al. 2016 (Italy)	Cross-sectional	Patients who died by suicide and MDD outpatients with and without history of suicide attempt (41.2±12.8 years)	150 (47.4% male)	Suicide mortality (declared by a relative)	TEMPS-A; reported by relative (psychological autopsy), self-report for controls	No difference in irritable temperament between patients who died by suicide and MDD controls with (0.40±0.25 vs 0.38±0.20, $t=-0.32$ , $p=0.75$ ) or without (0.40±0.25 vs 0.46±0.19, $t=-1.22$ , $p=0.23$ ) history of suicide attempt	None
Popovic et al. 2015 (Multiple)	Cross-sectional	Patients with major depressive disorder (NA years)	2,811 (31.2% male)	Suicide ideation (clinical assessment)	Clinical assessment	Irritable mood associated with history of suicidal ideation in univariate but not multivariate analysis (OR=1.55 [1.29–1.86])	None
Rihmer et al. 2009 (Hungary)	Cross-sectional	Suicide attempters and healthy controls (35.3 years)	452 (28.8% male)	Suicide attempt (hospital admission)	TEMPS-A; self-report	Irritable temperament was associated with suicidal attempt (OR=3.34 [1.47–7.56])	None

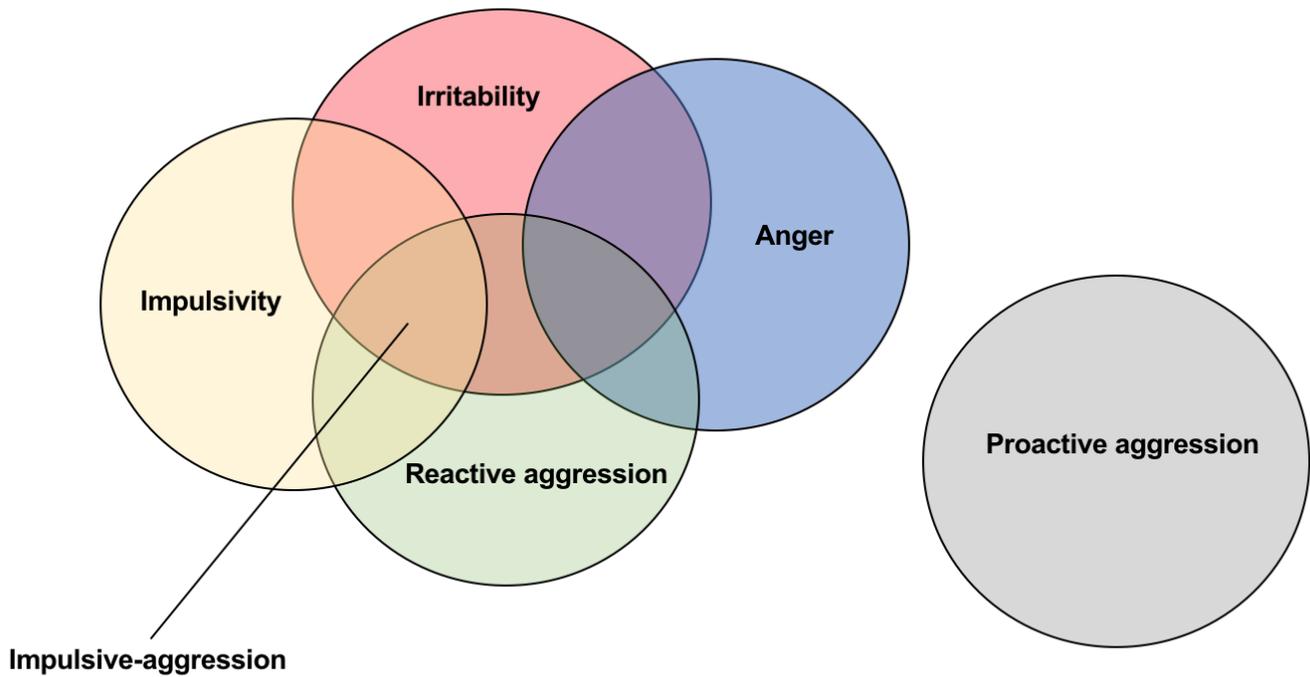
Rihmer et al. 2013 (Hungary)	Cross-sectional	General practice patients (20-90 years)	509 (38% male)	Suicide attempt (history) (clinical assessment)	TEMPS-A; self-report	Irritable temperament was not different among patients with and without history of suicidal attempt (median [IQR]: 4[2,6] vs 4[2,8.25], $p=0.188$ )	None
Stålenheim 2001 (Sweden)	Cross-sectional	Forensic psychiatry unit male patients (18-56 years)	61 (100% male)	Suicide attempt (SCID)	Karolinska Scales of Personality; self-report	Higher levels of irritability among attempters ( $60.5\pm 14.2$ vs $49.7\pm 14.7$ , $t=2.77$ , $p<0.01$ )	None
Tanabe et al. 2016 (Japan)	Cross-sectional	Patients admitted for intoxication or self-inflicted injuries (48.5±18.4 years)	116 (62.1% male)	Suicide attempt (clinician assessment)	TEMPS-A; self-report	Irritable temperament score was higher among patients admitted at the hospital and classified as suicide attempters than those admitted to the hospital but not classified as attempters ( $5.6\pm 5.0$ vs $2.8\pm 3.1$ , $t=-3.1$ , $p=0.003$ )	None
Umamaheswari et al. 2014 (India)	Cross-sectional	Patients with bipolar disorder (43.0±12.0 years)	140 (66.2% male)	Suicide ideation (BDI item 9)	Irritability Depression Anxiety Scale; self-report	Inward irritability, but not outward, was associated with suicidal ideation in multivariate analysis (OR=1.49 [1.04–2.13])	Religion, family history of mental disorders, duration of bipolar episode and intra-episodic period, history of hospitalization, depressive symptoms, life events, psychiatric symptoms
Westring et al. 1998 (Sweden)	Cross-sectional	Patients admitted for suicide attempt and matched healthy controls (38±14 years)	74 (43.2% male)	Suicide attempt (clinician assessment)	Karolinska Scales of Personality; self-report	Higher irritability score among suicide attempters; positive correlation between plasma-neuropeptide Y and irritability among attempters ( $r=0.44$ vs $r=-0.30$ , $p<0.01$ )	None
Berk et al. 2014 (Australia)	Longitudinal (2 years follow-up)	Adult outpatients with bipolar I or schizoaffective disorder (18–79 years)	239 (41.8% male)	Suicidality (1 item from HAMD21 scale)	1 item from the Young Mania Rating Scale; clinician-report	Higher levels of suicidality among irritable individuals in multivariate analysis (0.31 vs 0.18, $p=0.004$ )	Changes in mania, depression, SF-36 Physical and Mental health scores

*Abbreviations:* AOR=Adjusted Odds Ratio; BDI=Beck Depression Inventory; CESD=Centre for Epidemiological Study Depression scale; CIDI=Composite International Diagnostic Interview; CIRS= Cumulative Index Rating Scale; HAMD=Hamilton Depression Rating Scale; HARS=Hamilton Anxiety Rating Scale; PHQ-9=Patient Health Questionnaire-9; SF-36=Short Form Health Survey; MDD/E=Major Depressive Disorder/Episode; MINI=Mini-International Neuropsychiatric Interview; OR= Odds Ratio;

SCID=semi-structured interview for Axis I and II DSM-III-R diagnoses; SE=Standard Error; TEMPS-A= Temperament Evaluation of Memphis, Pisa, Paris and San Diego autoquestionnaire

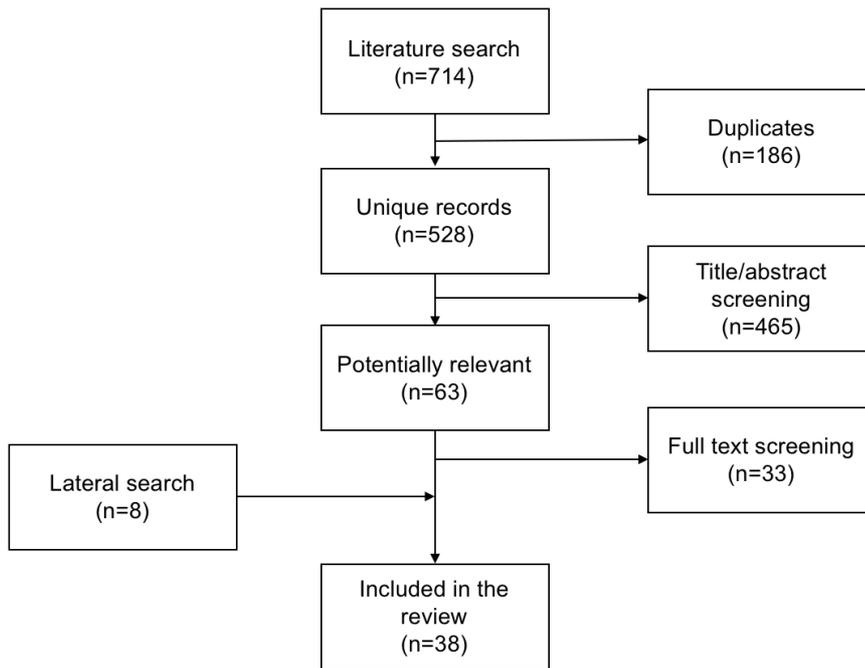
<sup>a</sup> Range or, if not available, mean  $\pm$  SD. For longitudinal studies, the age at irritability assessment was reported.

**Figure 1. Conceptual relation between irritability and related concepts**



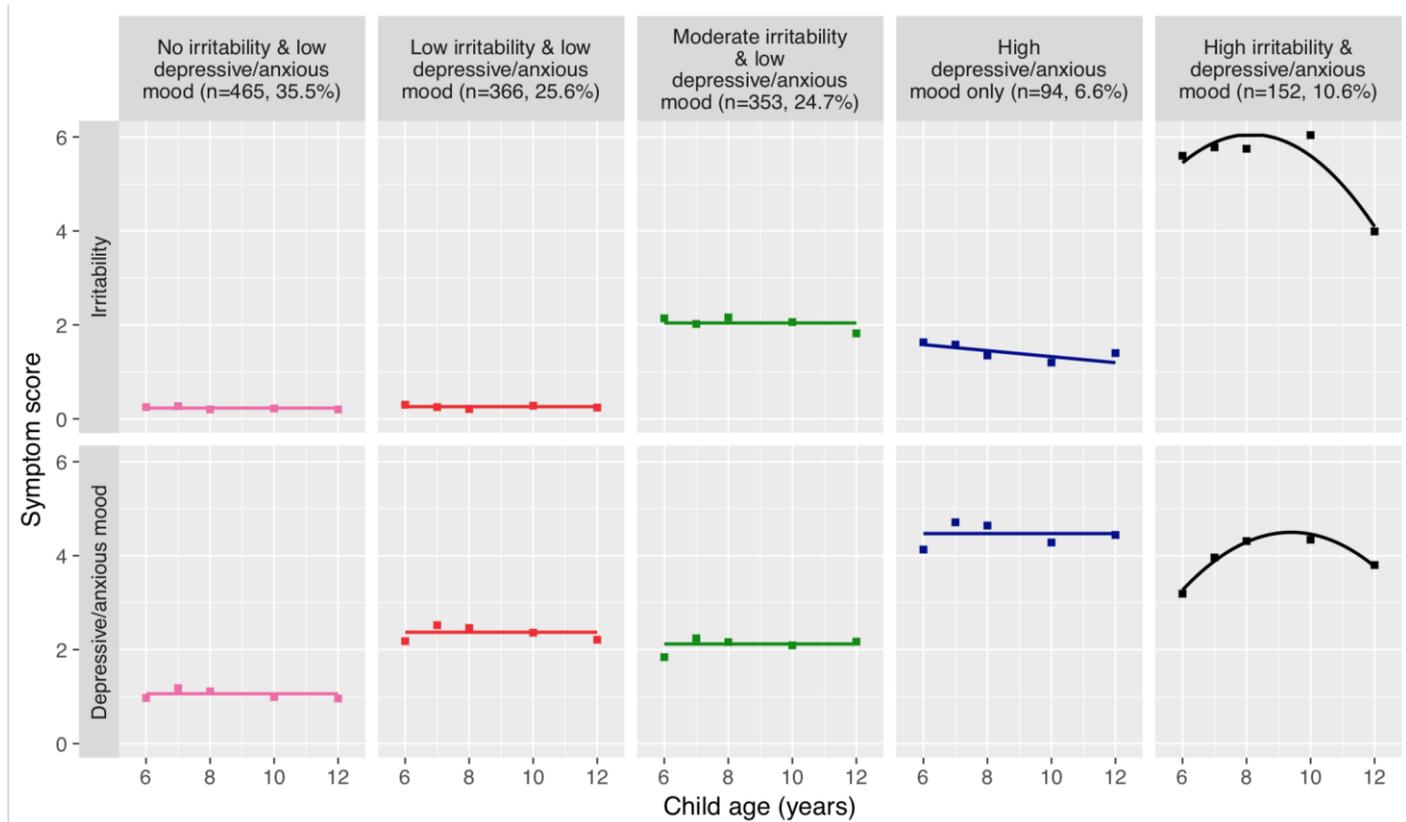
The figure conceptually represents the overlap between irritability and related concepts. Anger is related to irritability as irritability make individual more prone to experience anger. In the same way, irritability make an individual more prone to manifest reactive aggression (behavior manifesting in reaction to perceived provocation or threat, e.g., hitting someone who threatening you), but no proactice aggression (instrumental behavior used to achieve particular goal, e.g. yelling at others so they would do things for you) which is unrelated to irritability. Impulsive behaviors (deficit in inhibitory control mechanisms) can also manifest in association with irritability.

**Figure 2. Flowchart of literature search**



The systematic search was performed in January, 2018 on Medline (Pubmed) and PsycINFO (Ovid). Limits were: English language, and Human. The screening process were independently performed by 2 authors and discrepancies discussed with a third author. The reference list of all included studies was screened for additional references.

**Figure 3. Joint developmental profiles of irritability and depressive/anxious during childhood (6-12 years of age) in the Quebec Longitudinal Study of Child Development (n=1430)**



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Each column represents a different profile of joint irritability and depression/anxious mood development over middle childhood. Each profile is defined by the trajectory of irritability (upper panel) and depressive/anxious mood (lower panel) from 6 to 12 years of age (x-axis) of their member. Dots represent observed value, whether lines represent the fitted regression slopes in the group-based multi-trajectory model.