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Behavioral Inhibition and Risk for Developing Social Anxiety Disorder: A Meta-Analytic Study

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Abstract

Objective—Behavioral inhibition (BI) has been associated with increased risk for developing social anxiety disorder (SAD); however, the degree of risk associated with BI has yet to be systematically examined and quantified. The goal of the present study was to quantify the association between childhood BI and risk for developing SAD.

Method—A comprehensive literature search was conducted to identify studies that assessed both BI and SAD. Meta-analyses were performed to estimate the odds ratio (OR) of the association between BI and SAD in children.

Results—Seven studies met inclusion criteria. BI was associated with a greater than sevenfold increase in risk for developing SAD (odds ratio = 7.59, $p < .00002$). This association remained significant even after considering study differences in temperament assessment, control group, parental risk, age at temperament assessment, and age at anxiety diagnosis.

Conclusions—Identifying early developmental risk factors is critical for preventing psychiatric illness. Given that 15% of all children show extreme BI, and that almost half of these inhibited children will eventually develop SAD, we propose that BI is one of the largest single risk factors for developing SAD.

Keywords

behavioral inhibition; social anxiety disorder; inhibited temperament; meta-analysis; social phobia

Anxiety disorders are the most common class of psychiatric disorders, with more than one in four American adults affected by an anxiety disorder at some point in their lifetime¹ and approximately one in three adolescents affected by the age of 18 years.² Of the anxiety disorders, specific phobias and social anxiety disorder (SAD; social phobia) are the most common, with adolescent lifetime prevalence rates of 22.1% and 9.1%, respectively.² Unlike triggers for specific phobias, which can be easy to avoid, social situations are ubiquitous and inherently difficult to avoid, which makes the burden associated with social anxiety especially great. SAD has a median onset during adolescence,¹ and is defined as a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar individuals, or to possible scrutiny by others. Individuals with SAD experience intense distress and anxiety when exposed to feared situations, and especially when anticipating the feared situation.³

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Children and adolescents with SAD experience significant distress and functional impairment at school and with peers⁴ and are at risk for a variety of subsequent problems.⁵ Adults with SAD are more likely to experience the following: lower education attainment,^{6,7} lower wages,⁷ unemployment,⁸ and fewer or poorer quality of relationships with family, romantic partners, and friends.⁹ SAD is also frequently comorbid with other psychiatric and physical health disorders. In all, 70% of adults with SAD will eventually develop a comorbid psychiatric disorder,¹⁰ such as major depression or substance abuse,¹¹ and adults with SAD are at increased risk for attempting suicide.¹² Individuals with SAD often fail to seek treatment,¹³ resulting in a long duration of suffering. Given the early onset and long course of SAD, it is critical to identify risk factors that precede the development of SAD, so that individuals with these risk factors can be targeted in prevention and early intervention efforts.

One of the most clearly established developmental risk factors for SAD is behavioral inhibition (BI). BI is the chronic tendency to respond to novel persons, places, and objects with wariness or avoidant behaviors.¹⁴ BI is a heritable trait¹⁵ that emerges early in life.¹⁴ An estimated 15% to 20% of young children are born with extreme BI. Although BI was initially identified in toddlers,¹⁶ the trait is also evident during late childhood,¹⁶ adolescence,¹⁷ and adulthood.¹⁸

The characteristics of BI are well defined: behaviorally inhibited children are typically shy, fearful, and cautious.^{16,19} Relative to uninhibited children, inhibited children have increased physiological signs of arousal at rest, including a higher and more stable heart rate, increased pupil dilation, and higher cortisol levels²⁰ (reviewed by Fox *et al.*¹⁹). Temperament-based differences in brain profiles have been reported, including differences in electroencephalography (EEG) asymmetry,²¹ functional differences in amygdala response to faces,²²⁻²⁷ and structural differences in the ventral prefrontal cortex.²⁸ Interestingly, SAD is also characterized by high and stable heart rate²⁹ and amygdala hyperresponsivity,³⁰⁻³² pointing to possible shared biological underpinnings.

Several prospective studies have demonstrated that behaviorally inhibited children are at substantially increased risk for developing SAD during childhood and adolescence (e.g., Schwartz *et al.*³³); however, the effect sizes have been variable across studies. In addition, because statistical significance does not necessarily imply clinical significance, it is important to quantify the size of the association between BI and SAD, to determine how prevention efforts may affect clinical outcomes. To date, the degree of risk that BI confers for SAD has yet to be systematically examined and quantified.

To quantify the association between BI and risk for developing SAD in children, we conducted a meta-analytic study. We hypothesized that childhood BI would be associated with significantly increased risk for SAD later in childhood or during adolescence.

METHOD

Systematic Literature Review and Study Selection

A comprehensive and systematic literature search was conducted to identify longitudinal studies of children with BI that also included an assessment of social anxiety. Studies were identified by searching multiple search engines (PubMed and PsycINFO). We used the following search terms: (behavioral inhibition, behavioural inhibition, or inhibited temperament) and (social anxiety or social phobia) and (longitudinal, prospective, or follow-up). In addition, references from each study and from review articles were examined to find additional studies.

Studies were included in the analysis if they met the following inclusion criteria: longitudinal study; measured BI; and measured social anxiety symptoms. Of the 85 studies reviewed, 12 studies met inclusion criteria. However, because some studies reported on multiple samples, the 12 studies represented 8 independent longitudinal cohorts. To ensure independence, we included only one study from each longitudinal cohort. Because rates of SAD increase with age,³⁴ we selected the latest age group from each cohort to provide sufficient opportunity to observe the outcome of interest; the final sample included seven studies. Six of the seven studies reported on independent cohorts; however, one study³³ combined two samples. Studies were excluded for the following reasons: review article or nonempirical study (n = 25); not a human sample (n = 1); not longitudinal (n = 12); did not report on BI (n = 5); did not report on social anxiety (n = 21); no control group (n = 4); BI not assessed during early childhood (n = 2); and duplicate report on a longitudinal sample (n = 8).

Study Variables

The following information was extracted from each study: recruitment method; temperament classification method; age(s) at temperament classification; social anxiety evaluation method; age at SAD evaluation; recruited for parental psychopathology (yes/no); percentage of male subjects; percentage of Caucasian subjects; number of subjects in each temperament group; and number of subjects within each temperament group with a SAD diagnosis. One study included the correlation between level of BI and social anxiety symptoms; for this study, the correlation between BI and social anxiety symptoms was extracted. Sample characteristics are provided in Table 1,^{33,35-41} and details about recruitment, BI assessment, and SAD assessment are provided in Table 2.^{33,35-40}

Temperament Classification—Most of the studies measured BI at a single time point in early childhood: Three studies^{33,35,38} classified BI using a behavioral assessment; three studies^{36-39,40} used maternal report of temperament; and one study³⁷ used a composite measure of behavioral assessment, child self-report, maternal report, and teacher report of temperament. Several studies assessed temperament at multiple time points; when possible, we used the earliest temperament assessment (baseline) to categorize subjects. Two studies^{36,37} assessed temperament at multiple time points and computed a composite temperament score that was used to categorize subjects as chronically inhibited or noninhibited. Behavioral assessment of inhibition is often considered to be the gold standard because it provides an objective measure of behavior. Although parent report often corresponds quite well with behavioral assessment^{39,42} and may provide a more comprehensive perspective on the child's behavior, the possibility of reporter bias exists. Therefore, we also examined risk separately for the studies that categorized children based on a behavioral assessment of inhibition.

Control Group—Five studies defined the control group as noninhibited children, i.e., those without extreme BI,^{35-38,40} and two studies^{33,39} defined controls as children who were extremely behaviorally uninhibited. Although both methods have merit, interpretation of risk differs based on the control group; that is, estimates of risk may be higher in comparison to the extremely uninhibited group. We included both types of control group in the analysis; however, we also examined risk separately for the studies that included a noninhibited control group.

Recruited for Parental Psychopathology—Five studies^{36,37,39,40} recruited children of parents from the general population and two studies^{35,38} specifically recruited children of parents with a psychiatric disorder. Because studies which specifically recruited the children of parents with psychiatric disorders may artificially inflate estimates of risk, we also

performed a separate risk estimate for children of parents recruited from the general population.

Age at Assessment—Initial assessments of BI were made between 14 months and 7 years of age. For studies with repeated assessments of BI, the final assessments were made between 7 and 14.5 years of age. Across the studies, SAD was assessed between 6 and 15 years of age. The interval between the most recent BI assessment and the age at SAD assessment also varied, ranging from 0 years (in studies that made the final BI assessment concurrently with the anxiety diagnosis) to 12 years. We examined the potential moderator effects of each of these variables.

Statistical Analysis

Meta-analytic methods were used to derive a weighted average of risk for SAD in behaviorally inhibited children relative to controls. Effect sizes were calculated as odds ratios (OR), the differential odds for anxiety diagnosis between the two temperament groups. The single correlation was converted to an odds ratio. A random effects analysis was performed using the Comprehensive Meta Analysis, Version 2.2.057 software package (Biostat, Englewood, NJ).

To examine the impact of each of the study variables on the effect size estimates, we performed additional analyses. Given the number of studies included in the meta-analysis, we were concerned about having statistical power to detect significant effects of the study variables based on a direct comparison of two groups of studies. Instead, for each study variable, we computed the OR for a subsample of studies selected based on the most conservative approach (e.g., only studies with a general control group). For the continuous variables, we performed meta-regressions. Meta-regression is a method used to examine the impact of potential moderator variables on study effect size using regression-based techniques. We performed the analysis using the Comprehensive Meta-Analysis software (unrestricted ML method).

Finally, we used three complementary methods to test for possible publication bias: “fail-safe” number of studies, funnel plot, and Egger test.⁴³

RESULTS

Risk for Social Anxiety Disorder

To quantify the association between BI and SAD, we computed a weighted average of the ORs across all studies (Figure 1).^{33,35-40} Behaviorally inhibited children had significantly increased the odds of developing SAD (OR = 7.59; 95% confidence interval [CI] = 3.03–19.00; $z = 4.33$; $p = .00002$). In all, 43% of BI children (107 of 246) met criteria for SAD, compared with 12% of noninhibited children (57 of 446). To assess the contribution of each study to the overall effect size, we also computed the OR after removing one study at a time. Regardless of which study was removed, BI children still had significantly increased odds of developing SAD (Figure S1, available online).

To determine the potential impact of the categorical study variables, we performed meta-analyses on subsamples of the studies defined by the presence/absence of each study variable. BI was still associated with increased risk for SAD within each subsample: behavioral assessment of inhibition (OR = 3.41; CI = 1.95–5.94; $z = 4.32$; $p = .00002$); noninhibited control group (OR = 6.42; CI = 2.05–20.10; $z = 3.20$; $p = .002$); and not recruited for parental psychopathology (OR = 10.52; CI = 3.96–27.95; $z = 4.72$; $p = .000002$). For the continuous study variables, we performed meta-regressions. The ORs

representing the relationship between BI and SAD were not related to age at BI assessment (slope = 0.00; CI = -0.21–0.21; $z = 0.009$; $p = .99$) or age at anxiety assessment (slope = -0.16; CI = -0.38–0.05; $z = -1.50$; $p = .14$). However, the interval between assessment of BI and SAD was negatively correlated with the rate of SAD (slope = -0.16; CI = -0.32–-0.002; $z = -1.99$; $p = .05$).

Three methods were used to assess for publication bias. The “fail-safe” number was 164, reflecting that 164 unpublished studies with a null effect would be needed to reduce the current significant findings to a negligible level. Also, there was no evidence for systematic heterogeneity based on the funnel plot (Figure S2, available online) or Egger test ($B_0 = -0.54$; CI = -7.09–6.02; one-tailed $p = .42$). Thus, all three metrics suggest that the study results are not likely to be the result of publication bias.

DISCUSSION

Behavioral inhibition (BI) was associated with a significantly increased risk for developing social anxiety disorder (SAD). Based on the primary study analysis, risk was increased sevenfold for BI children, and even with the most conservative estimate, risk was increased more than threefold. Given that 15% to 20% of children are born with extreme BI,¹⁶ and that more than 40% of behaviorally inhibited children will eventually develop SAD, we propose that childhood BI is a principal predictor of SAD.

A key question is whether BI is the childhood manifestation of SAD. Questions about distinctions between BI (and related concepts, such as shyness) and SAD are a source of debate.^{44–48} BI and SAD share multiple common features, including behavioral characteristics, biological characteristics, and prevalence rates. For example, social inhibition is a central dimension of SAD⁴⁹ and is a major component in the assessment of BI. Both BI and SAD are characterized by high and stable heart rate^{29,50,51} and amygdala hyperresponsivity.^{26,27,30–32} Prevalence rates of SAD in adolescence (~11%) are very similar to the 15% estimate of extreme BI in the population and within samples, and the degree of BI and social anxiety symptom severity are highly correlated.^{18,52} However, not all BI children develop SAD. In the present study, 43% of the behaviorally inhibited children developed SAD, similar to a study of 2,200 individuals,⁵³ which found that 48% of highly shy (>90th percentile) young adults had SAD, compared with 18% of normatively shy (40th–60th percentile) young adults. These findings suggest multifinality—the principle that the same development starting point (e.g., extreme BI) can have divergent developmental pathways. SAD may be distinguished from BI by social-evaluative concerns and functional impairment, which are part of SAD but not BI. Thus, we propose that childhood BI forms a core component of later SAD, but that SAD also includes other components that may arise later in development, such as social-evaluative concerns and lack of coping skills, which contribute to functional impairment.

Although most studies included in this meta-analysis classified BI as an extreme temperament category, there is debate about whether BI should be conceptualized as a category or a continuum.⁵⁴ Kagan and colleagues have used a categorical approach based on an early finding suggesting that a categorical approach represented the data better than a continuum,²⁰ which was later confirmed by an empirical test of the data structure.⁵⁵ However, longitudinal studies that used continuous measures of BI and social anxiety, including that of Muris *et al.*,⁴⁰ have demonstrated that parent report of childhood BI significantly predicted degree of social anxiety symptoms both at 1 year ($r = 0.71$) and 2 years ($r = 0.72$) later. The similarity in findings suggests that both categorical and continuous (dimensional) approaches can be used to measure the relationship between childhood BI and later social anxiety. As such, we propose that an “and” approach to

categories and continua may be more fruitful than the current debate of category “or” continuum.

Multiple factors, such as assessment method, control group, time between assessments, and parental psychopathology, may have contributed to the overall estimate of risk for SAD. We examined the possible effects of each of these factors by performing analyses within each subgroup. BI was still associated with SAD in each of the subgroup analyses, although, as expected, the ORs were somewhat reduced for the analyses restricted to behavioral assessment of inhibition or noninhibited control group analyses. The age variables, namely, age at BI assessment and age at anxiety assessment, also had negligible impacts on study effect sizes. In contrast, the time between assessment of BI and SAD was associated with effect size, with shorter time periods associated with larger effect sizes. This finding mostly reflects two large studies with 2-year measurement intervals and large effect sizes. Importantly, the studies with the longest intervals between assessments of BI and SAD still show a significant association. For parental psychopathology, effect sizes were similar between the studies that specifically recruited children based on parental psychopathology compared with those that did not. However, it is important to note that parental rates of psychopathology are typically elevated for behaviorally inhibited children,⁵⁶ consistent with the strong genetic contribution to both BI and SAD. Therefore, it is likely that parents recruited from the general population also had some psychopathology. Although it is not possible to examine relative contributions of early BI and parental psychopathology in this meta-analysis, the study by Hudson *et al.* found that BI and parental psychopathology had an additive effect on later SAD.³⁹ Future studies should examine the contributions of BI and parental psychopathology to SAD to understand the unique risk associated with each, as this could have important implications for prevention and treatment.

The present study had several limitations. First, the meta-analysis was based on a small number of studies, which may affect the reliability or precision of the estimated odds ratios; however, the odds ratio remained fairly stable across multiple additional analyses, suggesting that the estimate is reliable. Second, the study samples had little racial or ethnic variability, limiting the generalizability of this study to Caucasian populations. Third, the rate of SAD in the control group was slightly greater than the 9% lifetime rate seen in adolescents (National Comorbidity Survey Replication—Adolescent Supplement [NCS-A] study²); however, there was considerable variance across studies, suggesting effects of demographic and other study variables on the rate. Fourth, only SAD was examined. It will be important for future studies to examine specificity of risk, particularly for other anxiety disorders and depression. Finally, unpublished data were not included. Although the inclusion of null findings from unpublished datasets might reduce the estimates of risk, the fail-safe estimate suggests that the risk would still be significant.

In conclusion, identifying childhood risk factors is critical for preventing psychiatric illness. We propose that BI is one of the strongest and most readily identifiable developmental markers of risk for SAD, given that BI is evident early in development, is relatively stable over time, and is easily observable during childhood. Prevention efforts can both reduce the prevalence of anxiety disorders and reduce the risk of developing comorbid disorders such as depression and substance dependence. Preliminary evidence for the promise of prevention comes from a recent study by Rapee *et al.*,⁵⁷ who demonstrated that a brief protocol targeting behaviors in parents of inhibited preschool children significantly reduced anxiety symptoms and diagnoses, but not BI, 3 years later. Therefore, significant resources should be devoted toward the development of brief and accessible temperament screening tools and toward the development of public health prevention efforts so as to preempt the development of SAD in behaviorally inhibited children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2005; 62:593–602. [PubMed: 15939837]
2. Merikangas KR, He JP, Burstein M, et al. Lifetime prevalence of mental disorders in U.S. adolescents: results from the National Comorbidity Survey Replication—Adolescent Supplement (NCS-A). *J Am Acad Child Adolesc Psychiatry*. 2010; 49:980–989. [PubMed: 20855043]
3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4. Arlington, VA: American Psychiatric Publishing; 2000.
4. La Greca AM, Lopez N. Social anxiety among adolescents: linkages with peer relations and friendships. *J Abnorm Child Psychol*. 1998; 26:83–94. [PubMed: 9634131]
5. Bittner A, Egger HL, Erkanli A, Costello EJ, Foley DL, Angold A. What do childhood anxiety disorders predict? *J Child Psychol Psychiatry*. 2007; 48:1174–1183. [PubMed: 18093022]
6. Van Ameringen M, Mancini C, Farrow P. The impact of anxiety disorders on educational achievement. *J Anxiety Disord*. 2003; 17:561–571. [PubMed: 12941366]
7. Katzelnick DJ, Kobak KA, DeLeire T, et al. Impact of generalized social anxiety disorder in managed care. *Am J Psychiatry*. 2001; 158:1999–2007. [PubMed: 11729016]
8. Moitra E, Beard C, Weisberg RB, Keller MB. Occupational impairment and social anxiety disorder in a sample of primary care patients. *J Affect Disord*. 2011; 130:209–212. [PubMed: 20934220]
9. Stein MB, Kean YM. Disability and quality of life in social phobia: epidemiologic findings. *Am J Psychiatry*. 2000; 157:1606–1613. [PubMed: 11007714]
10. Schneier FR, Johnson J, Hornig CD, Liebowitz MR, Weissman MM. Social phobia—comorbidity and morbidity in an epidemiologic sample. *Arch Gen Psychiatry*. 1992; 49:282–288. [PubMed: 1558462]
11. Kessler RC, Chiu WT, Demler O, Walters EE. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey-Replication (NCS-R). *Arch Gen Psychiatry*. 2005; 62:617–627. [PubMed: 15939839]
12. Cogle JR, Keough ME, Riccardi CJ, Sachs-Ericsson N. Anxiety disorders and suicidality in the National Comorbidity Survey-Replication. *J Psychiatr Res*. 2009; 43:825–829. [PubMed: 19147159]
13. Olfson M, Guardino M, Struening E, Schneier FR, Hellman F, Klein DF. Barriers to the treatment of social anxiety. *Am J Psychiatry*. 2000; 157:521–527. [PubMed: 10739410]
14. Kagan J, Reznick JS, Snidman N, Gibbons J, Johnson MO. Childhood derivatives of inhibition and lack of inhibition to the unfamiliar. *Child Dev*. 1988; 59:1580–1589. [PubMed: 3208569]
15. Robinson JL, Reznick JS, Kagan J, Corley R. The heritability of inhibited and uninhibited behavior—a twin study. *Dev Psychol*. 1992; 28:1030–1037.
16. Kagan J, Snidman N. Early childhood predictors of adult anxiety disorders. *Biol Psychiatry*. 1999; 46:1536–1541. [PubMed: 10599481]
17. Muris P, Merckelbach H, Schmidt H, Gadet B, Bogie N. Anxiety and depression as correlates of self-reported behavioural inhibition in normal adolescents. *Behav Res Ther*. 2001; 39:1051–1061. [PubMed: 11520011]

18. Reznick JS, Hegeman IM, Kaufman ER, Woods SW, Jacobs M. Retrospective and concurrent self-report of behavioral-inhibition and their relation to adult mental-health. *Dev Psychopathol.* 1992; 4:301–321.
19. Fox NA, Henderson HA, Marshall PJ, Nichols KE, Ghera MM. Behavioral inhibition: linking biology and behavior within a developmental framework. *Annu Rev Psychol.* 2005; 56:235–262. [PubMed: 15709935]
20. Kagan J, Reznick JS, Snidman N. The physiology and psychology of behavioral-inhibition in children. *Child Dev.* 1987; 58:1459–1473. [PubMed: 3691195]
21. Davidson RJ, Fox NA. Frontal brain asymmetry predicts infants' response to maternal separation. *J Abnorm Psychol.* 1989; 98:127–131. [PubMed: 2708653]
22. Blackford JU, Avery SN, Shelton RC, Zald DH. Amygdala temporal dynamics: temperamental differences in the timing of amygdala response to familiar and novel faces. *BMC Neurosci.* 2009; 10:145. [PubMed: 20003287]
23. Schwartz CE, Wright CI, Shin LM, Kagan J, Rauch SL. Inhibited and uninhibited infants “grown up”: adult amygdalar response to novelty. *Science.* 2003; 300:1952–1953. [PubMed: 12817151]
24. Perez-Edgar K, Roberson-Nay R, Hardin MG, et al. Attention alters neural responses to evocative faces in behaviorally inhibited adolescents. *Neuroimage.* 2007; 35:1538–1546. [PubMed: 17376704]
25. Clauss JA, Cowan R, Blackford JU. Expectation and temperament moderate amygdala and dorsal anterior cingulate cortex responses to fear faces. *Cogn Affect Behav Neurosci.* 2011; 11:13–21. [PubMed: 21264642]
26. Blackford JU, Avery SN, Cowan RL, Shelton RC, Zald DH. Sustained amygdala response to both novel and newly familiar faces characterizes inhibited temperament. *Soc Cogn Affect Neurosci.* 2010; 6:621–629. [PubMed: 20660534]
27. Schwartz CE, Kunwar PS, Greve DN, Kagan J, Snidman NC, Bloch RB. A phenotype of early infancy predicts reactivity of the amygdala in male adults. *Mol Psychiatry.* 2011 published online September 6, 2011. 10.1038/mp.2011.96
28. Schwartz CE, Kunwar PS, Greve DN, et al. Structural differences in adult orbital and ventromedial prefrontal cortex predicted by infant temperament at 4 months of age. *Arch Gen Psychiatry.* 2010; 67:78–84. [PubMed: 20048225]
29. Beidel DC, Turner SM, Dancu CV. Physiological, cognitive and behavioral aspects of social anxiety. *Behav Res Ther.* 1985; 23:109–117. [PubMed: 4004691]
30. Guyer AE, Lau JYF, McClure-Tone EB, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch Gen Psychiatry.* 2008; 65:1303–1312. [PubMed: 18981342]
31. Etkin A, Wager TD. Functional neuroimaging of anxiety: a meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry.* 2007; 164:1476–1488. [PubMed: 17898336]
32. Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME. Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry.* 2006; 59:424–429. [PubMed: 16256956]
33. Schwartz CE, Snidman N, Kagan J. Adolescent social anxiety as an outcome of inhibited temperament in childhood. *J Am Acad Child Adolesc Psychiatry.* 1999; 38:1008–1015. [PubMed: 10434493]
34. Burstein M, Ameli-Grillon L, Merikangas KR. Shyness versus social phobia in US youth. *Pediatrics.* 2011; 128:917–925. [PubMed: 22007009]
35. Biederman J, Rosenbaum JF, Bolducmurphy EA, et al. A 3-year follow-up of children with and without behavioral inhibition. *J Am Acad Child Adolesc Psychiatry.* 1993; 32:814–821. [PubMed: 8340303]
36. Chronis-Tuscano A, Degnan KA, Pine DS, et al. Stable early maternal report of behavioral inhibition predicts lifetime social anxiety disorder in adolescence. *J Am Acad Child Adolesc Psychiatry.* 2009; 48:928–935. [PubMed: 19625982]

37. Essex MJ, Klein MH, Slattery MJ, Goldsmith HH, Kalin NH. Early risk factors and developmental pathways to chronic high inhibition and social anxiety disorder in adolescence. *Am J Psychiatry*. 2010; 167:40–46. [PubMed: 19917594]
38. Hirshfeld-Becker DR, Biederman J, Henin A, et al. Behavioral inhibition in preschool children at risk is a specific predictor of middle childhood social anxiety: a five-year follow-up. *J Dev Behav Pediatr*. 2007; 28:225–233. [PubMed: 17565290]
39. Hudson JL, Dodd HF, Lyneham HJ, Bovopoulos N. Temperament and family environment in the development of anxiety disorder: two-year follow-up. *J Am Acad Child Adolesc Psychiatry*. 2011; 50:1255–1264. [PubMed: 22115146]
40. Muris P, van Brakel A, Arntz A, Schouten E. Behavioral inhibition as a risk factor for the development of childhood anxiety disorders: a longitudinal study. *J Child Fam Stud*. 2011; 20:157–170. [PubMed: 21475710]
41. Rosenbaum JF, Biederman J, Gersten M, et al. Behavioral inhibition in children of parents with panic disorder and agoraphobia. *Arch Gen Psychiatry*. 1988; 45:463–470. [PubMed: 3358645]
42. Bishop G, Spence SH, McDonald C. Can parents and teachers provide a reliable and valid report of behavioral inhibition? *Child Dev*. 2003; 74:1899–1917. [PubMed: 14669903]
43. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Br Med J*. 1997:315.
44. Gazelle H, Rubin KH. Social anxiety in childhood: bridging developmental and clinical perspectives. *New Direct Child Adolesc Dev*. 2010; 127:1–120.
45. Stein DJ, Ono Y, Tajima O, Muller JE. The social anxiety disorder spectrum. *J Clin Psychiatry*. 2004; 65:27–33. [PubMed: 15554786]
46. Rapee RM, Spence SH. The etiology of social phobia: empirical evidence and an initial model. *Clin Psychol Rev*. 2004; 24:737–767. [PubMed: 15501555]
47. Stein MB. How shy is too shy? *Lancet*. 1996; 347:1131–1132. [PubMed: 8609744]
48. Lane, C. *Shyness: How Normal Behavior Became a Sickness*. New Haven, CT: Yale University Press; 2007.
49. Schneider FR, Blanco C, Antia SX, Liebowitz MR. The social anxiety spectrum. *Psychiatr Clin N Am*. 2002; 25:757–774.
50. Schmidt LA, Fox NA, Schulkin J, Gold PW. Behavioral and psychophysiological correlates of self-presentation in temperamentally shy children. *Dev Psychobiol*. 1999; 35:119–135. [PubMed: 10461126]
51. Kagan J, Reznick JS, Clarke C, Snidman N, Garcia-Coll C. Behavioral inhibition to the unfamiliar. *Child Dev*. 1984; 55:2212–2225.
52. Gladstone G, Parker G. Measuring a behaviorally inhibited temperament style: development and initial validation of new self-report measures. *Psychiatr Res*. 2005; 135:133–143.
53. Chavira DA, Stein MB, Malcarne VL. Scrutinizing the relationship between shyness and social phobia. *J Anxiety Disord*. 2002; 16:585–598. [PubMed: 12405519]
54. Kagan, J.; Snidman, N. *The Long Shadow of Temperament*. Cambridge, MA: Harvard University Press; 2004.
55. Woodward SA, Lenzenweger MF, Kagan J, Snidman N, Arcus D. Taxonic structure of infant reactivity: evidence from a taxometric perspective. *Psychol Sci*. 2000; 11:296–301. [PubMed: 11273388]
56. Rosenbaum JF, Biederman J, Hirshfeld DR, et al. Further evidence of an association between behavioral inhibition and anxiety disorders: results from a family study of children from a non-clinical sample. *J Psychiatr Res*. 1991; 25:49–65. [PubMed: 2027095]
57. Rapee RM, Kennedy SJ, Ingram M, Edwards SL, Sweeney L. Altering the trajectory of anxiety in at-risk young children. *Am J Psychiatry*. 2010; 167:1518–1525. [PubMed: 20810472]

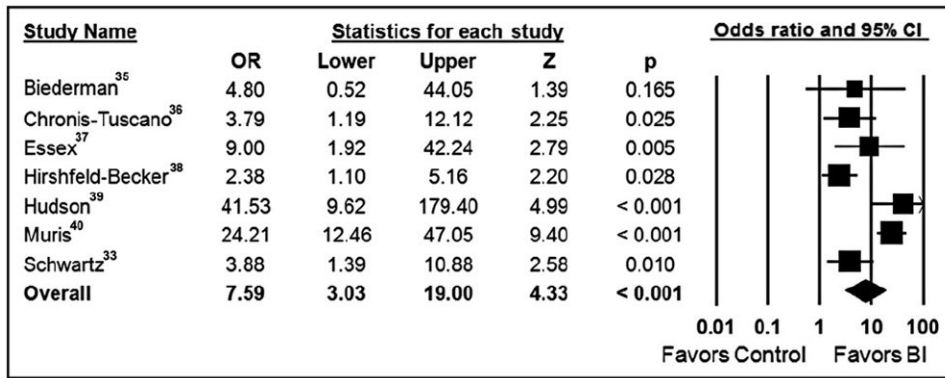


FIGURE 1. Childhood behavioral inhibition (BI) is associated with significantly increased risk for developing social anxiety disorder (SAD). Note: For each study, the odds ratio (OR), lower and upper 95% confidence intervals, z statistic, and *p* value are presented. The overall meta-analyses values are presented at the bottom, and the effect sizes for each study and the overall analysis are presented in the forest plot at the far right.

TABLE 1

Sample Characteristics, by Study

Citation (First Author)	Gender (% male)	Ethnicity (% Caucasian)	BI Subjects (n)	Control Subjects (n)	BI Subjects with SAD (%)	Control Subjects with SAD (%)	Correlation Between Level of BI and SAD Symptoms (r)	Age at Temperament Classification	Age at Anxiety Diagnosis		Mean Time Between Temperament Assessment and Diagnosis (y)
									y	mean	
Biederman ³⁵	53	100	26	17	23.1	5.9		2-7 y (X = 4.3) ^b	5-10	6.4	2.1
Chronis-Tuscano ³⁶	48	"Primarily white"	15	107	40.0	15.0		14 mo, 2, 4, and 7 y	14-16	15.1	8-14
Essex ³⁷	47	89	10	50	50.0	10.0		4.5 y, grades 1, 3, 5, 7, 9	Grade 9	14.5 ^c	0-10
Hirshfeld-Becker ³⁸	59	88	67	148	22.4	10.8		21 mo-6 y (X = 4.2)	6-15	9.6	5.4
Hudson ³⁹	50	84 Australian or European	87	91 ^d	48.3	2.2		4 y		6.0	2
Muris ⁴⁰	44	97	88	118			.66	6.6 y		8.6 ^d	2
Schwartz ³³	46	100	41	33 ^d	80.5	52.5		21 or 31 mo		13.0	12
Overall	50	91	343	534	43	12		4.1-5.6 y		10.0	4-6

Note: BI = behavioral inhibition; NA = not available; SAD = social anxiety disorder; x = mean; y = years.

^aAll controls were behaviorally uninhibited.

^bAge obtained from Rosenbaum et al.⁴¹

^cAge estimated from grade level included (study did not include average age at anxiety diagnosis).

^dAge estimated from age at initial assessment and time since initial assessment.

TABLE 2

Study Assessment and Recruitment Methods

Citation (First Author)	Recruitment Method	Temperament Classification Method	Anxiety Diagnosis Method	Recruited for Parental Psychopathology
Biederman (Massachusetts General Hospital [MGH] Sample) ³⁵	Caucasian children of outpatient parents with panic disorder and/or agoraphobia and comparison children of parents without those disorders who were treated at the Department of Psychiatry at MGH were recruited.	Children were categorized as inhibited or not inhibited based on behavior with unfamiliar adults and during cognitive tasks. Inhibited children had longer latencies to interact with adults, were more likely to stop playing when the unfamiliar adult was present, and vocalized less during cognitive tasks.	Maternal interview with the Diagnostic Interview for Children and Adolescents—Parent Version and the modules for social phobia, simple phobia, panic disorder, and agoraphobia from Kiddie–Schedule for Affective Disorder for School-Age Children (K-SADS)	Yes
Chronis-Tuscano ³⁶	Parents of young infants were contacted by mail. Infants were initially screened at 4 months (n = 443) to assess reactions to novelty and 178 children across a range of temperaments were selected.	A composite score of maternal report of behavioral inhibition was calculated based a latent class analysis of the Social Fearfulness subscale of the Toddler Behavior Assessment Questionnaire (ages 14 months and 2 years) and the Shyness/Sociability subscale of the Colorado Children’s Temperament Inventory (ages 4 and 7 years).	Interview with parent and child using the K-SADS present and lifetime (K-SADS-PL), supplemented with questions from the Anxiety Disorders Interview Schedule for Children	No
Essex ³⁷	A sample of 570 second-trimester pregnant women more than 18 years of age, who were living with the infant’s biological father, were recruited from prenatal clinics.	<i>Early Inhibition:</i> A composite score was calculated based on principal components analysis of ratings (5-point scale) of global shyness, initiative with tasks, exploration of unfamiliar objects, and social engagement during a home visit. <i>Longitudinal Inhibition:</i> Category based on sum of scores (1 = lowest 25%, 2 = middle 50%, 3 = highest 25%) at grades 1, 3, 5, 7, and 9. Scores at each age were based on a principal components analysis of mother and teacher reports on the social inhibition subscale of the MacArthur Health and Behavior Questionnaire and child report on the social subscale of the Berkeley Puppet Interview. Final categories summarizing longitudinal inhibition were chronic low, low-middle, middle, middle-high, and chronic high inhibition.	Interview with parent and children using the KSADS-PL	No
Hirshfeld-Becker ³⁸	Children of parents with panic disorder and/or depression plus comparison children of parents without either disorder were recruited.	Temperament was based on behavioral responses to unfamiliar toys and adults in a laboratory setting. Categorization of inhibited was based on meeting two or more of the following: bottom 20% on vocalizations/comments/smiles; global rating of behavioral inhibition, or top 20% on a composite score based on principal factor analysis of all assessed behaviors. Children who did not meet one of the criteria for behavioral inhibition were classified as noninhibited.	Interview with mothers and children (12 or older) using the KSADS Epidemiological version	Yes
Hudson ³⁹	Parents were recruited through local preschools and via an advertisement in a free parenting magazine.	Behavioral inhibition was based on maternal report on the Approach subscale of the Short Temperament Scale for Children. Children scoring 1 standard deviation above or below the normative mean on the Approach subscale were classified as inhibited or uninhibited, respectively. These categories corresponded well (74%) to categories based on a behavioral assessment of responses to novel persons and stimuli, and statistical findings were similar.	Maternal interview using the Anxiety Disorders Interview Schedule for the DSM-IV Parent Version plus a clinical severity rating of 4 or greater	No
Muris ⁴⁰	Parents of children in local primary schools were solicited via mail.	Parents completed the Behavioral Inhibition Instrument (BII); a matched sample of BI children and control children were solicited from the overall sample. Children were considered inhibited if their score on the Behavioral Inhibition Scale (BIS) part of the BII was 22	Parents completed the Screen for Child Anxiety Related Emotional Disorders. Social anxiety disorder	No

Citation (First Author)	Recruitment Method	Temperament Classification Method	Anxiety Diagnosis Method	Recruited for Parental Psychopathology
Schwartz ³³	<p>Cohort 1: Selected from a group of 305 white children whose mothers described them as tending to be either inhibited or uninhibited.</p> <p>Cohort 2: Children were recruited from a volunteer subject from a larger group of 175 children at 31 months of age.</p>	<p>or greater (out of 32) or when parents chose the description of high behavioral inhibition on the inhibition categories.</p> <p><i>Cohort 1:</i> Behavioral inhibition was based on reactions to multiple moderately unfamiliar events were rated. Inhibited toddlers had 9 or more inhibited behaviors, and uninhibited toddlers had fewer than 3 inhibited behaviors.</p> <p><i>Cohort 2:</i> Behavioral inhibition was based on reactions to unfamiliar peers, adults, and events. Children were classified based on time spent proximal to the mother, latency to approach novel toys or persons. To be rated as inhibited or uninhibited, the child had to meet one criterion for time spent proximal to the mother and two of five criteria for latency to approach novel stimuli.</p>	<p>symptoms were assessed using the social anxiety disorder subscale.</p> <p>Adolescents were interviewed using several modules adapted from the Diagnostic Interview Schedule for Children</p>	No