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LONGITUDINAL ASSOCIATION BETWEEN SELF-INJURIOUS THOUGHTS AND BEHAVIORS AND SUICIDAL BEHAVIOR IN ADOLESCENTS AND YOUNG ADULTS: A SYSTEMATIC REVIEW WITH META-ANALYSIS

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ABSTRACT

Background

Adolescents with previous self-injurious thoughts and behaviors (SITB) have over 2-fold risk of dying by suicide, higher than older ages. This meta-analysis aims to disentangle the association of each SITB with subsequent suicidal behavior in adolescence/young adulthood, the contribution of each SITB, and the proportion of suicide deaths with no previous suicide attempt.

Methods

We searched 6 databases until June 2015. Inclusion criteria: 1. Assessment of any previous SITB [a) suicidal thoughts and behaviors (ideation; threat/gesture; plan;

attempt); b) non-suicidal thoughts and behaviors (thoughts; threat/gesture; self-injury); c) self-harm] as a risk factor of suicide attempt or suicide death; 2. Case-control or cohort studies; 3. Subjects aged 12-26y. Random effect models, metaregression analyses including mental health and environmental variables, and population attributable risks (PAR)s were estimated.

Results

From 23,682 potentially eligible articles, 29 were included in the meta-analysis (1,122,054 individuals). While 68% of all youth suicide deaths had no previous suicide attempt, suicide death was very strongly associated with any previous SITB (OR= 22.53, 95%CI: 18.40-27.58). Suicide attempts were also associated with a history of previous SITB (OR= 3.48, 95%CI: 2.71-4.43). There were no moderating effects for mental health and environmental features. The PAR of previous SITB to suicide attempts is 26%.

Limitations

There is considerable heterogeneity between the available studies. Due to limitations in the original studies, an over-estimation of the proportion dying at their first attempt cannot be ruled out, since they might have missed unrecognized previous suicide attempts.

Conclusions

Although more than two thirds of suicide deaths in adolescence/young adulthood have occurred with no previous suicidal behavior, previous SITBs have a much higher risk of dying by suicide than previously reported in this age group.

LIST OF ABBREVIATIONS

CI, Confidence Intervals; MOOSE, Meta-Analysis of Observational Studies in Epidemiology; NOS, Newcastle-Ottawa Scale; NSSI, Non-Suicidal Self-Injury; NSSIT, Non-Suicidal Self-Injury Thoughts; OR, Odds Ratio; PAR, Population Attributable Risk; RR, Relative Risk; SE, Standard Error; SITB, Self-Injurious Thoughts and Behaviors; US, United States; WHO, World Health Organization

Key words: suicide; self-harm; non-suicidal self-injury; adolescents; youths

INTRODUCTION

The World Health Organization (WHO) has declared suicide a priority for global health. Overall more than 800,000 individuals of all ages commit suicide every year worldwide. Suicidal behaviors may be preventable using efficient prevention strategies at low cost. Nevertheless, over the past 45 years worldwide suicide rates have increased by 60%, youths being the group at highest risk in a third of countries (WHO, 2014), making it the second most important cause of death during adolescence and young adulthood in 2013 (Mokdad et al., 2016).

Suicide is rare in childhood and early adolescence, but it becomes more frequent with increasing age. Worldwide annual rates of suicide per 100,000 were 0.5 for females and 0.9 for males during childhood, and 12.0 for females and 14.2 for males during adolescence/young adulthood (Pelkonen and Marttunen, 2003). Adolescence and

young adulthood is a crucial developmental period with an increasing autonomy but is also subject to rapid psychological, biological and social changes. Such changes may make youths vulnerable to environmental stress (Aro et al., 1993) which may contribute to psychopathology, alcohol and drug misuse, and risk behaviors (Aro et al., 1993; Arpawong et al., 2015; Pelkonen and Marttunen, 2003), and thus increase suicide risk and repeated suicide-related thoughts and behaviors (Castellvi et al., 2016). SITBs are common in young people (Baetens et al., 2011), and 18% will repeat suicidal or non-suicidal behavior within a year (Hawton et al., 2007), which is strongly linked to suicide death with 40-60% of those who die by suicide having self-harmed in the past (Owens et al., 2002). Furthermore, self-harm has long-term health consequences such as mental illness and psychiatric hospitalization, even suicide death (Beckman et al., 2016).

Although, fortunately, suicide deaths are relatively uncommon in most populations (e.g. the one-year odds of dying by suicide in the United States is around 0.00013 persons/year ((CDC), 2012)), suicide has huge family and social consequences, even more when the victim is an adolescent or youth. Self-inflicted injuries are one of the main causes of disability-adjusted life-years lost (DALYs) worldwide. Each youth suicide represents a potential of 60 years of life lost (YLL)s and suicide attempts have a high potential impact in term of years lost because of disability (YLD)s (Mokdad et al., 2016).

Previous self-injurious thoughts and behaviors (SITB) are considered one of the strongest predictors of suicide attempts and suicide death (Bridge et al., 2006; McLoughlin et al., 2015). A large amount of research has been published linking the association between any previous SITB and further suicide attempts and suicide death among adolescents and youths. However, the real magnitude of the risks among this population remains unclear with large variations in the risk being reported (Conner et

al., 2014; Miranda et al., 2014; Wichstrom and Hegna, 2003), and some studies have even reported non-significant effects (Guan et al., 2012; Nock and Banaji, 2007; Nrugham et al., 2008). These discrepancies raise doubts about the true effect of previous SITBs on future suicidal behaviors among youths. A recent meta-analysis estimated that individuals with a history of any SITB had a more than 2-fold risk of subsequent suicide attempts (Ribeiro et al., 2016) and 1.5-fold risk of dying by suicide, when compared with those persons with no previous SITB. This association has been found across all ages. While the authors concluded that all ages are at risk when they have a history of any SITB, adolescents are the group most at risk of dying by suicide (Ribeiro et al., 2016), no meta-analyses have been conducted specifically to calculate the risks of suicidal behaviors during adolescence and youth in terms of previous specific SITB.

A recently meta-analysis showed that adolescents and young adults with a history of previous SITB are the most vulnerable group for presenting future SITBs (Ribeiro et al., 2016). Therefore, we conducted a new systematic review to deepen the understanding of these associations by assessing in this population: (i) the effect size of each previous SITB as a risk factor of suicide attempt and suicide death; (ii) whether there was a moderating effect by key psychopathological and environmental variables; (iii) the population attributable risk (PAR) of each previous SITB; and (iv) the proportion of suicide deaths with no previous suicide attempt. This knowledge should be useful for suicide prevention among adolescents and young adults. We hypothesized that young individuals with any type of SITB would have higher rates of suicide attempts and suicide deaths than their counterparts without any prior SITBs, and also that rates would be higher among those with previous suicidal thoughts and behaviors than among those presenting non-suicidal self-injurious thoughts and behaviors. As mentioned above, youths and adolescents with any previous SITB will be at risk of making a suicide

attempt or dying by suicide. In contrast to non-suicidal thoughts and behaviors, suicidal thoughts and behaviors include the intention to die. Additionally, the main motivation of non-suicidal behaviors is instead to communicate distress and/or to seek help from others (Nock and Kessler, 2006).

METHOD

Search strategy

This article is based on data extracted from a broad systematic review to identify a comprehensive list of risk factors of suicidal behaviors in individuals aged from 12 to 26 years. The original research protocol was previously registered at PROSPERO (Reg: CRD42013005775) (Alonso et al., 2013). Recommendations from the MOOSE guidelines for systematic reviews (Stroup et al., 2000) in relation to handling and reporting of results were considered (see MOOSE checklist at supplementary material Table S1). The search strategy was devised for Medline by two investigators with previous experience in performing systematic reviews of observational studies (PC; OPB) and adapted to the other databases. More information about the search strategy and selection criteria of the broad systematic review is provided in Text S1 (see supplementary material Text S1).

Inclusion and exclusion criteria

For this article, we added the following specific selection criteria: population-based longitudinal studies (non-clinical and non-institutionalized sample cohorts; or case-control studies where the control group was of the same age range as the case group and both non-clinical and non-institutionalized) which assessed any form of previous SITB as a risk factor of suicide attempts or suicide death. Initially, we adopted the conceptual

framework proposed by Nock for SITB definitions (Nock, 2010), differentiating previous suicidal and non-suicidal behaviors. However, inconsistent terms and definitions have historically been used for each SITB by previous authors and we included two additional terms which Nock's nomenclature did not contemplate: (i) self-harm as a separate risk behavior (NICE, 2011), and (ii) suicide threat as a suicidal behavior, because some authors consider suicide threat as a suicidal behavior due to intentionality (Silverman and Berman, 2007). Nock considers only suicide threat/gesture as non-suicidal behavior. So, our SITB final classification was: 1) Suicidal thoughts and behaviors (ideation; threat; plan; attempt); 2) Non-suicidal thoughts and behaviors (self-injurious thoughts [NSSIT]; threat/gesture; self-injury [NSSI]); and 3) Self-harm (which includes suicide attempt and NSSI) (See typology and definitions of each type of SITB in supplementary material Table S2). Information on eligible studies included: author; year of publication; study; country; study design; type of sample recruited; sample size; age range; mean age; number of females; type of outcome; type of SITB assessed; time prevalence of SITB; percentage of people exposed to SITB; instrument used; and variables included in multivariate analyses. From cohort studies, additional data were extracted relating to the follow-up: length; attrition rates; percentage of incident suicide attempt or completed suicides.

Information abstracted about risk factors consisted of: odds ratio (OR) and 95% confidence intervals (95% CI), or beta coefficients (b) and standard error (SE). The adjusted OR prevailed over the unadjusted OR. When papers provided estimates of the risk ratio (RR) or hazard ratio (HR), we used these as estimates of the OR. Although the OR is a valid measure of the association, it is often used as an approximation of the RR or HR, but OR biases the results to the null hypothesis. So, it tends to exaggerate the magnitude of the association. When the incidence of the outcome, such as suicide

attempt and even more suicide death is rare, this is acceptable, and the different effect estimates should be very similar in value (Sazklo and Nieto, 2000). Alternatively, when possible, we extracted corresponding risks from the article using 2x2 contingency tables containing numbers of cases and non-cases, and of exposed and non-exposed subjects. When two or more papers reported on the same sample they were included in the systematic review if they contributed to different meta-analyses or PAR calculations. Otherwise, we included results from the paper achieving the longest follow-up or with the largest sample.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of studies (Wells et al., 2014). The NOS uses a “star system” in which a study is evaluated on three broad perspectives: the Selection of the study groups; the Comparability of the groups; and the Ascertainment of either the exposure or outcome of interest for case-control or cohort studies respectively. The scale consists of eight items with different response categories; the category which indicates the highest quality gets a star, except for the item Comparability which can get two stars. The highest possible NOS score is nine stars. For some items specific criteria are required to give the star. Criteria used included: 1) For Comparability, one star was awarded when adjustment had been performed for one variable only; and two stars for two or more adjustment variables; 2) For Follow-up, one star was awarded for periods ≥ 3 years. 3) For Adequate follow-up, one star was given if attrition rate was $<30\%$ at the end of the study. The quality of identified studies was assessed by one reviewer, and another reviewer checked each item in the article.

Data analysis

A bottom-up analysis strategy was used to implement each of the meta-analyses. First, we assessed each basic form of SITB separately (Suicide ideation, threat/gesture, plan, attempt, NSSI, non-suicidal threat/gesture, NSSIT). When any of the included samples was a source of heterogeneity, we excluded it using sensitivity analyses when necessary. The samples finally selected were then included in the meta-analysis of the three aspects constituting the top level in the hierarchical breakdown of previous SITB (1. Suicidal thoughts and behaviors; 2. Non-suicidal thoughts and behaviors; and 3. Self-harm) according to its definition. Finally, we assessed the global risk estimates for any previous SITB.

STATA software version 13 was used to conduct these meta-analyses. For studies that provided results by subgroups (e.g. sex), we combined results using a fixed-effects model and included the pooled result in the analyses. The proportion of heterogeneity was calculated using Higgins test (I^2), and its significance determined using a Chi-square test, p-values <0.10 being considered statistically significant. Heterogeneity was defined as: low (<30%), moderate (30-50%), severe (>50%) (Higgins and Thompson, 2002). The following variables were considered *a priori* as sources of heterogeneity and we conducted sensitivity analyses excluding articles with: (i) <6 stars using NOS instrument; (ii) case-control design; (iii) attrition rate >30% during the follow up; (iv) length of follow-up <3y; (v) unadjusted estimates; (vi) population oversampled with known risk factors related with suicide (e.g. population-based subgroups with depressive symptoms); (vii) non-lifetime prevalence of previous SITB (e.g., 12-month prevalence); (viii) prior SITB not assessed by any validated instrument, clinical certification or semi-structured interview. Additionally, Galbraith plots were used to evaluate heterogeneity. We used a random-effects meta-analysis for pooled estimation

because we assumed that the studies identified differed among themselves in several factors, such as different populations, countries or study design.

Small-study effects or publication bias was determined using funnel plots and Egger test. In the presence of significant asymmetry, we used Duval and Tweedie's Trim and Fill test (Duval and Tweedie, 2000) to reduce the impact of publication bias by imputing potential new unpublished studies, and obtaining a new pooled estimate.

Metaregressions were conducted to assess the role of some mental health and environmental exposures: previous psychopathology, alcohol or substance use/disorder, impulsiveness, aggressiveness, stressful life event, and access to means as moderators of associations between previous SITB and future suicidal behavior. We estimated separate models for each variable, and subsequently considered them as co-variables in the multivariate models.

Population attributable risk (PAR) was also calculated from cohort studies using the formula:

$$PAR = \frac{P(RR-1)}{1+P(RR-1)}$$

where P is the prevalence of being exposed to any form of SITB obtained from data available in some of the cohort studies included in the meta-analysis, and RR is the relative risk of suicidal behaviours in exposed versus non-exposed individuals based on data from the studies included.

The RR was then converted to OR using :

$$RR = \frac{OR}{(1-P_0)+P_0OR}$$

where P_0 is the prevalence of suicide attempts in non-exposed (Zhang and Yu, 1998), calculated through meta-analysis using data available from the cohort studies.

RESULTS

Selection and inclusion of studies

From a total of 23,682 potentially eligible articles, we identified 1,575 full-text articles for eligibility, of which 1,544 were excluded. Twelve articles were excluded from this systematic review because they were about the same sample and they did not provide any additional information. Finally, 31 articles from 26 studies were included for qualitative synthesis, and 29 articles for the meta-analysis (1,122,054 individuals) (Figure 1).

Characteristics of included studies

Characteristics of the included studies are presented in Table 1. The majority were cohort studies ($n = 23$, 74.2%). A total of 25 (80.6%) articles assessed the risk of suicide attempt and 6 (19.4%) articles assessed the risk of suicide death. Most samples were from the US (64%). Of all the comparisons of previous SITB included, 43% were assessed as life-time, and 35% as 12-month prevalence. The majority (71%) of included studies used a non-validated instrument for assessing any previous SITB: 44% used one item, 19% two items, and 8% three items. (Table 1)

Quality assessment of studies

Over half (61%) of the studies achieved ≥ 6 stars. Most of the studies (69%) recruited the sample from general or student population, but other studies recruited specific high-risk groups (e.g., lesbian, gay, and bisexuals; with depressive symptoms or disruptive behaviors; or offspring of alcoholic parents) (Brezo et al., 2007; Conner et al., 2014; Lambert et al., 2008; Lewinsohn et al., 2001; McKeown et al., 1998; Miranda et al., 2014; Mustanski and Liu, 2013; Nruugham et al., 2008; Scott et al., 2015). In two studies (8%), previous SITB had been clinically validated (Brezo et al., 2007; Finkelstein et al., 2015). Eleven (48%) cohort studies had a length of follow-up < 3 years, and six (26%) had an attrition rate $> 30\%$. In five studies (19%), the estimates were unadjusted. (See quality assessment in supplementary material Table S3).

Previous self-injurious thoughts and behaviors (SITB)s as risk factor of suicide death

1. Previous Suicidal Thoughts and Behaviors

Five studies were case-control and only one was a cohort. In 88% of identified studies, suicidal behavior was significantly associated with suicide death.

Two comparisons assessed suicidal ideation and meta-analysis showed a significantly higher risk of suicide death (OR = 32.16; 95% CI: 6.99-147.92). Two comparisons assessed suicidal threat and a pooled risk of suicide death was obtained (OR = 11.46; 95% CI: 2.25-58.31). Four comparisons were included for previous suicide attempts, and the pooled OR was over 22 (OR = 22.58; 95% CI: 18.37-27.76) (Figure 2).

The pooled OR estimate of all previous suicidal thoughts and behaviors was 22.48 (95% CI: 18.35-27.54) (Figure 2).

2. *Previous Self-Harm*

Six comparisons were assessed, and a high pooled risk of suicide death was obtained (OR = 22.63; 95% CI: 18.42-27.80). (See online supplementary material, Figure S1).

None of the identified studies dealt with non-suicidal thoughts and behaviors.

3. *Any Previous Self-Injurious Thoughts and Behaviors*

The overall estimate including ten comparisons from five articles among adolescents and youths, comparing those with a history of any SITB with their non-exposed counterparts, was 22.53 (95% CI: 18.4-27.58).

No heterogeneity was found in any of these meta-analyses for suicide death.

Previous suicidal thoughts and behaviors (SITB)s as risk factors of suicide attempt

1. *Previous Suicidal Thoughts and Behaviors*

Over 60% of studies found a significant association between a history of suicide ideation and future suicide attempt, and over 90% for a history of suicide attempt.

The pooled OR including 19 comparisons of suicidal ideation was 3.26 (95% CI: 2.26-4.70). Heterogeneity was severe ($I^2 = 92\%$). However, by excluding those studies, detected through sensitivity analysis, which evaluated non-lifetime prevalence of SITB, we reduced heterogeneity to a moderate level ($I^2=48\%$), obtaining a lower estimate (OR = 2.08) Based on the Galbraith plot analysis, nine samples were excluded (Brezo et al., 2007; Fergusson et al., 2005; Garnefski et al., 1992; Guan et al., 2012; Ialongo et al., 2004; Lewinsohn et al., 2001; Reinherz et al., 1995; Wichstrom and Hegna, 2003; You and Lin, 2015) and as a result heterogeneity disappeared, while the estimate remained similar (OR = 3.14). No study was identified that assessed suicidal threat as a risk factor. We identified one sample which examined suicidal plan and the estimate was not significant (OR = 2.29; 95% CI: 0.12-43.16) (McKeown et al., 1998). Previous suicide attempt showed the largest average effect size (OR = 5.56; 95% CI: 3.32-9.30), but results presented severe heterogeneity ($I^2 = 66\%$). Sensitivity analyses showed that heterogeneity could only be slightly reduced by excluding those studies with a follow-up <3 years (OR = 6.67; $I^2 = 58\%$) resulting in a slightly higher estimate. Based on the Galbraith Plot, three studies were excluded (Conner et al., 2014; Fergusson et al., 2005; Miranda et al., 2014) and the analysis yielded a lower but similar estimate (OR = 4.93) with no heterogeneity (Figure 3).

After performing sensitivity analyses for each type of suicidal thoughts and behaviors (ideation, threat, plan, attempt), no reasons for excluding samples were found and we included 34 comparisons. The pooled estimate for any type of suicidal SITB was significant (OR = 3.88; 95% CI: 2.91-5.17). Heterogeneity was severe ($I^2 = 87\%$) (Figure 3).

2. *Previous Non-Suicidal Thoughts and Behaviors*

From five identified studies, four articles (80%) found NSSI a significant risk factor. We did not identify any article that assessed NSSIT (i.e. thoughts).

One study assessed non-suicidal threat/gesture as risk factor, and the OR was not significant (OR = 0.70; 95% CI: 0.35-1.40). A meta-analysis assessing NSSI was performed including five comparisons, and the estimate was significant (OR = 2.26; 95% CI: 1.26-4.07) with severe heterogeneity ($I^2 = 75\%$). Sensitivity analyses suggested that heterogeneity could be reduced by excluding studies evaluating non-lifetime prevalence of SITB; doing so we achieved moderate heterogeneity ($I^2 = 58\%$) and a lower estimate (OR = 1.60). Based on a Galbraith plot, two studies were excluded, (Guan et al., 2012; Whitlock et al., 2013) and the new estimate was lower (OR = 1.50) with no heterogeneity.

The pooled OR of all non-suicidal variables was 1.78 (95% CI: 1.04-3.05) with severe heterogeneity ($I^2 = 77\%$) (Figure 4).

3. *Previous Self-Harm*

Eighteen comparisons were included. The pooled estimate was significant (OR = 4.37; 95% CI: 2.88-6.63). Heterogeneity was severe ($I^2 = 80\%$) (See online supplementary material Figure S2).

4. *Any Previous Self-Injurious Thoughts and Behaviors*

Forty one comparisons were included. The pooled SITB risk was over 3-fold and significant (OR = 3.48; 95% CI: 2.71-4.43) showing severe heterogeneity ($I^2 = 88\%$).

All sensitivity analyses performed are available in supplementary material Table S4.

Small-study effects or publication bias

For suicide death, visual inspection and Egger test did not suggest evidence of any small study effects or publication bias for any previous SITB. The Trim and Fill method imputed 3 new comparisons for any previous SITB and the new pooled risk was reduced by 1.9%. For suicide attempt, Egger test and funnel plot suggested that publication bias was overestimating the risks for: any previous SITB ($P = 0.001$), any suicidal thoughts and behaviors ($P = 0.011$), and self-harm ($P < 0.001$). Accounting for small-study effects or publication bias would reduce the weighted OR for previous SITB by 44.3%, for previous suicidal thoughts and behaviors by 44.6%, and for previous self-harm by 56.8%..

Metaregression analyses

Metaregression analyses show that mental health and environmental variables included in the model have a non-significant effect and have very low heterogeneity due to adjusting variables in the association between previous SITB and suicidal behavior (see online supplementary material Table S5).

Population attributable risks (PAR) and proportion of first attempters to die by suicide

The contribution of any SITB to future suicide attempt was 26% (95% CI: 19% – 34%). Specifically for each SITB, PAR percentages were similar, ranging from 21% for previous self-harm, to 33% for suicide ideation. Data was not available for non-suicidal thoughts and behaviors. For suicide death, no PAR calculations were conducted because no data was available (Table 2).

Finally, using 2x2 contingency tables of exposed and non-exposed groups of suicide deaths we obtained the weighted proportion of young people who died by suicide with no previous suicide attempt. Random effects meta-analysis of proportions showed that 68% (95% CI: 60% - 75%) of all suicide deaths have no previous suicide attempt. For non-suicidal behaviors, no data was available. (Figure 5)

DISCUSSION

Summary of Main Findings

Our study adds new relevant scientific knowledge about the association between previous SITB and future suicidal behavior among adolescents and young adults: the results show that individuals with any previous SITB have had a much higher risk of dying by suicide than previously reported for this age group, thus suggesting SITB are one of the strongest risk factors of suicide death in this population. Furthermore, the association between previous SITB and suicidal behavior was not affected by mental health or environmental aspects, suggesting that previous SITB may be considered a risk of suicidal behavior independently of these factors. Based on PAR estimates, previous SITB could be considered as a major contributor because they accounted for

26% of future suicide attempts in adolescents and young adults. Finally, our results also indicate that more than two thirds (68%) of suicide deaths in adolescence and young adulthood have occurred in the absence of any previous suicide attempt. However, in none of those studies was previous suicide attempt directly assessed from individuals who die by suicide. Therefore, there may be an unrecognized number of previous suicide attempts in all suicide deaths.

Strengths and Limitations

Our systematic review has several strengths: (i) we only included longitudinal studies in our review, thus ensuring that exposure to the factors assessed preceded the outcome. Such a decision makes our findings more relevant to establish the temporal order of events, as well as minimizing bias. However, information about exposure in case-control studies is retrospective, and therefore subject to recall bias. Additionally, concurrent mental health factors at the moment of reporting may influence our results (Colman et al., 2016). For suicide attempt, most of them (84%) used a cohort design, but for suicide, mostly identified studies (83%) were case-control. Therefore, our inferences about causality and temporality are more robust for suicide attempt than for suicide death.

It is worth noting that our study overcame some limitations of previous systematic reviews (Bridge et al., 2006; Ribeiro et al., 2016) by measuring all forms of previous SITB exclusively in youths, and quantifying the strengths of their associations with suicide attempts and suicide separately, considering the role of key mental health and environmental variables in the analyses, estimating PAR values, and examining the proportion of suicide deaths with no previous suicide attempt. This has resulted in new

and relevant information about the true risk associated with each form of previous SITB in adolescence/young adulthood. Indeed, because the length of follow-up in some of the identified cohort studies was relatively short (i.e., less than three years), we may have underestimated risks. Given that the incidence of suicidal behavior in the general population is relatively low (WHO, 2014), it is important to take latency periods into account and promote studies allowing for longer periods (Stroup et al., 2000).

Other limitations of our review deserve discussion. First, including only population-based studies represents an advantage for interpretation of our results as it provides more valid estimates of the global magnitude of the impact of SITB, which may guide prevention and early-intervention strategies at the community level. However, at the same time, it may have resulted in high heterogeneity. It is noteworthy that after excluding studies which appeared to be sources of heterogeneity, almost all OR values remained similar. Second, we used the Newcastle-Ottawa Scale (NOS) to assess the quality of the studies reviewed, as recommended by the Cochrane Collaboration for observational studies. However, evidence about its validity is still limited (Wells et al., 2014).

Comparison with other studies

Consistently with previous studies (Brent et al., 1999; Conner et al., 2014; Garnefski et al., 1992; Miranda et al., 2014; Ribeiro et al., 2016; Shaffer and Gould, 1996; Shafii et al., 1985), we found significant associations for a history of SITB with subsequent suicide attempt and with suicide death during adolescence and youth. Our results showed that individuals with any previous SITB are at higher risk of both suicide

attempt, and suicide death than a recent meta-analysis which included both population-based and clinical population studies (Ribeiro et al., 2016). These differences may be due to the fact that we only included population-based studies (excluding clinical populations for which the risk is likely to be lower); or because we identified new articles which had not been included in that meta-analysis (Ribeiro et al., 2016). For example, we identified six new articles on suicide death not included by Ribeiro et al. (Brent et al., 1999; Brent et al., 1993; Davidson et al., 1989; Finkelstein et al., 2015; Shaffer and Gould, 1996; Shafii et al., 1985). With respect to suicide death, the risk for those exposed to any previous SITB was very high (OR= 22.53). We identified studies with risk increases of almost 70-fold risk (Brent et al., 1999), and 80-fold risk (Davidson et al., 1989) for suicide death. These estimates are consistent with data reported in a previous review (Bridge et al., 2006), showing that early suicidal behaviors increased the risk by from 10 to 60 times of future suicide death. However, as mentioned above, these results should be interpreted with caution because we identified only 6 samples, none of which had interviewed participants directly: 5 were case-controls published from 1985 to 1999 which used psychological autopsies; and the most recent study published in 2015 was about a cohort obtained from a National Registrar of deaths database. Our results are only partially consistent with our a priori hypothesis. Compared to non-suicidal behaviors, previous suicidal behaviors showed a stronger association with subsequent suicide attempt in adolescence/youth, although confidence intervals between these exposures slightly overlapped. We thus consider that our hypothesis, that previous suicidal behavior would confer an increased risk for future suicide attempts than non-suicidal behaviors, should not be rejected given the substantive risk estimate difference, even if it did not reach statistical significance. Additionally, previous suicide attempt showed the largest effect size for future suicide

attempt, being a more useful predictor than NSSI. There has been a historical disagreement about the effects of NSSI on the likelihood of future suicide attempts (Guan et al., 2012; Nruham et al., 2008; Whitlock et al., 2013; You and Lin, 2015), but our pooled risk estimates add new information about these behaviors because the association for future suicide attempt was significant. Our pooled analyses revealed that for 68% of all suicide deaths among adolescents and young adults no history of previous suicide attempt was reported. This suggests that a large proportion of deaths by suicide occur for first attempters. Nonetheless, we should interpret these results with caution because all the included studies have some limitations which might lead to overestimate the proportion of deaths as first attempters. Three out of the four studies were psychological autopsies and the remaining study was a follow-up which took data from databases. None had interviewed participants who died by suicide directly. So, we cannot know whether or not there were unrecognized suicide attempts in the past. In a previous study, the authors reported that 46% of all suicide deaths had never previously self-harmed, and that 43% never had a previous suicide attempt nor any suicide ideation (Rodway et al., 2016). While previous SITB seems to be the strongest predictor of suicide death among adolescence/youth, other risk factors may also contribute. Further research is needed to identify other causes of suicide death among youths who die on their first attempt.

Generalization of results

As discussed above, heterogeneity may pose a challenge to the generalization of our results. For suicide deaths, no heterogeneity was found, but this is probably due to the scarcity of data and the lack of precision of included studies. Much higher heterogeneity was found between studies for suicide attempts. The high degree of heterogeneity suggests that there is variability among populations and countries. It may

also be due to the fact that suicide attempt is a complex behavior phenomenon with different levels of severity, intentionality and intensity among attempters (Silverman and Berman, 2007). Another source of heterogeneity might be the different methods used for assessing suicide attempts (e.g., as one/two-item questions, longer validated instrument, semi-structured interviews, or clinical hospital admissions). Although our sensitivity analyses identified possible sources of heterogeneity, excluding them did not generally reduce the heterogeneity. Thus, heterogeneity could be due to factors that we did not consider. The only exceptions involved studies which assessed previous SITB using non-lifetime prevalence, and non-validated instruments, as excluding them reduced the heterogeneity of the estimates. These results indicate that heterogeneity was partially influenced by these features, but not by other methodological variables. Although high heterogeneity existed in our analyses for suicide attempts, the pooled estimates obtained excluding outliers according to the Galbraith visual plot were mostly similar. This supports the generalizability of our results. In addition, publication bias was observed for most SITBs as risk factors of suicide attempts, while no such bias was found for risk of suicide death. As the Trim & Fill imputation method and funnel plot suggested, small studies with statistically significant and positive results are more likely to be published than studies with negative or null findings. We cannot rule out that this may have caused inflated estimates of pooled risk of suicidal behaviors for these particular exposures. In summary, we are convinced that our results are generalizable to the general population but less generalizable to clinical samples where the strength of the association is likely to be lower, although the presence of publication bias in some meta-analyses may have led us to overestimate the risk.

Future research and recommendations

In this study, previous exposure to SITB, regardless of type, has been shown to be consistently associated with youth suicide behaviors. Future research is needed for a more accurate estimation of the magnitude of risks associated with suicide death. This is especially so for previous suicidal ideation and threat since only two studies were included and for which the pooled risks (OR) for the two exposures ranged from 26 to 60, and from 9 to 80, respectively, and for suicide plan which no study was found. Future research is needed to help in clarifying key warning signs that reflect a risk of suicide death in youths who have reported any previous SITB. In addition, Gene by Environment interaction studies are also needed to identify children highly prone to exhibit recurrent suicidal behaviors, and prone to die by suicide on the first attempt. Furthermore, research estimating the relationship between prior SITBs and suicidal behavior risk should be extended to developing countries.

From a public health perspective, effective prevention strategies and health policies should be developed and implemented in schools and neighborhoods to substantially reduce the number of youth suicidal behaviors and deaths (Wasserman et al., 2015), and to reduce the lethality of these behaviors among high risk groups. Based on our PAR calculations, and assuming that eliminating the exposure will not affect other risk factors, effective interventions among adolescents and youths exposed to any previous SITB could theoretically reduce suicide attempts by around 21% to 33%. Although the complete elimination of each SITB is unlikely, children and adolescents with these exposures should be considered a potential target for suicide prevention programs. Schools, primary care and emergency rooms should also have a pivotal role in the prevention, identification, and management of these behaviors. Screening of vulnerable groups, such as victims of violence or traumas, people with a current mental disorder, heavy alcohol consumers or substance users is recommended.

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TABLE 1. Description of identified studies

Author	Study	Country	Population	Study design	Sample at baseline (% of women)	Sample at end of follow-up (% attrition)	Age range	Mean age (SD)	Length of follow-up	Cumulative incidence of the outcome	SITB variable	Type of SITB prevalence assessed at baseline	Rate of risk factors at baseline (%)	Instrument assessed for each SITB	Controlled for any variable
Studies assessing suicide attempts															
Garnefski et al. 1992	Monitoring the future: Behavior and Health of High School Students	The Netherlands	Students	Cas-control	285 cases vs. 285 controls(65)	<i>b</i>	15-16	16	<i>b</i>	<i>b</i>	SA; SI	SA = Lifetime; SI = 1y	12.2 SI;	Two items	Yes
Wichstrom et al. 2003	Young Norway Study	Norway	Students	Cohort	9,769	2,460(75)	NI	22.1(1.9)	7y	NI	SA	Lifetime	4.4 SA	Two items	Yes
Vega et al. 1993	Dade County School District	United States	Students	Cohort	9,763(0)	6,010(38)	14-15	NI	1y	NI	SA; SI	SA = ever; SI = 6m	8.2 SA; 18.2 SI	Two items	Yes
Reifman et al. 1995	Two schools of New York	United States	Students	Cohort	NI	981	NI	NI	6m	4-6%	SA	6m	NI	Three items	<i>B</i>

State															
Reinherz et al. 1995	Northeastern United States	United States	Students	Cohort	404(51)	385(5)	NI	17.9	3y	NI	SI	NI	4.2 SA; 22.5 SI	YSR	B
McKeown et al. 1998	South Carolina school district	United States	Students	Cohort	NI	247	NI	NI	2y	NI	SB; SA; SI; SP; NSS	12m	B	KSA DS	Yes
Lyon et al. 2000	African American population	United States	Primary care	Cases vs. Control	38 vs. 76 control s(82)	b	12-17	14.8	b	b	SI	Lifetime	22 SI	One item	Yes
Lewinsohn et al. 2001	Urban and rural districts of Oregon	United States	Students	Cohort	1,709(57)	941(45)	24-24	24	8y	13.20%	SITB	Lifetime	NI	KSA DS	Yes
Ialongo et al. 2004	Baltimore city schools	United States	Students	Cohort	1,197(56)	747(38)	19-20	NI	11y	4.41%	SI	Current	NI	YARS; BHIF YR	Yes
Ferguson et al. 2005	Church Health and Development Study	New Zealand	General population	Cohort	1,265(50)	887(30)	NI	25	9y	NI	SA; SI	36m	5.4 SA; 17.2 SI	Interview	Yes
Rodriguez et al. 2006	NI	Spain	Students	Cohort	1,766(50)	1,076(39)	25-25	NI	2y	2.87%	SA; SI	Lifetime	2.6 SA, 12.7 SI, 8.6 NSS	Three items	Yes
Brezonick et al. 2007	Quebec	Canada	Students	Cohort	3017(32)	1,684(44)	19-24	21.4	6y	0.17%	SI	Lifetime	20 SI; 3.5 SA	DISC SIS	Yes
Nock et al. 2007	Harvard	United States	General population	Cases vs. Control	14 cases vs. 38 control s(77)	b	12-19	17.1(1.9)	b	b	SA; SH; SI	Lifetime	31.6 SI; 7.9 SA	SITBI; BSS	Yes
Wong et al. 2007	Cantonese speaking Hong Kong Chinese youth	China	Students	Cohort	2,176(39)	1,099(49)	13-19	NI	1y	4.45%	SA; SI	12m	2 SA; 14 SI	Two items	Yes
Lambert et al. 2008	NI	United States	Students	Cohort	473(47)	473	12-15	NI	2y	NI	SA	12m	NI	Two items	Yes
Nrugham et al. 2008	Central Norway	Norway	Students	Cohort	2,792(51)	242(17)	NI	20(0.6)	6y	NI	SA; SI; NSS	Lifetime	NI	KSA DS	B
Thompson et al. 2011; Watkins et al. 2013	Add health	United States	Students	Cohort	20,745(52)	10,828(48)	17-26	21.82(1.81)	SI = 6y; SA = 1y	NI	SI; SA	12m	13.2 SI; 3.9 SA	One item	Yes

Guan et al. 2012	NI	NI	Students	Cohort	712	399(44)	16-17	NI	2y	5.20%	SA; SI; NSSI; NST	12m	3.3 SA; 8.9 SI; 5.1 ST	SI = SIQ, NSSI = 6 items, SA = 1 item	Yes
Mustanski et al. 2013	NI	United States	LGB	Cohort	237(52)	212(10)	17-21	NI	1y	5.50%	SA	Lifetime	31.6 SA	DISC	Yes
Whitlock et al. 2012	Survey of student well-being	United States	Students	Cohort	5,214(58)	1,466(72)	NI	NI	2y	NI	NSSI	Lifetime	19.7 NSSI; 6.7 SA	NSSI AT	Yes
Conner et al. 2014	Collaborative Study on the Genetics of Alcoholism	United States	General population	Cohort	NI	418(22)	12-17	14.5	5y	4.50%	SA; SI	Lifetime	NI	Single Item	No
Miranda et al. 2014	Seven High Schools in the New York City Metropolitan Area	United States	Students	Cohort	641	506(21)	17-26	NI	5y	NI	SA; SI	SI = 3m; SA = lifetime	29 SSI; 15 SA	CSS; ASI	Yes
Scott et al. 2015	The Pittsburgh Girls Study	United States	General population	Cohort	2,450(100)	1,950(20)	18-21	NI	8y	1.80%	SI	12m	NI	CSI; ASI*; ASRI-4;	Yes
You et al. 2015	Eight coeducational high schools in Hong Kong	China	Students	Cohort	5,423(53)	3,600(34)	13-19	NI	1y	2.90%	SI; NSSI	12m	2.6 SA; 16 SI; 18.7 NSSI	Single item	Yes
Studies assessing suicide death															
Shafii et al. 1985	Psychological Autopsy of Jefferson County Texas	United States	General population	Cases vs. Controls	20 cases vs. 17 controls(11)	<i>b</i>	12-19	NI	<i>b</i>	<i>b</i>	SA; SI; ST	NI	18 SI; 12 ST; 6 SA.	109 items	Yes
Davidson et al. 1989	Texas	United States	Students	Cases vs. Controls	14 cases vs. 38 controls	<i>b</i>	14-19	15.6	<i>b</i>	<i>b</i>	SA; SH; ST	SA = Lifetime; SH = Lifetime; ST = 12m	NI	Interview	Yes
Brent et al. 1993; 1999	Western Pennsylvania	United States	General population	Cases vs. Controls	140 cases vs. 131 controls(22)	<i>b</i>	13-19	14	<i>b</i>	<i>b</i>	SI; SA	SI = Current; SA = Lifetime	SI = NI; SA = 0.76	SI = KSA DS; SCS; SA = BSIS	Yes

Shaffer et al. 1996	New Jersey, Litchfield, Fairfield, New Haven, Connecticut, New York, Nassau, Suffolk, Putnam, Rockland, Westchester.	United States	General population	Cases vs. control	120 cases vs. 147 controls(21)	<i>b</i>	NI	16.7	<i>b</i>	<i>b</i>	SA; SH	NI	0.7 SA	SSDB	Yes
Finkelstein et al. 2015	Residents of Ontario	Canada	General population	Cohort	1,043, 958	1,043, 958 (74.2)	22-31	NI	7y	NI	SA	Current	NI	Clinical Database	Yes

ASI = Adolescent suicide interview; ASI* = Adolescent symptom inventory; ASRI = Adult self-report inventory; BHIFYR = Baltimore how I feel youth report; BSIS = Beck suicide intent scales; BSS = Beck scale for suicidal ideation; CSI = Child symptom inventory; CSS = Columbia Suicide Screen; DISC = Diagnostic interview schedule for children; KSADS = Kiddie Schedule for Affective Disorders and Schizophrenia; LGBT = Lesbian, gay, bisexuals; m = month; NI = Not information; NSSI = Non Suicidal Self Injury; NSSIAT= Non-suicidal self-injury assessment tool; SA = Suicide attempt; SB = Suicidal behavior; SCS = Suicide circumstance schedule; SH = Self harm; SI = Suicide ideation; SIQ = Suicidal ideation questionnaire; SIS = Suicidal Ideation Scale; SITB = Self injurious thoughts and behavior; SITBI = Self injurious thoughts and behavior interview; SP = Suicide plans; SSDB = Scale self-damaging behavior; ST= Suicide threat; y = year; YARSC = Young adult report of suicide; YSR = Youth self-report. *b* = Not applicable.

Table 2. Population Attributable Risk (PAR) calculations for each form of self-injurious thoughts and behaviors (SITB)s and suicide attempts

Type of SITB exposure	Prevalence of each SITB (%)	P ₀ (%)	RR	PAR (%)
SITB	15 (10 - 22)	2	3.31	26 (18.7 – 33.7)
Suicidal behaviour	15 (9 - 21)	2	3.67	29 (19.4 – 35.9)
Suicide attempt	9 (5 - 14)	3	4.89	26 (16.3 – 35.3)
Suicidal plan	---	---	---	---
Suicidal threat	---	---	---	---
Suicidal ideation	23 (17 - 30)	2	3.12	33 (26.5 – 38.9)
Non-suicidal behaviour	---	---	---	---
NNSI	---	---	---	---
Non-suicidal threat	---	---	---	---
Self-harm	9 (5 - 14)	3	3.97	21 (12.9 – 29.4)

Prevalence of prior SITB was calculated based on data from studies reporting the number of exposed and non-exposed people among cases and non-cases.

P₀: prevalence of suicide attempts in people with no prior SITB.

RR: relative risk.

PAR: population attributable risk.

Figure 1. Modified version of PRISMA diagram of included articles.

Figure 2. Forest Plot of suicidal thoughts and behaviors (SITB)s as risk factor for future suicide death.

Figure 3. Forest Plot of suicidal thoughts and behaviors (SITB)s as risk factor for future suicide attempts.

Figure 4. Forest Plot of non-suicidal thoughts and behaviors (SITB)s as risk factor for future suicide attempts.

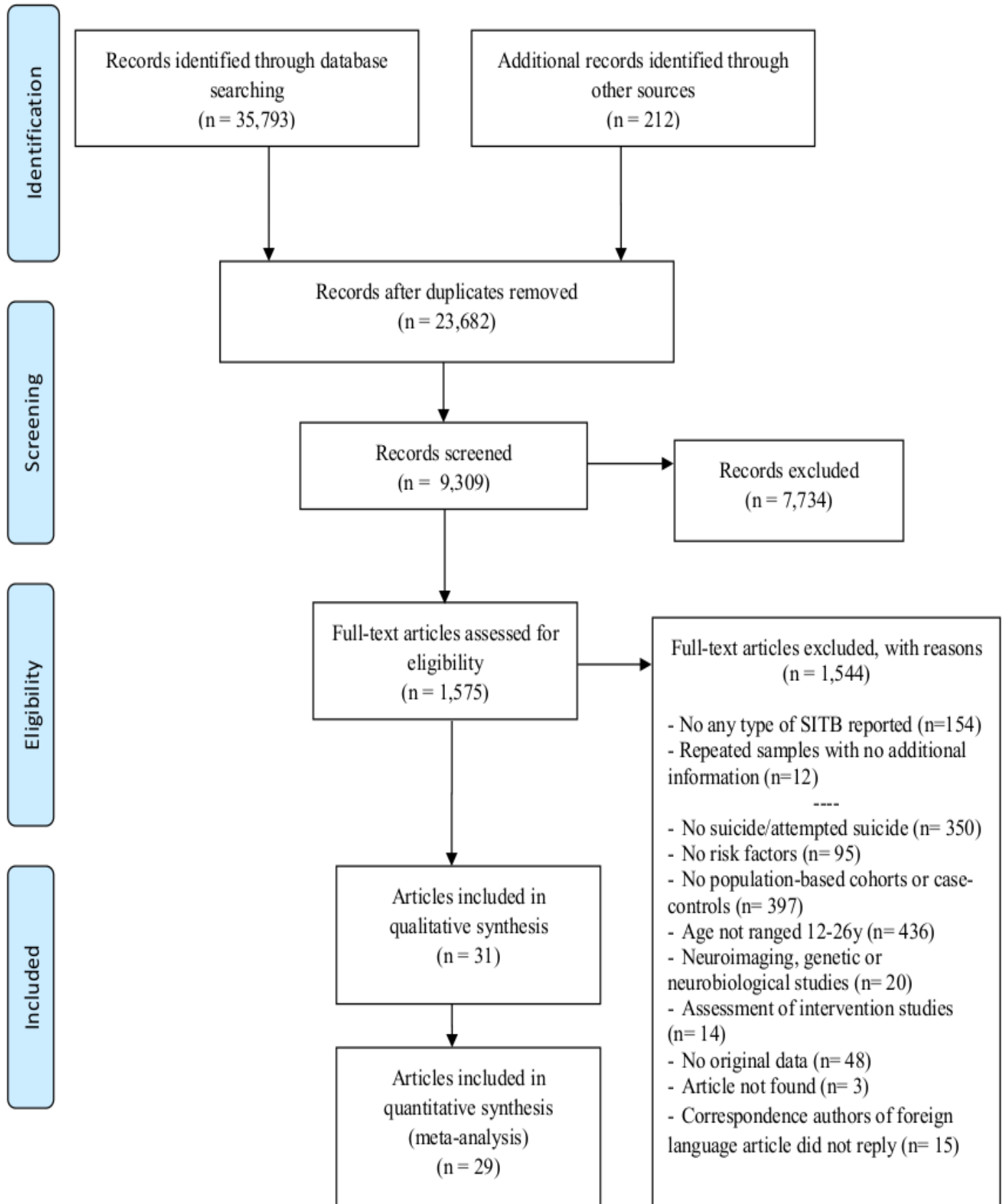
Figure 5. Forest plot of proportions of suicide deaths with no previous suicide attempts.

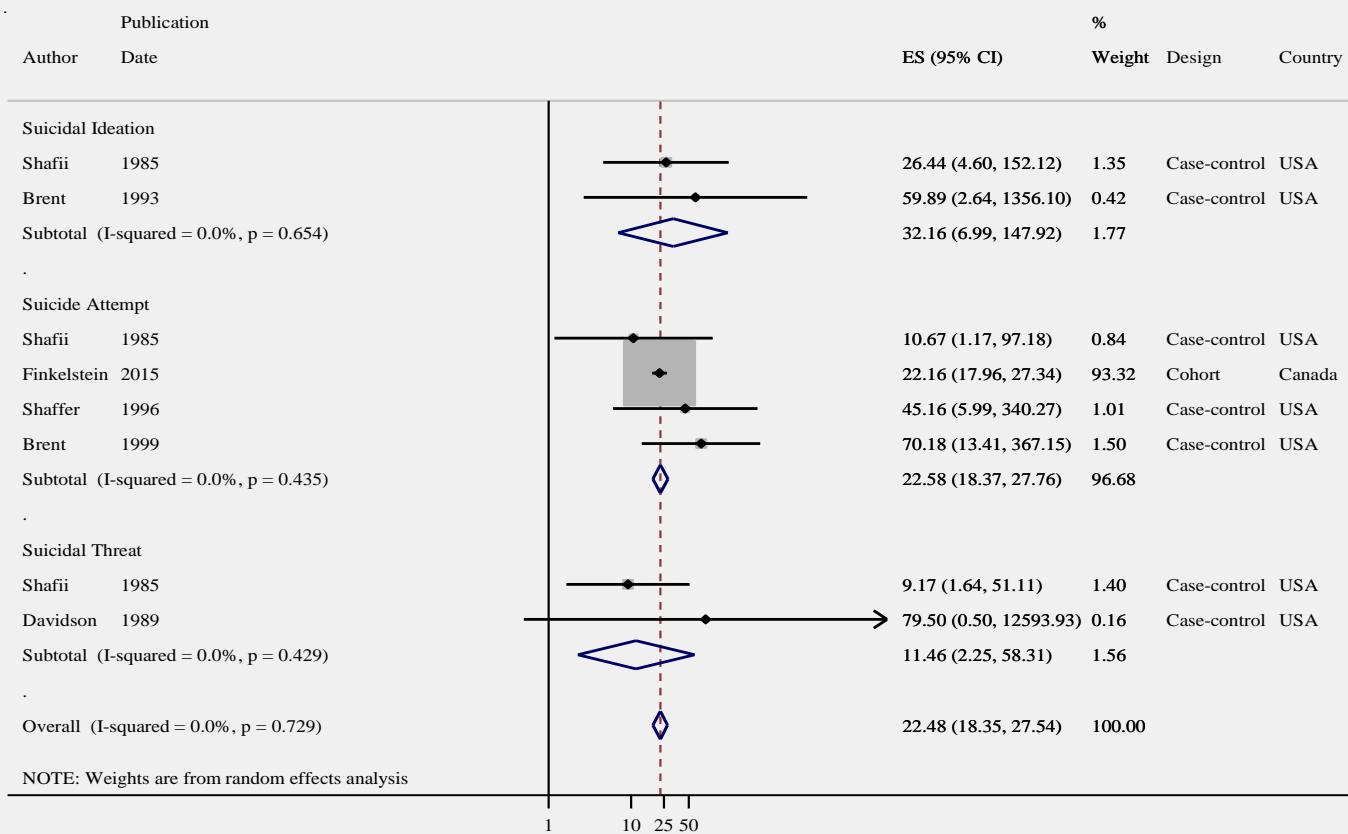
HIGHLIGHTS

- Over two thirds of suicide deaths among adolescents and young people occur with no previous suicide behavior.
- A much higher risk of dying by suicide among adolescents and young people was found than previously reported meta-analysis.
- These associations were not moderated by mental health and environmental variables.
- The contribution of any SITB to future suicide attempt was 26% (95% CI: 19% – 34%).



PRISMA 2009 Flow Diagram





Accepted manuscript

