**Association between suicidal spectrum behaviors and**

**Attention-Deficit/Hyperactivity Disorder: A systematic review and meta-analysis**

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**ABSTRACT**

The relationship between ADHD and suicidal spectrum behaviors (SSBs) remains uncertain. We conducted the first meta-analysis on the association between ADHD and SSBs taking possible confounders into account. Based on a pre-registered protocol (PROSPERO-CRD42018093003), we searched Pubmed, Ovid and Web of Knowledge databases through April 6th, 2018, with no language/publication type restrictions, and contacted study authors for unpublished data/information. From a pool of 2,798 references, we retained 57 studies. Random-effects models were performed. Study quality was rated using the Newcastle-Ottawa Scale. After pooling crude ORs, we found a significant association between ADHD and suicidal attempts (2.37, 95% CI = 1.64 to 3.43; I2 = 98.21), suicidal ideations (3.53, 2.94 to 4.25; I2 = 73.73), suicidal plans (4.54, 2.46 to 8.37; I2 = 0), and completed suicide (6.69, 3.24 to 17.39; I2 = 87.53). Results did not substantially change when pooling adjusted ORs. Findings were also in general robust to sensitivity analyses to assess possible moderators. Awareness of the association between ADHD and SSBs should contribute to more effectively prevent SSBs.

**Keywords:** ADHD; suicide; children; adults

1. **INTRODUCTION**

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by age inappropriate, pervasive, and impairing symptoms of inattention and/or impulsivity/hyperactivity (American Psychiatric Association, 2013). ADHD is one of the most common neurodevelopmental disorders, with a worldwide prevalence estimated between 5% and 6% in school-aged children (Moffitt et al., 2015; Polanczyk et al., 2014) and between 2.5% and 3% in adults (Caci et al., 2014; Moffitt et al., 2015; Simon et al., 2009). Based on the recommended and more conservative scoring method (using the Adult ADHD Symptoms Self-Report), the overall prevalence of impairing ADHD symptoms is estimated to be 2.99% in adults, with no sex ratio or difference in the severity of symptoms between the sexes or between younger and older adults (Caci et al., 2014; Corbisiero et al., 2017).

According to Polanczik et al. (2014), there is no evidence to suggest an increase during the last three decades in the prevalence of children in the population who meet criteria for ADHD when standardized diagnostic procedures are followed. Increasing rates of diagnosis and treatment of ADHD are mostly explained by methodological characteristics of the studies and are likely a reflection of increasing awareness, access to treatment or changing clinical practices (Polanczyk et al., 2014). Recent studies (Caye et al., 2016; Moffitt et al., 2015) suggest that, at least in some cases, ADHD may have its onset in adulthood, although this remains controversial.

ADHD represents a major public health issue (Feldman and Reiff, 2014) and is often comorbid with a number of psychiatric and somatic conditions (Brevik et al., 2017; Cortese et al., 2018, 2016). Because of its core symptoms and comorbid disorders, ADHD imposes an enormous burden on society. Average annual incremental costs of ADHD were estimated at $143-$266 billion in the U.S. (Doshi et al., 2012) and are substantial in other countries as well (Le et al., 2014; Quintero et al., 2018).

 Suicidal spectrum behaviors (SSBs) are a continuum including suicidal ideations, suicidal attempts, suicidal plans, and eventually completed suicides. For some authors the term should also include deliberate-self-harm (Gvion et al., 2015). Indeed, patients frequently move from one type of suicidal behavior to another during the evolution of their psychopathology. The majority of individuals with suicidal ideation do not put their thoughts in action but the transition from suicidal ideation to suicidal action is a common pathway. One-third (33.4%) of adolescent ideators go on to develop a suicide plan, and 33.9% make an attempt (Nock et al., 2013). The proportions of ideators who go on to make an attempt is estimated at around 60% of those with a plan, compared with 20.4% of those without a plan. Eventually, 60% of first attempts have been found to be planned (57% among boys and 66% among girls) (Nock et al., 2013).

Among adults, Nock et al. found that the cross-national lifetime prevalence of suicidal ideation, plans, and attempts was 9.2%, 3.1%, and 2.7%, respectively. Across all countries, 60% of transitions from ideation to plan and attempt occur within the first year after ideation onset. The strongest diagnostic risk factors have been found to be the presence of mood disorders in developed countries, and of impulse-control disorders in developing countries (Nock et al., 2008a). Among adolescents 13 to 18 years old, the estimated lifetime prevalence of suicide ideations, plans, and attempts has been reported at 12.1%, 4.0%, and 4.1%, respectively. Most adolescents with these behaviors meet lifetime criteria for at least one mental disorder (Nock et al., 2013). The gender ratio of suicidal behaviors varies by country but in general its prevalence is higher in females than males (Hee Ahn et al., 2012).

However, whilst complete suicide is more prevalent among men, nonfatal suicidal behaviors are more prevalent among women (Nock et al., 2008b). Furthermore, young males seems to have less suicidal behavior and higher rates of suicide mortality (Möller-Leimkühler, 2003). Serious suicide attempts have been found to be more frequent in males than in females (Freeman et al., 2017) and a recent review based on WHO data has shown that men commit suicide almost twice as often as women (Bachmann, 2018).

Suicide is a leading cause of death worldwide as it accounts for 1.5 % of all deaths in developed countries (Hawton and van Heeringen, 2009). Many factors influence SSBs, especially comorbid psychiatric disorders, impulsivity and impaired decision-making (Gvion et al., 2015). Anorexia nervosa (AN), for example, is known to be associated with a high suicidal risk. Suicide-specific standardized mortality ratio is 19.6 times higher among AN subjects than in a community sample (IC 95%: 12.3 – 31.4) (Keshaviah et al., 2014) but in fact, each psychiatric disorder seems associated, albeit with different degrees, with SSBs, especially after hospitalization discharge (Chung et al., 2017).

 Whilst ADHD has been associated with a wide range of functional impairment and negative outcomes in the psychosocial, academic and occupational domains (Shaw et al., 2012), its association with suicidal spectrum behaviors (SSBs) remains uncertain, due to mixed findings from available studies. Indeed, whereas some studies reported a significant association between ADHD and suicidal ideations, suicidal attempts or completed suicides (Barbaresi et al., 2013; Hinshaw et al., 2012; Impey and Heun, 2012), others failed to replicate these findings (Arias et al., 2008; Kılıç et al., 2017). Furthermore, it is unclear to which extent possible associated factors, such as comorbid psychiatric disorders (e.g., mood disorders or substance use disorders) and psychosocial variables may confound, mediate, or moderate a possible association between ADHD and SSBs.

Given the clinical and public health relevance of SSBs, gaining insight into their potential association with a frequent neurodevelopmental disorder such as ADHD is a priority in the field, as it may have important implications in terms of diagnostic assessment and preventive strategies. To fill this knowledge gap, we conducted a systematic review and meta-analysis of published and unpublished data to estimate the association between ADHD and SSBs considering possible confounding factors. Given the exploratory nature of the study, no *a priori* hypotheses were formulated.

1. **METHODS**

We followed the recommendations of the Meta-Analysis of Observational Studies in Epidemiology group (MOOSE) (Stroup et al., 2000) and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) (see eMethods 1 in the Supplement). The protocol of this systematic review and meta-analysis was pre-registered in PROSPERO (CRD42018093003).

*2.1 Search strategy*

The following electronic databases were searched until April 6th 2018, with no language/date/type of document restrictions: PubMed, Ovid (including PsycINFO, Ovid MEDLINE®, and Embase+Embase Classic), and Web of Knowledge (Web of Science, Biological abstracts, BIOSIS, FSTA). Additional details on the search strategy/syntax are reported in eMethods 2 in the Supplement. References of included studies were hand-searched to find any potentially pertinent study not detected with the electronic search. In addition, we systematically contacted study authors when their study met our inclusion criteria but the published paper did not report data on the association between ADHD and SSBs or data allowing the estimation of this association (e.g., conference proceedings with pertinent design but not reporting data of interest for the present meta-analysis).

*2.2 Type of studies*

Empirical observational studies reporting data on the association between ADHD and SSBs (or data from which this association could be estimated) were included. We excluded case reports. Trials were also excluded since they usually include selected populations, which would have hampered the estimate of the association between SSBs and ADHD. For longitudinal studies, we extracted data at baseline. We also contacted experts in the field to ask for any relevant unpublished data. When several reports were available from the same cohort, to avoid duplication of data, we included the publication reporting the largest number of participants.

*2.3 Types of participants*

The population of interest included children (aged 6-12), adolescents (aged 13-17) or adults (aged > 18) with a diagnosis of ADHD according to DSM (DSM-III, III-R, IV IV-TR, 5) or ICD (9 or 10) criteria. We also planned to include studies on individuals with ADHD defined based on a symptom threshold on a validated ADHD rating scale (eMethods 3 in the Supplement), a diagnosis of ADHD recorded in medical files/registries or, for adults, a positive answer to the question: “Did your doctor ever tell you that you have ADHD”. We excluded studies where participants presented with ADHD symptoms but without a formal diagnosis of the disorder or with a diagnosis of minimal brain dysfunction, which would not be comparable with DSM criteria of ADHD or ICD definition of hyperkinetic syndrome (HKD). We also excluded studies reporting only data on self-injuries without suicidal intentionality.There was no restriction on ADHD subtype/presentation, presence of co-morbid psychiatric or neurologic disorders, gender, intelligent quotient (IQ) or socio-economic status of participants. Studies were retained regardless of their setting (clinical or population-based).

*2.4 Outcomes*

The primary outcome was the unadjusted odds ratio (OR) expressing the association between ADHD and SSBs. The secondary outcome was the OR adjusted for possible confounding factors, when available from the publication. Of note, the variables adjusted for inevitably varied across studies. For each analysis, we split SSBs into: suicidal attempts, suicidal ideations, suicidal plans (defined as "a proposed method of carrying out a design that will lead to a potentially self-injurious outcome, a systematic formulation of a program of action that has the potential for resulting in self-injury", as per Silverman et al., 2007), and (completed) suicides. When the nature of SSBs was not adequately described in the article, we classified them under the category "unspecified suicidal behaviors."

*2.5 Study selection and data extraction*

Retrieved references were independently screened and blindly double-coded for eligibility by two study authors (CS, MS). Any disagreement was resolved by a senior author (SC). Data were extracted from the published reports of the studies or obtained by contacting the study authors when not available in the published article. Papers in languages other than English were translated by the authors or their collaborators.

*2.6 Assessment of study quality/bias*

As suggested by the Cochrane collaboration, (<http://handbook-5-1.cochrane.org/>) we used the Newcastle-Ottawa Scale (NOS) (<http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp>). Details of the NOS are reported in eMethods 4.

*2.7 Statistical analysis*

We used a random-effects model allowing the true population effect size to differ among

studies. We pooled unadjusted (primary outcome) as well as adjusted (secondary outcome) ORs. Whenever data were available from each study, we also calculated the pooled prevalence of SSBs in individuals with ADHD. We planned sensitivity meta-analyses focusing on studies: 1) using a cross-sectional and longitudinal design, respectively; 2) in clinical and population-based samples, respectively; 3) including only current (as opposed to lifetime) prevalence of SSBs; 4) with a formal diagnosis of ADHD (i.e., confirmed by a (semi-) structured interview as per DSM/ICD criteria); 5) including only ADHD medication naïve participants. We also planned a meta-regression analysis including unadjusted ORs as outcomes and the year of study publication, age group (children/adolescents, adults), gender, study setting (clinical, population-based), study continent, and the rating on the Newcastle-Ottawa Scale as regressors. The meta-analyses and meta-analytic regressions were weighted by the reciprocal of the effect size variance, which allowed greater weight to larger studies (DerSimonian and Laird, 1986). We used the I² index to assess the effect size heterogeneity. The I² index estimated the percentage of variation among effect sizes that could be attributed to heterogeneity (Higgins and Thompson, 2002). A significant I² indicated that the degree of heterogeneity was greater than would be expected by chance. We used funnel plots and Egger’s test to assess publication bias (Egger et al., 1997). Analyses were performed using Comprehensive Meta-Analysis (<http://www.meta-analysis.com/index.php>). Clarifications in relation to the pre-registered protocol are reported in eMethods 5 in the Supplement.

1. **RESULTS**

The study selection process is described in Figure 1 and reported in detail in eTables 1 and 2 in the Supplement (list of excluded studies with reasons for exclusion, and list of retained studies, respectively). From 2,798 potentially eligible, de-duplicated citations, 57 studies (datasets) were retained for the meta-analysis (see eTable 3 in the Supplement for study characteristics). The included studies encompassed a total of 90,805 participants with ADHD and 239,778 without ADHD. Overall, 45.5% of studies recruited participants from Europe, 38.2% from America, 10.9% from Asia, 3.6% from Africa and 1.8% from Oceania. Variables adjusted for in each individual study are reported in the eTable 4 in the Supplement. The results of the assessment of the study bias using the Newcastle- Ottawa Scale are reported in eTable 5 in the Supplement. In case-control studies, the average scores in each domain were as follows: *Selection* = 3.02 (out of 4); *Comparability =* 0.95(out of 2); *Outcome: =* 2.4(out of 3). In cohort studies, average ratings were: *Selection* = 3.71 (out of 4); *Comparability =* 1.2(out of 2); *Outcome: =* 2.5(out of 3).

Results of all the meta-analyses (primary meta-analyses on unadjusted ORs, meta-analyses of adjusted ORs and sensitivity meta-analyses) are reported in Tables 1-3, Figures 2-4, and eResults 1.

The primary analysis (unadjusted ORs) (Table 1) indicated a significant association between ADHD and suicide attempts (pooled OR = 2.37, 95% CI = 1.64 to 3.43; for forest plot, see Figure 2), suicidal ideations (3.53, 2.94 to 4.25; for forest plot, see Figure 3), and (completed) suicide (6.69, 3.24 to 13.79; for forest plot, see Figure 4), albeit for all these three analyses, a significant heterogeneity was found (I2 = 98.21, 73.73, and 87.53, respectively). We also found a significant association between ADHD and suicidal plans (4.54, 2.46 to 8.37; for forest plot, see Figure 5), with no significant heterogeneity (I2 = 0). By contrast, we did not find any significant association between ADHD and unspecified symptoms associated with SSBs, that we labeled as “unspecified suicidal behaviors” (1.05, 0.43 to 2.55, I2 =91.45; for forest plot, see Figure 6). Egger test in relation to the primary analysis outcomes indicated a possible publication bias for *suicidal attempts* (p = 0.03), but not for other outcomes. The pooled prevalence of suicide attempts in individuals with and without ADHD was 18.9% (95% CI =14.2 to 24.6) and 9.3% (95% CI = 5.2 to 16.2 %), respectively. The pooled prevalence of suicide ideations in individuals with and without ADHD was 40.8% (95% CI = 29.8 to 52.8) and 15.2% (95% CI = 8.3 to 26.4 %), respectively. The pooled prevalence of unspecified suicidal behaviours in individuals with and without ADHD was 29.5% (95% CI = 13.6 to 52.6) and 17.4% (95% CI = 6.9 to 37.5 %), respectively. The pooled prevalence of (completed) suicide in individuals with and without ADHD was 0.7% (95% CI = 0.2 to 2.9) and 0.2% (95% CI = 0.0 to 4.1 %), respectively.

Findings were substantially replicated in the analyses focusing on adjusted ORs (Table 1).

We found a significant association between ADHD and suicidal attempts (pooled aOR = 2.08, 95% CI = 1.27 to 3.47; I2 = 93.65; for forest plot, see Figure e1 in eResults1) as well as suicidal ideations (4.48, 1.72 to 11.63; I2 = 79.62; for forest plot, see Figure e2 in eResults1). Egger test in relation to these two analyses of adjusted ORs indicated no publication bias (p = 0.145 for suicidal attempts and p = 0.08 for suicidal ideations). No data were available to conduct analyses of adjusted ORs for (completed) suicide, suicidal plans and unspecified suicidal behaviors.

Results were in general robust to the sensitivity analyses. In the ~~subgroups~~ sensitivity analyses focusing on clinical samples (Table 2), we found a significant association between ADHD and suicidal attempts (unadjusted: OR = 2.18, 95% CI = 1.59, 2.98; I2 = 62.66; adjusted: OR = 2.74, 95% CI: 0.67, 11.30; I2 = 87.52), as well as suicidal ideation (unadjusted OR = 2.28, 95% CI= 1.64, 3.16; I2 = 43.27; no data available for adjusted OR), but not for suicidal attempts, adjusted (OR = 2.74, 95% CI: 0.67, 11.30; I2 = 87.52) and for unspecified suicidal behaviors (unadjusted OR = 0.57, 95% CI = 0.13, 2.53; I2 = 92.37 no data available for adjusted OR). Forest plots for the sensitivity meta-analyses focused on clinical samples are reported in Figures e3-e6 in eResults1. As shown in these figures, in none of these sensitivity analyses there was evidence of publication bias at the Egger’s test.

In the sensitivity analyses focusing on epidemiological samples (Table 2), we found a significant association between ADHD and suicidal attempts (unadjusted: OR = 2.52, 95% CI = 1.51, 4.20; I2 = 99.03; adjusted: OR = 1.91, 95% CI = 1.03, 3.56; I2 = 94.10), suicidal ideation (unadjusted OR: 4.22, 95% CI = 3.45, 5.16; I2 = 74.33; no data available for adjusted OR), and also unspecified suicidal behaviors (unadjusted OR = 2.41, 95% CI = 1.75, 3.33; I2 = 0.00; no data available for adjusted OR). Forest plots for the sensitivity meta-analyses focused on epidemiological samples are reported in Figures e7-e10 in eResults1. As shown in these figures, in none of these sensitivity analyses there was evidence of publication bias at the Egger’s test.

In the sensitivity analyses focusing on studies with a formal diagnosis of ADHD (Table 3), we found a significant association between ADHD and suicidal attempts (unadjusted: OR = 2.64, 95% CI = 1.56, 4.48; I2 = 97.96) as well as suicidal ideation (unadjusted: OR = 2.89, 95% CI = 2.29, 3.65; I2 = 46.17) but not unspecified suicidal behaviors (unadjusted: OR = 1.60, 95% CI = 0.65, 3.96; I2 = 91.59). No data were available for analyses of adjusted ORs. Forest plots for the sensitivity meta-analyses focused on studies with a formal diagnosis of ADHD are reported in Figures e11-e13 in eResults1. As shown in these figures, among these sensitivity analyses, there was evidence of publication bias at the Egger’s test only for “unadjusted ORs for suicidal attempts (formal diagnosis of ADHD)”.

In the sensitivity analyses focusing on studies based on current outcomes (Table 3), we found a significant association between ADHD and suicidal attempts (unadjusted: OR = 2.31, 95% CI = 1.44, 3.70; I2 = 97.88) and suicidal ideation (unadjusted: OR = 3.46, 95% CI = 2.67, 4.49; I2 = 75.14). No data were available for analyses of adjusted ORs. Forest plots for the sensitivity meta-analyses focused on studies based on current outcomes are reported in Figures e14-e15 in eResults1. As shown in these figures, among these sensitivity analyses, there was evidence of publication bias at the Egger’s test only for “unadjusted ORs for suicidal attempts, current”.

In the sensitivity analyses focusing on studies based on lifetime outcomes (Table 3), we found a significant association between ADHD and suicidal attempts (unadjusted: OR = 2.87, 95% CI = 1.87, 4.39; I2 = 58.92) as well as suicidal ideation (unadjusted: OR = 3.58, 95% CI = 2.88, 4.44; I2 = 48.95). No data were available for analyses of adjusted ORs. Forest plots for the sensitivity meta-analyses focused on studies based on current outcomes are reported in Figures e16-17 in eResults1. As shown in these figures, there was no evidence of publication bias at the Egger’s test.

In the sensitivity analyses focusing on study design (Table 4), we found a significant association between ADHD and a) suicidal attempts, based on cross sectional studies (unadjusted: OR = 2.13, 95% CI = 1.02, 4.44; I2 = 96.8; adjusted: OR = 1.49, 95% CI = 1.18, 1.89; I2 = 0.00), prospective studies (unadjusted: OR = 2.28, 95% CI = 1.70, 3.407; I2 = 80.51; no data for adjusted OR), and retrospective studies (unadjusted: OR = 3.95, 95% CI = 2.21, 7.07; I2 = 95.01); b) suicidal ideation based on cross-sectional studies (unadjusted OR = 4.05, 95% CI = 3.17, 5.18; I2 = 72.46; no data for adjusted ORs), and prospective studies (unadjusted OR = 2.84, 95% CI = 1.84, 4.37; I2 = 63.30; no data for adjusted ORs), as well as retrospective studies (unadjusted OR = 2.96, 95% CI = 1.69, 5.20; I2 = 70.74; no data for adjusted ORs). However, no significant association was found between ADHD and suicidal attempts, based on retrospective studies, considering adjusted OR (2.02, 95% CI = 0.95, 4.30) and unspecified suicidal behaviors, based on cross-sectional studies (unadjusted OR = 0.87, 95% CI = 0.16, 4.79; I2 = 93.49; no data for adjusted ORs) or retrospective studies (unadjusted OR= 1.24, 95% CI: 0.47, 3.27; I2 = 87.79; no data for adjusted ORs). Forest plots for the sensitivity meta-analyses focused on study design are reported in Figures e18-e27 in eResults1. Egger’s test indicated a possible publication bias only for the analysis of suicidal attempts, unadjusted OR, retrospective.

Due to insufficient data, the planned sensitivity analyses focusing on studies including only ADHD medication-naive participants could not be performed.

The meta-regression analyses showed that none of the included covariates available in the retained studies (data available for suicidal attempts and suicidal ideation: study design, setting, type of diagnosis, age, continent, study publication year, and study quality as rated at the NOS) significantly impacted on the results (see eResults 3 in the Supplement).

1. **DISCUSSION**

To our knowledge, this is the first meta-analysis, based on a systematic review, on the association between SSBs and ADHD. By analysing different types of SSBs, we were able to provide a fine-grain description of the relationship between ADHD and SSBs, which we believe may be informative for the daily clinical practice. After pooling published and unpublished data from 57 datasets, including a total of more than 300,000 participants, we found meta-analytic evidence of a significant association of ADHD to suicidal attempts, suicidal ideations, suicidal plans, and suicide. The magnitude of the pooled OR, as well as the increased percentage of SSBs prevalence in individuals with compared to those without ADHD, show that our findings are not only statistically but also clinically significant.

Our results extend the conclusions of previous reviews that suggest an overall significant association between ADHD and suicidal behaviors (Balazs and Kereszteny, 2017; Furczyk and Thome, 2014; Giupponi et al., 2018; Impey and Heun, 2012; James et al., 2004) but did not use a formal meta-analytic approach to quantitatively pool mixed evidence from available studies and estimate the magnitude of the association. Previous reviews also failed to quantitatively assess the impact of possible confounding, mediating, or moderating factors (such as psychiatric comorbidities), which may lead to a biased estimation of the association between ADHD and a risk of SSBs. For instance, some authors concluded that the link between ADHD and SBBs (Renaud et al., 1999) is mediated by the cumulative effects of externalizing disorders (conduct and oppositional defiant disorders), substance use disorders, affective disorders (emotional problems in males and depression in females) or somatic conditions (Bácskai et al., 2012; Berkol et al., 2014; Donev et al., 2011; Patros et al., 2013; Penney et al., 2012; Sáez-Francàs et al., 2012) rather than being accounted for by ADHD *per se*. In this regard, it is important to note that our results were in general replicated when pooling ORs adjusted for a number of variables. Therefore, early views according to which ADHD would not be a risk factor for SSBs *per se* are not supported by our results. However, as the factors adjusted for inevitably varied from study to study, additional studies simultaneously adjusting for all these factors are needed to fully appreciate to which extent ADHD may independently increase the risk of SSBs.

# Our findings were in general robust to variation in study setting (clinical or epidemiological), study design (cross-sectional, prospective, or retrospective), method used to diagnose ADHD, and temporality (lifetime or current) of SSBs. Regarding the higher OR for association between ADHD and suicidal ideation in epidemiological *vs.* clinical samples, it is possible that individuals in population based, non-clinical studies feel less constrained and report suicidal ideation via questionnaires more spontaneously than in a face-to-face interview in a clinical setting. On the contrary, suicidal acts may be recorded in healthcare systems (following admission to Emergency Departments), so less likely to be underestimated in the clinical setting. The lack of significant findings in the subgroup meta-analyses focusing on suicidal attempts, adjusted OR, in the clinical setting and suicide attempts, adjusted OR, retrospective design should be considered with caution given the limited number of studies (two and three, respectively) they were based on. Additionally, our meta-regression analysis showed that none of the variables that we considered (study design, setting, type of diagnosis, age, continent, study publication year, and study quality) had a significant impact on the results. No data were available to explore the impact of gender in the meta-regression models. Whilst these results are at odds with the conclusions of early reviews (e.g., increased risk of SSBs in males only, (James et al., 2004) they lend meta-analytic support to a recent systematic review highlighting how ADHD is related to increased risk of SSBs across age groups (Balazs and Kereszteny, 2017). This study also found that gender did not impact on the rates of SSBs in ADHD, which we could not explore with our meta-regression due to lack of data.

The strong association between ADHD and SSBs points to potential shared mechanisms or/and reciprocal influences of both disorders in their determinism. Since our analysis focused on cross-sectional relationships, it is not informative on cause-effect relationships. As such, a number of possible mechanisms should be considered to explain the link between ADHD and SSBs. A first hypothesis is that ADHD contributes to SSBs. Impulsivity, a core symptom of ADHD, along with impaired decision-making and risk taking, that characterize a number of individuals with ADHD (Shoham et al., 2016), may lead to SSBs (Hadlaczky et al., 2018). Additionally, a sizeable portion of individuals with ADHD present with deficits in executive functions (Willcutt et al., 2005). As executive functions are implicated in the regulation of impulse control and emotions, executive dysfunctions may contribute to SSBs (Barkley, 2001). Furthermore, as ADHD significantly impacts on daily functioning in a number of areas (such as social, academic, work-related), it entails high levels of stress, which may increase the vulnerability to SSBs. A second hypothesis is that common underlying factors, such as a shared genetic vulnerability, play a role. Indeed, SSBs and impulsivity have been found to be genetically linked (Hawton and van Heeringen, 2009). Meta-analytic evidence points to a role of serotonergic dysfunction in suicidality and impulsivity, with significant associations between variations on *TPH1* and *5-HTTLPR* genes, and impulsive and suicidal behaviours (Antypa et al., 2013).

We initially planned to assess, via meta-analytic methods, the possible effect of ADHD pharmacological treatment on the risk of SSBs. To avoid important confounding by indication, a study design that is suitable to address this question is represented by the so called *within subject* or *self-case control* design, reporting the risk of SSBs in the same individual when exposed or not to ADHD medications. After a systematic search across several databases and contacting all the authors of the studies included in our meta-analysis, we were able to identify only two self-case control studies (Chen et al., 2014; Man et al., 2017). As such, we did not deem it appropriate to perform any meta-analysis. However, both studies found no evidence of a significant association between SSBs and the use of psychostimulants in ADHD. Indeed, both these studies suggests that treatment by methylphenidate may have a protective effect on SBBs. More specifically, the study by Man et al. (2017) reported that the risk of suicide attempts for individuals treated with methylphenidate returned to a baseline level of risk (compared to general population) after 90 days of drug treatment. According to the study authors, the increased risk of SSBs in the period immediately following the start of methylphenidate may be accounted for by the increased severity of the psychopathological distress which triggers the referral of the patient to a specialist to seek appropriate treatment.

The results of our systematic review/meta-analysis should be considered in the light of its strengths and limitations. As for the strengths, we pre-registered the protocol in a publicly available repository (PROSPERO), reducing the risk of reporting bias. Furthermore, we performed a comprehensive and systematic search of several databases, with no restrictions in terms of language or document type, and we gathered unpublished data from study authors. Additionally, we used a state-of-the-art tool, the Newcastle-Ottawa scale, to assess the quality of the retained studies. In terms of study limitations, heterogeneity, measured by I2, was significant and high for the majority of our analyses and, with a few exceptions, it tended to remain high even when restricting the analyses to more homogeneous study groups. Although this does not invalidate the results, it indicates that the pooled OR cannot appropriately summarise results from all datasets. Finally, although study quality ratings indicated that poor representativeness was not an issue, comparability between cases and controls was the domain with the lowest score, being scored as problematic in 5.26% of the studies.

Despite these caveats, our study provides meta-analytic evidence - even after pooling ORs adjusted for possible confounders- that ADHD is associated with a major risk of SSBs, specifically suicide. We believe that our findings have important clinical and public health implications. Awareness of this association should prompt practitioners to systematically screen for SSBs in patients with ADHD at the first assessment and at each follow-up, which in turns should contribute to decrease the risk of SSBs. This is particularly noteworthy considering that questionnaires/scales commonly used to screen/assess ADHD symptoms generally do not include suicide related items. Our findings highlight how such screening should start with young patients, rather than just in adults. There is preliminary evidence that, once SSBs have been detected, they are not worsened by ADHD pharmacological- if anything, ADHD medications might indeed contribute to reduce the severity of SSBs.

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**DECLARATION OF CONFLICTS OF INTEREST**

The authors declare no conflict of interest

**Figures legend**

Figure 1. PRISMA flowchart

Figure 2. Forest plot. Unadjusted ORs for suicidal attempts (SA)

Figure 3. Forest plot. Unadjusted ORs for suicidal ideation (SI)

Figure 4. Forest plot. Unadjusted ORs for (completed) suicide

Figure 5. Forest plot. Unadjusted ORs for suicidal plan (SP)

Figure 6. Forest plot. Unadjusted ORs for unspecified suicidal behaviors

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