# The Separation Anxiety Hypothesis of Panic Disorder Revisited: A Meta-Analysis

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**Objective:** Evidence suggests that childhood separation anxiety disorder may be associated with a heightened risk for the development of other disorders in adulthood. The authors conducted a meta-analysis to examine the relationship between childhood separation anxiety disorder and future psychopathology.

**Method:** PubMed, PsycINFO, and Embase were searched for studies published through December 2011. Case-control, prospective, and retrospective cohort studies comparing children with and without separation anxiety disorder with regard to future panic disorder, major depressive disorder, any anxiety disorder, and substance use disorders were included in the analysis. Effects were summarized as pooled odds ratios in a random-effects model.

**Results:** Twenty-five studies met all inclusion criteria (14,855 participants). A meta-analysis of 20 studies indicated that children with separation anxiety disorder were more likely to develop panic disorder later on (odds ratio=3.45; 95% CI=2.37–5.03). Five studies suggested that a childhood diagnosis of separation anxiety disorder increases the risk of future anxiety (odds ratio=2.19; 95% CI=1.40–3.42). After adjusting for publication bias, the results of 14 studies indicated that childhood separation anxiety disorder does not increase the risk of future depression (odds ratio=1.06; 95% CI=0.78–1.45). Five studies indicated that childhood separation anxiety disorder does not increase the risk of substance use disorders (odds ratio=1.27; 95% CI=0.80–2.03). Of the subgroup analyses performed, differences in comparison groups and sample type significantly affected odds ratio sizes.

**Conclusions:** A childhood diagnosis of separation anxiety disorder significantly increases the risk of panic disorder and any anxiety disorder. These results support a developmental psychopathology conceptualization of anxiety disorders.

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Separation anxiety disorder is characterized by persistent, excessive, and developmentally inappropriate fear of separation from major attachment figures, usually parents (1). It is one of the most frequently diagnosed childhood anxiety disorders, with lifetime prevalence rates between 4.1% and 5.1% (2, 3).

Suggestions of a specific link between separation anxiety in childhood and adult panic disorder can be found in the early work of Klein (4), who noted that imipramine blocked the key panic attacks in patients hospitalized for agoraphobia. Review of the patients' histories indicated that those with early onset also had separation anxiety. Klein's separation anxiety hypothesis stimulated much research leading to ambiguous results. At present, the consequences of childhood separation anxiety disorder for future mental disorders are not clear. Some studies have identified it as a specific risk factor for adult panic disorder (4), others have identified it as a general risk factor for multiple adult anxiety and nonanxious disorders (5–7), and yet others have demonstrated that it may continue into adulthood (8).

One of the first attempts to review the literature on the relationship between separation anxiety disorder and mental disorders in adulthood was by Silove et al. (9), who analyzed the early evidence for an association between childhood separation anxiety disorder and adult panic disorder with agoraphobia. They concluded that there was evidence supporting the link, although the specificity of that relationship required further clarification. However, they focused exclusively on the link between separation anxiety disorder and panic disorder with agoraphobia. Since then, a considerable number of retrospective, as well as longitudinal, studies have been published (5–7, 10–13), indicating that the volume of evidence on this topic has rapidly increased. To our knowledge, however, no systematic review or meta-analysis addressing the outcomes of childhood separation anxiety disorder has been published. Consequently, a meta-analysis examining the outcomes of childhood separation anxiety disorder is of highest clinical and conceptual relevance.

To test the relationship between childhood separation anxiety disorder and subsequent mental disorders in adolescence and adulthood, we performed meta-analyses of epidemiological studies investigating the association between childhood separation anxiety disorder and panic disorder, anxiety disorders in general, major depressive disorder, or substance use disorders. Selected outcomes were

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chosen because of their theoretical relation to separation anxiety disorder (8), as well as a sufficient number of empirical studies investigating the associations. In addition, possible moderators were identified by examining subgroup analyses.

## Method

### Search Strategy and Inclusion Criteria

We performed searches in PubMed, PsycINFO, and Embase of studies published through December 31, 2011, using the keyword "separation anxiety." In addition, the references of all included articles were reviewed, and researchers in the field were contacted and asked if they were aware of additional relevant publications. Eligibility judgments were performed independently by two reviewers (J.K. and C.L.). Inconsistencies were resolved in consensus meetings and confirmed with a third reviewer (M.C.P.) when necessary. We included peer-reviewed published articles comparing children with separation anxiety disorder with children without separation anxiety disorder or with other mental disorders with regard to future mental disorders in adolescence and adulthood. Case-control, prospective, and retrospective cohort studies that were in either English or German were included. Only studies using explicit, reliable, and reproducible diagnostic criteria for separation anxiety disorder and outcome variables, which were based on DSM-III, DSM-III-R, DSM-IV, or ICD-10, were included. Outcomes had to be reported as odds ratios or in other ways that allowed for their calculation. Prospective studies with a follow-up period less than 2 years were excluded, as were case reports, comments, letters, and reviews. Any disagreements were discussed, and a consensus was reached. With these criteria, 25 studies were identified and included in our analysis (5–7, 10, 11, 13–32) (Table 1).

### Quality Assessment

Two of the reviewers (M.C.P. and C.L.) independently evaluated the methodological quality of the studies using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement (33). Items 11, 12c, 16b, 16c, 17, and 22 of the STROBE were disregarded because they were either not applicable to the studies under investigation or did not appropriately differentiate between studies of low and high quality. For items 7 and 16a, the studies were rated by assigning 0, 0.5, or 1 point as appropriate. For the remaining items, the studies were rated by assigning 0 or 1 point. Disagreements regarding data extraction or quality of the studies were resolved by consensus among reviewers.

### Data Extraction and Analysis

Data were extracted independently by two of the reviewers (J.K. and M.C.P.). Inconsistencies were resolved in consensus meetings. Extracted data were converted to odds ratio effect sizes and 95% confidence intervals reflecting the probability of unfavorable outcomes, with odds ratios above 1 reflecting a greater likelihood of future psychopathology in individuals with a history of childhood separation anxiety disorder compared with those without. Data management, log-transformation of effect sizes, and calculation of the pooled mean effect sizes were performed using Comprehensive Meta-Analysis, version 2.0 (www.meta-analysis.com). Since considerable heterogeneity was expected, all analyses were performed with a random-effects model. We used this model because it is preferable to fixed-effects models, particularly with relatively small numbers of studies with expected high heterogeneity (34). Log-transformed odds ratio estimates were pooled using the inverse of their variance as weights (35).

The majority of cohort studies prospectively investigated separation anxiety disorder samples compared with non-separation anxiety disorder samples, which included individuals with no history of childhood separation anxiety disorder but with other potential present or lifetime diagnoses. Case-control studies retrospectively investigated the clinical population under investigation (i.e., individuals with panic disorder, major depressive disorder, other anxiety disorders, or substance use disorders) compared with either a clinical comparison group including subjects with a variety of current disorders other than the outcome variable under investigation (these disorders are listed in Table 1) or a nonclinical comparison group (i.e., healthy or nonpsychiatric comparison subjects), with regard to a history of separation anxiety disorder. Two studies included data for both nonclinical and clinical comparison subjects (7, 21). To avoid the problem of correlated data, the odds ratios for these studies were calculated for a pooled comparison group and not included in the subgroup analysis differentiating between the comparison groups. One study included two separate samples (15), and the data were treated as belonging to separate cohorts.

To assess heterogeneity between studies, we used the Q statistic. A statistically significant Q indicates a heterogeneous distribution of odds ratios between studies, meaning that systematic differences, possibly influencing the results, are present (36). In addition, the degree of inconsistency was quantified by the $I^2$ statistic, which measures the percentage of variation across studies that is a result of heterogeneity rather than chance (37). A value of 0% means no heterogeneity, and higher values indicate greater heterogeneity. Generally, heterogeneity is considered low at an $I^2$ value of 25%, moderate at a value of 50%, and high at a value of 75% (37).

Additional sensitivity analyses explored the effects of various possible sources of artifact or bias on the results. First, we assessed the presence of publication bias visually by funnel plot (38) and formally by its direct statistical analogues, the Begg adjusted-rank correlation test (39) and the fail-safe N method (40). Sensitivity to the estimate of publication bias was assessed by the trim-and-fill method (41). Second, we performed subgroup analyses to test for significant differences between odds ratios in different categories of studies. Of greatest interest were differences with regard to comparison groups, study type, study population, diagnostic criteria (i.e., DSM-III, DSM-IV), differential symptom assessments (i.e., participant report, parental report, or both), data collection methods (i.e., questionnaire, structured interview), sociodemographic characteristics (i.e., age, sex, family background, familial stress, parental psychopathology), and severity of and age at onset of separation anxiety disorder. Furthermore, we assessed the impact of study quality on the meta-analysis results. To evaluate the statistical stability of results, studies rated as "poor" in quality (i.e., STROBE values $<10$) were removed in a separate analysis, and the pooled odds ratio, with 95% confidence interval, was recalculated and compared with the original results. Differences between odds ratios were calculated using a z test (42).

## Results

### Study Selection

The study selection procedure is summarized in Figure 1.

### Association Between Separation Anxiety Disorder and Future Mental Disorders

In investigating the association between separation anxiety disorder and panic disorder, we first assessed

**TABLE 1. Selected Characteristics of Studies Investigating the Association Between Childhood Separation Anxiety Disorder and Subsequent Mental Illnesses[a]**

| Study | Group (Disorder) | Study Participants N | Mean Age or Range | SD | Female (%) | Study Design | Sample Type |
|---|---|---|---|---|---|---|---|
| Aschenbrand et al. (2003) | Clinical control; separation anxiety disorder | 67<br>18 | 19.3<br>(Total sample) | 1.7 | 36 | Prospective cohort | Clinical |
| Ayuso et al. (1989) | Nonclinical control; panic disorder | 50<br>107 | No data<br>35.1 | 9.0 | 65 | Case control | Clinical |
| Balon et al. (1989) | Nonclinical control; panic disorder | 100<br>100 | 29.5<br>32.8 | 5.9<br>8.0 | 55 | Case control | Clinical |
| Bandelow et al. (2001) | Nonclinical control; panic disorder | 124<br>115 | 36.8<br>38.1 | 11.6<br>10.6 | 58 | Case control | Clinical |
| Battaglia et al. (1995) | Nonclinical control; panic disorder | 131<br>231 | 37.3<br>36.3 | 12.0<br>11.0 | 68 | Case control | Clinical |
| Biederman et al. (2005)[b] | Nonclinical control referred; | 61 | 38.3 | 5.1 | 48 | Case control | Population |
| | panic disorder in referred sample; | 131 | 38.8 | 5.4 | 85 | | |
| | nonclinical control nonreferred; | 587 | 42.4 | 5.8 | | | |
| | panic disorder in nonreferred sample | 58 | 40.5 | 6.4 | | | |
| Biederman et al. (2005)[c] | Nonclinical control; panic disorder; major depressive disorder | 686<br>23<br>225 | 42.1<br>42.5<br>41.8 | 6.0<br>5.5<br>5.9 | 51 | Case control | Population |
| Biederman et al. (2006) | Nonclinical control; panic disorder | 960<br>58 | 42.0<br>40.5 | 6.0<br>6.4 | 51 | Case control | Population |
| Biederman et al. (2007) | Separation anxiety disorder; non-separation anxiety disorder | 41<br>192 | 6.4<br>(Total sample) | No data | No data | Prospective cohort | Population |
| Bittner et al. (2007) | Separation anxiety disorder; non-separation anxiety disorder | 68<br>812 | 9–19<br>(Total sample) | | 50 | Prospective cohort | Population |
| Brückl et al. (2007) | Separation anxiety disorder; subthreshold separation anxiety disorder; symptomatic separation anxiety disorder; non-separation anxiety disorder | 17<br>99<br>86<br>888 | 14–17<br>(Total sample) | | 52 | Prospective cohort | Population |
| Flakierska-Praquin et al. (1997) | Nonclinical control<br>clinical control; separation anxiety disorder | 35<br>35<br>35 | 7–12<br>(Total sample) | | 54 | Prospective cohort | Clinical |
| Gregory et al. (2007) | Nonclinical control; clinical control; panic disorder | 640<br>307<br>16 | 32<br>(Total sample) | No data | 62 | Case control | Population |

[a] OCD=obsessive-compulsive disorder; STROBE=Strengthening the Reporting of Observational Studies in Epidemiology.
[b] The data refer to the Biederman et al. study on childhood antecedents to panic disorder (13).
[c] The data refer to the Biederman et al. study on patterns of comorbidity in panic disorder and major depression (17).

| Outcome | Comparison Group | Clinical Control Disorder | Separation Anxiety Disorder Measure | Separation Anxiety Disorder Measure Criteria | Informant | STROBE Score |
|---|---|---|---|---|---|---|
| Anxiety disorders; major depressive disorder; panic disorder | Clinical control | Generalized anxiety disorder; social phobia | Interview | DSM-III-R | Parent and child | 18.5 |
| Panic disorder | Nonclinical control | | Checklist | DSM-III | Proband | 11 |
| Panic disorder | Nonclinical control | | Checklist | DSM-III | Proband | 7 |
| Panic disorder | Nonclinical control | | Interview; checklist | DSM-IV | Proband | 16.5 |
| Panic disorder | Nonclinical control | Panic disorder; major depressive disorder; social phobia; simple phobia | Checklist | DSM-III-R | Proband | 14.5 |
| Panic disorder | Nonclinical control | | Interview | DSM-III-R | Proband | 17.5 |
| Major depressive disorder; panic disorder | Nonclinical control | | Interview | DSM-III-R | Proband | 15.5 |
| Panic disorder | Nonclinical control | | Interview | DSM-III-R | Proband | 17.5 |
| Major depressive disorder; panic disorder | Non-separation anxiety disorder | | Interview | DSM-III-R | Parent and child | 16.5 |
| Major depressive disorder; substance dependence | Non-separation anxiety disorder | | Interview | DSM-IV | Parent and child | 17 |
| Anxiety disorders; major depressive disorder; panic disorder; substance dependence | Non-separation anxiety disorder | | Interview | DSM-IV | Child | 15.5 |
| Anxiety disorders; major depressive disorder; panic disorder; substance dependence | Clinical control, nonclinical control | Oppositional disorder; attention deficit disorder; dysthymia; anxiety disorders; OCD; tics; reading disorder; enuresis/encopresis; atypical stereotyped movement disorder; adjustment disorder | Medical records | DSM-III | No data | 15.5 |
| Panic disorder | Non-separation anxiety disorder | | Interview; checklist | DSM-III | Parent and child | 12 |

*continued*

**TABLE 1. Selected Characteristics of Studies Investigating the Association Between Childhood Separation Anxiety Disorder and Subsequent Mental Illnesses[a] (*continued*)**

| Study | Group (Disorder) | Study Participants N | Mean Age or Range | SD | Female (%) | Study Design | Sample Type |
|---|---|---|---|---|---|---|---|
| Hayward et al. (2000) | Major depressive disorder; | 124 | 15.4 (Total sample) | 0.9 | 47 | Prospective cohort | Population |
| | non-separation anxiety disorder | 1,917 | | | | | |
| Hayward et al. (2003) | Panic disorder; | 12 | 15.4 | 0.9 | 47 | Case control | Population |
| | clinical control | 2,342 | (Total sample) | | | | |
| Lewinsohn et al. (2008) | Nonclinical control; | 457 | 16.1 | No data | No data | Prospective cohort | Population |
| | clinical control; | 389 | (Total sample) | | | | |
| | separation anxiety disorder; | 42 | | | | | |
| | anxiety disorders | 88 | | | | | |
| Lipsitz et al. (1994) | Panic disorder; | 156 | 34.5 | 8.4 | 59 | Case control | Clinical |
| | social phobia; | 106 | (Total sample) | | | | |
| | OCD; | 51 | | | | | |
| Mroczkowski et al. (2011) | Clinical control; | 390 | 42.2 | 14.7 | 71 | Retrospective cohort | Clinical |
| | separation anxiety disorder | 80 | 34.2 | 12.9 | | | |
| Otto et al. (2001) | Panic disorder; | 133 | 36.4 | 9.7 | 34 | Case control | Clinical |
| | social phobia | 97 | | | | | |
| Pine et al. (1998) | Non-separation anxiety disorder; | 601 | 9–18 (Total sample) | No data | 50 | Prospective cohort | Population |
| | separation anxiety disorder | 111 | | | | | |
| Pini et al. (2005) | Nonclinical control; | 15 | 27.1 | 6.0 | 54 | Case control | Clinical |
| | panic disorder; | 24 | 32.5 | 9.3 | | | |
| | major depressive disorder | 20 | 45.6 | 8.3 | | | |
| Pini et al. (2010) | Non-separation anxiety disorder; | 250 | 42.0 | 12.1 | 66 | Case control | Clinical |
| | adult separation anxiety disorder with history of childhood separation anxiety; | 110 | 39.4 | 13.3 | | | |
| | separation anxiety disorder | 43 | 36.9 | 10.5 | | | |
| Raskin et al. (1982) | Clinical control; | 16 | 21–54 | No data | 70 | Case control | Clinical |
| | panic disorder | 17 | 24–60 | | | | |
| Silove et al. (2002) | Non-separation anxiety disorder; | 20 | 45.0 (Total sample) | 15.0 | 65 | Retrospective cohort | Population |
| | separation anxiety disorder | 52 | | | | | |
| Yeragani et al. (1989) | Nonclinical control; | 30 | 33.4 | 6.2 | 54 | Case control | Clinical |
| | panic disorder; | 35 | 29.6 | 6.3 | | | |
| | major depressive disorder | 24 | 31.7 | 5.1 | | | |

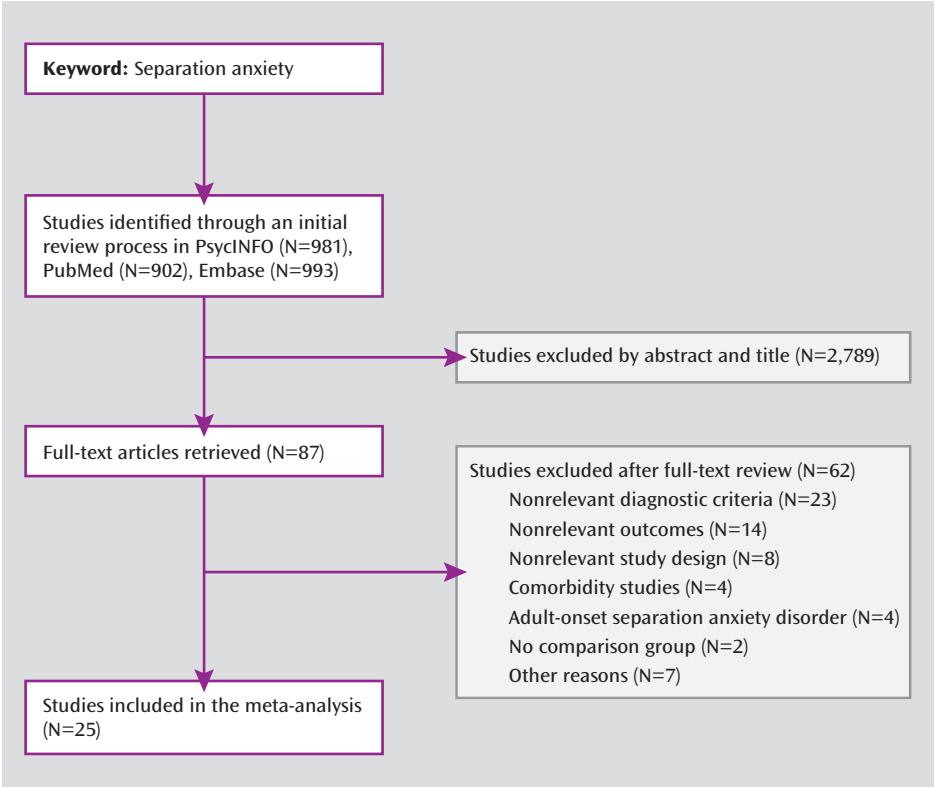
whether there was a difference between the independent studies investigating the association between separation anxiety disorder and panic disorder and the association between separation anxiety disorder and panic disorder with agoraphobia. We found that this was not the case (odds ratio=3.59; 95% confidence interval [CI]=2.92–4.42, compared with odds ratio=4.19; 95% CI=2.15–8.15; p=0.66). We therefore combined the two panic disorder groups.

Twenty-five studies were included in the meta-analysis (Table 1). Meta-analysis revealed that children with a history of separation anxiety disorder were more likely than those without to develop panic disorder later on (odds ratio=3.45, 95% CI=2.37–5.03) (Figure 2). We identified significant heterogeneity across studies (Q=79.01, df=23, $p<0.001$; $I^2=70.89$, $tau^2=0.50$). There was no evident publication bias in a funnel plot. The Begg's test result was not statistically significant, and the fail-safe N indicated that 782 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method did not lead to any adjustment of the odds ratio.

| Outcome | Comparison Group | Clinical Control Disorder | Separation Anxiety Disorder Measure | Separation Anxiety Disorder Measure Criteria | Informant | STROBE Score |
|---|---|---|---|---|---|---|
| Major depressive disorder | Non-separation anxiety disorder | | Interview | DSM-III-R | Child | 13.5 |
| Panic disorder | Nonclinical control | No data | Interview | DSM-III-R | Child | 12.5 |
| Anxiety disorders; major depressive disorder; panic disorder; substance dependence | Clinical control, nonclinical control | Affective disorder; nonaffective disorder; psychotic disorder; adjustment disorder | Interview | DSM-III-R | Child | 17.5 |
| Panic disorder | Clinical control | Panic disorder; social phobia; OCD | Interview | DSM-III-R | Proband | 13.5 |
| Major depressive disorder; panic disorder; substance dependence | Non-separation anxiety disorder | | Interview | DSM-IV | Proband | 13 |
| Panic disorder | Clinical control | Social phobia | Interview | DSM-III-R | Proband | 13.5 |
| Major depressive disorder; panic disorder | Non-separation anxiety disorder | | Interview | DSM-III; DSM-III-R | Parent and child | 15 |
| Major depressive disorder; panic disorder | Nonclinical control | | Interview | DSM-IV | Proband | 13.5 |
| Major depressive disorder; panic disorder; anxiety disorders | Non-separation anxiety disorder | | Interview | DSM-IV | Proband | 14.5 |
| Panic disorder | Clinical control | Generalized anxiety disorder | No data | DSM-III | Proband | 10.5 |
| Major depressive disorder; panic disorder | Non-separation anxiety disorder | | Interview; checklist | DSM-IV | Proband | 14 |
| Major depressive disorder; panic disorder | Nonclinical control | | Checklist | DSM-III | Proband | 7.5 |

Five studies were included to test the association between separation anxiety disorder and any anxiety disorder (Table 1). Because of the problem of adult anxiety comorbidity in case-control studies, it was not possible to combine various anxiety disorder groups for those studies. We therefore included only studies that specifically included any anxiety disorder as an outcome. Two of the five studies included odds ratios for any anxiety disorder other than panic disorder (5, 7), while three studies included odds ratios for any anxiety disorder including panic disorder (6, 21, 29). However, the odds ratios of the former and the latter studies did not differ from each other. All five studies exhibited moderate heterogeneity ($Q=7.55$, $df=4$, $p=0.11$; $I^2=47.04$, $tau^2=0.11$). Results suggested that a childhood diagnosis of separation anxiety disorder significantly increases the risk of any anxiety disorder (odds ratio=2.19; 95% CI=1.40–3.42). Because of the low number of studies, no sensitivity analyses or publication bias was assessed.

**FIGURE 1. Study Selection Procedure for a Meta-Analysis of the Association Between Childhood Separation Anxiety and Future Psychopathology**




Fourteen studies were included to test the association between separation anxiety disorder and major depressive disorder (Table 1, Figure 3). We identified significant moderate heterogeneity across studies (Q=31.71, df=13, p=0.003; $I^2$=59.01, $tau^2$=0.14). Results suggested that a childhood diagnosis of separation anxiety disorder significantly increases the risk for the development of major depressive disorder (odds ratio=1.36; 95% CI=1.01–1.83). However, there was evidence of some possible publication bias in a funnel plot. The Begg's test result was not significant, and the fail-safe N indicated that 26 unpublished null studies would be needed to remove the significance from the findings. The trim-and-fill method led to a nonsignificant corrected odds ratio of 1.06 (95% CI=0.78–1.45).

Five studies were included to test the association between separation anxiety disorder and substance use disorders (Table 1). These studies revealed good between-study homogeneity (Q=5.84, df=4, p=0.21; $I^2$=31.41, $tau^2$=0.09). Results suggested that a childhood diagnosis of separation anxiety disorder does not increase the risk of substance use disorders (odds ratio=1.27; 95% CI=0.80–2.03). Because of the low number of studies, no sensitivity analyses or publication bias was assessed.

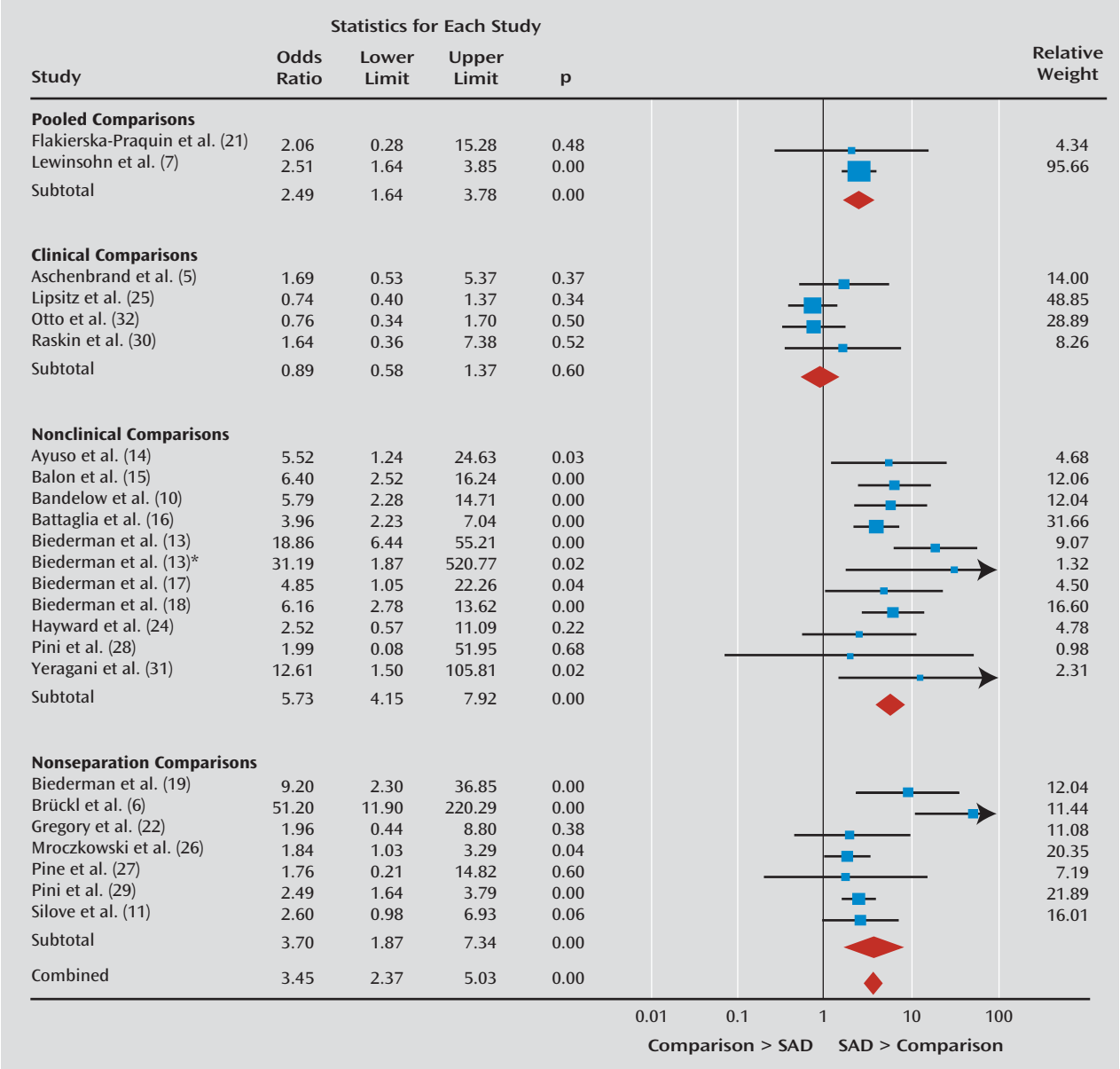
### *Sensitivity Analyses and Moderator Variables*

Because of the small number of studies investigating substance use disorders and any anxiety disorder as outcomes, sensitivity analyses were performed only for the association between separation anxiety disorder, panic disorder, and major depressive disorder (Table 2). Studies with nonclinical comparison subjects revealed that individuals with separation anxiety disorder were more likely to develop panic disorder ($p<0.001$) and major depression (p=0.02) than individuals in studies with clinical comparison subjects. Furthermore, population studies reported a significantly higher association with panic disorder (p=0.03) and major depression ($p<0.01$) than clinical studies. The nonclinical comparison subjects were similarly distributed between the two sample types.

No differences were found between the different types of studies (i.e., case-control, prospective, and retrospective cohort studies), diagnostic criteria, data collection methods, and differential symptom assessments. However, only five studies included both parents and participants as informants, while the remaining studies relied solely on participants. To evaluate the statistical stability of the results, the two studies with low STROBE scores (15, 31) were removed. The removal of these studies decreased the overall effect on the separation anxiety disorder-panic disorder link by only 6% and the link to major depression by 1.5%.

No meta-analyses were performed for the moderator variables described below because of the low number of studies including these moderator variables. However, we

**FIGURE 2. Meta-Analysis of Studies Investigating the Association Between Childhood Separation Anxiety Disorder (SAD) and Future Panic Disorder (Random Effects)[a]**




[a] The red diamonds indicate the combined effect sizes for studies with clinical, nonclinical, and non-separation anxiety disorder comparison groups, as well as the overall effect size of the meta-analysis (top to bottom). An asterisk indicates that the study included two separate separation anxiety disorder samples, and the data were treated as belonging to separate cohorts.

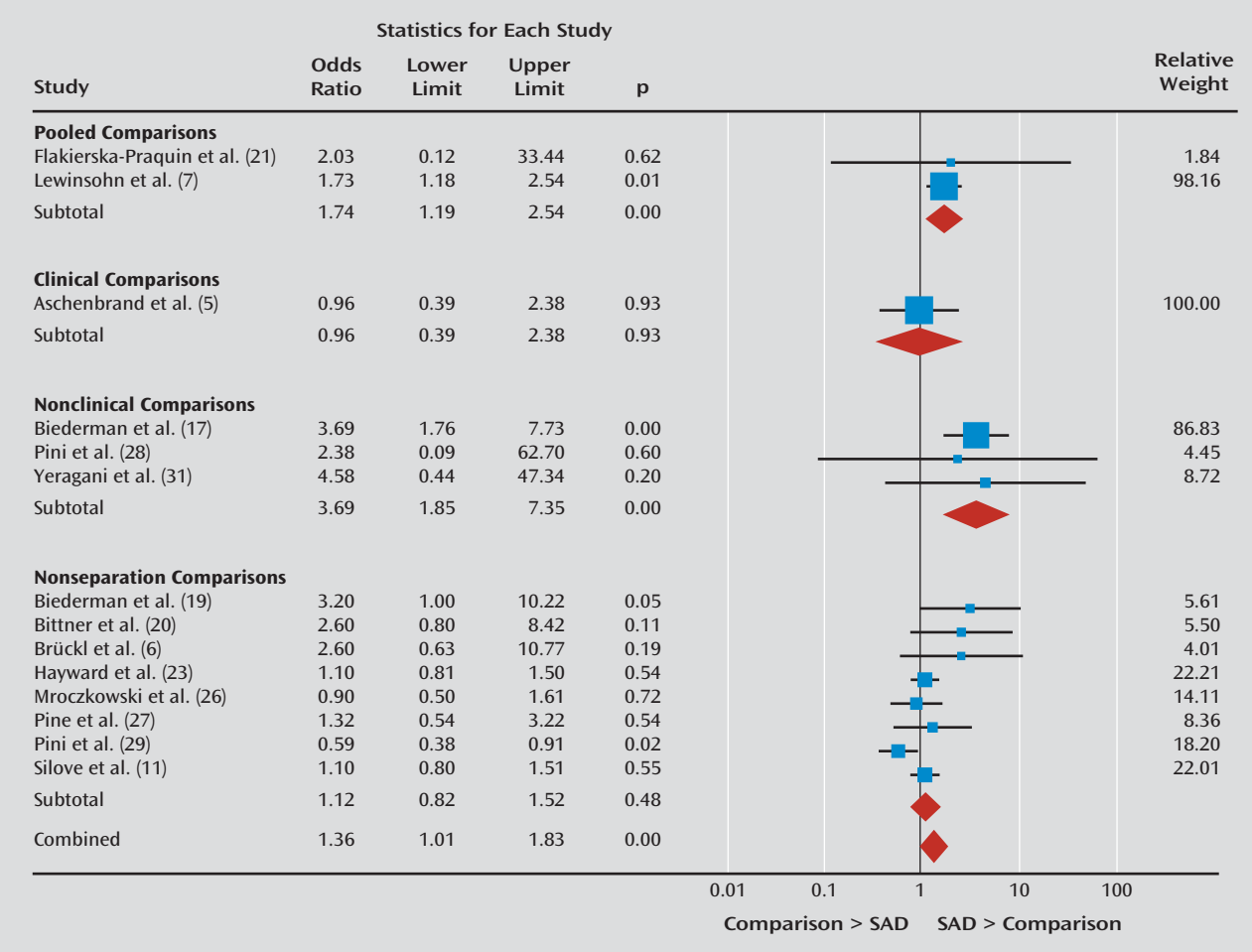
summarize the study results here because of their potential relevance to future psychopathology.

Aschenbrand et al. (5) observed no significant differences between individuals who were successfully treated as children and those who were not successfully treated as children with regard to the frequency of clinical panic disorder at long-term follow-up evaluation. No other studies compared these two groups.

Only two studies (15, 16) explicitly investigated the link between separation anxiety disorder and panic disorder separately for male and female subjects, yielding conflicting results, and only three studies (6, 7, 27) included sex as a covariable.

Four studies provided information about the age at onset of separation anxiety disorder (6, 7, 26, 29), but none examined the influence of this variable on the development of future psychopathology. One study examined parental psychopathology and found that the familial risk of panic disorder was similar for patients both with and without separation anxiety disorder (16). Only three studies (7, 20, 27) included comorbidities during childhood as a covariable in the analyses. None of the studies clearly

**FIGURE 3. Meta-Analysis of Studies Investigating the Association Between Childhood Separation Anxiety Disorder (SAD) and Future Major Depressive Disorder (Random Effects)[a]**




[a] The red diamonds indicate the combined effect sizes for studies with clinical, nonclinical, and non-separation anxiety disorder comparison groups, as well as the overall effect size of the meta-analysis (top to bottom).

controlled for comorbid adult anxiety disorders or investigate the influence of separation anxiety disorder severity level.

## Discussion

Our meta-analysis addressed the possible development of panic disorder, any anxiety disorder, major depressive disorder, and substance use disorders in children with separation anxiety disorder. The results indicate that a childhood diagnosis of separation anxiety disorder significantly increases the risk of panic disorder but also of other anxiety disorders, as indicated by the association with any anxiety disorder as well as the nonsignificant association with panic disorder when compared with other anxiety disorders. After adjusting for possible publication bias, no association with major depression or substance use disorders was found.

There was evidence of both clinical and statistical heterogeneity in the included studies. Studies using nonclinical comparison subjects as reference groups often obtained significantly higher overall odds ratios than studies using clinical comparison and non-separation anxiety disorder reference groups and demonstrated that children with separation anxiety disorder have almost six times the odds of developing panic disorder than children without separation anxiety disorder. However, the nonsignificant association of separation anxiety disorder with panic disorder in studies with clinical comparison subjects with various anxiety disorders indicates that children with separation anxiety disorder do not have a greater risk of developing panic disorder than of developing other anxiety disorders. Even in studies using comparable reference groups, odds ratios were substantially influenced by the amount of separation anxiety symptoms in the reference group. For example, the odds ratios for lifetime panic disorder in one study (6) was 51.2 when compared with a reference group with no separation anxiety symptoms, compared with an odds ratio of 28.2 when a subthreshold reference group with symptoms was used (T. Brückl, personal communication, March 2012). In summary, the lack of a clear standard with regard

to comparison groups makes it difficult to compare the effects of other possible moderators and their possible interactions. The use of a standardized comparison group would allow for more accurate statements regarding the described confounding effects of heterogeneity.

Two interesting nonfindings deserve emphasis. The association between separation anxiety disorder and major depressive disorder was nonsignificant after correcting for publication bias. Many reasons for publication bias and ways of dealing with it have been identified (43, 44). The trim-and-fill method imputes the number and most probable results of unpublished experiments to calculate an estimate of what the effect size would be in the absence of publication bias (41). However, even without eliminating publication bias, the association was borderline significant. In summary, the data suggest that the association with major depression is weak, but more studies, especially longitudinal studies, are necessary to clarify the issue. The nonfinding of substance use disorders might be due to the samples investigated. Studies differentiating between men and women might uncover possible sex-specific courses and outcomes, such as substance use disorders, which are commonly found in men but not women. Although unexpected, the nonsignificant effect owing to study type and informant type cannot be explained by the possible confounding effect of a strong coincidence with either nonclinical or clinical comparison subjects.

This study has several limitations. First, we included articles published in English and German but not in other languages. Second, methodological differences between the studies limit the generalizability of the results. Similarly, because of the low number of outcome studies investigating anxiety in general and substance use disorders, these results should be considered preliminary and require further investigation. Third, lifetime diagnoses based on retrospective report may be subject to recall bias (45), although we found no difference between retrospective and prospective studies. It may be that separation anxiety is less vulnerable to recall bias because of the prominent and observable nature of the disorder and the impairment it causes in daily life activities. Fourth, despite the fact that our data suggest an association between separation anxiety disorder and future pathology, they do not allow for comments about causality. Although it is possible that separation anxiety disorder is a causal agent for subsequent psychopathology, it is also possible that childhood separation anxiety disorder and adult anxiety and panic pathology may be caused by a common underlying vulnerability. Lewinsohn et al. (7) proposed that if the latter is true, then it might also be true that separation anxiety disorder is a marker for severity of the underlying vulnerability. The use of a quantitative measure of separation anxiety disorder severity, such as the Separation Anxiety Symptom Inventory (46), might help in shedding light on the issue. Finally, because only few studies addressed the issue of childhood or adult anxiety comorbidity, our results do not address the specificity of the association between separation anxiety disorder and the outcomes in adulthood. It remains unclear whether the individual studies were adequately powered to detect a difference between panic disorder and other anxiety disorders. This problem posed by a naturalistic study design and the consequent naturalistic problem of positive publication cannot be rectified by statistical adjustment procedures, such as the trim-and-fill method. It is further plausible that links between childhood separation anxiety disorder and future psychopathology are attributable, completely or partially, to the presence of the comorbid condition (e.g., adult separation anxiety disorder) (11). Studies specifically comparing children with other psychopathologies and healthy children with regard to future psychopathology and controlling for adult comorbidity would be necessary to correctly estimate the specific and nonspecific effect of separation anxiety disorder and whether it is a specific risk factor for panic disorder or a general risk factor for future anxiety disorders.

Despite these limitations, we found clear indications for an association between childhood separation anxiety disorder and future anxiety and panic disorders. These results support a developmental psychopathology conceptualization of anxiety disorders, a perspective that is expected to be strengthened in DSM-5 (47). Preliminary evidence suggests a developmental pathway that may start with exaggerated stranger anxiety in infancy (48). Understanding stranger anxiety as an age-dependent developmental task may provide new insight to our understanding of the etiology of separation anxiety disorder. Developmental cascades and developmental tasks are integrally related (49). Thus, the effects of maladaptive functioning in a domain early in development can become more pervasive or diffuse as that function affects the quality of the child's experience, amplifying its effect and ultimately becoming entrenched as a more significant disorder (50). Children suffering from separation anxiety disorder may be hindered early in life in developing skills to help cope with anxiety and strong emotions, both being important for healthy development.

The pathophysiological processes behind the developmental pathway in separation anxiety disorder remain unclear. However, the early onset of separation anxiety disorder suggests that genetic factors and shared environmental factors may be of particular importance (51). It can be assumed that shared environmental influences in the family decrease with age, having their greatest effects during childhood (52). Consistent with this assumption, twin studies have revealed no or only small shared environmental influences on anxiety disorders in adulthood (53–55) but a significant influence in children and adolescents (52, 56, 57), accounting for approximately 14%–21% of the variance (58, 59). Current psychophysiological

**TABLE 2. Selected Results of Publication Bias and Sensitivity Analyses**

| Variable | Outcome | | | |
|---|---|---|---|---|
| | Panic Disorder | df or 95% CI | Major Depressive Disorder | df or 95% CI |
| Publication bias | | | | |
| Funnel plot distribution | Symmetrical | | Asymmetrical | |
| Begg's adjusted-rank correlation (p value) | 0.45 | | 0.29 | |
| Classic fail-safe N | 782 | | 26 | |
| Comparison group | | | | |
| **Separation anxiety disorder compared with clinical control** | | | | |
| Heterogeneity[a] | 0.00 | 3 | 0 | 0 |
| Heterogeneity[b] | 0 | | 0 | |
| Odds ratio | 0.89 | 0.58–1.37 | 0.96 | 0.39–2.38 |
| **Separation anxiety disorder compared with non-separation anxiety disorder** | | | | |
| Heterogeneity[a] | 71.09** | 6 | 53.28* | 7 |
| Heterogeneity[b] | 0.51 | | 0.09 | |
| Odds ratio | 3.70 | 1.87–7.34 | 1.04 | 0.87–1.24 |
| **Separation anxiety disorder compared with nonclinical control** | | | | |
| Heterogeneity[a] | 0.00 | 10 | 0.00 | 2 |
| Heterogeneity[b] | 0 | | 0 | |
| Odds ratio | 5.73 | 4.15–7.92 | 3.69 | 1.85–7.35 |
| Odds ratio of nonclinical control compared with odds ratio of clinical control[c] | 6.78*** | | 2.32* | |
| Odds ratio of nonclinical control compared with odds ratio of non-separation anxiety disorder[c] | 1.13 | | 3.49*** | |
| Odds ratio of clinical control compared with odds ratio of non-separation anxiety disorder[c] | 3.45*** | | 0.17 | |
| Study type | | | | |
| **Case control** | | | | |
| Heterogeneity[a] | 74.80*** | 15 | 79.71*** | 4 |
| Heterogeneity[b] | 0.58 | | 0.63 | |
| Odds ratio | 3.36 | 2.09–5.41 | 1.43 | 0.59–3.45 |
| **Prospective** | | | | |
| Heterogeneity[a] | 68.50** | 6 | 12.57 | 7 |
| Heterogeneity[b] | 0.79 | | 0.02 | |
| Odds ratio | 4.08 | 1.75–9.52 | 1.43 | 1.11–1.86 |
| **Retrospective cohort** | | | | |
| Heterogeneity[a] | 0 | 0 | 0 | 0 |
| Heterogeneity[b] | 0 | | 0 | |
| Odds ratio | 2.60 | 0.98–6.93 | 1.10 | 0.80–1.51 |
| Odds ratio of case control compared with odds ratio of prospective[c] | 0.39 | | 0 | |
| Odds ratio of case control compared with odds ratio of retrospective[c] | 0.46 | | 0.55 | |
| Odds ratio of prospective compared with odds ratio of retrospective[c] | 0.68 | | 1.25 | |
| DSM criteria | | | | |
| **DSM-III/DSM-III-R** | | | | |
| Heterogeneity[a] | 69.61*** | 18 | 70.85*** | 8 |
| Heterogeneity[b] | 0.47 | | 0.24 | |
| Odds ratio | 3.18 | 2.11–4.81 | 1.45 | 0.94–2.23 |
| **DSM-IV/DSM-IV-TR** | | | | |
| Heterogeneity[a] | 82.65*** | 3 | 1.51 | 4 |
| Heterogeneity[b] | 1.58 | | 0 | |
| Odds ratio | 4.79 | 1.13–20.29 | 1.14 | 0.87–1.50 |
| Odds ratio of DSM-III compared with odds ratio of DSM-IV[c] | 0.53 | | 0.92 | |

*continued*

**TABLE 2. Selected Results of Publication Bias and Sensitivity Analyses (*continued*)**

| Variable | Outcome | | | |
|---|---|---|---|---|
| | Panic Disorder | df or 95% CI | Major Depressive Disorder | df or 95% CI |
| Sample type | | | | |
| **Clinical** | | | | |
| Heterogeneity[a] | 67.55*** | 13 | 3.14 | 5 |
| Heterogeneity[b] | 0.38 | | 0.01 | |
| Odds ratio | 2.40 | 1.53–3.76 | 0.77 | 0.55–1.07 |
| **Population** | | | | |
| Heterogeneity[a] | 68.22*** | 10 | 56.51* | 7 |
| Heterogeneity[b] | 0.65 | | 0.10 | |
| Odds ratio | 5.63 | 3.01–10.50 | 1.63 | 1.18–2.25 |
| Odds ratio of clinical compared with odds ratio of population[c] | 2.17* | | 3.17** | |

[a] The data represent the variance between studies as a proportion of the total variance; heterogeneity was tested using the $I^2$ statistic (low heterogeneity=25%; moderate heterogeneity=50%; high heterogeneity=75%). The p values refer to significance of the Q statistic (the $I^2$ statistic does not include a test of significance).
[b] Heterogeneity was tested using the $tau^2$ statistic, which estimates the between-study variance.
[c] The data represent the Z value of the test of interaction between different categories of studies (Altman and Bland [42]).
* p≤0.05. ** p≤0.01. *** p≤0.001.

studies postulating a unique genetic association between separation anxiety disorder and the development of adult-onset panic attacks have shown that children with separation anxiety disorder exhibit manifest $CO_2$ sensitivity (60–62). The study of further pathological mechanisms shared by both separation anxiety disorder and panic disorder patients is needed, such as the role of attachment (63). With regard to clinical care, the meta-analytical evidence of an association with future anxiety and panic disorder calls attention to the importance recognizing and treating separation anxiety disorder as early as possible. Treatment studies have shown that separation anxiety disorder can be successfully treated with disorder-specific parent-child cognitive-behavioral therapy (64).

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