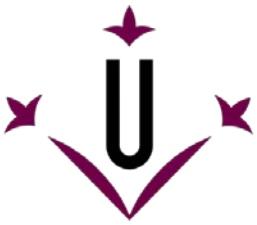

Title: Stressful life events during adolescence and risk for externalizing and internalizing psychopathology: a meta-analysis

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Abstract

The main objective of the present research was to analyze the relations between stressful life events and the externalizing and internalizing spectra of psychopathology using meta-analytical procedures. After removing the duplicates, a total of 373 papers were found in a literature search using several bibliographic databases, such as the PsycINFO, Medline, Scopus, and Web of Science. Twenty-seven studies were selected for the meta-analytical analysis after applying different inclusion and exclusion criteria in different phases. The statistical procedure was performed using a random/mixed-effects model based on the correlations found in the studies. Significant positive correlations were found in cross-sectional and longitudinal studies. A transactional effect was then found in the present study. Stressful life events could be a cause, but also a consequence, of psychopathological spectra. The level of controllability of the life events did not affect the results. Special attention should be given to the usage of stressful life events in gene–environment interaction and correlation studies, and also for clinical purposes.

Keywords: stressful life events, externalizing spectrum, internalizing spectrum, meta-analysis, transaction

Introduction

Adolescence is a period of change. Pubertal maturation mixed with social demands lead adolescents to assume adult roles [1, 2]. These vital changes are often experienced as stressful [1]. During adolescence, stressors increase stress reactivity, decrease hippocampal volumes and alter neural plasticity [3, 4]. Changes in neurobiological stress should be a natural response to properly adapt the organism to the challenges of adolescence [5]. However, the consequence of these brain changes in adolescents with individual and/or genetic predispositions for heightened affective processing could be a stress dysregulation process, increasing their vulnerability to psychopathology [1, 3, 5].

According to most recent reviews, the prevalence of mental disorders, without specify which, during adolescence ranges from 25% to 45% [6–8]. Some mental disorders begin their prodromal phase or show an increase in prodromal symptoms at this stage of life [9–12]. Identifying adolescents with prodromic symptoms is crucial for proper intervention and prevention programs [10].

One difficulty for the diagnostic process and also for selecting proper interventions according to evidence-based guidelines is that some disorders tend to co-occur in a non-random fashion [13, 14]. Epidemiological studies estimate that comorbidity tends to occur in around 40% of affected adolescents [6, 7]. For example, social phobia, specific phobias and depression are common co-occurring disorders with other mental illnesses [6, 7]. Although the concomitance of different affections has been considered a conceptual problem and a clinical difficulty [15], there is now evidence to confirm that, at least in mental disorders, some cases of comorbidity could be explained by common latent liability factors [16]. The most prevalent mental disorders can be grouped into two clusters of symptomatology [16–18], the internalizing and externalizing spectra. The internalizing spectrum is considered a general liability toward the disorders characterized by negative affect, while the externalizing spectrum should be understood as a liability toward disinhibitory disorders [16]. With a few exceptions [19, 20], the externalizing/internalizing categorization has been found in children and adolescents [18, 21, 22]. In addition, the psychopathological spectra are important in clinical settings. When such symptomatology emerges during childhood and/or adolescence, it can evolve into adult psychiatric disorders [23, 24]. Such symptoms could also be considered as prodromic states of emotional and impulsive mental disorders. Hence, research to identify the risk factors for externalizing and internalizing spectra during childhood and adolescence is essential.

Regarding the association between stress and psychopathology, some of the stressors that an adolescent can experience are derived from adverse life events. The death of a family member, a divorce or a separation, or a romantic breakup are specific life events that have been found to increase the likelihood of developing psychiatric symptoms [25–27]. The effect of stressful life events seems to be strengthened when some of them are lived in an aggregated fashion. Swartz et al. [28] found that adolescents who had experienced more life events with a severe negative impact during the last 12

months showed a long-term alteration in amygdala reactivity, influencing their risk for depression. Besides its neurobiological implications, the aggregation of life events has proved to be clinically relevant. In healthy adolescents and clinical samples, a significantly higher number of stressful life events during a short period of time increased the likelihood of developing depression and emotional disorders [29, 30], substance use behaviours and addictions [27, 31], hyperactivity and conduct problems [30], and suicide attempts [2]. Furthermore, experiencing stressful life events during adolescence can predict psychopathology in adult life, for example, by disrupting the reward circuit function [32, 33]. Hence, the association between stressful life events and psychopathology has been consistently replicated in one direction: stress may induce the symptomatology; this effect is the one tested in gene–environment interaction studies [34–36].

However, exposure to certain life events is partly under genetic control for depression [37] and impulsive and aggressive behavior [38]. This is known as the gene–environment correlation [35, 39]. Commonly, the directionality of the association between stressful life events and psychopathology has been studied by separating the effects of "dependent" and "independent" life events [37]. The life events that are dependent on one's actions are considered controllable or dependent life events. On the contrary, those life events that are unpredictable by nature, that do not rely on the behavior of the person in order to happen, are considered uncontrollable or independent. In a systematic review, Kendler & Baker [39] showed that the heritability of dependent negative life events was higher than for independent life events. This effect has since been replicated [40]. In addition, McAdams et al. [38] found that the same genes that affect dependent stressful life events are involved in delinquency, physical aggression and depression. On the other hand, it seems that, in interaction with other environmental variables, a stress sensitization effect on psychopathology is caused by independent life events rather than by dependent ones [41, 42]. Hence, independent life events could causally affect psychopathology, while people with certain psychopathological symptoms and other intrinsic characteristics would show increased exposure to dependent life events. In other words, independent life events are involved in gene–environment interactions while dependent life events are associated with psychopathology through gene–environment correlations [36, 39]. The experience of stressful dependent life events could increase the chronicity of some disorders, such as depression [43, 44], and also increase the risk of suicide in adolescents [45].

The directionality of the association between stressful life events and psychopathology has also been tested using longitudinal designs [37]. With this methodology, Hammen [46] introduced the concept of stress generation to describe the finding that people with past episodes of depression were more likely to be exposed to stressful life events than people with a lack of past depressive states. Stress generation has been replicated in different studies involving depression [47], and also in other mental disorders [48]. Taking into account the controllability of the life events in a longitudinal study, Kercher et al. [49] found that exposure to dependent negative life events partially mediated the relation between depressive symptomatology between time 1 and time 2, while independent stressful life events

predicted depressive symptoms at time 2 but were not predicted by the depressive symptoms at time 1. Hence, the directionality of the relation between the psychopathological spectra and stressful life events is controversial nowadays. Moreover, as far as we know, no studies in this field have been performed using a meta-analytical methodology. The main aim of the present study was to systematically review all available studies concerning the relation between the aggregated experience of stressful life events and the internalizing and externalizing spectra during adolescence. The internalizing spectrum is understood as "a general liability toward negative-affect-laden mood and anxiety disorders" [16]; and externalizing as "a general liability toward disinhibitory disorders such as substance use disorders and antisocial behavior disorders" [16]. In the present study, aggregate stressful life events are considered to be the sum of incidents that could occur during adolescence (our target stage of life) which have a negative impact on the person because they potentially increase stress. Moreover, we tried to test the causation in this relation, paying particular attention to longitudinal studies and the dependent/independent stressful life events classification. Moderators accounting for systematic variations were also analyzed.

Methods

The present study was performed following the MOOSE guidelines [50]. Two independent researchers selected the studies found in a systematic review of the literature by applying pre-specified inclusion and exclusion criteria. Heterogeneity and sensitivity analyses were performed to assess different biases in the studies. Proper meta-analytical statistics were applied in order to test the hypotheses.

Selection of studies

Literature search.--We carried out a literature search using four bibliographic databases: PsycINFO, Medline, Scopus and Web of Science. The search items were limited to the title, abstract and keywords. Search terms were generated from the synonyms found in the MeSH and Cochrane Library databases and by inspecting the common terminology used in the stressful life events literature. The keyword combination was: (life event OR adolescent adverse* OR social adverse OR lifetime trauma OR traumatic event* OR life-history calendar OR life history calendar OR Event*, Life Change OR Life Change Event* OR Event*, Stressful OR Stressful Event* OR Analys*, Event History OR Event History Analys* OR Experience*, Life OR Life Experience*) AND (externalizing behavi* OR externalizing symptom* OR externalizing psychopath* OR externalizing path* OR externalizing disorder* OR externalizing problem* OR externalizing difficult* OR internalizing behavi* OR internalizing symptom* OR internalizing psychopath* OR internalizing path* OR internalizing disorder* OR internalizing problem* OR internalizing difficult*) AND (adolescen*). The same equation was repeated with the British form of 'externalising'/'internalising' terms. Reference lists of available reviews were also screened.

Phases of the study.--Three basic screenings (phases 1 to 3) were carried out in the present study. After eliminating duplicated articles found in the different databases, a screening by titles was performed. Second, the abstract was screened to look for the inclusion and exclusion criteria. Finally, the full text was analyzed. Figure 1 is a flow diagram of the present study, reporting the number of studies included and excluded in each phase.

Insert Figure 1 here

Inclusion and exclusion criteria.-- In phase 1 and 2, the strategy used to select the papers was conservative. We found that the main objective of a study was rarely to analyze the relations between externalizing/internalizing psychopathology and life events. However, some studies in which the main objective was not to test the association between psychopathological clusters and life events presented a correlation matrix that was suitable for the analysis we conducted in the present study. Hence, in phase 1 and 2, the only papers that were excluded were those that completely matched the exclusion criteria and did not meet the inclusion criteria. Any ambiguities were resolved in phase 3, after reading the full text. So, in the third phase, the strategy was rigid, and only those studies that completely fitted the inclusion criteria were selected for further analysis.

The inclusion criteria were: (a) Externalizing and internalizing clusters were assessed by means of a validated methodology. If a paper reported the assessment of the spectra with measures that did not use specific scales to assess them, then only if that paper estimated the externalizing and internalizing factors empirically was it included. (b) Aggregated major life events were assessed. Daily hassles were not taken into account. (c) The study contained empirical data on the association between the stressful life events and the externalizing/internalizing spectra. (d) The sample was between 10 and 19 years of age, the period of time defined by the WHO as demarcating adolescence [51]. (e) Cross-sectional and longitudinal studies were included. Studies that focused on the effect of stressful life events on the externalizing/internalizing spectra or vice versa that began before 10 years of age or finished after 19 years of age were excluded. However, if a study with these characteristics included empirical data at different time points in the range of 10–19 years of age, then these data were included.

The exclusion criteria were: (a) The topic of the paper was not concerned with either externalizing/internalizing symptoms or with stressful life events. (b) The reports were dissertations, books or book chapters, conference abstracts and reviews. (c) The study did not report data about adolescence, such as life events assessed before the adolescent period or a longitudinal analysis of the prediction of young adult outcomes. (d) There is currently the lack of an operational definition of trauma. In some studies [52, 53] the concept of trauma was used as a synonym of stressful life events. However, the standard measures of life events mix major life events (e.g. the death of a parent) that could be really considered as traumatic events with minor life events (e.g. new partner moved into the home) that should not be

considered traumatic. Moreover, some papers [54] restricted the usage of this terminology to major stressful life events, often making reference to sexual abuse, etc. Hence, another exclusion criterion was that no life event was measured in the study. Measures of daily hassles were also excluded. (e) Regarding the measures of psychopathology, the only studies that were accepted were those that assessed the internalizing and/or externalizing spectra. Although some papers argue that they assessed the internalizing/externalizing spectra, some of them only related the life events to separate disorders, and not with the cluster of disorders. These papers were excluded. (f) Studies that were not based on correlations, or on simple statistics suitable for transformation into correlations (e.g. simple odds ratios), were also excluded. (g) Finally, we tried to contact several authors in order to clarify some aspects of their studies. Four of them replied and the studies were thus included in the meta-analysis; the three that did not reply were excluded from the meta-analysis.

Problem of multiplicity.--When different papers based on the same study were found, the key article referring to the main results was selected.

Coding

Two independent raters, the first and the last author of the present study, coded the study features and extracted the effect size data. The coding procedure was blind. In each phase of the study, both raters worked separately. They pooled their conclusions and if there was any substantial discrepancy, the other authors of the paper, experts in this field, were consulted. The final decision depended on a consensus on all parts of the study. The percentage of agreement between the two raters was 80% in phase one ($\kappa = 0.57$; 95% CI: 0.48, .65; $p < 0.001$), 86% in phase two ($\kappa = 0.72$; 95% CI: 0.64, 0.81; $p < 0.001$), and 95% in phase three ($\kappa = 0.83$; 95% CI: 0.71, 0.94; $p < 0.001$). There were more inconsistencies between the raters in the first two phases due to the ambiguity and unclear information of some titles and abstracts.

For the purpose of the present study, the papers were classified into nine categories. (a) The type of stressful life events. Studies that did not assess subtypes of life events were coded as studies on general stressful life events. Those that assessed only the impact of life events uncontrolled by the subject were labelled as studies on independent stressful life events. Life events controlled by the subjects were coded as dependent stressful life events. Some studies separated those life events that can occur because of relations with other people (coded as interpersonal stressful life events), from life events that happen without the intervention of others (coded as non-interpersonal stressful life events). (b) The measure used to assess the life events: by interviewing and by administering a checklist. Another classification was attempted based on the specific measure used. However, only four studies used the same methodology to assess life events. (c) The duration of time assessed by the measure of life events (number of months in which the life events could happen). (d) Who reported the life events: self-reports by the adolescents, hetero-evaluation by the parents or the teachers or multi-informant assessment (self-report plus hetero-evaluations). (e) Regarding the psychopathological

measures, the type of externalizing/internalizing spectra assessed. Most of the studies assessed both externalizing and internalizing symptoms, although some of them only presented data on one of them. (f) The specific measure used to assess the spectra was coded. (g) Who reported the psychopathology: self-report, hetero-evaluation, and multi-informant. (h) Regarding the design, the studies were coded as cross-sectional if they included measures of the stressful life events and the clusters of psychopathology at the same time, or as longitudinal if the basic measures were separated in time. In some cases, the same study contained cross-sectional and longitudinal data. These articles were coded as both designs but the cross-sectional data were used in the cross-sectional analyses and the longitudinal data were used in the longitudinal analyses. (i) The longitudinal studies were also classified according to the classic distinction between the two main directional hypotheses described: the stress-generation hypothesis [46, 48, 55–57] and the sensitivity-stress hypothesis [58, 59]. In some longitudinal designs, the clusters of psychopathology were assessed at Time 1 and the life events at Time 2. In these cases, the time lapse reported for the life events was from the first to the second assessment. These studies were coded as relating to the stress-generation hypothesis. On the contrary, in other longitudinal studies, the stressful life events were assessed at Time 1 and the psychopathological clusters were assessed at Time 2. These studies were coded as relating to the sensitivity-stress hypothesis. As the cross-sectional studies were merely correlational, they were not suitable for testing the directionality of the association. These studies were coded as correlational.

In addition to this process, each study was assessed using a quality assessment tool. Seven criteria were formulated to judge the quality of the research articles: (a) Operationalization of negative life events: if negative life events were measured and described in the paper by a standardized procedure, the study received two points; if the measure used was an ad-hoc instrument not validated previously or a non-validated modification of a standardized procedure, the study received one point; if there was not enough information to deduce the quality, the study received zero points; (b) continuity of the life events measure: if the study used the sum of life events in a continuous measure, the study received two points; if the study categorized the measure into more than two categories, the study received one point; if the study dichotomized the measure, the study received zero points; (c) time period for which life events were reported: if the paper clearly described the time period that the participants had to think about in order to report whether the life events had occurred or not, the study received one point; if this time period was not specified, the study received zero points (in such cases, the data were obtained by inspecting the stressful life events measure or by asking the authors); (d) appropriate statistical analyses: if the researchers used adequate analyses to answer the research question and a correlation matrix was clearly depicted, the study received one point; if the statistical procedure was not appropriate or the correlations were derived from latent variables despite the inclusion of observational variables, the study received zero points; (e) continuity of the psychopathological measure: if the study used the standard estimation of the externalizing/internalizing spectra that entailed a continuous measure, the study received two points; if the study

categorized the measure into more than two categories, for example by dividing the sample according to the standard deviations, the study received one point; if the study dichotomized the measure, for example by applying a percentile criterion, the study received zero points; (f) description of the sample: if the sample description was complete, by reporting at least the mean age with the standard deviation, the percentage of girls and boys and the ethnicity of the sample, the study received two points; if there were missing data on the above descriptors, the study received one point; if no descriptors were reported, the study received zero points; (g) selection of the sample: if the authors performed a selection procedure resulting in a representative group of participants and the differences between the sample who agreed to participate and the sample who declined was analyzed (or the attrition process), the study received two points; if the sample assessed was a representative group, but no analysis of the differences between those who participated and those who declined was described (or the attrition process), the study received one point; if the sample selection procedure was not explained, the study received 0 points. The quality score ranged from 0 to 12. According to the MOOSE proposal [50] a sensitivity analysis was performed rather than weighting the studies or not including some of them due to the quality score. The quality assessment was performed separately by two researchers. There was 95% agreement between them ($\kappa = 0.80$; 95% CI: 0.69, 0.91; $p < 0.001$). The discrepancies were solved by consensus. In most cases, the discrepancies were due to unclear information in the papers.

Effect size computation

The present meta-analysis was based on correlations. Most of the papers reported the exact values of the *r* measures. If the study described beta values of simple, not multiple, regressions, then the square root of the R^2 was used. This was required in one study. No studies presented simple, rather than multiple, odds ratios, so no transformation was needed to estimate the *r* value.

Decisions were made about four types of multiplicity: multiple assessment points, multiple measures for the externalizing/internalizing clusters, multiple measures for negative life events, multiple stressful life events individually estimated. With respect to the first type, a multivariate meta-analysis model of estimation was performed, as will be described in the next section. Regarding the other types of multiplicity, the multiple associations were averaged.

Statistical analysis

We applied a random/mixed-effects model that provided unconditional inference about a larger set of studies from which the k studies included in the meta-analysis were assumed to be a random sample [60]. The outcome was the Fisher's r-to-z transformation, a variance stabilizing transformation for correlation coefficients with the added benefit of also being a rather effective normalizing transformation [61].

Procedure to fit meta-analytical model.-- All analyses were conducted using the metafor-package, a comprehensive collection of functions in R for fitting meta-analytical multivariate random models with or without moderators via linear (mixed-effects) models. We used the rma.mv function to specify the correlated structure between samples derived from

the same study. The rma.mv function assumes that outcomes with different values in the grouping factor come from independent studies, while effects or outcomes with the same value in the grouping factor share correlated random effects.

To properly test the hypotheses of the present study three main analyses for each psychopathological spectrum were performed: one with the correlational (cross-sectional design) studies, one with the sensitivity-stress hypothesis (longitudinal design), and third with the stress-generation hypothesis (longitudinal design). In addition, different meta-regressions were performed in order to test the effect of nine covariates: (a) the quality score, in order to test the sensitivity analysis according to the design specifications in the studies, (b) the female ratio, (c) the differences between samples from the general population vs. samples with special characteristics, such as ADHD, etc., (d) the type of life events, tested by comparing those studies that evaluated nonspecific general stressful life events vs. those based on the independent life events and the interpersonal life events (dependent life events and non-interpersonal life events were not taken into account because there were too few studies evaluating them), (e) interview methodologies to assess the life events vs. checklists, (f) comparisons were also performed taking into account who reported the stressful life events (self-reports, hetero-evaluation and multi-informant), (g) the same comparisons were performed regarding the reports of the psychopathology (self-reports, hetero-evaluation and multi-informant), (h) the time (in months) referred to in the life events measure, (i) the number of life events that appeared in the life event checklists/interviews used in each study. Moreover, for longitudinal studies only, time between assessments was tested.

Finally, in order to analyze whether life events correlated better with externalizing or internalizing spectra, we performed the Hotellings-Williams test [62]. As the Williams test is only an approximation as is not based on a mean difference, we did not carry out a meta-analysis (to convert t-values into outcomes accepted by the metafor package involves repeating a transformation similar to Fisher r-to-z normalization). Instead, we determined a bootstrap confidence. We only performed this statistical test on the papers (n=24) that assessed both externalizing and internalizing spectra in the same sample and in the same study with cross-sectional designs. This analysis was not performed to the longitudinal studies because too few papers met the criteria of reporting the correlations with both spectra (4 regarding the stress-generation hypothesis and 3 for the stress-sensitivity hypothesis).

Results

Description of study features

Twenty-seven publications fulfilled the inclusion criteria (See the Table S1 of the supplementary material for an overview of the studies and their features). Eleven contained cross-sectional and longitudinal data, fifteen studies were only cross-sectional and one contained only longitudinal data. The earliest studies were published in 1995, and the most

recent was published in 2015. The quality of studies was good, ranging from 8 to 12 (mean = 10.2, SD = 1.21). The meta-analysis was performed in an aggregated sample of 13,340 participants.

Eighteen studies included general population samples. The non-general population samples included children of alcoholics, children with ADHD and referred samples, and adolescents who lived in particular environments such as violent neighborhoods. Eighteen studies assessed nonspecific life events, five assessed independent life events only, one assessed dependent life events only, one assessed interpersonal life events only, one assessed both interpersonal and non-interpersonal life events, and one study assessed nonspecific, dependent and independent life events. Twenty-one studies used checklists, five studies used interviews and one study used both methods. Twenty studies used a self-report measure, two studies used a hetero-evaluation measure, and five studies used a multi-informant measure of life events. Regarding the measurement of the psychopathological spectra, sixteen studies used a self-report measure, one study used a hetero-evaluation measure, and ten studies used a multi-informant measure. Two studies included two different samples (the life events and the psychopathological variables were assessed with different measures in each sample). The mean time period asked about in the life events measure was 15.23 months (SD = 16.64).

Twenty-seven studies had cross-sectional data with the externalizing spectrum. Eleven included more than one correlation. Regarding the internalizing spectrum, twenty studies had cross-sectional data, six of them including more than one correlation. Seven studies were included in the sensitivity-stress hypothesis longitudinal analysis with the externalizing spectrum, two of them with more than one correlation, while four studies included longitudinal data to test this hypothesis with the internalizing spectrum, all of them with a single correlation. Finally, ten studies were included in the stress-generation hypothesis longitudinal analysis regarding the externalizing spectrum, four of them with more than one correlation. The internalizing spectrum analysis of this hypothesis was performed with seven studies, only one reporting more than one correlation.

Correlational and longitudinal hypothesis analysis

All the analyses showed high levels of heterogeneity, ranging from $Q(41) = 311.01$ ($p < 0.001$) for the cross-sectional analysis with the externalizing spectrum to $Q(8) = 21.08$, ($p = 0.007$) for the stress-generation longitudinal analysis with the internalizing spectrum. These results justified the use of random models to perform the statistical analyses.

The effect sizes estimated were significant in the six analyses (see Figure 2 for the Forest plots of the cross-sectional studies. See the supplementary material, Figure S1 and S2, for the Forest plots of the longitudinal analyses). All of them were positive, indicating that the greater the number of life events experienced, the higher the level of the psychopathological spectrum found. The highest effect sizes were found in the cross-sectional correlational studies (externalizing spectrum: $r = 0.35$, $z = 14.59$, $p < 0.0001$, 95% CI: 0.30, 0.40; internalizing spectrum: $r = 0.33$, $z = 14.92$, $p < 0.0001$, 95% CI: 0.29, 0.38), and the lowest effect sizes were found in the stress-generation hypothesis analyses (externalizing spectrum: $r = 0.28$, $z = 6.41$, $p < 0.0001$, 95% CI: 0.19, 0.37; internalizing spectrum: $r = 0.23$, $z = 7.98$, p

< 0.0001, 95% CI: 0.18, 0.29). The effect size regarding the externalizing spectrum in the sensitivity-stress hypothesis analysis was 0.28 (z = 6.41, p < 0.0001, 95% CI: 0.19, 0.37), while in the internalizing spectrum it was 0.29 (z = 3.92, p < 0.0001, 95% CI: 0.14, 0.43).

By means of a bootstrapping procedure applied to the Hotteling-Williams t-test, the correlations between life events and both psychopathological spectra were compared in 24 cross-sectional studies. The average correlation between life events and the externalizing spectrum was 0.34 (95% CI: 0,29, 0.38), and the average correlation between life events and the internalizing spectrum was 0.31 (95% CI: 0,26, 0.35). The difference between both correlations was not significant (t = 0.439, p = 0.332, 95% CI: -0.521, 1.334).

Symmetric and sensitivity analyses

All the Funnel plots were symmetrical (see Figure 3 for the Funnel plots of the cross-sectional studies. See the supplementary material, Figure S3 and S4, for the Funnel plots of the longitudinal analyses). The tau values ranged from □ = 0.33 (p = 0.75) for the internalizing spectrum sensitivity-stress hypothesis longitudinal analysis to □ = -0.08 (p = 0.75) for the internalizing spectrum stress-generation hypothesis longitudinal analysis. Hence, no bias of publication was found.

According to the MOOSE standards [50], the sensitivity analysis could be performed by controlling for the effect of the quality score. The studies were divided into two groups, those considered to be of higher quality (more than 10 in the quality score) and those of lower quality (less than or equal to 10 in the quality score). A meta-regression was performed by introducing the dichotomous variable as a covariate. In all analyses, the effect size estimated was independent of the studies' quality (highest value: Z = 1.62, p = 0.11; lowest value: Z = -0.31, p = 0.75).

Insert Figure 2 here

Analyses of possible confounders

Seven extra meta-regressions were performed in the six basic analyses in order to test the effect of different confounders. No significant differences were found in any analysis regarding gender (highest value: Z = -1.79, p = 0.07; lowest value: Z = 0.12, p = 0.90). The comparison between the general population samples versus those with special characteristics also showed no significant differences (highest value: Z = -1.72, p = 0.08; lowest value: Z = -0.26, p = 0.79). This analysis could not be performed for the sensitivity-stress hypothesis with the internalizing spectrum because all the studies included were based on general population samples. In line with the other analyses, the interviewing methodology used to assess the life events did not change the results significantly compared to the use of checklists (highest value: Z = 0.77, p = 0.44; lowest value: Z = -0.60, p = 0.55). Furthermore, the time period asked about in the

life events assessment was also not significant in any analysis (highest value: Z = -1.72, p = 0.09; lowest value: Z = -0.68, p = 0.50).

The analysis of the effect of the type of life events assessed was restricted only to those studies that used an independent life events measure. This was because none of the other types of life event were found in a minimum number of studies (n = 4) to have reliable data. So, the effect size reference was the general nonspecific life events measures. No analysis showed significant differences between the use of a specific independent life events measure and a general nonspecific life events measure (highest value: Z = -1.50, p = 0.13; lowest value: Z = -0.17, p = 8.87).

Significant differences were found when taking into account the reporter of the life events measure. In the cross-sectional studies regarding the externalizing spectrum, lower effect sizes were found in those studies with multiple reporters compared with the self-report method (Z = -3.94, p < 0.0001). However, in the cross-sectional studies of the internalizing spectrum, the lowest effect sizes were found in the studies with a single hetero-reporter (Z = -2.19, p < 0.05). In the longitudinal analyses no significant differences were found regarding the reporter of the life events.

In line with the previous findings, a significant effect of the reporter was found for the assessment of the psychopathological clusters. In the cross-sectional studies, those studies that used multiple reporters to estimate the externalizing spectrum resulted in lower correlations than those that used only self-reports (Z = -3.94, p < 0.0001). The same result (lower correlations in studies with multiple reporters) was found in the stress-generation hypothesis analysis regarding the externalizing spectrum (Z = -2.13, p < 0.05). The other analyses showed no significant differences between the ways in which the psychopathology was evaluated.

Furthermore, for the longitudinal studies only, the time between the two assessments was introduced as a covariate. In the sensitivity-stress hypothesis analysis for the externalizing spectrum, a significant effect was found (Z = -3.51, p < 0.001). The longer the time between the two evaluations, the lower was the correlation coefficient. In the other three longitudinal analyses no significant effect was found.

Finally, the number of life events in the checklists/interviews was also introduced as a covariate. Only for the externalizing spectrum a significant effect was found in cross-sectional studies (Z = 2.82, p < 0.01) and in the stress-generation hypothesis (Z = 2.98, p < 0.01). As more life events were questioned, the higher was the correlation coefficient.

Insert Figure 3 here

Discussion

The main aim of the present study was to study the relation between stressful life events during adolescence and externalizing/internalizing spectra using a meta-analytical methodology. Twenty-seven studies were included in the meta-analysis. Population effect sizes were estimated based on the correlations using a random/mixed-effects model. In each study, the effect of aggregated stressful life events, rather than specific life events, was analyzed. Moreover, the life events investigated were those that occurred during adolescence, so no effects from other life periods were investigated. Hence, the present study focused only on recent life events during adolescence.

Some of the studies included were cross-sectional, while others used longitudinal designs. According to the empirical guidelines of Hemphill [63], the meta-analytical correlations found in cross-sectional studies could be interpreted as high. This is consistent with past research focused on individual disorders [29, 31].

As longitudinal designs are useful to deduce which variable precede the other in correlational analyses, the present meta-analysis also used longitudinal data. Theoretically, the directional relation between stressful life events and psychopathology can be understood according to two hypotheses. The first one, the sensitivity-stress hypothesis, implies that the aggregation of stressful experiences should be a risk factor for psychopathology [58, 59]. Those studies that showed correlations between the stressful life events assessed at Time 1 and the psychopathological clusters evaluated at Time 2 were selected to test the sensitivity-stress hypothesis. According to Hemphill [63], the correlations found for the externalizing and internalizing spectra could be interpreted as a medium effect size. The second directional association between the stressful life events and the psychopathology is described by the stress-generation hypothesis. This suggests that a mental disorder increases exposure to more stressful life events or could lead to a more stressful interpretation of the life events experienced [46, 48, 55–57]. Hence, studies in which psychopathological clusters were assessed at Time 1 and stressful life events were assessed at Time 2 were selected to test the stress-generation hypothesis. According to Hemphill [63], the two correlations found could be interpreted as medium effect size. Hence, in line with past research [55, 64, 65], the directional association between the aggregation of stressful life events and the externalizing/internalizing spectra could be considered as transactional. The psychopathological spectra could be a consequence but also a cause of the stressful situations that could be experienced during adolescence. This developmental process of reciprocal relations should evolve due to mutual interactions with other biopsychosocial factors [56].

According to the definition of the psychopathological spectra [16], the present study suggests that the aggregation of stressful life events must be considered as a general risk factor (and sometimes a consequence) for the common liability factors that underlie impulsive and emotional disorders, and not specific mental problems. This could be important in clinical settings. For example, if a patient has a diagnosis of a specific phobia and the psychiatrist or psychologist detects that in recent months this patient has experienced a significant increase in stressful life events, it should be pointed out that the patient will have an increased likelihood of developing another internalizing disorder, such as

depression. On the other hand, which specific life events have been experienced could be important when hypothesizing which particular mental disorder could develop. For example, the death of a family member predicted major depression but not general anxiety syndrome [66]. This could also be applicable for gene–environment interaction/correlation studies.

One objective of the present study was to analyze the directionality of the association between the stressful life events and psychopathology, taking into account the difference between dependent and independent life events. The heritability component of independent life events is estimated to be lower than that of dependent life events [39]. Thus it could be assumed that independent life events influence the individual through gene–environment interactions (sensitivity-stress hypothesis), whereas dependent life events are related to psychopathology through gene–environment correlation effects (stress-generation hypothesis) [36, 39]. However, when metaregressions controlling for the type of life events were performed, no significant results were found. Those studies that assessed life events using an undifferentiated measure showed the same pattern of relations as those studies that assessed independent life events only. One problem with the studies accepted for the meta-analysis is that most of them analyzed the effect of life events using an undifferentiated measure or they only assessed independent life events. As the undifferentiated measures mixed dependent and independent life events, we could not rule out the possibility that the main results of the present study were due exclusively to independent life events. Future studies in this field should differentiate more frequently between the types of life events.

In addition, only four out of the 27 studies assessed stressful life events using the same measure as any other of the 27 studies (2 using the Adolescent Life Events Questionnaire (ALEQ [67]) and 2 using a selection of items from the Life Events Checklist (LEC [68]). As all four of these studies did not use the same instrument, they did not reach the minimum number of studies (n = 4) necessary to provide reliable data for subgroup analysis. Hence, we could not test the effect of specific tests on the results directly. This heterogeneity in the measurement of life events makes it difficult to perform adequate meta-analysis, as not all the measures consider the same life events or use the same questions. This problem is also typical in meta-analysis focused on single disorders [69]. Taking into account that the life events considered by these measures are intended to be a representative sample of the most likely life events that a person could experience, not enquiring about a specific life event that was significant to the respondent means underestimating the real stress lived through by that person. Thus, a test of the effect of the number of life events measured in each study was performed in order to gain indirect information concerning the significance of using one measure or another. We found that the number of life events included in the tests moderated the associations between the aggregate life events and the externalizing spectrum. Hence, the checklist/interview that a researcher decides to use is relevant when estimating the effect of life events on some mental disorders. So, a suggestion for the scientific community in this field would be to standardize the measurement of stressful life events, conceptually but also technically.

Another limitation of the present study is related to the outcome used. The fact that the meta-analysis was performed with the correlations of the studies presents two main drawbacks. The first is that we could not control for confounders in the relations between life events and psychopathology. Some of the confounders tested in past studies have been the family socioeconomic position, gender and the parental psychopathology [70–72]. In non-meta-analytic studies, controlling these confounders is usually done by performing regressions. But it is very difficult to carry out a meta-analysis by taking the standardized betas of regressions as the unit of measurement. This could be done if a sufficient number of studies performed the same regression methodology with the same dependent, independent and confounder variables. But there are too few studies with these characteristics in the literature. However, the empirical studies that have controlled for confounders found that the relation between the stressful life events and the psychopathological spectra remained stable and significant [70–72]. Another problem derived from using the correlations as the unit to perform the meta-analysis is that we could not control for the baseline levels of the variables of interest in the longitudinal studies. For example, if we wanted to test whether the stressful life events at Time 1 predicted the psychopathological spectra levels at Time 2, we would have to control for the effect of the psychopathological spectra levels at Time 1. This methodological control is the basic step necessary to ensure assessment of causation in a longitudinal design, while also performing regressions in empirical studies. In line with the first limitation, the longitudinal studies that have controlled for this effect also found that the transactional relations between the stressful life events and the psychopathological spectra remained significant [64, 65].

To conclude, the present study assessed the relations between stressful life events and the externalizing/internalizing spectra of psychopathology using a meta-analytical methodology. In cross-sectional studies, the association between these variables was significant and empirically high. From a longitudinal perspective, both the sensitivity-stress hypothesis and the stress-generation hypothesis were supported. These results would mean that the aggregation of stressful life events during adolescence should be considered as a risk factor for externalizing or internalizing symptoms, which increase the likelihood of developing specific psychiatric disorders. At the same time, having high levels of the liability to develop externalizing or internalizing disorders would increase exposure to more stressful life experiences. Hence, the relation between the variables studied seems to be reciprocal and transactional. More research in this field should be performed in order to show whether different types of life events (dependent vs. independent) explain the associations found in the present study.

The manuscript does not contain clinical studies or patient data. The authors declare that they have no conflict of interest.

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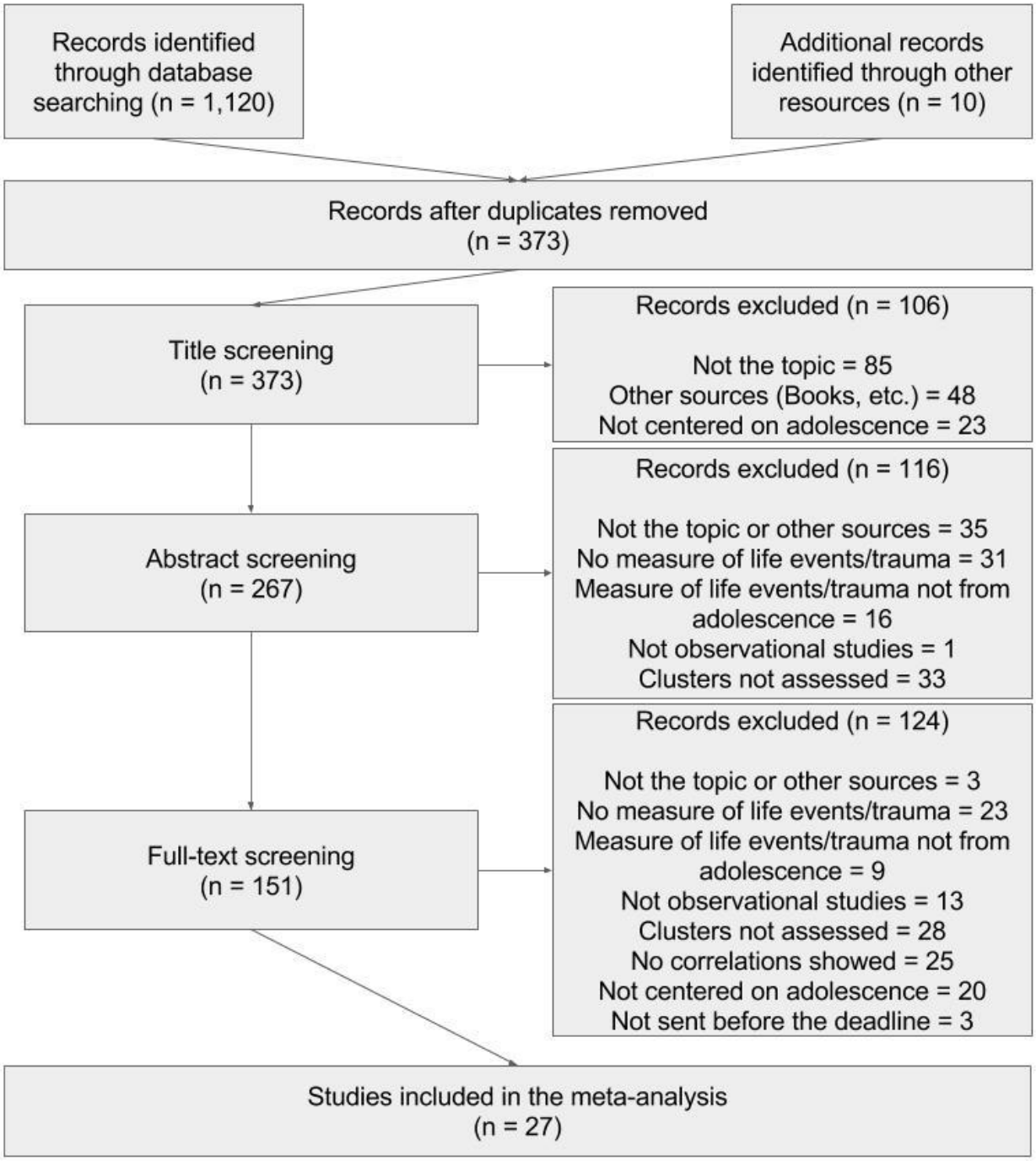
Figure captions

Fig. 1 Flowchart for study selection.

Fig. 2 Forest plot for the externalizing spectrum (A) and internalizing spectrum (B) of cross-sectional studies. Forest plot of average effect size and 95% confidence interval of each individual study (represented by a square) and summary effect (represented by a diamond).

Fig. 3 Funnel plot of standard error by effect size for all cross-sectional studies (A: externalizing spectrum; B: internalizing spectrum).

Fig. 1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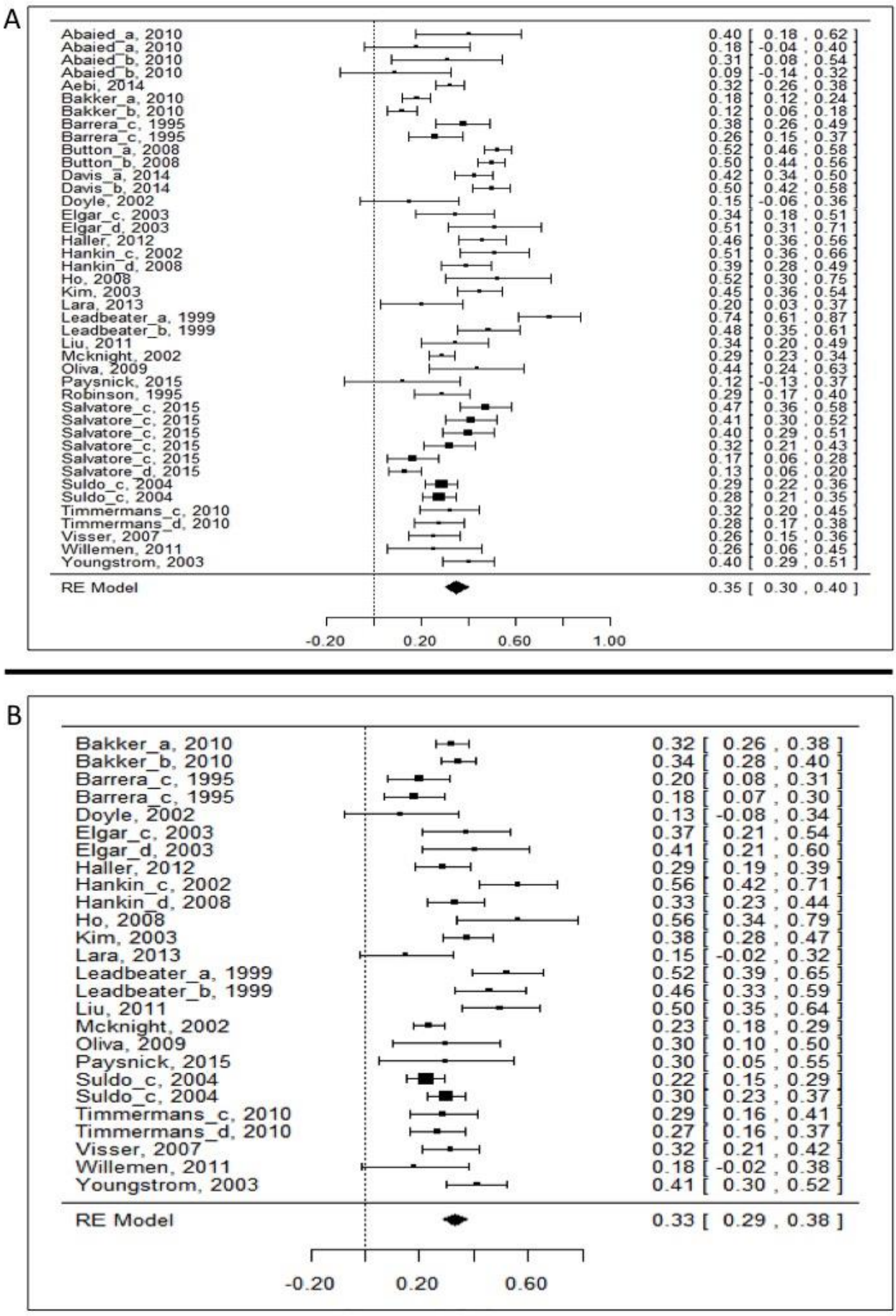
Additional records identified through other resources (n = 10)
Records after duplicates removed (n = 373)
Title screening (n = 373)
Records excluded (n = 106)
Not the topic = 85
Other sources (Books, etc.) = 48
Not centered on adolescence = 23
Abstract screening (n = 267)
Records excluded (n = 116)
Not the topic or other sources = 35
No measure of life events/trauma = 31
Measure of life events/trauma not from adolescence = 16
Not observational studies = 1
Clusters not assessed = 33
Full-text screening (n = 151)
Records excluded (n = 124)
Not the topic or other sources = 3
No measure of life events/trauma = 23
Measure of life events/trauma not from adolescence = 9
Not observational studies = 13
Clusters not assessed = 28
No correlations showed = 25
Not centered on adolescence = 20
Not sent before the deadline = 3
Studies included in the meta-analysis (n = 27)

Fig. 2


A
Abaied_a, 2010 0.40 [0.18 , 0.62]
Abaied_a, 2010 0.18 [-0.04 , 0.40]
Abaied_b, 2010 0.31 [0.08 , 0.54]
Abaied_b, 2010 0.09 [-0.14 , 0.32]
Aebi, 2014 0.32 [0.26 , 0.38]
Bakker_a, 2010 0.18 [0.12 , 0.24]
Bakker_b, 2010 0.12 [0.06 , 0.18]
Barrera_c, 1995 0.38 [0.26 , 0.49]
Barrera_c, 1995 0.26 [0.15 , 0.37]
Button_a, 2008 0.52 [0.46 , 0.58]
Button_b, 2008 0.50 [0.44 , 0.56]
Davis_a, 2014 0.42 [0.34 , 0.50]
Davis_b, 2014 0.50 [0.42 , 0.58]
Doyle, 2002 0.15 [-0.06 , 0.36]
Elgar_c, 2003 0.34 [0.18 , 0.51]
Elgar_d, 2003 0.51 [0.31 , 0.71]
Haller, 2012 0.46 [0.36 , 0.56]
Hankin_c, 2002 0.51 [0.36 , 0.66]
Hankin_d, 2008 0.39 [0.28 , 0.49]
Ho, 2008 0.52 [0.30 , 0.75]
Kim, 2003 0.45 [0.36 , 0.54]
Lara, 2013 0.20 [0.03 , 0.37]
Leadbeater_a, 1999 0.74 [0.61 , 0.87]
Leadbeater_b, 1999 0.48 [0.35 , 0.61]
Liu, 2011 0.34 [0.20 , 0.49]
Mcknight, 2002 0.29 [0.23 , 0.34]
Oliva, 2009 0.44 [0.24 , 0.63]
Paysnick, 2015 0.12 [-0.13 , 0.37]
Robinson, 1995 0.29 [0.17 , 0.40]
Salvatore_c, 2015 0.47 [0.36 , 0.58]
Salvatore_c, 2015 0.41 [0.30 , 0.52]
Salvatore_c, 2015 0.40 [0.29 , 0.51]
Salvatore_c, 2015 0.32 [0.21 , 0.43]
Salvatore_c, 2015 0.17 [0.06 , 0.28]
Salvatore_d, 2015 0.13 [0.06 , 0.20]
Suldo_c, 2004 0.29 [0.22 , 0.36]
Suldo_c, 2004 0.28 [0.21 , 0.35]
Timmermans_c, 2010 0.32 [0.20 , 0.45]
Timmermans_d, 2010 0.28 [0.17 , 0.38]
Visser, 2007 0.26 [0.15 , 0.36]
Willemen, 2011 0.26 [0.06 , 0.45]
Youngstrom, 2003 0.40 [0.29 , 0.51]
RE Model 0.35 [0.30 , 0.40]
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Bakker_a, 2010 0.32 [0.26 , 0.38]
Bakker_b, 2010 0.34 [0.28 , 0.40]
Barrera_c, 1995 0.20 [0.08 , 0.31]
Barrera_c, 1995 0.18 [0.07 , 0.30]
Doyle, 2002 0.13 [-0.08 , 0.34]
Elgar_c, 2003 0.37 [0.21 , 0.54]
Elgar_d, 2003 0.41 [0.21 , 0.60]
Haller, 2012 0.29 [0.19 , 0.39]
Hankin_c, 2002 0.56 [0.42 , 0.71]
Hankin_d, 2008 0.33 [0.23 , 0.44]
Ho, 2008 0.56 [0.34 , 0.79]
Kim, 2003 0.38 [0.28 , 0.47]
Lara, 2013 0.15 [-0.02 , 0.32]
Leadbeater_a, 1999 0.52 [0.39 , 0.65]
Leadbeater_b, 1999 0.46 [0.33 , 0.59]
Liu, 2011 0.50 [0.35 , 0.64]
Mcknight, 2002 0.23 [0.18 , 0.29]
Oliva, 2009 0.30 [0.10 , 0.50]
Paysnick, 2015 0.30 [0.05 , 0.55]
Suldo_c, 2004 0.22 [0.15 , 0.29]
Suldo_c, 2004 0.30 [0.23 , 0.37]
Timmermans_c, 2010 0.29 [0.16 , 0.41]
Timmermans_d, 2010 0.27 [0.16 , 0.37]
Visser, 2007 0.32 [0.21 , 0.42]
Willemen, 2011 0.18 [-0.02 , 0.38]
Youngstrom, 2003 0.41 [0.30 , 0.52]
RE Model 0.33 [0.29 , 0.38]
-0.20
0.20
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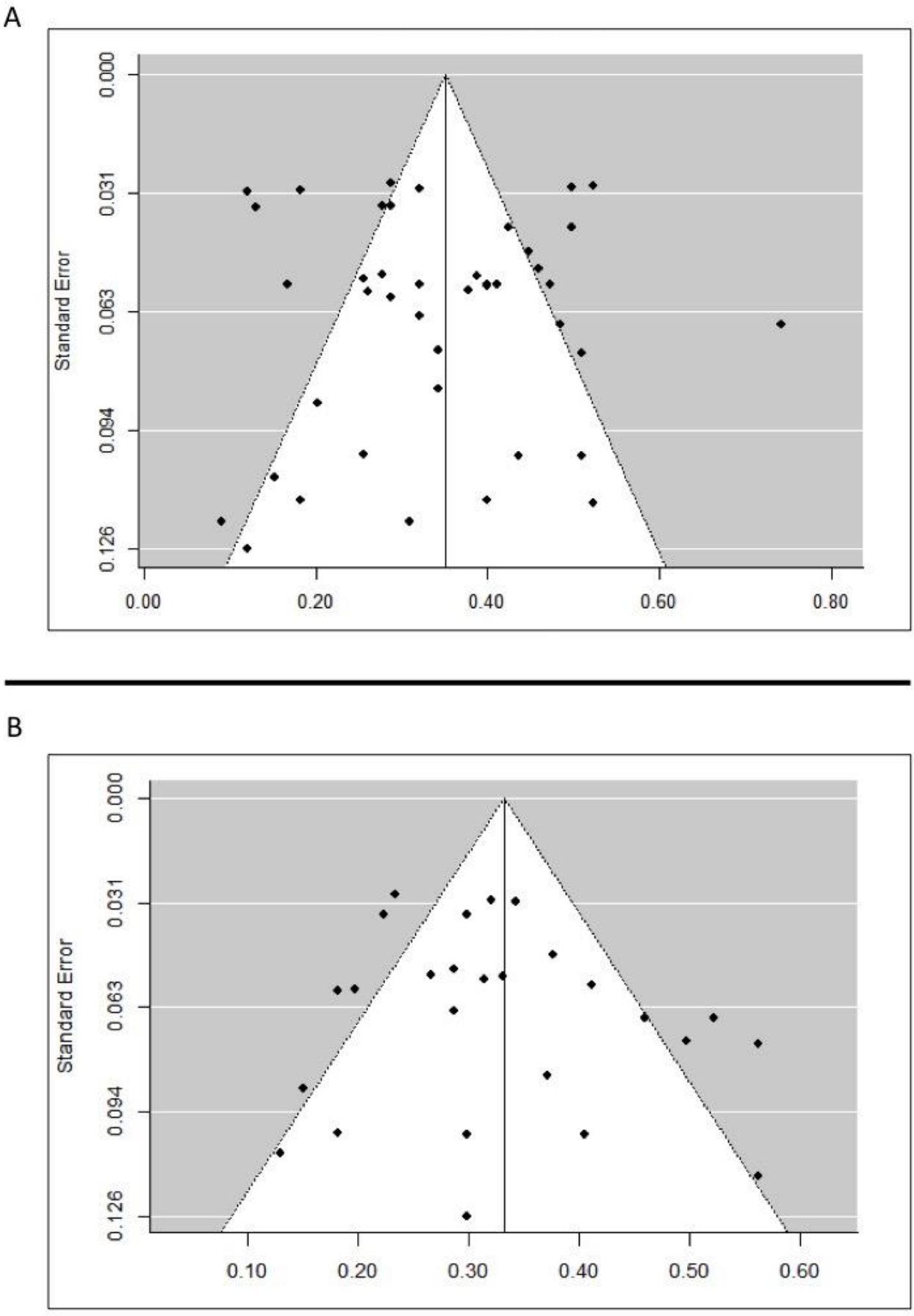
Fig. 3


A
Standard Error
0.000
0.031
0.063
0.094
0.126
0.00
0.20
0.40
0.60
0.80
B
Standard Error
0.000
0.031
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0.50
0.60