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Oppositional Defiant Disorder: Meta-Analysis, Predictive Validity, and Mediation of Psychopathology Outcomes

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Oppositional Defiant Disorder:

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A dissertation submitted in partial satisfaction

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in Psychology

by

Kristen Lea Jezior

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ABSTRACT OF THE DISSERTATION

Oppositional Defiant Disorder:

Meta-Analysis, Predictive Validity, and Mediation of Psychopathology Outcomes

by

Kristen Lea Jezior

Doctor of Philosophy in Psychology

University of California, Los Angeles, 2018

Professor Steve S. Lee, Chair

Background: Oppositional defiant disorder (ODD) is a youth disorder characterized by developmentally atypical defiance, hostility, disobedience, and angry/irritable mood. ODD predicts diverse negative outcomes such as psychopathology, antisocial behavior (ASB), and impairment. This dissertation included three studies unified around testing youth ODD's prediction of future psychopathology and impairment, and identifying potential mechanisms underlying the development from ODD dimensions to ASB.

Study I: The aim of Study I was to estimate the prevalence of psychopathology outcomes among youth with prior ODD. Meta-analyses included 1137 participants across 17 studies. Among youth with ODD, 13% developed a subsequent anxiety disorder, 5% a depressive disorder, and 21% conduct disorder (CD)/antisocial personality disorder. Meta-regression identified that older youth at baseline had a higher prevalence of later depression. More prevalent psychotropic

medication use at baseline was associated with elevated rates of later depression and CD/antisocial personality disorder.

Study II: The aim of Study II was to test the predictive validity of irritable and oppositional ODD dimensions with respect to multiple psychopathology outcomes (i.e., anxiety, depression, CD), ASB, psychopathic traits, substance use, and functional impairment, with control of baseline negative emotionality, attention-deficit/hyperactivity disorder (ADHD), and psychopathology/impairment in each model by employing generalized linear models. Oppositional ODD inversely predicted parent-rated Total Anxiety and Depression, several parent-rated anxiety subscales, and youth-rated Total Anxiety and Depression. Irritable ODD positively predicted parent-rated obsessions and compulsions. Negative emotionality did not significantly predict any outcomes. Notably, baseline measures of ADHD and psychopathology/impairment predicted the majority of outcomes.

Study III: The aim of Study III was to test reactive and proactive aggression as simultaneous, temporally-ordered mediators of predictions of multi-informant rated ASB from irritable and oppositional ODD symptoms in a prospective sample. Individual differences in Wave 2 reactive aggression significantly mediated the prediction of Wave 3 youth-rated ASB from baseline irritable ODD. Wave 1 irritable ODD positively predicted Wave 2 reactive aggression in all prediction models.

Conclusion: The theoretical and clinical implications of the results from Studies I – III were discussed, as well as future directions for research.

Keywords: Oppositional defiant disorder (ODD); Meta-analysis; Prospective psychopathology; Irritability; Oppositionality; Predictive validity; Multiple mediation

The dissertation of Kristen Lea Jezior is approved.

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Introduction

Oppositional defiant disorder (ODD) is characterized by developmentally aberrant levels of defiance, hostility, disobedience, as well as angry and irritable mood. ODD is among the earliest predictors of later antisocial behavior (ASB) and robustly predicts early-onset conduct disorder (CD), even with control of co-occurring attention-deficit/hyperactivity disorder (ADHD) (Burke, Waldman, & Lahey, 2010). Notably, early-onset CD predicts diverse negative outcomes including antisocial personality disorder, depression, adult criminal behavior, incarceration, substance abuse, risk for injury, and early mortality (Lahey, Loeber, Burke, & Applegate, 2005; Loeber & Farrington, 1998). Beyond predictions of psychopathology, ODD symptoms often portend enduring functional impairment such as academic failure, psychosocial maladjustment, family conflict, and unemployment (Burke, Rowe, & Boylan, 2014; Burke, Waldman, et al., 2010; Burt, Krueger, McGue, & Iacono, 2003; Knapp, King, Healey, & Thomas, 2011; Pardini & Fite, 2010). Moreover, youth ASB is among the most economically costly and socially burdensome mental health problems in North America (Welsh et al., 2008). Given the serious clinical and public health problems associated with ODD, improved understanding of its naturalistic course, dimensions, and the processes underlying its predictions of negative outcomes is a significant priority.

Historically, ODD was conceptualized unidimensionally (Bauermeister, 1992; Burns, Boe, Walsh, Sommers-Flanagan, & Teegarden, 2001; Burns & Patterson, 2000; Pelham, Gnagy, Greenslade, & Milich, 1992). However, efforts to improve the nosology of mental disorders for DSM-5 (American Psychiatric Association, 2013; Pardini, Frick, & Moffitt, 2010) revealed that ODD consisted of separable dimensions. Specifically, some ODD symptoms (e.g., “often angry or resentful”) differentially loaded onto an irritable or affective dimension, which predicted

internalizing (e.g., anxiety, depression) *and* externalizing problems; other ODD symptoms (e.g., "often argues with adults") loaded onto an oppositional/defiant dimension that was more specifically associated with CD and related ASB (Burke, 2012; Burke et al., 2014; Burke, Hipwell, & Loeber, 2010; Drabick & Gadow, 2012; Rowe, Costello, Angold, Copeland, & Maughan, 2010; Stringaris & Goodman, 2009a, 2009b). Based on these preliminary findings, some suggested that ODD is better conceptualized as an emotion regulation disorder (Cavanagh, Quinn, Duncan, Graham, & Balbuena, 2014); consistent with their formulation, the irritable ODD dimension is positively associated with anxiety and mood disorder symptoms (Althoff, Kuny-Slock, Verhulst, Hudziak, & van der Ende, 2014; Drabick & Gadow, 2012; Ezpeleta, Granero, de la Osa, Trepat, & Domenech, 2016; Kuny et al., 2013; Leadbeater & Homel, 2015; Stringaris & Goodman, 2009b), as well as suicidality (Aebi et al., 2015). Although this emergent literature has already affected diagnostic criteria for ODD in DSM- 5 (American Psychiatric Association, 2013; Hawes, 2014) with the creation of separate designations for "angry/irritable mood," "argumentative/defiant behavior," and "vindictiveness" typologies, testing the predictive validity of both ODD dimensions with respect to later mental health outcomes is critical.

Across development, surprisingly little is known about the mental health outcomes of youth with ODD. To establish a basis for the potential utility of separable ODD dimensions, the prevalence of internalizing and externalizing outcomes among youth with ODD must first be rigorously characterized. This is necessary to substantiate the clinical significance of ODD, as well as highlight logical directions for future research. Meta-analysis is arguably the most appropriate and compelling technique to assess these important questions. Given the increasing number of studies of psychopathology outcomes of youth with ODD, a meta-analysis is strategically positioned to increase the generalizability of the current evidence base. One recent

meta-analysis (Loth, Drabick, Leibenluft, & Hulvershorn, 2014) found that childhood externalizing psychopathology predicted unipolar depression in adulthood, however they did not examine ODD specifically and the outcome was limited to depression. This dissertation improved upon these limitations by separately meta-analyzing the prevalence of anxiety disorders, depressive disorders, and CD/antisocial personality disorder (ASPD) among children with ODD specifically. To inform future mechanistic research (e.g., identification of causal mediators) and to facilitate intervention development, we exclusively analyzed prospective longitudinal studies.

Next, although there is increasing evidence that ODD consists of separable dimensions, there is inconsistency with respect to the construct thought to represent each dimension, the individual symptoms that load onto these dimensions, the number of ODD dimensions identified, and the methodological approaches used. Most studies identified two ODD dimensions (Drabick & Gadow, 2012; Herzhoff & Tackett, 2015; Lavigne, Bryant, Hopkins, & Gouze, 2015; Leadbeater & Homel, 2015; Rowe et al., 2010), but others have found three dimensions (Burke, Hipwell, et al, 2010; Stringaris & Goodman, 2009b); one study fit a bifactor model for ODD symptoms (Burke et al., 2014) and other studies identified three to four latent classes that optimally fit ODD symptoms (Aebi et al., 2015; Althoff et al., 2014; Kuny et al., 2013). As outlined in Study II, the current dissertation featured two ODD dimensions. The ODD dimension conceptualized as reflecting negative affect and that is associated with both internalizing and externalizing psychopathology is hereafter referred by as *irritable* ODD. The dimension characterized by behavioral facets and specific association with externalizing problems is hereafter referred to as *oppositional* ODD.

The clinical and diagnostic validity of these ODD dimensions remain largely unknown (Frick & Nigg, 2012), which is reflected in clinical concerns about potential stigma associated with diagnosing youth with ODD without strong evidence of its validity (Frick & Nigg, 2012; Poulton, 2010). Predictive validity, the degree to which a test/scale predicts an independent criterion measured in the future (Cronbach & Meehl, 1955), is arguably the most important and stringent test of validity (Strauss & Smith, 2009). Particularly in the context of psychological assessment, given significant social and political consequences, predictive validity is necessary for meaningful inference (Messick, 1995). Although a rigorous test of the predictive validity of irritable ODD should account for baseline internalizing psychopathology, this is infrequently employed (see Burke, Hipwell, et al., 2010 for a key exception). Similarly, predictions of later internalizing symptoms from ODD dimensions were dramatically weakened, including to non-significance, when baseline internalizing symptoms were controlled (Lavigne, Gouze, Bryant, & Hopkins, 2014). Recent calls to distinguish between important correlated, but separable constructs such as irritability, negative affect, "temperamental dysregulation," anxiety, and depression early in development, especially in models pertaining to ODD dimensions (Burke, 2012; p. 9) further underscore the timeliness of this work. Given that emotion regulation is central to the development of disruptive behavior disorders with comorbid conditions, temperament, as an index of emotion regulation, should be considered in models examining risk factors for comorbid psychopathology (Steinberg & Drabick, 2015). Consideration of baseline psychopathology and temperament would constitute among the most important and conservative tests of the predictive validity of irritable and oppositional ODD that afford meaningful inferences and catalyze treatment innovations. For example, if ODD dimensions show strong predictive validity, even with control of baseline psychopathology and temperament, ODD

would constitute a unique precursor of later negative outcomes. Alternatively, if temperament better predicts psychopathology than ODD dimensions, temperament may be a more relevant target for prevention efforts, easier to assess, and less stigmatizing than a diagnosis of ODD.

Wakschlag et al. (2015) argued that a vital next step for the field is to empirically examine the potential utility of separable ODD dimensions in clinical decision-making and treatment response. Given that identification of mediating pathways and processes constitutes unique evidence of validity (Boorsbom et al., 2004), improves causal models of psychopathology, and advances development of innovative interventions (MacKinnon, 2015; Rose, Holmbeck, Coakley, & Franks, 2004), elucidation of potential mechanisms underlying predictions of later psychopathology and impairment from irritable and oppositional ODD dimensions is critical. Although there is research on potential pathways underlying predictions of later ASB from ODD overall, relatively little is known about predictions from irritable versus oppositional facets. Potentially important mediators between irritable ODD and oppositional ODD with later ASB are reactive aggression and proactive aggression, respectively. Reactive aggression is retaliatory or in response to provocation, whereas proactive aggression is organized and goal-oriented (Raine et al., 2006). Similar to how irritable ODD is associated with negative affect, emotion dysregulation, and internalizing problems, reactive aggression is associated with similar correlates (e.g., anxiety; Raine et al., 2006). Like oppositional ODD, which is characterized by deliberate defiance of rules, proactive aggression is intentional, goal-oriented, and predicts delinquency (Raine et al., 2006). Reactive and proactive aggression are separable (Hubbard, McAuliffe, Morrow, & Romano, 2010), but are also both associated with components of ASB (Raine et al., 2006). Thus, reactive aggression is a plausible mediator for youth with

irritable ODD, and proactive aggression a putative mediator of youth with oppositional ODD, both on the trajectory for significant ASB.

Addressing important limitations in the field, this three-study dissertation is unified around the centrality of testing ODD as a predictor of future psychopathology and impairment, as well as identifying potential factors underlying predictions of ASB from early dimensions of ODD (i.e., irritable and oppositional). Study I is a meta-analysis of prospective longitudinal studies that estimates the prevalence of psychopathology outcomes (i.e., anxiety/fear disorders, depressive disorders, and CD/ASPD) among youth with ODD. Advantaged by aggregating participants across studies, enhancing the diversity of participants (e.g., socioeconomic status, ethnicity) and improving external validity, Study I followed established guidelines for meta-analysis, such as reporting effect sizes, testing heterogeneity among effect sizes, and probing potential moderators. Next, in a six-year, three-wave prospective longitudinal study of school-age children, Study II examined the predictive validity of irritable and oppositional dimensions of ODD with respect to psychopathology (i.e., anxiety, depression, CD, ASB, psychopathic traits, and alcohol use) and functional impairment, controlling for baseline negative emotionality, psychopathology, and ADHD symptoms. Finally, Study III investigated reactive and proactive aggression as putative mediators underlying predictions of ASB from irritable and oppositional ODD dimensions, respectively. An improved understanding of the pathways underlying the development from ODD to prospective ASB will lay the groundwork for future research that comprehensively integrates the role of complex transactional roles of variables such as genotype and emotion regulation that factor into these models, thus setting the stage for more thoughtfully targeted interventions. Studies II and III utilized data from the UCLA ADHD and Development Study, a longitudinal study of 223 5 to 10-year-old children with and without ADHD followed

prospectively for six years. This sample consists of diverse laboratory-based methods, including structured interviews and normed rating scales, gathered from multiple informants (e.g., parent, youth) at three separate assessments. Collectively, all three studies are well-positioned to substantiate knowledge with respect to the validity and clinical significance of ODD, ultimately informing key areas for prevention and intervention efforts to improve youth mental health.

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Study I: Prospective Psychopathology Outcomes of Youth with ODD: A Meta-Analytic Review

Abstract

Context: The prevalence of internalizing and externalizing outcomes of youth with oppositional defiant disorder (ODD), particularly across development, is poorly understood. Reliable estimation of the prevalence of psychopathology among youth with ODD followed prospectively is necessary to clarify the clinical significance of ODD and to facilitate identification of targets for prevention and intervention efforts.

Objective: The aim of the present study was to meta-analyze the proportion of youth with ODD who subsequently developed later psychopathology (i.e., anxiety/fear disorders, depressive disorders, and conduct disorder [CD] or antisocial personality disorder [ASPD]).

Method: Literature searches identified publications from longitudinal studies of youth with ODD. Effect sizes were the proportion of youth with ODD who prospectively developed psychopathology. 1137 participants across 17 studies were included. Meta-analyses were conducted with random-effects models followed by heterogeneity tests; meta-regression evaluated moderators as potential explanatory factors underlying significant heterogeneity.

Results: Among youth with ODD, 13% developed a subsequent anxiety disorder, 5% a depressive disorder, and 21% CD or ASPD. Meta-regression identified that older youth at baseline had a higher prevalence of later depression. Higher psychotropic medication use at baseline was associated with elevated rates of later depression and CD/ASPD.

Conclusions: Individuals with ODD exhibited both heterotypic and homotypic psychopathology outcomes. We discussed future research priorities and clinical implications for youth with ODD.

Keywords: ODD; Meta-Analysis; Anxiety; Depression; Conduct disorder

Prospective Psychopathology Outcomes of Youth with ODD: A Meta-Analytic Review

Historically, ODD was conceptualized unidimensionally (Bauermeister, 1992; Burns, Boe, Walsh, Sommers-Flanagan, & Teegarden, 2001; Burns & Patterson, 2000; Pelham, Gnagy, Greenslade, & Milich, 1992). However, efforts to improve the nosology of mental disorders revealed that ODD consisted of separable dimensions: specifically, some ODD symptoms (e.g., "often angry or resentful") differentially loaded onto an irritable or affective dimension, which predicted internalizing (e.g., anxiety, depression) *and* externalizing problems. Other ODD symptoms (e.g., "often argues with adults") loaded onto an oppositional/defiant dimension that was more specifically associated with CD and related ASB (Burke, 2012; Burke, Rowe, & Boylan, 2014; Burke, Hipwell, & Loeber, 2010; Drabick & Gadow, 2012; Rowe, Costello, Angold, Copeland, & Maughan, 2010; Stringaris & Goodman, 2009a, 2009b). This nascent evidence affected diagnostic criteria for ODD in the DSM-5 (American Psychiatric Association, 2013; Hawes, 2014) with the creation of separate designations for "angry/irritable mood," "argumentative/defiant behavior," and "vindictiveness" ODD symptoms.

To substantiate the potential utility of separable ODD dimensions, the developmental course and psychopathology outcomes of youth with ODD must be well-characterized. Meta-analytic estimates of the prevalence of internalizing and externalizing outcomes of youth with ODD would persuasively contextualize the clinical significance of ODD. For example, elevated psychopathology in youth with ODD would strongly justify subsequent efforts to build predictive models and to elucidate causal mechanisms. Given the increasing number of prospective longitudinal studies of psychopathology outcomes of youth with ODD (e.g., Burke et al., 2014), a meta-analysis is both timely and strategically positioned to synthesize this expanding literature. Although one recent meta-analysis (Loth, Drabick, Leibenluft, &

Hulvershorn, 2014) found that childhood externalizing psychopathology predicted adult unipolar depression, they did not examine ODD specifically and outcomes were limited to depression. To critically improve upon these and other important limitations, the current study meta-analyzed the prevalence of anxiety disorders, depressive disorders, CD, and antisocial personality disorder (ASPD) outcomes among children with ODD specifically. To accelerate the development of predictive and explanatory models, as well as facilitate innovations in intervention development, we exclusively analyzed prospective longitudinal studies.

By virtue of its strong prediction of CD and ASB (e.g., Drabick, Steinberg, & Shields, 2016), ODD has traditionally been conceptualized as an externalizing disorder. However, more recent work suggests that it is also a significant risk factor for internalizing disorders (Frick & Nigg, 2012). Given persistent concerns of the construct validity and clinical significance of ODD (Frick & Nigg, 2012), there is a pressing need to adequately characterize the fundamental association of ODD with psychopathology outcomes. Several innovations define the current meta-analysis: (1) properly differentiated dimensions of psychopathology including internalizing disorders (i.e., fear/anxiety disorders and depressive disorders) and externalizing disorders (i.e., CD, ASPD) were analyzed separately. Although fear and anxiety are empirically separable (e.g., differential correlates; Sylvers, Lilienfeld, & LaPrairie, 2011), there is little consensus on what *specifically* constitutes an anxiety versus fear disorder (Craske et al., 2009); thus, fear and anxiety disorders were combined into a single outcome. (2) The current meta-analysis attended to crucial terminological distinctions given examination of both *homotypic continuity* (e.g., externalizing problems are manifested across the lifespan; ODD develops into CD) and *heterotypic continuity* (e.g., ADHD results in depression) (Angold, Costello, & Erkanli, 1999; Nikolas, 2016). Attention to terminological distinctions will strengthen efforts to elucidate risk

factors and causal risk processes. For example, homotypic comorbidity may suggest that similar causal mechanisms underlie similar clinical presentations across development whereas heterotypic comorbidity may signify clinical severity, designate important subtypes, that two disorders share underlying causes, or that one disorder is the manifestation of another disorder (see Angold et al., 1999 for a thorough discussion; Costello, Mustillo, Erkanli, Keeler, & Angold, 2003).

Moreover, the current study prioritized *successive comorbidity*, the succession of mental disorders over time, relative to *concurrent comorbidity*, or simultaneous co-occurrence of psychopathology (Angold et al., 1999). Studies of successive comorbidity are ideally designed to reveal temporal associations between and among dimensions of psychopathology. For example, the "dual failure" model suggests that negative social (e.g., peers, parent-child relationships) and academic consequences secondary to externalizing problems mediate the development of internalizing problems (Humphreys et al., 2013; Patterson & Stoolmiller, 1991). Next, the prospective longitudinal studies included in this meta-analysis are also advantaged insofar as testing potential moderators of predictive associations. In the presence of significant heterogeneity, we tested several theoretically- and empirically-derived (e.g., sex, age) variables as moderators of heterogeneity (Lipsey & Wilson, 2001). Collectively, the design of the current meta-analysis was significantly influenced by key developmental psychopathology principles including prioritizing prospective designs as well as elucidation of moderators of significant predictive associations (Cicchetti, 1984; Kazdin & Kagan, 1994).

The goal of this meta-analysis was to determine the prevalence of adolescent/adult psychopathology (i.e., anxiety/fear disorders, depressive disorders, and CD/ASPD) among youth with prior ODD. This knowledge is necessary to spur subsequent, mechanism-informed research

to improve understanding of the significant heterogeneity underlying ODD and later psychopathology, including important differences in treatment response secondary to comorbidity (Beauchaine, Webster-Stratton, & Reid, 2005; Connell et al., 2008; Frick, Ray, Thornton, & Kahn, 2013). We hypothesized that a significant proportion of children with ODD would exhibit prospective psychopathology, but did not propose specific prevalence estimates.

Method

Study Selection

Inclusion criteria for each study was as follows: (1) DSM-IV, DSM-IV-TR, or DSM-5 criteria (given that DSM III had different criteria for ODD) were employed and the study was published after January 1994 (when DSM-IV was published), (2) written in English, (3) use of a prospective, longitudinal design, (4) youth were assessed for ODD (either full diagnostic or symptom criteria, i.e., at least 4 symptoms), (5) used fully structured interviews, semi-structured interviews, and/or rating scales, (6) contained at least 10 individuals with ODD, (7) assessed for symptom or diagnostic criteria for at least one of the following: anxiety/fear disorders, depressive disorders, CD, or ASPD, and (8) ODD assessments temporally preceded prospective psychopathology follow-up assessments by at least one year. Studies that included dimensional measures of ODD and other psychopathology data were considered for inclusion on a case-by-case basis; for example, if diagnostic status could be calculated, or if study authors could re-analyze or provide data upon request, they were included. Exclusion criteria included: (1) studies that included participants with an IQ < 70, (2) studies that included participants with an autism spectrum disorder, (3) intervention studies or studies that recruited participants from a study that provided intervention, and (4) studies that did not use standard, well-established measures to diagnose psychopathology (e.g., unstructured clinical interview; retrospective diagnoses).

Search Procedure

Potential studies were identified using separate searches for each psychopathology outcome (i.e., anxiety/fear disorders, depressive disorders, and CD/ASPD outlined through the Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart (see Figure 1). First, we conducted computer-based searches using Google Scholar and PubMed databases limited to articles published since 1994. Google Scholar searches targeted articles that included *oppositional defiant disorder, ODD, attention deficit hyperactivity disorder, ADHD, conduct disorder,* or *CD* in the title, as well as key search terms for the outcome of interest in the remainder of the article. Search terms included ADHD and CD in the title given that many ADHD and CD studies assess for ODD and comorbid conditions. Keywords were combined by using the Boolean operators *"AND"* and *"OR."* In cases when the entire search phrase exceeded the character limit for the database, multiple searches were run to ultimately include all relevant search terms (candidate studies were summed across searches to yield the total number of hits; duplicates were screened out—see data extraction section). For example, the search for depressive disorders was: *allintitle:("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "CD" OR "conduct disorder")("major depressive disorder" OR "MDD" OR "depression" OR "depressive" OR "dysthymia" OR "dysthymic").* PubMed searches used parallel search terms to target studies with ODD and psychopathology outcomes of interest in the title or abstract. For example, the search for depressive disorders was: *("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "CD" OR "conduct disorder"[Title/Abstract]) AND ("major depressive disorder" OR "MDD" OR "depression" OR "depressive" OR "dysthymia" OR*

"dysthymic"[Title/Abstract])." For PubMed searches, we also activated filters based on eligibility criteria (see study selection section above): Article types: Journal Article; Publication dates from 01/01/1994 to 12/31/2016; Species: Humans; Language: English. All initial searches presented herein were completed in early April 2016 (see Table 1 for all search terms and hits by database). The initial search yielded the following number of citations or "hits" for each outcome: anxiety/fear disorders (Google Scholar = 365; PubMed = 1256), depressive disorders (Google Scholar = 718; PubMed = 2903), and CD or ASPD (Google Scholar = 524; PubMed = 1573). There was a total of 7339 hits.

Data Extraction

We (1) screened out duplicate studies, (2) filtered citations based on expected exclusionary factors (e.g., cross-sectional studies; did not assess for ODD), (3) filtered hits by inclusionary and exclusionary criteria, and (4) contacted study authors to determine additional eligibility criteria and to request data necessary for analyses. For *all* likely eligible studies, we contacted authors because the data that were central to the aims of this study were not reported in publications (i.e., psychopathology outcomes among *only* the participants with prior ODD).

There were 1712 hits screened out as duplicates. After reviewing remaining studies based on inclusionary and exclusionary criteria, 54 study samples from 105 hits (i.e., often multiple hits from the same study sample) were retained for potential inclusion. After contacting study authors to determine additional eligibility criteria and/or to request data necessary for analyses, three samples from five hits were excluded because authors actively declined to participate and four samples from nine hits were excluded because authors passively declined to participate (e.g., did not respond to multiple inquiries or did not follow through on requests after responding to the initial inquiry). We remain in communication with authors from 32 samples that came from 52

hits, most of whom promised to share data later this year. We will continue efforts to include these data before this project is ultimately submitted for publication. We obtained data from 15 study samples represented by 39 hits, as well as two additional samples offered from authors. Authors either directly provided the data that would typically be extracted from a publication, or provided raw data and we extracted the necessary values. The current meta-analysis was based on data from 17 study samples.

Data: Primary and Moderator Variables

We extracted the following data from eligible studies: (1) the number of individuals with ODD (i.e., full diagnostic criteria or at least 4 symptoms) at the earliest available assessment at which participants were evaluated for ODD based on DSM-IV, DSM-IV-TR, or DSM-5 criteria; among this group, we calculated the number of individuals at the latest follow-up assessment with any (2) anxiety/fear disorder, (3) depressive disorder, and/or (4) CD or ASPD. Additionally, to estimate the prevalence of specific disorders, we requested data on the number of participants with baseline ODD that were diagnosed with the following diagnoses at the last follow-up assessment: (1) generalized anxiety disorder (GAD), (2) social phobia/social anxiety disorder, (3) separation anxiety disorder, (4) specific phobia, (5) panic disorder (with or without agoraphobia), (6) agoraphobia, (7) obsessive compulsive disorder, (8) selective mutism, (9) posttraumatic stress disorder (PTSD), (10) acute stress disorder, (11) major depressive disorder (MDD), (12) dysthymia/persistent depressive disorder, (11) CD, and (12) ASPD.

Next, to explain significant heterogeneity among effect sizes for each outcome, hypothesized demographic and methodological variables were requested for evaluation as potential moderators. Sample characteristics were coded as follows: (1) type of sample (i.e., oversampled for ADHD, internalizing problems, externalizing problems, trauma exposure, twins,

adoptees, or other), and (2) referral source (i.e., clinic, community, mixture of clinic and community, juvenile justice/detention-based sample, or other). Variables that were requested for individuals with baseline ODD included: (1) mean age (years), (2) sex (% male), (3) racial composition (% Caucasian), (4) informant for ODD (i.e., parent, teacher, self, combination, or other), (5) assessment measure type (i.e., fully- or semi-structured interview, or rating scale or questionnaire), (6) DSM version (i.e., DSM-IV or DSM-IV-TR versus DSM-5), (7) percent of youth with ODD ever treated with psychotropic medication, and (8) percent of youth with ODD ever treated with psychotherapy. Moderator variables requested at follow-up were the same, with the exception of being asked separately for participants with ODD who developed (1) *any* anxiety/fear disorder, (2) *any* depressive disorder, and (3) CD or ASPD. An additional requested moderator variable was: mean time (years) between ODD and follow-up assessment for each respective outcome.

Calculation of Effect Sizes

Effect sizes were proportions—that is the number of youth with prospective psychopathology (variable by outcome assessed) as the numerator, divided by the number of youth with baseline ODD at least one year prior as the denominator. Proportions ranged from 0 (i.e., no participants with ODD were diagnosed with later psychopathology) to 1 (i.e., all youth with ODD were diagnosed with later psychopathology). Because of known biases associated with effect size calculations based on proportions, including underestimation of confidence intervals (CIs) and overestimation of heterogeneity as the proportion approaches 0 or 1, the logit method was implemented (Lipsey & Wilson, 2001). Logits are not restrained to values between 0 and 1 and approximate a normal distribution with a mean of 0; thus, they produce less biased results than directly observed proportions. When numerators/cells were 0 for the number of

participants with prospective psychopathology, they were transformed to 0.5 to utilize the logit transformation and to allow for inclusion in the meta-analysis (Lipsey & Wilson, 2001). Final results were converted from logits back to proportions to facilitate interpretation. Separate effects sizes were estimated for the proportion of individuals with ODD diagnosed with each of the following dichotomous psychopathology outcomes at the follow-up at least one year later: (1) anxiety/fear disorders, (2) depressive disorders, and (3) CD/ASPD.

There is no consensus about the number of samples required for meta-analysis, ranging from 2-3 studies (Lipsey & Wilson, 2001; Valentine, Pigott, & Rothstein, 2010) to recommendations of cautious interpretation when 5-10 samples are employed, especially if accompanied by significant heterogeneity (Kontopantelis & Reeves, 2010). To balance these considerations, we meta-analyzed specific outcomes if at least five samples were available. Thus, in addition to meta-analyses of broad diagnostic outcomes (i.e., anxiety disorders, depressive disorders, and CD/ASPD), we analyzed nine specific diagnostic outcomes: GAD, social phobia/social anxiety disorder, separation anxiety disorder, specific phobia, panic disorder, PTSD, MDD, dysthymia/persistent depressive disorder, and CD. Because a given study sample could yield separate effect sizes (i.e., study assessed for several prospective psychopathology outcomes), a single study could yield multiple effect sizes.

Data Analytic Procedures

Analyses were conducted in STATA. Meta-analyses were based on the *metaprop_one* command using random-effects models and the DerSimonian and Laird method, which assumes that variability in effect sizes is attributed to factors beyond subject-level sampling error and the existence of a distribution of effect sizes rather than a single, true effect size (Borenstein, Hedges, Higgins, & Rothstein, 2009; Egger, Smith, & Altmand, 2001; Lipsey & Wilson, 2001).

The mean effect size for each psychopathology outcome was weighted by its respective inverse variance, and additionally the 95% CI of each effect size was estimated.

Next, we conducted likelihood ratio tests comparing the fixed- and random-effects models to test for inter-study heterogeneity for each outcome. Heterogeneity among effect sizes reflects sources other than subject-level sampling error (e.g., study characteristics; Lipsey & Wilson, 2001). When significant heterogeneity was present, we conducted random-effects meta-regression analyses to test whether moderator variables explained significant variability across effect sizes. Because most moderator variables at follow-up reflected youth with ODD across outcomes (e.g., mean age of participants with baseline ODD who had *any* prospective anxiety disorder versus mean age for only those with a specific anxiety disorder), the following moderators were considered for specific diagnostic outcomes: (1) mean time (years) between ODD and follow-up assessment, (2) informant for prospective psychopathology (i.e., parent, teacher, self, combination, or other), (3) assessment measure type (i.e., fully- or semi-structured interview, or rating scale or questionnaire), and (4) DSM version (i.e., DSM-IV or DSM-IV-TR versus DSM-5).

We also evaluated for potential publication bias by employing Egger's test[1] for meta-analyses without significant heterogeneity across studies[2] (Egger, Smith, Schneider, & Minder, 1997). That is, statistically significant findings and those with relatively large effects are more likely to be published, and therefore included in meta-analyses, relative to studies with null

[1] We chose Egger's test over Begg's test (Begg & Mazumdar, 1994) because Begg's test is not recommended for meta-analyses with fewer than 25 individual studies.
[2] The trim and fill method, which corrects for publication bias, is inappropriate for meta-analyses where heterogeneity is present because it can spuriously adjust for bias and underestimate the effect size (Peters, Sutton, Jones, Abrams, & Rushton, 2007; Terrin, Schmid, Lau, & Olkin, 2003). For meta-analyses with significant heterogeneity, the meta-regression approach should be prioritized over the trim and fill method to correct for publication bias.

findings and small effect sizes. Egger's test begins with creating funnel plots (i.e., plotting each study's effect sizes on the x-axis against its standard error on the y-axis) where unbiased meta-analyses form a symmetrical "funnel." Egger's test then uses linear regression where the effect size divided by its standard error is regressed against the estimate's "precision" (i.e., the inverse of the standard error; Egger et al., 1997). An unbiased meta-analysis yields a y-intercept equal to zero, whereas the further the intercept is from zero, the more biased the meta-analysis. Duval and Tweedie's trim and fill method is then implemented (Duval & Tweedie, 2000) to correct for bias. Trim and fill uses an iterative procedure to remove the most extreme small studies from the funnel plot, and then estimates the number and effect sizes of "missing" studies, incorporating these missing data to estimate an "unbiased" estimate effect size (Borenstein et al., 2009). When the trim and fill method was utilized, we then estimated heterogeneity across studies after the new unbiased proportion was derived, using the Cochran's *Q* Test, which approximates a χ^2 distribution with $k - 1$ *df*, where *k* is the number of effect sizes and indicates consistency of findings across studies (Hedges & Olkin, 1985).

Results

Across 17 independent samples (15 samples from 39 hits; two additional samples), 1137 youth with ODD were included in analyses (see Tables 2-7 for sample characteristics, descriptive data at the baseline ODD assessment, and descriptive data at the follow-up assessments).

ODD and Prospective Anxiety/Fear Disorder Status

Ten studies were included in this meta-analysis, and 13% of youth with ODD developed subsequent anxiety/fear disorders (pooled proportion = 0.13; 95% CI [0.07, 0.23]; see Figure 2 for forest plot) with significant heterogeneity observed across studies (χ^2 (8) = 39.06, p < .01).

None of the moderators evaluated with meta-regression significantly explained this heterogeneity, however.

ODD and Prospective Depressive Disorders Status

Fourteen studies were included in this meta-analysis, and 5% of youth with ODD developed a subsequent depressive disorder (pooled proportion = 0.05; 95% CI [0.02, 0.12]; see Figure 3 for forest plot), with significant heterogeneity observed across studies (χ^2 (12) = 121.50, p < .01). Two moderators significantly explained heterogeneity: mean age at baseline, such that older participants had elevated rates of depressive disorders (β = .36, *SE* = .13, p < .01). Similarly, medication status at baseline explained heterogeneity such that greater use of psychotropic medication use was associated with more prevalent depressive disorders (β = .03, *SE* = .01, p = .03).

ODD and Prospective CD or ASPD Status

Fifteen studies were included in this meta-analysis, and 21% of youth with ODD developed CD/ASPD (pooled proportion = 0.21; 95% CI [0.13, 0.31]; see Figure 4 for forest plot); once again significant heterogeneity was observed across studies (χ^2 (13) = 129.32, p < .01). Medication status at baseline explained heterogeneity such that more psychotropic medication use yielded more prevalent CD or ASPD (β = .04, *SE* = .01, p < .01).

ODD and Prospective Specific Diagnostic Outcomes

GAD. Ten studies were included in this meta-analysis, and 3% of youth with ODD developed subsequent GAD (pooled proportion = 0.03; 95% CI [0.01, 0.05]; see Figure 5 for forest plot) with no evidence of significant heterogeneity across studies (χ^2 (8) = 1.62, p = .10). Egger's test for publication bias was significant (*t* = -3.13, p = .01). After adjusting for potential bias using the trim and fill method, the proportion of youth with ODD who developed later GAD

remained consistent (pooled proportion = 0.04; 95% CI [0.03, 0.07], without significant heterogeneity across studies (Q = 9.53, df = 9, p = .39).

Social phobia/social anxiety disorder. Eight studies were included in this meta-analysis, and 5% of youth with ODD developed social phobia/social anxiety disorder (pooled proportion = 0.05; 95% CI [0.03, 0.08]; see Figure 6 for forest plot) with significant heterogeneity observed across studies (χ^2 (6) = 3.73, p = .03). Four moderators significantly explained heterogeneity. Fewer boys at baseline (β = -.02, SE = .01, p < .01) and at follow-up (β = -.02, SE = .01, p < .01) predicted lower prevalence of social phobia/social anxiety disorder at follow-up. Studies with a higher baseline usage of psychotropic medication (β = .02, SE = .01, p = .02) and studies with longer durations between baseline and follow-up (β = .17, SE = .06, p < .01) produced higher rates of social phobia/social anxiety disorder.

Separation anxiety disorder. Five studies were included in this meta-analysis, and 8% of youth with ODD prospectively developed separation anxiety disorder (pooled proportion = 0.08; 95% CI [0.06, 0.12]; see Figure 7 for forest plot). There was no evidence of heterogeneity across studies (χ^2 (3) = 0, p = 1) or of publication bias (Egger's test: t = -.78, p = .49).

Specific phobia. Six studies were included in this meta-analysis, and 5% of youth with ODD developed later specific phobia (pooled proportion = 0.05; 95% CI [0.01, 0.20]; see Figure 8 for forest plot) with significant heterogeneity across studies (χ^2 (4) = 46.57, p < .01). Several moderators explained heterogeneity: (1) studies oversampled for externalizing problems yielded a higher proportion of later specific phobia relative to studies that oversampled for ADHD (β = 4.07, SE = 1.02, p < .001); (2) older youth at baseline had less prospective specific phobia (β = -.55, SE = .22, p = .01); (3) studies with elevated psychotropic medication use at baseline yielded lower proportions of later specific phobia (β = -.11, SE = .02, p < .001); and (4) studies with

higher psychotherapy at baseline yielded a lower prevalence of specific phobia (β = -.06, *SE* = .02, p < .001).

Panic disorder (with or without agoraphobia). Five studies were included in this meta-analysis, and no youth with ODD were estimated to develop later panic disorder (pooled proportion = 0.00; 95% CI [0.00, 0.5]; see Figure 9 for forest plot), but significant heterogeneity was observed across studies (χ^2 (3) = 13.87, p < .01). Several significant moderators were identified: first, studies that oversampled for youth with externalizing problems had a lower prevalence of later panic disorder relative to studies that oversampled for ADHD (β = -3.07, *SE* = 1.47, p = .04). Next, older participants at baseline had elevated rates of panic disorder (β = .39, *SE* = .17, p = .02). Studies with more boys at baseline (β = -.04, *SE* = .01, p < .01) and at follow-up (β = -.04, *SE* = .01, p < .01) yielded less panic disorder at follow-up. Also, studies with higher psychotropic medication use (β = .07, *SE* = .03, p < .01), psychotherapy use (β = .05, *SE* = .02, p < .01), and longer follow-up periods from baseline (β = .32, *SE* = .10, p < .01) produced higher proportions of panic disorder at follow-up. Finally, in studies where there was a combination of informants at the follow-up assessment, there were higher rates of panic disorder relative to studies that had a parent informant only (β = 2.16, *SE* = .90, p = .02).

PTSD. Five studies were included in this meta-analysis, and 1% of youth with ODD developed prospective PTSD (pooled proportion = 0.01; 95% CI [0.00, 0.07]; see Figure 10 for forest plot) with significant heterogeneity observed across studies (χ^2 (3) = 13.87, p < .05). Studies with more psychotropic medication use (β = .06, *SE* = .03, p = .03) and psychotherapy use at baseline (β = .04, *SE* = .02, p < .05), yielded a higher prevalence of PTSD at follow-up.

MDD. Fourteen studies were included in this meta-analysis, and 4% of individuals with ODD developed MDD (pooled proportion = 0.04; 95% CI [0.01, 0.10]; see Figure 11 for forest

plot) with significant heterogeneity observed across studies (χ^2 (12) = 80.04, p < .01). Mean age at baseline significantly explained heterogeneity such that older participants at baseline had a higher proportion of prospective MDD (β = .35, *SE* = .13, p < .01).

Dysthymia/persistent depressive disorder. Ten studies were included in this meta-analysis, and 3% of youth with ODD developed later dysthymia/persistent depressive disorder (pooled proportion = 0.03; 95% CI [0.01, 0.10]; see Figure 12 for forest plot) with significant heterogeneity observed across studies (χ^2 (8) = 123.13, p < .01). The only significant moderator was methodological: studies that assessed ODD with a rating scale yielded higher proportions of participants with prospective dysthymia relative to studies that assessed ODD with a fully structured or semi-structured interview (β = 3.48, *SE* = .98, p < .001).

CD. Thirteen studies were included in this meta-analysis, and 18% of youth with ODD developed prospective CD (pooled proportion = 0.18; 95% CI [0.11, 0.28]; see Figure 13 for forest plot). Although significant heterogeneity was observed across studies (χ^2 (11) = 104.50, p < .01), none of the moderators significantly explained heterogeneity.

Discussion

Including data from 17 prospective longitudinal studies, we meta-analyzed anxiety disorder, depressive disorder, and CD/ASPD outcomes among 1137 youth with ODD (mean age 3.7- to 10.3-years old). Among youth with ODD: 13% developed a subsequent anxiety disorder, ranging from 0% for panic disorder to 8% for separation anxiety disorder (mean age ranging from 6.5- to 19.4-years-old across studies at follow-up). Next, 5% developed depressive disorders (mean age ranging from 6.5- to 24.1-years-old across studies at follow-up) with 4% and 3% who developed MDD and dysthymia, respectively. Finally, 21% developed subsequent CD or ASPD (18% developed CD specifically; mean age ranging from 6.5- to 24.1-years-old

across studies at follow-up). Meta-regression analyses were conducted in the presence of significant heterogeneity among study effect sizes, and revealed that older participants at baseline had elevated rates of later depression and higher psychotropic medication use at baseline yielded higher rates of later depression and CD/ASPD.

To contextualize the clinical significance of these results, consider the prevalence of psychopathology among youth and young adults from population-based estimates. According to the National Comorbidity Survey-Adolescent Supplement (Kessler, 2011), 23.9% to 25.4% (12-month prevalence) of 13- to 18-year-old youth exhibited anxiety disorders. In this same sample of nationally-representative adolescents, 4.4% to 10.0% were diagnosed with MDD or dysthymia, with increasing prevalence for older youth. For young adults (18-29 years old), 6.4% and 1.5% were diagnosed with MDD and dysthymia, respectively (Hasin, Goodwin, Stinson, & Grant, 2005; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). For CD, the 12-month prevalence rate ranged from 2.8% for 13-year-olds to 7.1% among 16-year-olds (Kessler, 2011), whereas 3.6% of adults exhibited ASPD in the previous 12 months (Grant et al., 2005). Relative to these epidemiologically-based 12-month prevalence rates, findings from the current meta-analysis suggest that individuals with ODD had lower prevalence rates of anxiety disorders, comparable rates of depressive disorders, and higher rates of CD/ASPD.

Although there was evidence of both heterotypic and homotypic continuity among youth with ODD, prevalence rates were substantially higher for externalizing problems relative to internalizing problems in our findings. Thus, the nature of childhood ODD as a significant risk factor for development of later anxiety and depressive disorders remains ambiguous with these data. For example, one study found that internalizing comorbidity with ODD was present across development, but the degree of comorbidity varied over time, perhaps reflecting that subgroups

of youth (e.g., based on age, sex, symptoms) may have different trajectories for comorbidity (Boylan, Vaillancourt, Boyle, & Szatmari, 2007). Perhaps also reflecting important methodological differences, the samples included in this meta-analysis were not enriched for internalizing problems, which may have yielded different patterns of association between ODD and internalizing disorders, relative to the majority of studies that were enriched for ADHD or externalizing problems (Weiss, Jackson, & Süsser, 1997). Relatedly, because ODD has historically been conceptualized as an externalizing disorder, and it has only recently gained more attention as a possible risk factor for internalizing problems (Cavanagh, Quinn, Duncan, Graham, & Balbuena, 2014; Frick & Nigg, 2012), ODD and comorbid anxiety may be understudied and thus, unlikely to be included in the present study. Now that ODD is recognized as a potential risk factor for internalizing problems, future prospective studies would benefit from studying both ODD and internalizing problems (e.g., anxiety and depression), along with data on other factors that may help explain their relationship (e.g., irritability, temperament, negative affect, genetics, psychophysiology, family accommodation, parenting).

Youth with ODD in this meta-analysis exhibited significantly elevated rates of CD/ASPD relative to nationally representative samples, which is consistent with prevailing evidence that ODD is a potent developmental precursor to CD. For example, 40% to 60% of boys with ODD developed subsequent CD in the influential Great Smoky Mountains Study and Developmental Trends Study, respectively (Lahey, Loeber, Quay, Frick, & Grimm, 1997; Moffitt et al., 2008; Rowe, Maughan, Pickles, Costello, & Angold, 2002). Although 21% of youth developed subsequent CD or ASPD in this meta-analysis, previous estimates have relied on clinic-referred youth. For example, the Developmental Trends Study consisted of clinic-referred boys, and was therefore susceptible to known biases including elevated impairment and comorbidity as well as

a higher proportion of boys (Goodman, Lahey, Fielding, Dulcan, Narrow, & Regier, 1997). Additionally, we note that the vast majority of youth with ODD did not develop later anxiety disorders, depressive disorders, or CD/ASPD. Knowledge of what differentiates youth with ODD who develop subsequent psychopathology versus those who do not could advance prevention and intervention efforts. Previous evidence has implicated parental factors (e.g., emotion coaching) and psychosocial factors (e.g., peer acceptance) as being protective against negative outcomes for youth with ODD (Dunsmore, Booker, & Ollendick, 2013; Tung & Lee, 2014). With respect to factors that explained heterogeneity among effect sizes, we consider additional issues. Older participants at baseline had elevated depression, likely reflecting its sensitivity to developmental factors including the salience of pubertal status to depression onset, as well as related sex differences (Kessler, 2011; Negriff & Susman, 2011). Finally, studies with youth who reported more psychotropic medication use at baseline yielded higher estimates of depression and CD/ASPD, which likely reflects the intervention selection bias (Larzelere, Kuhn, & Johnson, 2004). That is, in the absence of random assignment or quasi-experimental control, treatment status (e.g., pharmacological, psychosocial) is likely an indicator of clinical severity.

Several study limitations should be underscored. Although meta-analyses are advantaged by aggregating participants across studies, including enhanced external validity given the improved representation of key constructs (e.g., socioeconomic status, ethnicity, referral sources), this study lacks specificity. First, despite ADHD being critical to ODD, especially early in development (Harvey, Breaux, & Lugo-Candelas, 2016), baseline ADHD and co-occurring psychopathology were not controlled. Relatedly, it is important to consider whether constructs such as temperamental negative emotionality, negative affect, or irritability may better explain the development of prospective psychopathology rather than ODD itself (Lahey, Rathouz,

Applegate, Tackett, & Waldman, 2010; Stingaris et al., 2012). Although several key developmental aspects were incorporated (e.g., ODD and psychopathology outcomes were temporally ordered) into this study, it did not address others. For example, youth with ODD at baseline ranged from a mean age of 3.8- to 10.3-years-old, and mean ages ranged from 6.5- to 24.1-years-old at follow-up assessments. These "censored" samples are susceptible to misrepresenting these developmentally-sensitive phenomena. For example, youth with early-onset CD versus adolescent onset CD are separable based on risk factors and causal influences (Moffitt, Caspi, Dickson, Silva, & Stanton, 1996), but such distinctions could not be separately assessed in this study. Finally, we are still actively collecting data, corresponding with investigators who have promised to share data in the near future.

In summary, we found that youth with ODD prospectively developed psychopathology at varying levels, with 13% for any anxiety disorder, 5% for depressive disorders, and 21% with CD/ASPD, demonstrating both heterotypic and homotypic continuity for youth with ODD. Relative to 12-month epidemiological data, anxiety outcomes were lower, depression was comparable, and CD/ASPD was higher among youth with ODD in this study. Thus, these findings continue to demonstrate the inconsistent role of ODD with respect to the development of internalizing problems, however, they converge with prior evidence that ODD is a precursor to CD. Future work must continue to differentially examine separable ODD dimensions, consider their clinical and predictive utility, and delineate the nomological network of ODD dimensions relative to other well-characterized and consequential constructs such as negative emotionality, negative affect, and irritability.

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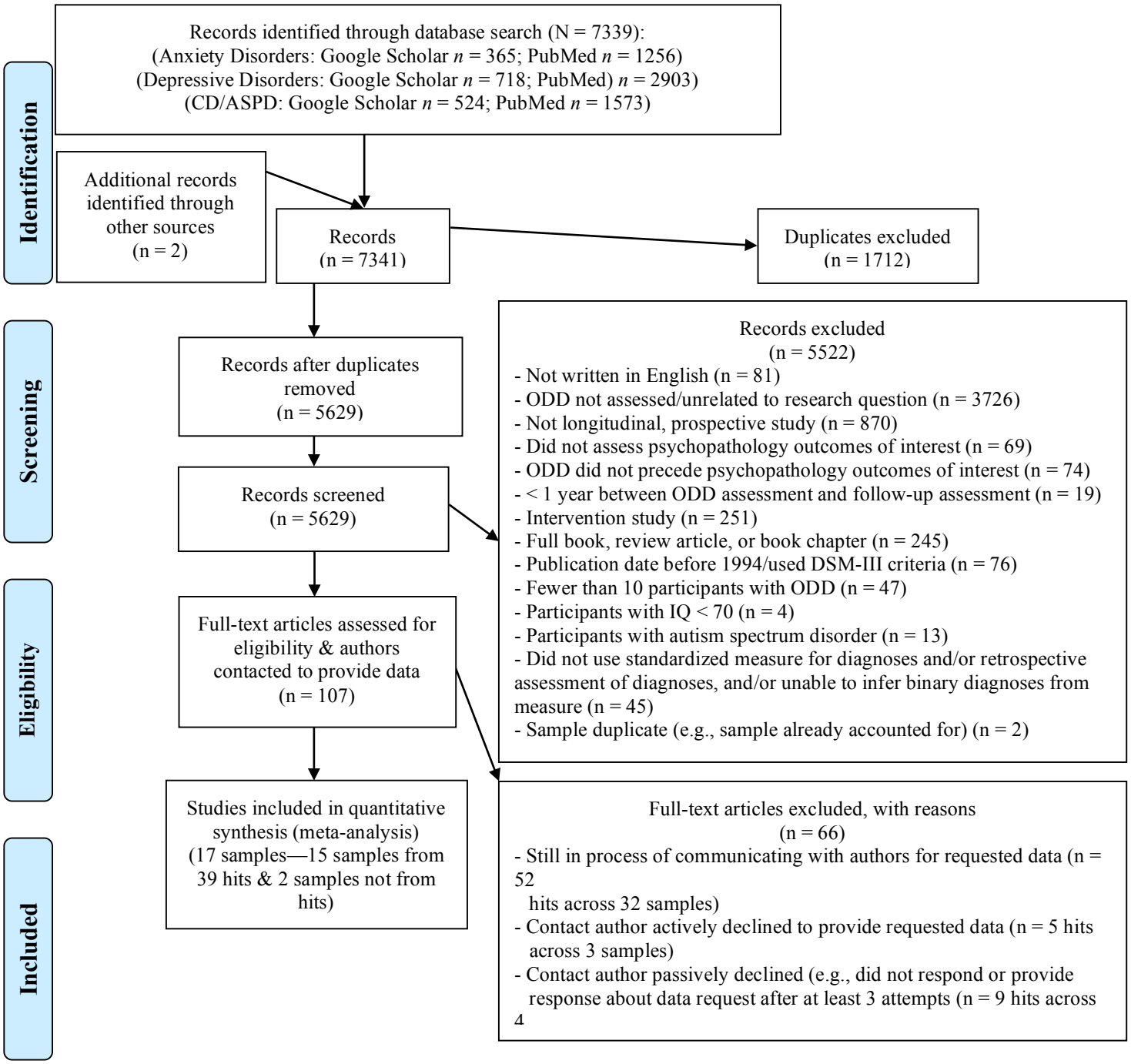


Figure 1. Flowchart of study inclusion.

Table 1. Meta-Analysis Search Terms

Outcome of Interest	Key Disorders Included	Database	Filters	Exact Search Phrase/s	Hits
Anxiety/fear Disorders	• Panic Disorder with/without Agoraphobia • Agoraphobia without History of Panic Disorder • Social Phobia/Social Anxiety Disorder (SAD) • Separation Anxiety Disorder (SAD) • Obsessive-Compulsive Disorder (OCD) • Generalized Anxiety Disorder (GAD) • Selective Mutism • Specific Phobia • Posttraumatic Stress Disorder (PTSD) • Acute Stress Disorder	Google Scholar	Date Range: 1994-2016	allintitle:("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "CD" OR "conduct disorder")("anxiety disorder" OR panic OR agoraphobia OR "SAD" OR "obsessive compulsive" OR OCD OR GAD OR "selective mutism") allintitle:("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "CD" OR "conduct disorder")("phobia" OR "posttraumatic stress" OR "PTSD" OR "acute stress") **Total** *Note: 2 separate searches due to character limit	302 63 365
“”	“”	PubMed	Article Types: Journal Articles Publication Dates: 01/01/1994 – 12/31/2016 Species: Humans Language: English	("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "CD" OR "conduct disorder"[Title/Abstract]) AND ("anxiety disorder" OR "panic" OR "agoraphobia" OR "phobia" OR "SAD" OR "obsessive compulsive" OR "OCD" OR "posttraumatic stress" OR "PTSD" OR "acute stress" OR "GAD" OR "selective mutism"[Title/Abstract])	1256
Depressive Disorders	• Major Depressive Disorder • Dysthymia/Persistent Depressive Disorder	Google Scholar	Date Range: 1994-2016	allintitle:("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "CD" OR "conduct disorder")("major depressive disorder" OR "MDD" OR "depression" OR "depressive" OR "dysthymia" OR "dysthymic")	718
“	“”	PubMed	Article Types: Journal Articles Publication Dates: 01/01/1994 – 12/31/2016 Species: Humans Language: English	("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder" OR "CD" OR "conduct disorder"[Title/Abstract]) AND ("major depressive disorder" OR "MDD" OR "depression" OR	2903

				"depressive" OR "dysthymia" OR "dysthymic"[Title/Abstract])	
Conduct Disorder or Antisocial Personality Disorder	• Conduct Disorder • Antisocial Personality Disorder	Google Scholar	Date Range: 1994-2016	allintitle:("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder")("conduct disorder" OR "CD" OR "antisocial personality disorder" OR "ASPD" OR "APD")	524
“”	“”	PubMed	Article Types: Journal Articles Publication Dates: 01/01/1994 – 12/31/2016 Species: Humans Language: English	("oppositional defiant disorder" OR "ODD" OR "ADHD" OR "attention deficit hyperactivity disorder"[Title/Abstract]) AND ("conduct disorder" OR "CD" OR "antisocial personality disorder" OR "ASPD" OR "APD"[Title/Abstract])	1573

Table 2. General Study Characteristics

Citation	Sample Name	Type of Sample (e.g., oversampled for particular population)	Referral Source	Notes
Beauchaine et al., 2008	Development of Conduct Problems & Depression in Middle Childhood Study	Externalizing problems	Community	-
Bufferd et al., 2012	The Temperament Study	-	Community	-
Burke et al., 2010	Pittsburgh Girls Study (PGS)	Other	Community	-
Carter et al., 2010	Connecticut Early Development Project	Other (original sample randomly selected from birth records; enriched sample oversampled for internalizing and externalizing problems)	Other	Outside record; not retrieved from hits.
Dierker et al., 2004	Service Use, Need, & Outcomes in Puerto Rican Children Study	-	Community	-
Harvey et al., 2009	UMass Amherst Longitudinal Study of Preschool-Aged Children	Externalizing problems	Mixture of clinic & community	Baseline ODD data is based on symptom criteria from the DISC, not full diagnostic criteria with impairment.
Humphreys et al., 2012	UCLA ADHD & Development Lab Longitudinal Study	ADHD	Mixture of clinic & community	Did not formally assess for autism spectrum disorder, but participants who were suspected to have the disorder were excluded.
Keenan et al., 2011	Diagnostic Validity Study	Externalizing problems	Mixture of clinic & community	Did not formally assess for autism spectrum disorder and exclude those participants.
Lahey et al., 2004	Chicago & Pittsburgh Longitudinal ADHD Study	ADHD	Mixture of clinic & community	-
Lavigne et al., 2009	Parents and Children Together (PACT)	-	Mixture of clinic & community	-
Lecendreux et al., 2015	French Epidemiological Telephone Survey	-	Community	Did not formally assess for or exclude autism spectrum disorder or intellectual disability.
Lee & Hinshaw, 2006	Berkeley Girls with ADHD Longitudinal Study (BGALS)	ADHD	Mixture of clinic & community	-
Loeber et al., 2000	Developmental Trends Study (DTS)	-	Clinic	Did not formally assess for autism spectrum disorder and exclude those participants.

Shaw et al., 2001	Pitt Mother & Child Project (PMCP)	Externalizing problems	Community	Did not formally assess for or exclude autism spectrum disorder or intellectual disability.
Staikova et al., 2010	Longitudinal Study of Urban Youth with ADHD	ADHD	Mixture of clinic & community	-
Whittinger et al., 2007	Cardiff Longitudinal ADHD Sample Study (CLASS)	ADHD	Clinic	-
Wiggins et al., 2017	Multidimensional Assessment of Preschoolers Study (MAPS)	Other (oversampled for externalizing problems and trauma exposure to gather participants with high irritability)	Clinic	Outside record; not retrieved from hits.

Note. When there were multiple hits/citations, the earliest citation was selected.
– indicates not provided, not assessed, or not applicable

Table 3. Diagnostic Data Provided by Studies

Citation	Any Anxiety/ Fear Disorder	Any Depressive Disorder	CD or ASPD	GAD	Social Phobia/ Social Anxiety Disorder	Separation Anxiety Disorder	Specific Phobia	PD	Agora-phobia	OCD	SM	PTSD	MDD	Dysthymia/ Persistent Depressive Disorder	CD	ASPD
Beauchaine et al., 2008	-	X	X	-	-	-	-	-	-	-	-	-	X	X	X	-
Bufferd et al., 2012	X	-	-	X	X	X	X	-	X	X	-	-	-	-	-	-
Burke et al., 2010	-	X	X	-	-	-	-	-	-	-	-	-	X	-	X	-
Carter et al., 2010	X	X	X	X	X	X	X	X	X	X	-	X	X	X	X	-
Dierker et al., 2004	X	X	X	X	X	X	-	X	-	-	-	X	X	X	X	-
Harvey et al., 2009	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	-
Humphreys et al., 2012	X	X	X	X	X	-	X	-	-	-	-	-	X	X	X	-
Keenan et al., 2011	-	X	X	-	-	-	-	-	-	-	-	-	X	-	X	-
Lahey et al., 2004	-	X	X	-	-	-	-	-	-	-	-	-	X	X	X	-
Lavigne et al., 2009	X	X	-	X	-	-	-	-	-	-	-	-	X	-	-	-
Lecendreux et al., 2015	-	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
Lee & Hinshaw, 2006	X	X	X	X	X	-	X	X	-	X	-	X	X	X	X	X
Loeber et al., 2000	-	X	X	-	-	-	-	-	-	-	-	-	X	X	-	X
Shaw et al., 2001	X	X	X	X	-	-	-	-	-	-	-	-	X	-	-	X
Staikova et al., 2010	X	X	X	X	X	-	-	-	-	-	-	-	X	X	X	X
Whittinger et al., 2007	-	-	X	-	-	-	-	-	-	-	-	-	-	-	X	-
Wiggins et al., 2017	X	X	X	X	X	X	X	X	X	-	X	X	X	X	X	-

Note. No studies provided data for acute stress disorder. CD = conduct disorder; ASPD = antisocial personality disorder; GAD = generalized anxiety disorder; PD = panic disorder; OCD = obsessive compulsive disorder; SM = selective mutism; PTSD = posttraumatic stress disorder; MDD = major depressive disorder.
X indicates data provided
- indicates data not provided or not assessed

Table 4. Study Characteristics at Baseline ODD Assessment

Citation	N w/ ODD	Minimum Age (years)	Maximum Age (years)	Mean Age (years)	% Male	% Caucasian	Informant	Assessment Measure	% Ever Treated w/ Psychotropic Medications	% Ever Treated w/ Psychotherapy
Beauchaine et al., 2008	71	7	12	9.7	78.9	63.4	Parent	CSI	-	-
Bufferd et al., 2012	51	3.1	4.1	3.7	62.7	96.1	Parent	PAPA	10	-
Burke et al., 2010	100	5	8	6.5	0	45	Parent	CSI	-	-
Carter et al., 2010	30	5	7	6.1	67	70	Parent	DISC	-	-
Dierker et al., 2004	107	4	17	10.2	57.6	-	Parent	DISC	12.6	48.5
Harvey et al., 2009	120	3	4.2	3.7	55	52	Parent	DISC	0.8	10
Humphreys et al., 2012	52	6	10	7.9	69.2	51.9	Parent	DISC	21.2	48.1
Keenan et al., 2011	84	3.0	6.0	4.5	50	11.9	Parent	K-DBDS	-	-
Lahey et al., 2004	79	4	6	5.3	89.9	62	Combination	DISC	23.1	38
Lavigne et al., 2009	36	4	4	4.5	41.7	69.4	Parent	DISC (Young Child Version)	-	-
Lecendreux et al., 2015	27	6	12	8.9	74.1	-	Parent	K-SADS	-	-
Lee & Hinshaw, 2006	85	6.6	12.9	9.8	0	66.3	Parent	DISC	48.8	82.6
Loeber et al., 2000	103	7	12	10.3	100	72.8	Parent	DISC	42.7	-
Shaw et al., 2001	11	5	5.7	5.3	100	36.4	Parent	K-SADS (Epidemiologic Version)	-	-
Staikova et al., 2010	25	7.3	11.1	8.9	84	20	Combination	DISC	64	-
Whittinger et al., 2007	95	6	12.9	9.3	94	100	Parent	CAPA	-	-
Wiggins et al., 2017	61	3	6	3.8	56	23	Parent	PAPA	-	-

Note. All studies used DSM-IV or DSM-IV-TR criteria. CSI = Child Symptom Inventory; PAPA = Preschool Age Psychiatric Assessment; DISC = Diagnostic Interview Schedule for Children; K-DBD-S = Kiddie Disruptive Behavior Disorder Schedule; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children; CAPA = Child and Adolescent Psychiatric Assessment.
– indicates not provided, not assessed, or not applicable

Table 5. Study Characteristics at Follow-up Anxiety Assessment

Citation	Minimum Time Between Baseline & Follow-up (years)	Maximum Time Between Baseline & Follow-up (years)	Mean Time Between Baseline & Follow-up (years)	Mean Age (years)	% Male	% Caucasian	Informant	Assessment Measure	% Ever Treated w/ Psychotropic Medications	% Ever Treated w/ Psychotherapy
Bufferd et al., 2012	8.3	10.1	9.0	12.6	61.5	100	Combination	K-SADS	30.8	53.8
Carter et al., 2010	1	3	1.3	7.8	50	67	Parent	DISC	-	-
Dierker et al., 2004	1	1	1	11.9	92.9	-	Combination	DISC	52.5	87.4
Harvey et al., 2009	2.7	3.6	3	6.7	47	49	Parent	DISC	17.8	44.4
Humphreys et al., 2012	3.6	6.3	4.8	13.1	50	100	Parent	DISC	100	50
Lavigne et al., 2009	3	3.5	-	6.5	0	0	Parent	DISC (Young Child Version)	0	0
Lee & Hinshaw, 2006	8.6	11.1	9.7	19.4	0	60	Combination	DISC	92	100
Shaw et al., 2001	16.4	17.2	16.7	-	-	-	Self	SCID	-	-
Staikova et al., 2010	7.9	8.9	8.3	17.0	100	0	Combination	K-SADS	0	-
Wiggins et al., 2017	1	3	2.3	6.8	73	9	Parent	K-SADS	-	-

Note. Data presented are for participants who had baseline ODD that developed *any* prospective anxiety/fear disorder. All studies used DSM-IV or DSM-IV-TR criteria except for Wiggins et al., 2017, who used DSM-5 criteria at follow-up. K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children; DISC = Diagnostic Interview Schedule for Children; SCID = Structured Clinical Interview for DSM-IV.
– indicates not provided, not assessed, or not applicable.

Table 6. Study Characteristics at Follow-up Depression Assessment

Citation	Minimum Time Between Baseline & Follow-up (years)	Maximum Time Between Baseline & Follow-up (years)	Mean Time Between Baseline & Follow-up (years)	Mean Age (years)	% Male	% Caucasian	Informant	Assessment Measure	% Ever Treated w/ Psychotropic Medications	% Ever Treated w/ Psychotherapy
Beauchaine et al., 2008	1.8	3.9	2.3	12	82.1	66.7	Parent	CSI	-	-
Burke et al., 2010	9	12	11	17	0	40	Parent	ASI	-	-
Carter et al., 2010	2	2	2	8	100	100	Parent	DISC	-	-
Dierker et al., 2004	1	1	1	14.0	74.0	-	Combination	DISC	29.5	58.8
Harvey et al., 2009	2.9	3.2	3	6.8	66	100	Parent	DISC	67	100
Humphreys et al., 2012	3.6	6.3	4.8	-	-	-	Parent	DISC	-	-
Keenan et al., 2011	2.7	4.1	3.0	-	-	-	Parent	ECI & CGAS	-	-
Lahey et al., 2004	-	-	9	14	89.7	62	Combination	DISC	53.2	58.2
Lavigne et al., 2009	3	3.5	-	6.5	0	0	Parent	DISC (Young Child Version)	0	0
Lee & Hinshaw, 2006	8.9	10.8	9.7	19.3	0	-	Combination	DISC	100	100
Loeber et al., 2000	12	17	14.5	24.1	100	72.8	Self	DISC	18.5	-
Shaw et al., 2001	16.4	17.2	16.7	-	-	-	Self	SCID	-	-
Staikova et al., 2010	7.2	9.0	8.1	17.9	66.7	33.3	Combination	K-SADS	66.7	-
Wiggins et al., 2017	2	2	2	7	100	100	Parent	K-SADS	-	-

Note. Data presented are for participants who had baseline ODD that developed *any* prospective depressive disorder. All studies used DSM-IV or DSM-IV-TR criteria except for Wiggins et al., 2017, who used DSM-5 criteria at follow-up. CSI = Child Symptom Inventory; ASI = Adolescent Symptom Inventory; DISC = Diagnostic Interview Schedule for Children; ECI = Early Childhood Inventory; CGAS = Children's Global Assessment Scale; SCID = Structured Clinical Interview for DSM-IV; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children.
– indicates not provided, not assessed, or not applicable.

Table 7. Study Characteristics at Follow-up CD/ASPD Assessment

Citation	Minimum Time Between Baseline & Follow-up (years)	Maximum Time Between Baseline & Follow-up (years)	Mean Time Between Baseline & Follow-up (years)	Mean Age (years)	% Male	% Caucasian	Informant	Assessment Measure	% Ever Treated w/ Psychotropic Medications	% Ever Treated w/ Psychotherapy
Beauchaine et al., 2008	1.8	3.9	2.3	12.2	83	68.1	Parent	CSI	-	-
Burke et al., 2010	9	12	10.4	17	0	19	Parent	ASI	-	-
Carter et al., 2010	1	2	1.7	8	100	100	Parent	DISC	-	-
Dierker et al., 2004	1	1	1.3	13.3	70.4	-	Combination	DISC	30.5	65.4
Harvey et al., 2009	2.8	3.8	3.1	6.8	69	46	Parent	DISC	23	62
Humphreys et al., 2012	3.6	6.3	4.8	10.9	100	0	Parent	DISC	100	100
Keenan et al., 2011	2.8	3.6	3.0	7.5	81.0	14.3	Parent	K-DBDS	61.9	23.8
Lahey et al., 2004	-	-	9	14	-	-	Combination	DISC	53.2	58.2
Lecendreux et al., 2015	4	4	4	14.2	100	-	Parent	K-SADS	-	-
Lee & Hinshaw, 2006	8.4	13.2	9.6	19.4	0	73.2	Combination	DISC	92.7	97.6
Loeber et al., 2000	12	17	14.5	24.1	100	72.8	Self	DIS	18.5	-
Shaw et al., 2001	16.7	17.2	16.9	22.2	100	100	Self	SCID	-	-
Staikova et al., 2010	7.5	9.2	8.6	17.0	100	11.1	Combination	K-SADS & SCID	77.8	-
Whittinger et al., 2007	3.4	6.8	5.2	14.6	95	100	Combination	CAPA	-	-
Wiggins et al., 2017	1	2	1.8	7	75	0	Parent	K-SADS	-	-

Note. Data presented are for participants who had baseline ODD that developed prospective CD *or* antisocial personality disorder. All studies used DSM-IV or DSM-IV-TR criteria except for Wiggins et al., 2017, who used DSM-5 criteria at follow-up. CSI = Child Symptom Inventory; ASI = Adolescent Symptom Inventory; DISC = Diagnostic Interview Schedule for Children; K-DBD-S = Kiddie Disruptive Behavior Disorder Schedule; K-SADS = Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Aged Children; DIS = Diagnostic Interview Schedule; SCID = Structured Clinical Interview for DSM-IV; CAPA = Child and Adolescent Psychiatric Assessment.
– indicates not provided, not assessed, or not applicable.

Figure 2. Forest Plot: Prevalence of Anxiety/Fear Disorder Outcomes

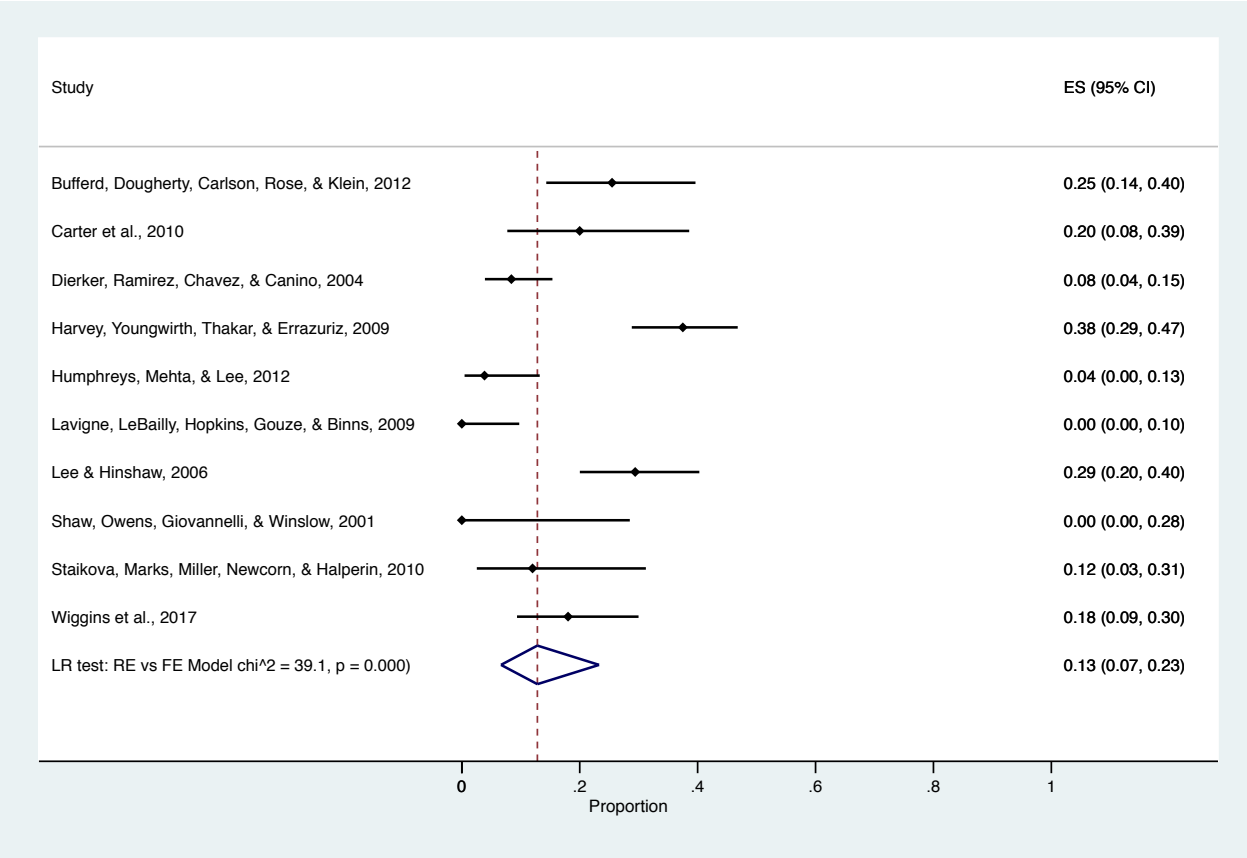


Figure 3. Forest Plot: Prevalence of Depressive Disorder Outcomes

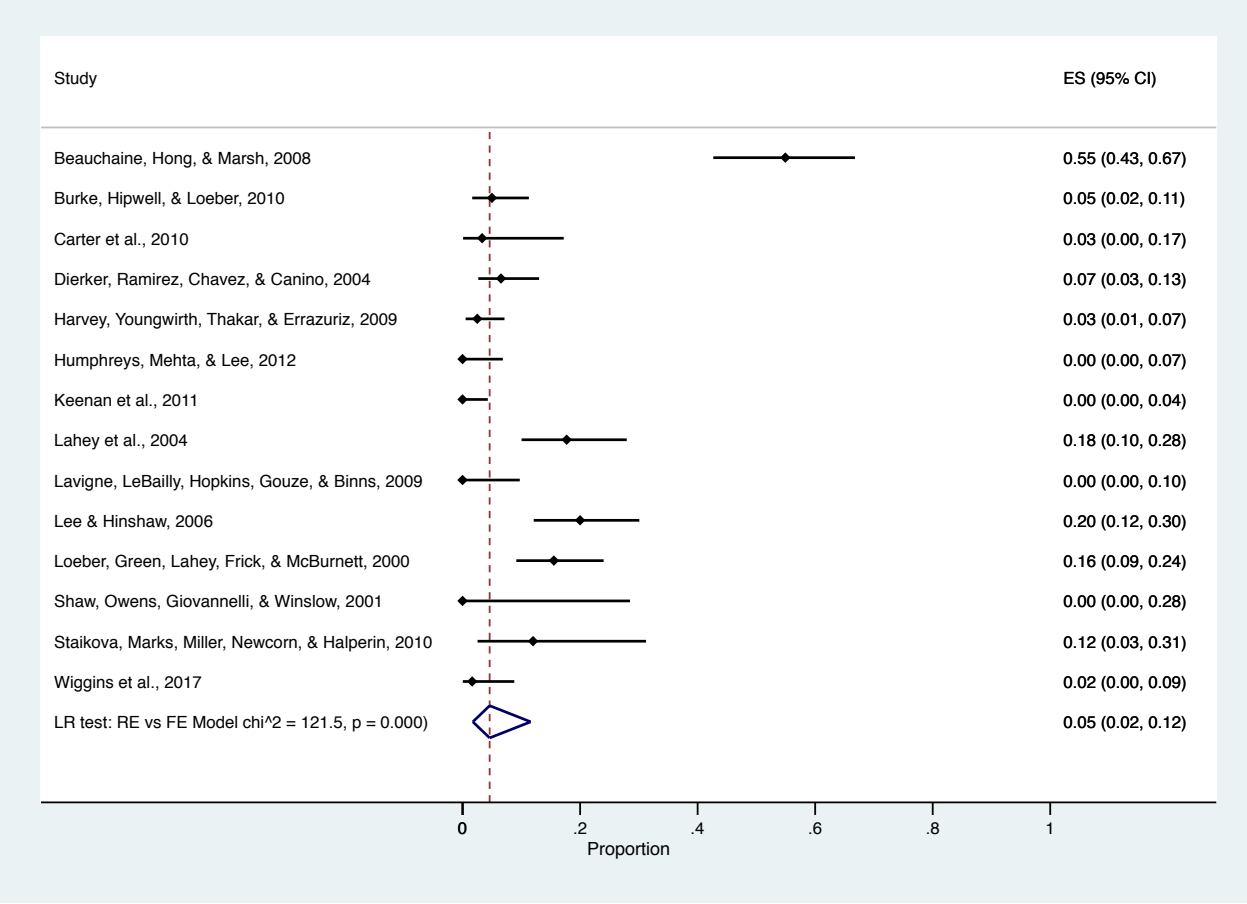


Figure 4. Forest Plot: Prevalence of CD or ASPD Outcomes

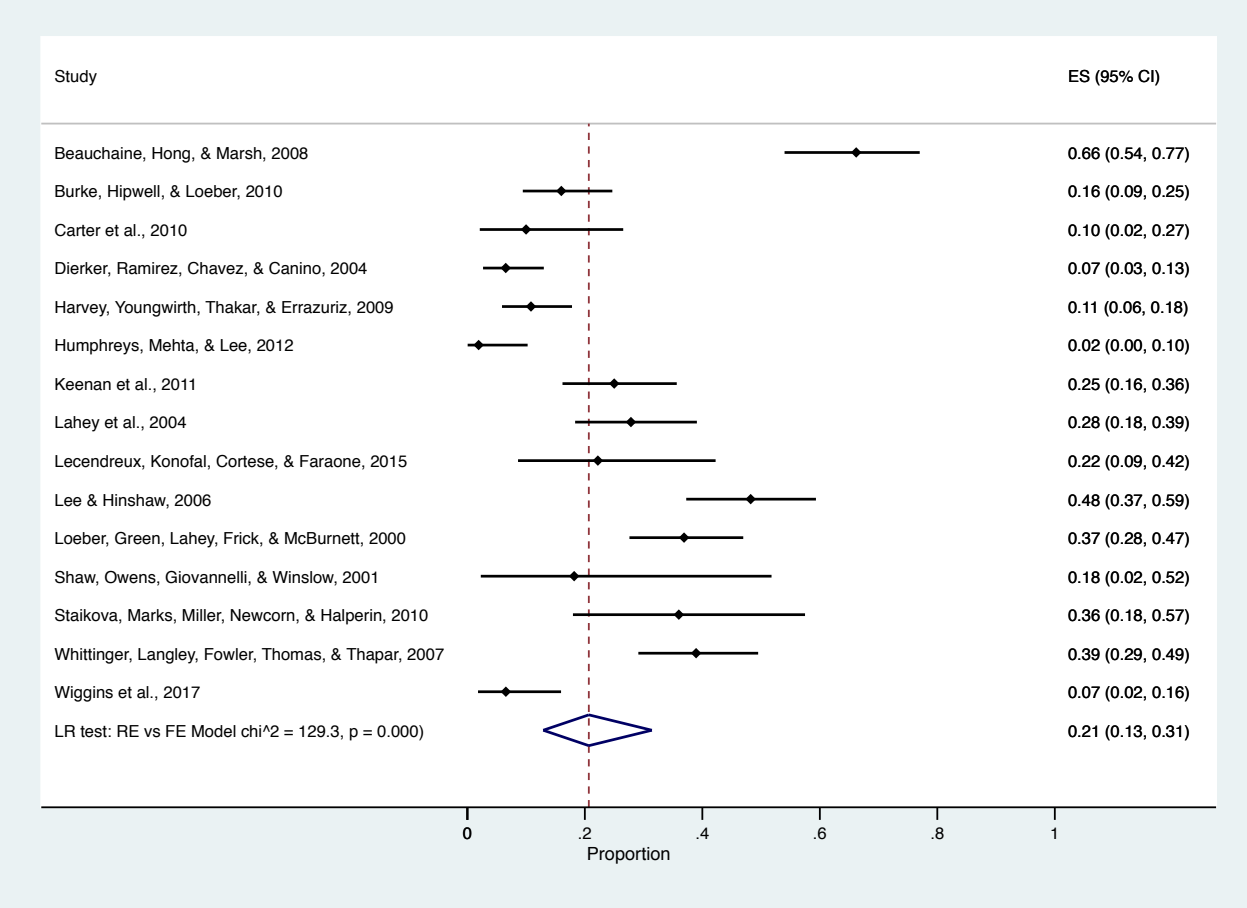


Figure 5. Forest Plot: Prevalence of GAD Outcomes

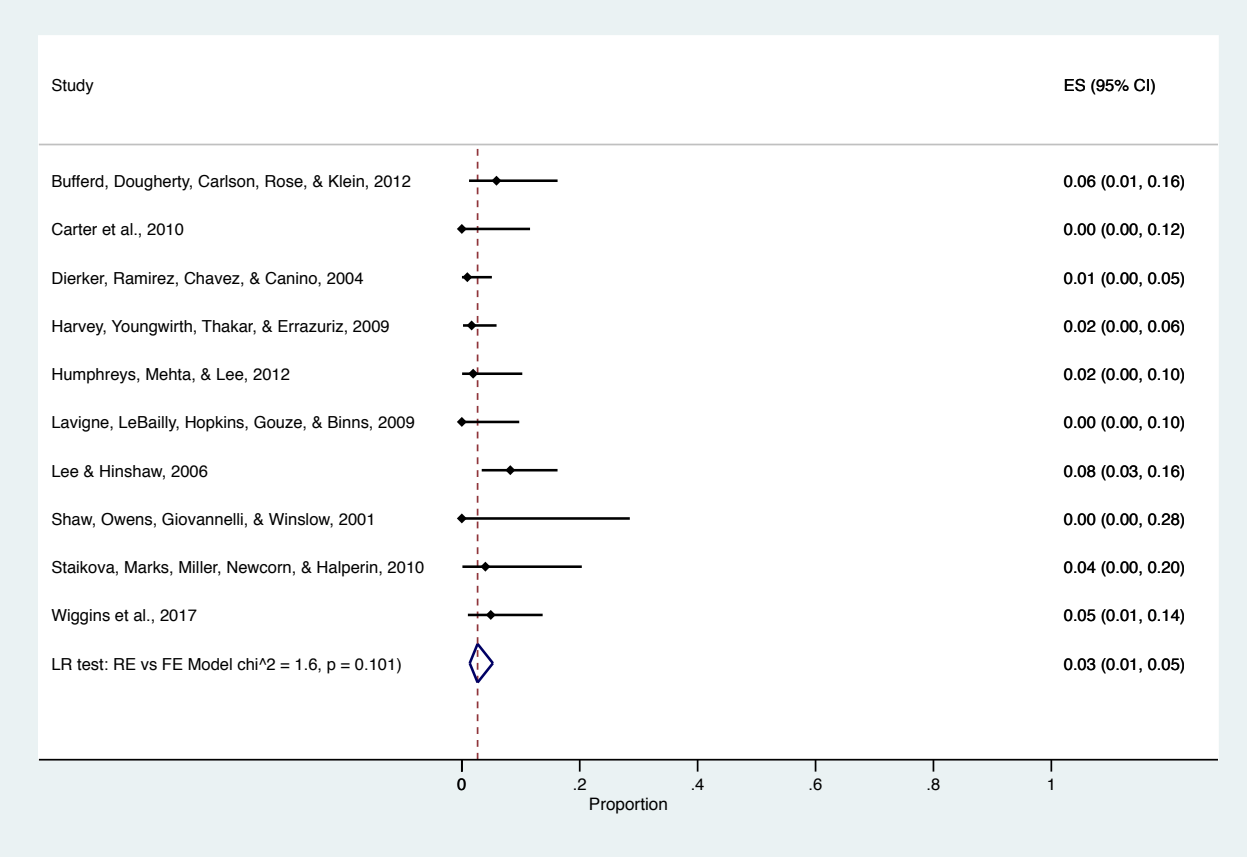


Figure 6. Forest Plot: Prevalence of Social Phobia/Social Anxiety Disorder Outcomes

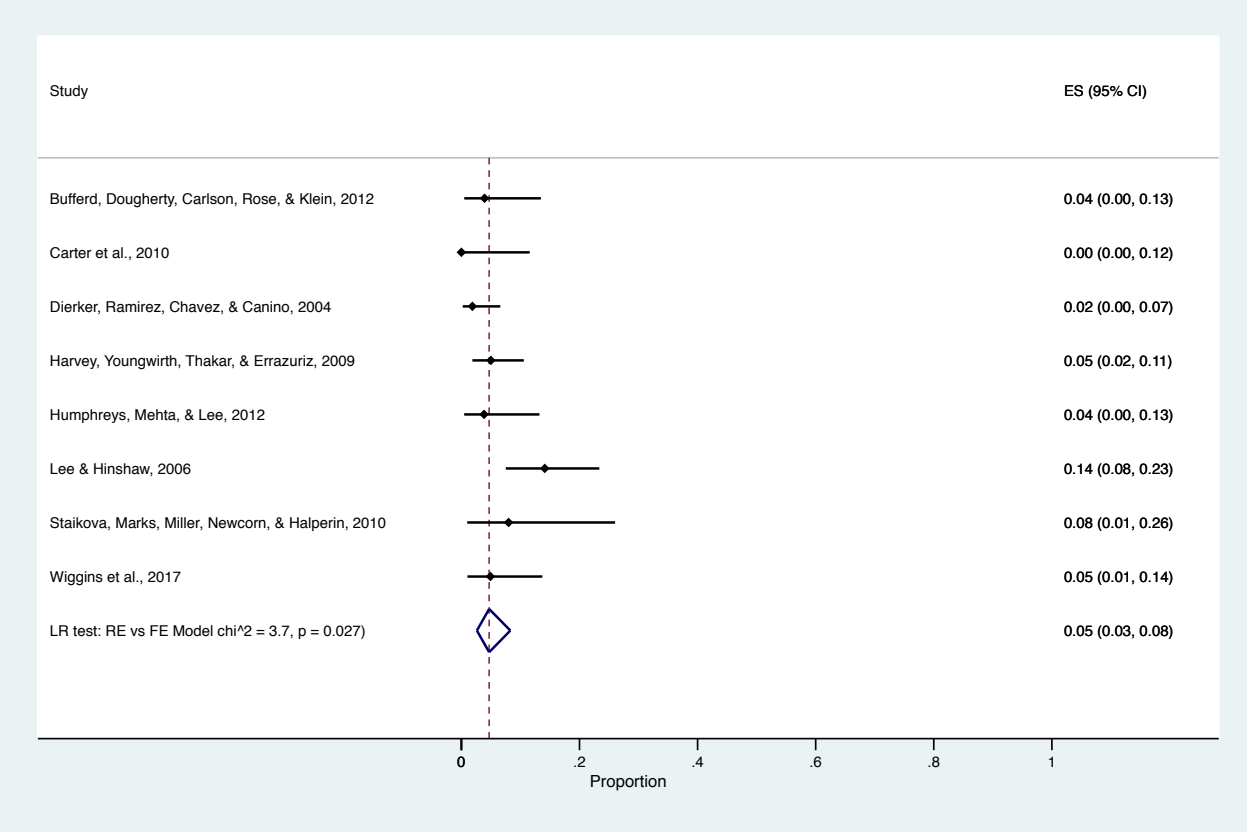


Figure 7. Forest Plot: Prevalence of Separation Anxiety Disorder Outcomes

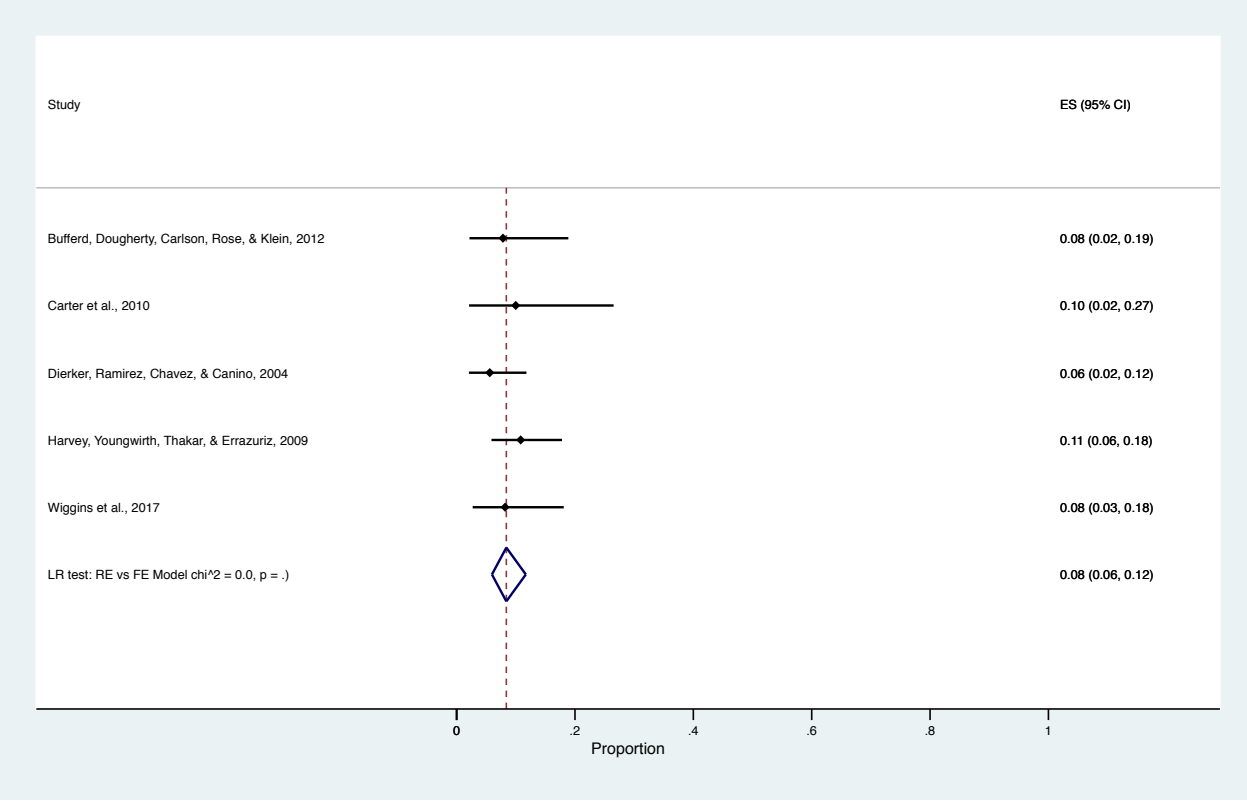


Figure 8. Forest Plot: Prevalence of Specific Phobia Outcomes

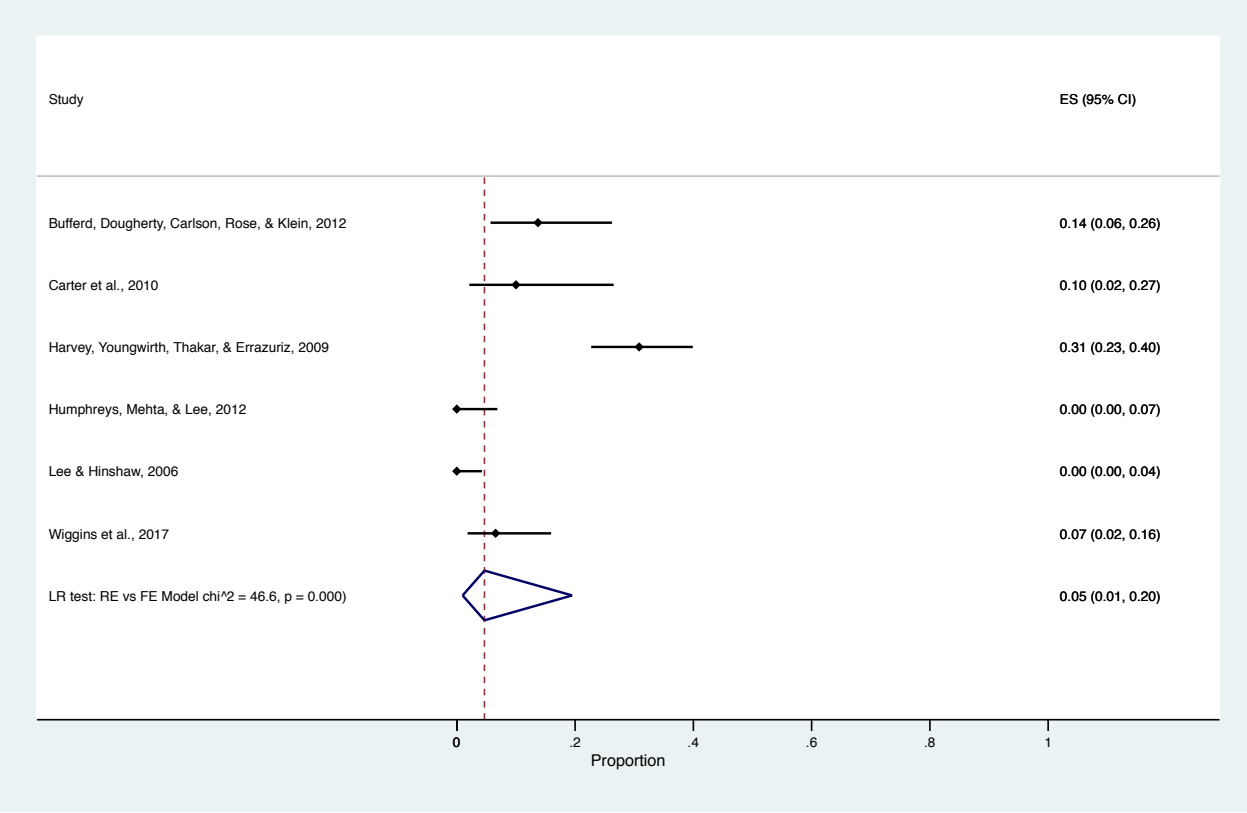


Figure 9. Forest Plot: Prevalence of Panic Disorder (with or without Agoraphobia) Outcomes

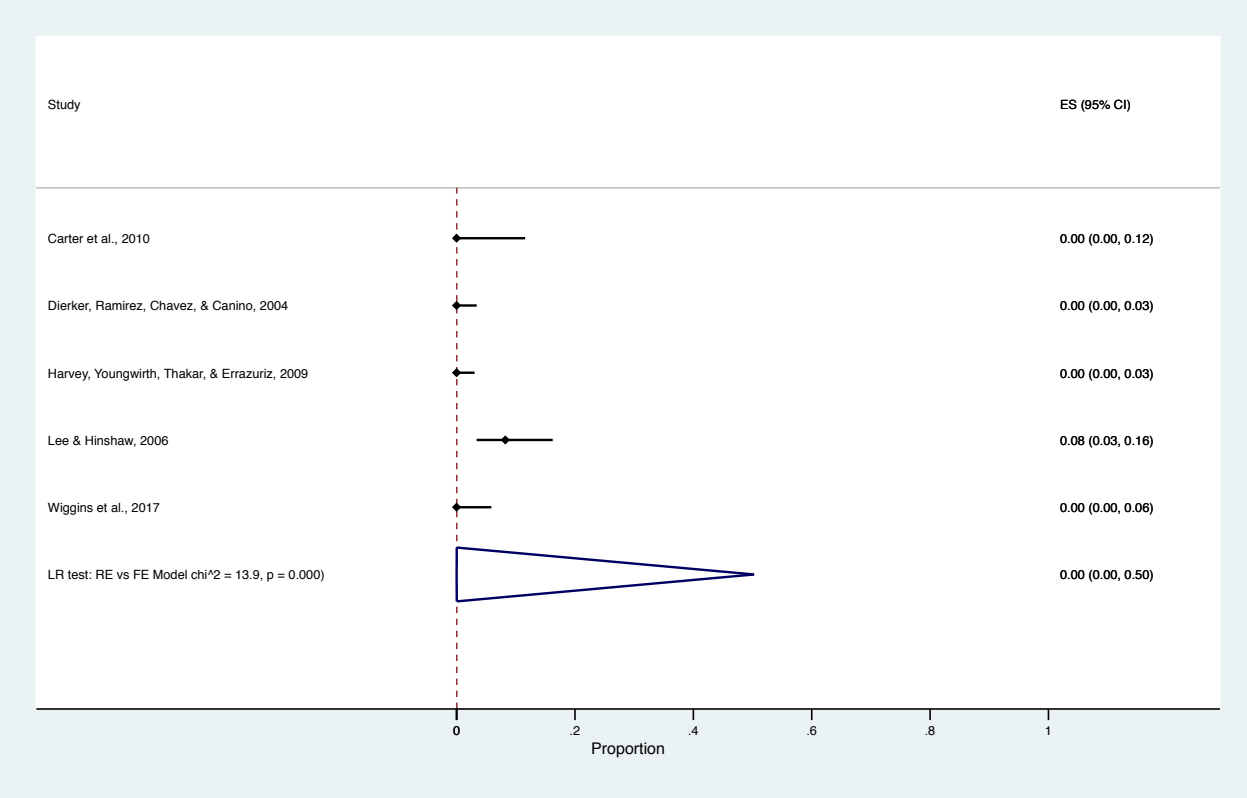


Figure 10. Forest Plot: Prevalence of PTSD Outcomes

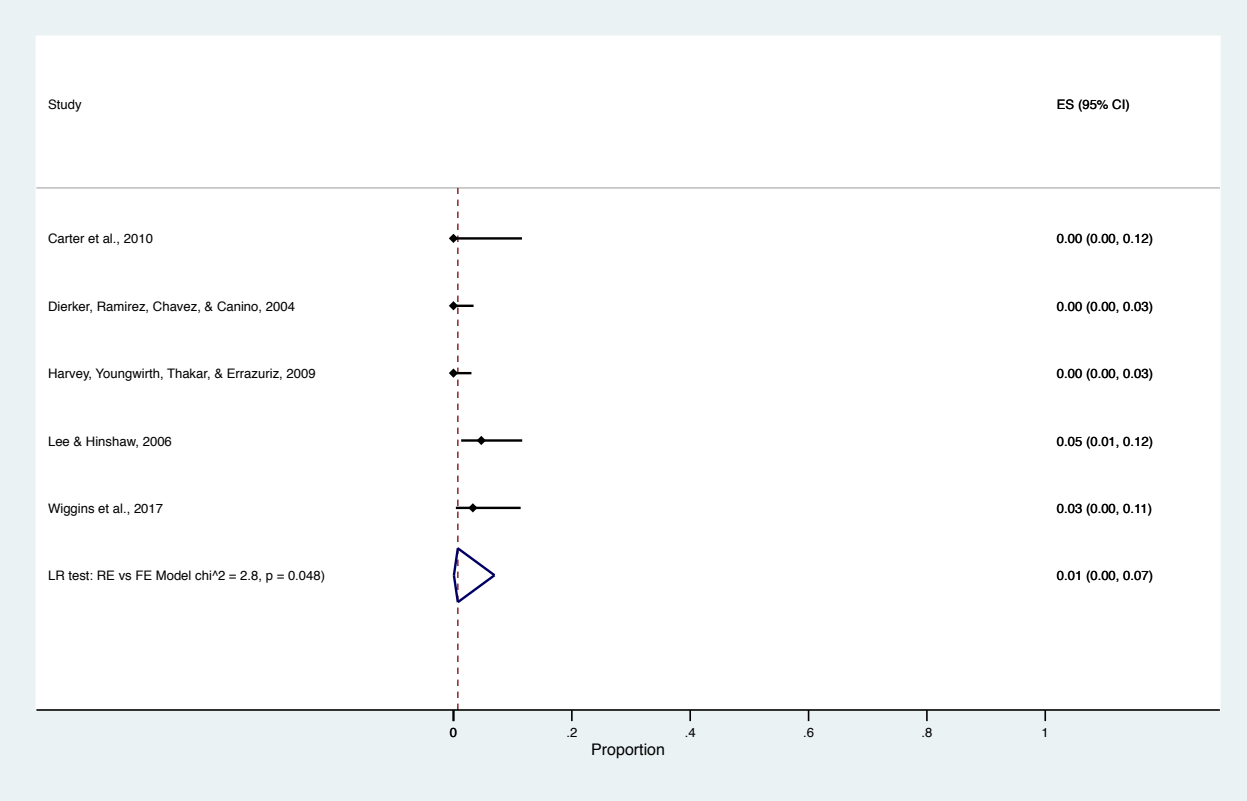


Figure 11. Forest Plot: Prevalence of MDD Outcomes

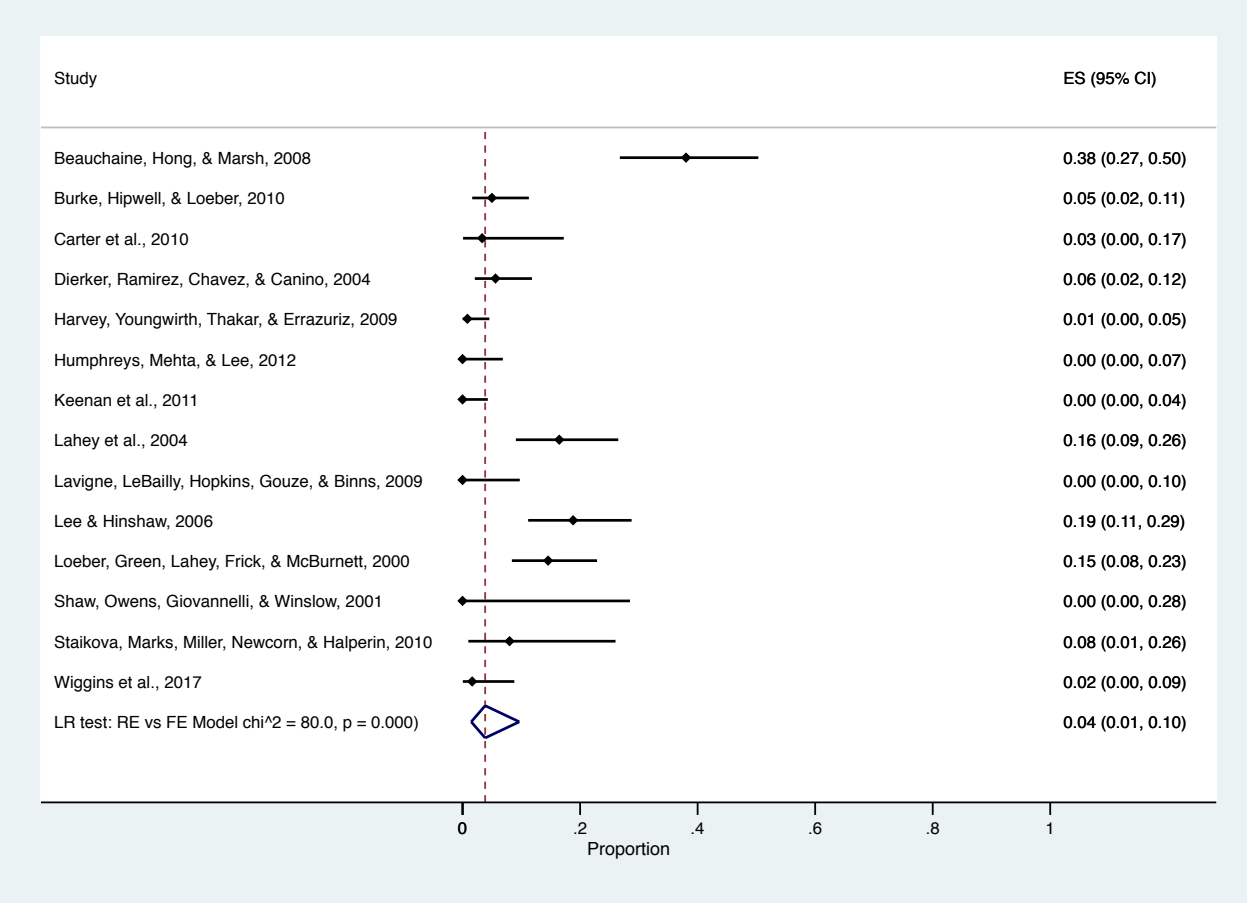


Figure 12. Forest Plot: Prevalence of Dysthymia/Persistent Depressive Disorder Outcomes

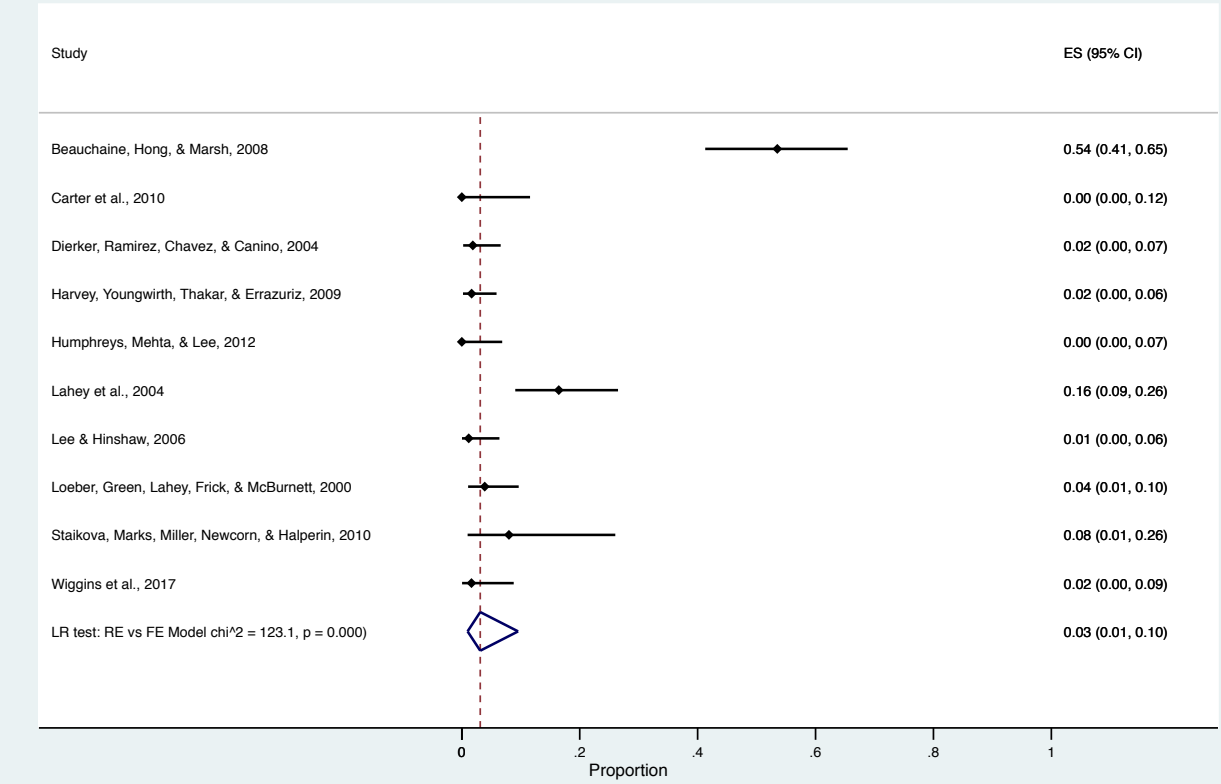
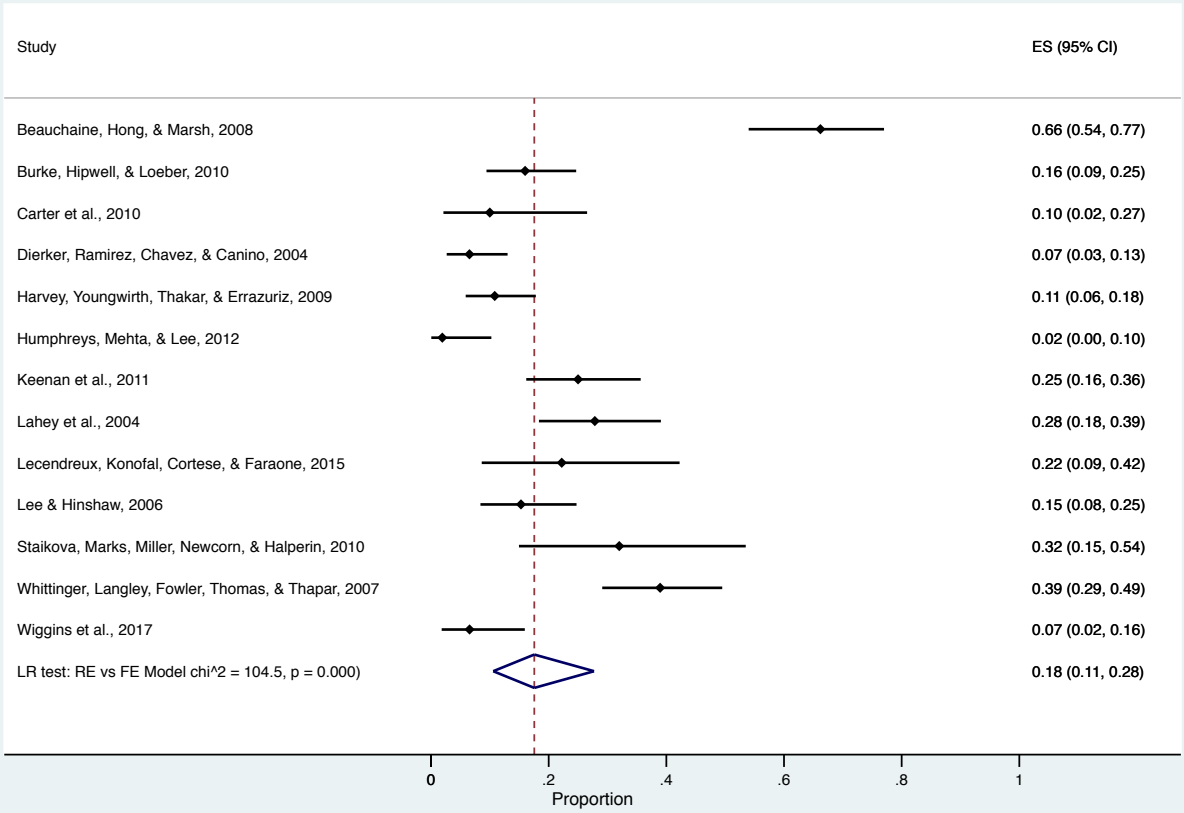


Figure 13. Forest Plot: Prevalence of CD Outcomes



Study II: Predictive Validity of Irritable and Oppositional ODD Dimensions

Abstract

Objective: The clinical and diagnostic validity of recently identified oppositional and irritable dimensions of oppositional defiant disorder (ODD) are largely unknown, necessitating efforts to evaluate their separability with respect to key constructs. The present study tested the predictive validity of irritable and oppositional ODD dimensions with respect to diverse psychopathology outcomes (i.e., anxiety, depression, conduct disorder), antisocial behavior, psychopathic traits, alcohol use, and functional impairment, with control of baseline negative emotionality, attention-deficit/hyperactivity disorder (ADHD), and baseline levels of outcomes.

Method: Participants were 145 ethnically-diverse youth (52% with ADHD at baseline; 69% male; 52.4% Caucasian; mean age 7.9 years at baseline) who were followed prospectively from childhood into early adolescence (mean age 12.6 years at the final follow-up). Generalized linear models examined the predictive validity of baseline irritable and oppositional ODD with respect to prospective psychopathology and functional impairment.

Results: Oppositional ODD inversely predicted parent-rated Total Anxiety and Depression, individual parent-rated anxiety subscales, as well as youth-rated Total Anxiety and Depression. Irritable ODD positively predicted parent-rated obsessions and compulsions only. Negative emotionality was unrelated to all outcomes, whereas baseline ADHD and baseline levels of psychopathology and impairment more consistently predicted negative outcomes.

Conclusions: Given their inconsistent prediction of key clinical and functional outcomes, the predictive validity of irritable and oppositional ODD dimensions should be interpreted cautiously, especially given the superior predictive qualities of other childhood risk factors.

Keywords: ODD dimensions; Irritability; Oppositionality; Negative emotionality

Predictive Validity of Irritable and Oppositional ODD Dimensions

Historically, ODD was conceptualized unidimensionally (Bauermeister, 1992; Burns, Boe, Walsh, Sommers-Flanagan, & Teegarden, 2001; Burns & Patterson, 2000; Pelham, Gnagy, Greenslade, & Milich, 1992). However, efforts to improve the nosology of mental disorders for DSM-5 (American Psychiatric Association, 2013; Pardini, Frick, & Moffitt, 2010) revealed that ODD consisted of separable dimensions: specifically, some ODD symptoms (e.g., "often angry or resentful") differentially loaded onto an irritable or affective dimension, which predicted internalizing (e.g., anxiety, depression) *and* externalizing problems. Other ODD symptoms (e.g., "often argues with adults") loaded onto an oppositional/defiant dimension that was more specifically associated with CD and related ASB (Burke, 2012; Burke, Rowe, & Boylan, 2014; Burke, Hipwell, & Loeber, 2010; Drabick & Gadow, 2012; Rowe, Costello, Angold, Copeland, & Maughan, 2010; Stringaris & Goodman, 2009a, 2009b). This nascent evidence affected diagnostic criteria for ODD in the DSM-5 (American Psychiatric Association, 2013; Hawes, 2014) where separate designations for "angry/irritable mood," "argumentative/defiant behavior," and "vindictiveness" ODD symptoms were codified.

Although there is increasing evidence that ODD consists of separable dimensions, there is inconsistency with respect to the latent construct thought to represent each dimension, the individual symptoms that load onto these dimensions, the number of ODD dimensions, and the methodological approaches used. Most studies identified two ODD dimensions (Drabick & Gadow, 2012; Herzhoff & Tackett, 2015; Lavigne, Bryant, Hopkins, & Gouze, 2015; Leadbeater & Homel, 2015; Rowe et al., 2010), but others have found three dimensions (Burke et al., 2010; Stringaris & Goodman, 2009b); one study fit a bifactor model for ODD symptoms (Burke et al., 2014), and others identified three to four latent classes that optimally fit ODD symptoms (Aebi et

al., 2015; Althoff et al., 2014; Kuny et al., 2013). The current study similarly featured two ODD dimensions—the first was conceptualized as reflecting negative affect and irritability that predicts both internalizing and externalizing psychopathology (i.e., *irritable* ODD), whereas the second dimension was characterized by behavioral facets and theorized to have a specific association with externalizing problems (i.e., *oppositional* ODD).

The clinical and diagnostic validity of these two ODD dimensions remain largely unknown (Frick & Nigg, 2012), which is reflected in concerns about potential stigma associated with diagnosing youth with ODD without strong evidence (Poulton, 2010). Predictive validity, which evaluates the degree to which a test/scale predicts a future, independent criterion measured (Cronbach & Meehl, 1955) is arguably the most important and stringent test of validity (Strauss & Smith, 2009). Particularly in the context of psychological assessment with significant social and political consequences, predictive validity is necessary for meaningful inference (Messick, 1995). Although a rigorous test of the predictive validity of irritable ODD should account for baseline psychopathology, this is infrequently employed (see Lavigne, Gouze, Bryant, & Hopkins, 2014 for a key exception). In one study, predictions of later internalizing symptoms from ODD dimensions were dramatically weakened, including to non-significance, when baseline internalizing symptoms were controlled (Lavigne et al., 2014). Thus, future research must distinguish between important correlated, but separable constructs such as irritability, negative affect, "temperamental dysregulation," anxiety, and depression early in development, especially in models pertaining to ODD dimensions (Burke, 2012; p. 9). Because emotion regulation is central to the development of disruptive behavior disorders with comorbid conditions, temperament must be accounted for in models with ODD (Steinberg & Drabick, 2015). In the context of predictive validity of irritable and oppositional ODD, incorporating

baseline psychopathology and dimensions of temperament constitutes a particularly conservative test with important implications for intervention. For example, if ODD dimensions showed strong predictive validity with control of baseline psychopathology and temperament, they would constitute a unique target for intervention. Alternatively, if negative outcomes were better predicted from other dimensions of temperament and psychopathology, ODD dimensions may be more incidental. Finally, if temperament predicted negative outcomes beyond ODD dimensions and psychopathology, it would suggest that temperament is a meaningful risk factor for mental health problems, and it would be easier to assess and less stigmatizing than a clinical diagnosis.

Consisting of individual differences in irritability, anger, hostility, anxiety, and sadness, neuroticism is central to conceptual models of personality and it uniquely predicts diverse comorbid conditions (Costa & McCrae, 1992; Lahey, 2009; McCrae & Costa, 1997). Given its phenomenological similarity to ODD (e.g., irritability, hostility), the construct validity of ODD must adequately attend to neuroticism and related constructs. Temperament appears early in development, is narrower in scope, and is more process-oriented relative to personality and neuroticism (Caspi & Shiner, 2008; Rothbart, Ahadi, & Evans 2000). Thus, individual differences in temperament are critical to consider in predictions of future psychopathology and impairment, especially with respect to the potential utility of separable irritable and oppositional ODD dimensions (Steinberg & Drabick, 2015). Negative emotionality is strongly associated with neuroticism, and a developmentally-sensitive construct to consider in studies of ODD and comorbid psychopathology (Lahey, Rathouz, Applegate, Tackett, & Waldman, 2010). Because studies rarely examine the extent to which ODD is separable from constructs such as negative emotionality, the current study examined the predictive validity of irritable and oppositional ODD dimensions with stringent control of negative emotionality and baseline psychopathology.

Virtually all theoretical and empirical models of temperament include a component of negative affect, irritability, and/or emotionality (Buss & Plomin, 1984; Chess & Thomas, 1966; Rothbart, 1981; Zentner & Bates, 2008). A recent review highlighted that temperament plays a critical role in the etiology, expression, and maintenance of most common dimensions of psychopathology (Krieger & Stringaris, 2016). Even across multiple theoretical models of temperament dimensions, there is consensus that temperament is highly heritable (Cyphers, Phillips, Fulker, & Mrazek, 1990; Saudino, 2005), is expressed in infancy (Buss & Plomin, 1984; Rothbart, 1981), and demonstrates considerable rank order stability (Shiner et al., 2012). Relatedly, the mechanisms that underlie the association of temperament and psychopathology are diverse. Whereas the *vulnerability association* theory argues that temperamental traits increase risk for- or the development of psychopathology (Krieger & Stringaris, 2016; Lahey, 2004; Shiner & Caspi, 2003), the *spectrum association* theory posits that psychopathology is an expression of extreme ends of individual differences in temperament and personality (Jensen et al., 1997; Shiner & Caspi, 2003; Widiger, Trull, Clarkin, Sanderson, & Costa, 2002). The current study evaluated both models by simultaneously testing negative emotionality and ODD dimensions as predictors of prospective psychopathology. That is, individual differences in temperament solely predicting psychopathology would be consistent with the vulnerability association theory whereas if both temperament and ODD dimensions similarly predicted psychopathology, this would support the spectrum association model.

In the current study, we prioritized the *negative emotionality* dimension from the developmental propensity model of temperament where children high on negative emotionality are "easily and intensely upset by frustrations, threats, and losses" (Lahey et al., 2008, p. 795). Crucially, the assessment of this construct is superior to other models of temperament and

psychopathology because it excludes items overlapping with psychopathology, thus avoiding artificially inflating intercorrelations (Lahey, 2004; Lahey et al., 2008; Lengua, West, & Sandler, 1998). Negative emotionality assessed in this particular way predicted ODD specifically, comorbid externalizing and internalizing problems, and psychopathology more generally in prior research (Krueger, 1999; Stringaris, Maughan, & Goodman, 2010; Tackett et al., 2013). Given its association with negative affect, irritability, and emotion regulation, as well as its prediction of ODD and comorbid problems, it is important to control for negative emotionality in tests of the predictive validity of ODD dimensions.

The aim of the present study was to test the predictive validity of irritable and oppositional ODD dimensions with respect to psychopathology outcomes (i.e., anxiety, depression, CD), ASB, psychopathic traits, alcohol use, and functional impairment, with control of baseline negative emotionality, ADHD symptoms, and psychopathology/impairment in each respective model. Given that few studies on the predictive validity of irritable and oppositional ODD dimensions controlled for baseline psychopathology, and no studies accounted for negative emotionality, we did not propose directional hypotheses.

Method

Participants

Participants were 223 ethnically-diverse children (67% male; 50.7% Caucasian; 8.5% Black; 10.8% Hispanic; 3.6% Asian; 21.9% mixed; 4.5% other or declined) children with (52%) and without ADHD (48%). There were no ADHD diagnostic group differences with respect to age, sex, race-ethnicity, or socioeconomic status. Subjects were 5- to 10-years-old (M = 7.9 years, SD = 1.2 years) at baseline (i.e., Wave 1), 7- to 13-years-old (M = 10.2 years, SD = 1.3 years) at their two- to three- year follow-up (i.e., Wave 2), and 9 to 15-years-old (M = 12.6 years,

SD = 1.3 years) at the Wave 3 follow-up. Approximately 88% of the original sample was assessed at Wave 2 and 78% of the original sample (i.e., *n* = 174) participated at all three waves. This study exclusively examined data from Wave 1 and Wave 3. Expectedly, however, there is variation in the statistical "N" for each measure. Table 1 includes demographic characteristics for the participants with complete data at Waves 1 and 3 included in the present study (N = 145).

At baseline, participants were recruited from community-based sources (e.g., advertisements in local schools) as well as referrals from pediatricians and local mental health service providers in a large metropolitan city in the Western United States. Youth were required to live with at least one biological parent at least half-time, be enrolled in school full-time, and be fluent in English. Participants with a Full Scale IQ less than 70, an autism spectrum disorder (including if was suspected and not formally assessed), seizure, or neurological disorder were excluded from participation. Non-ADHD comparison children who met diagnostic criteria for mental disorders other than ADHD were included in the study to avoid exaggerating diagnostic group differences. All participants were recruited, screened, and assessed using identical procedures.

Procedures

At baseline, interested families completed an initial telephone screen to determine their study eligibility based on the inclusionary and exclusionary criteria listed above. Rating scales were mailed to eligible families and they were subsequently invited for in-person laboratory-based assessments. After parental consent and child assent was obtained, clinical psychology doctoral students and/or bachelor of arts-level trained staff assessed children's academic achievement, cognitive ability, and socio-emotional functioning while a second member of the research staff concurrently interviewed parents about their child's psychopathology. All

interviewers were initially blind to the child's diagnostic status, but the blind could not always be preserved given the extensive information gathered about the child. Parents (85% mothers at Wave 1, 88% at Wave 2, and 84% at Wave 3) were asked to rate each child based on his or her unmedicated behavior. Parents were administered the Diagnostic Interview Schedule for Children, 4th edition (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), a fully structured diagnostic interview including questions on DSM-IV criteria, age of onset, and functional impairment. All *diagnostic* information for the sample, including ADHD proband status (i.e., ADHD versus non-ADHD comparison) and psychopathology (e.g., ODD, CD) outcomes, were ascertained via the DISC-IV. Additional disorder and/or construct-specific measures were also administered. Thus, diagnostic and impairment outcomes were assessed with the DISC-IV *and* through additional comprehensive measures. The majority of participants were evaluated unmedicated during the assessment (i.e., 94% and 92% of children at Wave 1 and Wave 3, respectively).

Approximately two years after the initial assessment, families were invited to participate in a follow-up laboratory assessment (i.e., Wave 2). A Wave 3 assessment was completed approximately two to three years after Wave 2, consisting of highly similar assessment procedures as those at Waves 1 and 2, with relevant domains such as youth psychopathology and functional impairment, but with developmentally-appropriate modification and expansions (e.g., delinquency and alcohol use interviews). There were no demographic or diagnostic status (i.e., age, sex, ethnicity, family income, baseline ADHD diagnostic status, baseline ODD diagnostic status, and baseline CD status) differences between families that participated at all three waves of the study versus non-participants at Wave 3. All study procedures were approved by the IRB.

Measures

ODD, ADHD, and CD symptoms. ODD, ADHD, and CD symptoms were assessed at every wave by parents with the Disruptive Behavior Disorders Rating Scale (DBD; Pelham et al., 1992). The DBD is an evidence-based assessment measure of ADHD, ODD, and CD symptoms with excellent psychometric properties (Lahey et al., 2004; Pelham, Fabiano, & Massetti, 2005; Shemmassian & Lee, 2016). The measure consists of 8 ODD items (e.g., "often argues with adults" and "often loses temper"), 18 ADHD items (e.g., "often fidgets with hands or feet or squirms in seat"), and 15 CD items (e.g., "has been physically cruel to people" and "has deliberately destroyed others' property.") All items were rated as being present "not at all," "just a little", "pretty much," or "very much." To maximize variance because disruptive behavior problems are often infrequent in young children, we examined ODD, ADHD, and CD symptoms dimensionally (i.e., 0-3 range for each item summed across the 8, 18, and 15 total items, respectively). At Wave 1, Cronbach alphas were .89 for ODD, .96 for ADHD, and .67 for CD. At Wave 3, Cronbach alphas were .88 for ODD, .95 for ADHD, and .54 for CD.

Wave 1 ODD dimensions. Irritable and oppositional ODD dimensions were calculated with confirmatory factor analysis using the Wave 1 DBD (see Table 2 for factor loadings; consistent with prior factor analyses in this sample- McKenzie & Lee, 2014) which yielded results similar to those in other samples where ODD was best characterized as two separate dimensions (e.g., Lavigne et al., 2015). Irritable ODD consisted of "is often spiteful or vindictive," "is often angry and resentful," "is often touchy or easily annoyed by others," and "often loses his/her temper." Oppositional ODD is composed of "often argues with adults," "often blames others for his/her mistakes or behavior," "often actively defies or refuses to comply with adults' requests or rules," and "often deliberately annoys people." The Cronbach alpha was .84 for the irritable dimension and .81 for the oppositional dimension.

Wave 1 temperament: Negative emotionality. The Child and Adolescent Dispositions Scale (CADS) is a parent-reported measure of children's temperament with items that were intentionally developed for studies of psychopathology by omitting synonyms or antonyms of psychiatric symptoms (Lahey et al., 2008). Parents rated youth emotional behavior as occurring "not at all," "just a little," "pretty much," or "very much" on 48 items. The CADS yields three factors: prosociality, daring, and negative emotionality, however, negative emotionality was exclusively examined in the current study. Examples of negative emotionality items include: "gets upset easily," "reacts intensely when he/she gets upset" and "is emotional." Previous studies have reported that the CADS has high test-retest reliability, construct validity, and external validity, and good internal consistency (Lahey et al., 2008; Trentacosta, Hyde, Shaw, & Cheong, 2009). The Cronbach alpha was .77 for the negative emotionality factor at Wave 1.

Anxiety and depression.

Wave 1 covariate. Parents completed the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), a 113-item rating scale of child psychopathology, impairment, and social competence at Wave 1. Items were rated as "not true," "somewhat or sometimes true," or "very true or often true," and scored 0 to 2, respectively. The CBCL is strong for use in multi-cultural populations (Achenbach et al., 2008), demonstrates adequate to excellent psychometrics and was normed on a large sample of 6- to 18-year-old youth (Achenbach & Rescorla, 2001). The CBCL Internalizing Scale discriminated youth with versus without anxiety disorders and externalizing disorders (Seligman, Ollendick, Langley, & Baldacci, 2004).

Wave 3 internalizing outcomes. At Wave 3, youth and their caregivers separately completed the Revised Children's Anxiety and Depression Scale (RCADS; Chorpita, Yim, Moffitt, Umemoto, & Francis, 2000), a 47-item scale of youth anxiety and depression. The

RCADS consists of 5 normed subscales (i.e., Separation Anxiety Disorder, Social Phobia, Generalized Anxiety Disorder, Panic Disorder, Obsessions/Compulsions, and Major Depressive Disorder), a Total Anxiety Scale (sum of 5 anxiety subscales), and Total Anxiety and Depression scale (sum of all 6 subscales). Items were rated as occurring "never," "sometimes," "often," or "always," ranging from 0 to 3, respectively (Weiss & Chorpita, 2011). The RCADS has high internal consistency and convergent validity, as well as clinical and research utility (Chorpita et al., 2000; Chorpita, Moffitt, & Gray, 2005; Ebesutani, Bernstein, Nakamura, Chorpita, & Weisz, 2010). We analyzed Wave 3 Total Anxiety & Depression T-scores (Cronbach alpha = .92 for parent-informants and .94 for youth-informants); when significantly predicted, we then examined individual Depression and Total Anxiety T-scores. Furthermore, if irritable or oppositional ODD dimensions significantly predicted the Total Anxiety T-score, we similarly examined the individual anxiety subscales (e.g., Separation Anxiety, and so on).

Self-reported ASB. At Wave 3, youth completed the 32-item Self-Reported Antisocial Behavior (SRA; Loeber, Stouthamer-Loeber, Van Kammen, & Farrington, 1989) semi-structured interview of ASB and delinquency (e.g., theft, aggression, vandalism). The frequency of behaviors was rated as "never," "once," "twice," or "more often," in the past 6 months and coded 0-3, respectively. Given that the alcohol and substance use were assessed in a separate measure, all substance use items were excluded, thus yielding 26 total items. We utilized the sum of all item ratings (possible range = 0 to 78), and the SRA scale had a Cronbach alpha of .68.

Psychopathic traits. At all waves, parents rated child psychopathic traits on the Antisocial Process Screening Device (APSD; Frick & Hare, 2001), a 20-item rating scale of youth callous-unemotional traits, narcissism, and impulsivity/conduct problems. Items measuring impulsivity/conduct problems were excluded in this study given their redundancy with ODD and

ADHD symptoms, which were accounted for with other measures.[3] The psychopathic traits composite score consisted of the sum of six callous-unemotional (e.g., "does not show feelings or emotions") and six narcissism (e.g., "can be charming at times, but in ways that seem insincere or superficial," "teases or makes fun of other people") items. All items were endorsed as "not at all true," "sometimes true," or "definitely true," and ranked 0-2, respectively. The Cronbach alpha of parent-rated psychopathic traits was .76 at Wave 1 and .84 at Wave 3.

Alcohol use. Youth alcohol use was assessed at Wave 3 with the Substance Use Questionnaire (SUQ; Molina & Pelham, 2003), a semi-structured youth interview adapted from national survey samples of substance use (e.g., Donovan, 1994; Jessor, Donovan, & Costa, 1989). The frequency and quantity of current (past 6 months) and lifetime use of licit substances (e.g., chewing tobacco, cigarettes, alcohol), inappropriate or non-prescribed medications, and illicit substances (e.g., marijuana, street drugs) were ascertained. In the present study, early alcohol use was estimated from youth self-reports of the number of lifetime sips of alcohol (excluding alcohol in the context of religious activities). Participants endorsed categorical options (e.g., once, twice, 3 to 5 times, 6 to 10 times, and so on) which were transformed into counts where the midpoint of ranges was used (e.g., 6 to 10 sips of alcohol was coded as 8 sips).

Functional impairment.

Wave 1 covariate. Following completion of the DISC-IV at Wave 1, parents and interviewers rated the child's impairment with the Children's Global Assessment Scale (CGAS; Shaffer et al., 1983). They rated the child's most significant impairment (e.g., behavior, emotion)

[3] To ensure that psychopathic trait items did not share significant variance with ODD symptoms, we conducted an exploratory factor analysis with remaining Wave 1 APSD and Wave 1 ODD items. Based on these results, one narcissism item (i.e., "becomes angry when corrected or punished") was omitted because it better fit an ODD factor than a narcissism factor (results available upon request; consistent with Jezior, McKenzie, & Lee, 2015).

in the past six months at school as well as with family, friends, and during leisure time. Youth were rated from 1 ("extremely impaired") to 100 ("doing very well"). The CGAS demonstrates good construct validity, as well as moderately strong inter-rater reliability (Bird et al., 1996; Lundh, Kowalski, Sundburg, Gumpert, & Landén, 2010; Shaffer et al., 1983). Parent and interviewer ratings were significantly correlated ($r = .66$, $p < .01$); thus, the mean of parent- and interviewer-rated impairment was used to estimate baseline functional impairment.

Wave 3 functional impairment. At Wave 3, parents completed the Barkley Functional Impairment Scale-Children and Adolescents (BFIS-CA; Barkley, 2012), a nationally-representative, empirically-supported measure of youth functional impairment. Possessing utility in both clinical and research settings (Barkley, 2012), the BFIS-CA was explicitly designed for use in longitudinal ADHD studies and related problems. The BFIS-CA is a 23-item rating scale that includes 15 items rated on a 10-point rating scale ranging from "not at all" to "severe" and coded 0 to 9, respectively, that assesses 15 domains of major life activities (e.g., parent interactions, academic performance). The BFIS-CA yields normed percentiles for each of the 15 domains of major life activities, as well as normed percentiles for a Home-School Impairment Scale, Community Impairment Scale, and Number of Impaired Domains Scale. We examined the Number of Impaired Domains as a dependent variable. See Table 3 for inter-correlations among key variables.

Data Analytic Procedures

Generalized linear models with robust estimation of the covariance matrix were employed to examine the predictive validity of Wave 1 irritable and oppositional ODD with respect to Wave 3 psychopathology and functional impairment outcomes. Appropriate distributions were specified based on the characteristics of each model (e.g., negative binomial),

an important consideration with psychopathology data. Wave 1 irritable and oppositional symptoms were entered simultaneously as unique predictors of Wave 3 outcomes, controlling for Wave 1 negative emotionality. Additionally, to account for the case-control design and ADHD as a risk factor for later psychopathology, Wave 1 ADHD symptoms were controlled in all models. Next, we controlled for baseline levels of each outcome: for example, in predictions of Wave 3 anxiety and depression, we controlled for Wave 1 anxiety and depression. Finally, we evaluated Wave 1 youth age, sex, and family income as potential covariates but only Wave 1 age significantly correlated with Wave 3 parent and child-rated anxiety and depression. However, given that the RCADS accounts for age in its T-scores for anxiety and depression, we did not separately control for Wave 1 age in predictions of anxiety and depression.

Internalizing outcomes. We fit generalized linear models with a normal distribution to separately predict Wave 3 parent- and youth-rated anxiety and depression from the RCADS. As described above, if the RCADS Total Anxiety and Depression T-score was significantly predicted by irritable or oppositional ODD, we examined the individual Depression and Total Anxiety subscales. If irritable or oppositional ODD dimensions significantly predicted the Total Anxiety T-score, we then predicted individual anxiety subscales where Wave 1 irritable and oppositional ODD symptoms were entered simultaneously with control of Wave 1 negative emotionality, ADHD symptoms, and baseline internalizing problems (i.e., Wave 1 CBCL Internalizing T-scores).

Externalizing and alcohol use outcomes. Employing highly parallel models as those described above and specifying a negative binomial distribution, we separately predicted Wave 3 parent-rated CD symptoms, Wave 3 youth-reported ASB, Wave 3 parent-rated psychopathic traits, and Wave 3 youth-reported alcohol use from Wave 1 irritable and oppositional ODD

symptoms, controlling for Wave 1 ADHD symptoms and negative emotionality. Additionally, Wave 1 CD symptoms were controlled in predictions of Wave 3 CD symptoms and Wave 3 youth-reported ASB; Wave 1 psychopathic traits were controlled in the model predicting Wave 3 psychopathic traits. However, because of the young sample, alcohol use data were not collected at Wave 1 and thus, were not adjusted for in predictions of Wave 3 alcohol use.

Impairment outcomes. Next, we predicted Wave 3 functional impairment (i.e., with the number of impaired domains measured by the parent-rated BFIS at Wave 3) specifying a negative binomial distribution, from Wave 1 irritable and oppositional ODD symptoms, controlling for Wave 1 negative emotionality, Wave 1 ADHD symptoms, and Wave 1 impairment measured from the CGAS (i.e., average of parent and interviewer). Once again, we predicted individual impairment subscales from irritable and oppositional ODD symptoms only if the composite impairment measure was significantly predicted.

Results

To review, across all models, baseline *parent-rated* irritable and oppositional ODD were tested as predictors, and baseline *parent-rated* ADHD, negative emotionality, and baseline levels of the outcome (with the exception of alcohol use; see below for details) were conservatively controlled. When the omnibus model was not significant, we did not interpret individual parameters. If a composite variable/outcome (e.g., RCADS Total Anxiety and Depression) was sensitive to oppositional or irritable ODD dimensions, we then probed individual subscales.

Internalizing.

Parent-reported anxiety and depression. We predicted Wave 3 RCADS Total Anxiety and Depression T-scores from baseline irritable and oppositional ODD with control of baseline negative emotionality, ADHD, and parent-rated CBCL Internalizing scores. The overall model

was significant (χ^2 (5) = 41.46, p < .001) where oppositional ODD inversely predicted (β = -1.2, *SE* = .36, p < .001), but irritable ODD was unrelated to (β = .61, *SE* = .51, p = .23) Wave 3 Total Anxiety and Depression. We subsequently tested separate Total Anxiety, and Depression subscales (χ^2 (5) = 32.84, p < .001 and χ^2 (5) = 51.51, p < .001, respectively). Oppositional ODD inversely predicted (β = -1.1, *SE* = .37, p < .01 and β = -.98, *SE* = .44, p = .03) but irritable ODD was unrelated to (β = .71, *SE* = .52, p = .17 and β = .05, *SE* = .42, p = .90) Wave 3 Total Anxiety and Depression subscales, respectively.

Given that oppositional ODD inversely predicted Wave 3 Total Anxiety, we separately examined all Wave 3 parent-rated anxiety subscales; all models were significant (individual omnibus test results available by request). Oppositional ODD significantly inversely predicted the following anxiety subscales: Separation Anxiety (β = -1.56, *SE* = .46, p < .001), Panic (β =-.84, *SE* = .33, p = .01), and Obsessions/Compulsions (β =-.91, *SE* = .34, p < .01). Irritable ODD significantly, positively predicted the Obsessions/Compulsions subscale only (β = .85, *SE* = .43, p = .04). Baseline negative emotionality was unrelated to all Wave 3 anxiety and depression subscales, whereas CBCL Internalizing T-scores predicted all subscales. Baseline ADHD significantly predicted Total Anxiety and Depression and the separate Depression subscale (see summary of results in Tables 4 and 5).

Youth self-reported anxiety and depression. We predicted Wave 3 RCADS Total Anxiety and Depression T-scores from irritable and oppositional ODD with control of baseline negative emotionality, ADHD, and parent-rated CBCL Internalizing T-scores. The model was significant (χ^2 (5) = 12.24, p = .03), where oppositional ODD inversely predicted (β = -1.18, *SE* = .56, p = .04), but irritable ODD was unrelated to (β = .36, *SE* = .47, p = .44) Wave 3 Anxiety and Depression. We subsequently tested separate Total Anxiety, and Depression subscales (χ^2

(5) = 9.43, p = .09 and χ^2 (5) = 19.18, p < .01, respectively). The omnibus model in predictions of Wave 3 Total Anxiety was not statistically significant; thus, we did not interpret individual parameters or further examine anxiety subscales. Irritable (β = -.08, *SE* = .53, p = .88) and oppositional ODD (β = -.82, *SE* = .55, p = .14) were unrelated to the Depression subscale. Negative emotionality was unrelated to all Wave 3 anxiety and depression measures, but baseline CBCL Internalizing T-scores positively predicted the Wave 3 Depression subscale. Baseline ADHD significantly predicted both Wave 3 Total Anxiety and Depression and the individual Depression subscale (see Table 6 for a summary of statistically significant results).

Externalizing and Alcohol Use.

First, controlling for baseline negative emotionality, ADHD, and parent-reported CD, we tested predictions of Wave 3 parent-rated CD from baseline irritable and oppositional ODD. Despite a significant overall model (χ^2 (5) = 24.89, p < .001), neither irritable (β = -01, *SE* = .06, p = .90) nor oppositional ODD (β = .03, *SE* = .05, p = .56) significantly predicted Wave 3 CD. Second, consisting of the same covariates and predictors for Wave 3 CD, we then examined the prediction of Wave 3 youth self-reported ASB. The overall model was not significant (χ^2 (5) = 10.02, p = .08). Next, controlling for baseline negative emotionality, ADHD, and parent-rated psychopathic traits, the overall model predicting Wave 3 parent-rated psychopathic traits was significant (χ^2 (5) = 92.23, p < .001), but baseline irritable ODD (β = .01, *SE* = .03, p = .82) and oppositional ODD (β = -.02, *SE* = .03, p = .47) did not predict Wave 3 psychopathic traits. Finally, controlling for baseline negative emotionality and ADHD, the overall model predicting wave 3 youth-reported alcohol use from irritable and oppositional dimensions was not significant (χ^2 (4) = 5.30, p = .26). Negative emotionality was unrelated to all Wave 3 externalizing outcomes. Baseline ADHD and CD positively predicted Wave 3 CD, and baseline psychopathic

traits positively predicted Wave 3 psychopathic traits (see summary in Table 7 of significant models).

Parent-reported Functional Impairment.

Finally, we evaluated the prediction of Wave 3 functional impairment from irritable and oppositional ODD, controlling for baseline negative emotionality, ADHD, and the average of parent and interviewer CGAS impairment ratings. Although the overall model for Wave 3 functional impairment was significant (χ^2 (5) = 24.89, p < .001), neither irritable ODD (β = .08, *SE* = .06, p = .21) nor oppositional ODD (β = -.06, *SE* = .06, p = .33) predicted Wave 3 functional impairment; thus, individual impairment subscales were not examined. Finally, negative emotionality was unrelated to Wave 3 functional impairment. However, baseline CGAS impairment ratings inversely predicted[4] and ADHD positively predicted Wave 3 functional impairment (see Table 8).

Discussion

To review, we rigorously evaluated the predictive validity of irritable and oppositional ODD with respect to multi-informant ratings of psychopathology (i.e., anxiety, depression, CD), ASB, psychopathic traits, and functional impairment, controlling for baseline negative emotionality, ADHD symptoms, and baseline levels of outcomes[5]. Oppositional ODD inversely predicted parent-rated combined anxiety and depression, individual parent-rated subscales (i.e., Total Anxiety, Separation, Panic, Obsessions/Compulsions, and Depression subscales), and youth-rated combined anxiety and depression. Irritable ODD positively predicted parent-rated

[4] Note that the BFIS and CGAS are on opposite scales (high BFIS = high impairment; high CGAS = low impairment).
[5] Note there was an exception that baseline alcohol use was not controlled given that it was not indicated developmentally, and therefore, not collected at baseline.

obsessions and compulsions only. Finally, negative emotionality was unrelated to clinical and functional outcomes, whereas baseline ADHD and psychopathology were the most consistent predictors of negative outcomes.

There is replicated evidence that irritable or negative affective dimensions of ODD predict both internalizing and externalizing problems, whereas oppositional ODD more specifically predicts externalizing problems (e.g., Aebi et al., 2015; Althoff et al., 2014; Burke et al., 2010). However, previous studies did not control for baseline negative emotionality, which is central to developmental models of psychopathology (Lahey, 2004). For example, given its positive association with negative affect (Zastrow, Martel, & Widiger, 2016) as well as shared genetic influences (Singh & Waldman, 2010), trait negative emotionality must be considered in concert with ODD (Mikolajewski, Hart, & Taylor, 2017). In one other study, with control of baseline internalizing problems, predictions of anxiety and depression from ODD dimensions were substantially attenuated (Lavigne et al., 2014). Thus, without adequate incorporation of other potent risk factors for psychopathology outcomes, the validity of separable ODD dimensions should be cautiously interpreted. Next, the inverse prediction of anxiety and depression from oppositional ODD in the current study should be interpreted relative to evidence that anxious youth rigidly impose rules on others due to anxiety-provoking stimuli (Lebowitz, Omer, & Leckman, 2011; Thompson-Hollands, Kerns, Pincus, & Comer, 2014). Relatedly, the finding that irritable ODD positively predicted obsessions and compulsions may reflect that obsession-related distress and avoidance of distress-provoking stimuli/situations can manifest as disruptive behavior, oppositionality, and aggression (Lebowitz et al., 2011; Storch et al., 2012) among youth with OCD.

Our primary aim was to test the validity of individual oppositional and irritable ODD dimensions as prospective predictors of psychopathology and impairment outcomes. However, the current study did not examine potential *interactive* influences of oppositional and irritable ODD dimensions on later psychopathology, which would correspond with longstanding developmental psychopathology principles such as interactive influences underlying typical and atypical development (Sroufe, 2009). However, in other studies, latent class analysis revealed four latent classes or subgroups of ODD (i.e., typically No symptoms, Irritable, Defiant, and All Symptoms classes) (Aebi et al., 2015; Althoff et al., 2014; Kuny et al., 2013). For example, individuals in the Irritable class had low concurrent ODD diagnoses, but increased odds of adulthood mood disorders, and those in the Defiant class had low concurrent ODD diagnoses, but increased odds for adulthood violence; finally, individuals in the All Symptoms class had increased frequency of concurrent ODD diagnoses and violence in adulthood (Althoff et al., 2014). Next, although outcomes were treated independently in the present study, irritable and oppositional ODD dimensions may relate to a general psychopathology factor, which powerfully explains covariation among psychopathology outcomes and constitutes its own latent factor (Caspi et al., 2014; Tackett et al., 2013; Laceulle, Vollebergh, & Ormel, 2015). Finally, the irritable ODD dimension represents one specific assessment of the latent irritability construct, although others may be more useful and explanatory. For example, Stringaris et al. (2012) developed the Affective Reactivity Index, which is intended to be a measure of irritability and negative affect that can quickly and efficiently (seven items) be utilized in both clinical and research settings without dependence on a full diagnostic assessment (Stringaris et al., 2012).

Developmentally, we consider a number of important themes that may usefully contextualize emergent evidence on the predictive validity of ODD dimensions. First, in the

present study, ODD dimensions were factor-analytically derived from school-age youth (mean = 7.9 years old). However, there may be developmental invariance given that basic taxonomic and phenomenological aspects of these ODD dimensions may change with development. For example, Burke et al. (2010) and Lavigne et al., (2015) assessed the factor structure of ODD dimensions at multiple time points, but not at considerably different developmental stages (i.e., 3-4 year spans in early childhood). Relatedly, another sample evaluated ODD dimensions by grouping individuals in 2-year age intervals spanning from age 12-25 years; the model fit varied such that in age groups on the extreme ends (i.e., separate 12-13 and 24-25 groups), the 2-factor model was not an ideal fit compared to in other age groups (Leadbeater & Homel, 2015). Additionally, evaluating how predictions of psychopathology from ODD dimensions vary across time may critically clarify key developmental time periods and areas for intervention. A cross-lagged panel analysis (Kearney, 2017), for example, would be well-positioned to understand reciprocal relationships among ODD dimensions, related constructs such as irritability and neuroticism, as well as other forms of psychopathology (e.g., anxiety, depression, and CD) across time.

Several study limitations should be highlighted. First, we examined individual differences in symptoms of irritable and oppositional ODD rather than youth who exclusively met full diagnostic criteria for ODD, which may have afforded more severity, additional impairment, and subsequent risk for later psychopathology. Next, the relatively low number of girls in this study (31% of youth) prevented meaningful tests of sex differences in predictive patterns, an important consideration given sex differences in key outcomes in this study (e.g., depression, CD, psychopathic traits). For example, girls have higher negative affect and an earlier onset of depression in early adolescence relative to boys (Burke et al., 2010; Martel, 2013). Similarly, a

negative affect dimension of ODD predicted depression in an all-female sample (Burke et al., 2010). Given that girls with early externalizing problems exhibit co-occurring psychopathology at rates that are comparable to, or even exceed risk ratios for boys, future research should ensure adequate representation of girls (Tung et al., 2016). Finally, our study did not detect effects with respect to emerging substance misuse outcomes—other sampling strategies may have been needed to detect substance misuse (e.g., older youth in adolescence; specifically recruiting youth of parents with substance use disorders).

In summary, we found limited evidence of the predictive validity of irritable and oppositional ODD dimensions when we conservatively controlled for baseline negative emotionality, ADHD, and relevant psychopathology. Oppositional ODD only *inversely* predicted separate parent and youth ratings of anxiety and depression, and irritable ODD predicted parent-rated obsessions and compulsions only. These findings suggest that the predictive utility of separable ODD dimensions should be interpreted cautiously, particularly without consideration of other developmentally-sensitive childhood psychopathology risk factors. Future research should prioritize models that are better positioned to assess irritable and oppositional ODD's prediction of a general psychopathology factor and that are developmentally-sensitive with respect to the assessment of ODD dimensions (e.g., accounting for developmental changes in ODD factors across time). Additionally, the field would benefit from more consistent and developmentally-sensitive measurements of irritability and negative affect across the lifespan, and mechanisms underlying these constructs' relationships with psychopathology to guide meaningful prevention and intervention efforts.

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Table 1. Descriptive Statistics of Key Variables (N = 145)

Variable	Wave 1	Wave 3
Age (years)	7.9 (0.1)	12.6 (0.1)
Sex (% Male)	69.0%	69.0%
Race (% Caucasian)	52.4%	52.4%
Household Income (% <$70k/yr)	23.4%	23.4%
% Parent-Rated ODD Diagnosis (DISC)	30.3%	12.7%
% Parent-Rated ADHD Diagnosis (DISC)	52.0%	27.5%
% Parent-Rated Anxiety Disorder Diagnosis (DISC)	32.6%	4.8%
% Parent-Rated Depressive Disorder Diagnosis (DISC)	0.7%	2.1%
% Parent-Rated CD Diagnosis (DISC)	2.8%	0.7%
Parent-Rated Irritable ODD Symptoms (DBD)	2.4 (0.2)	-
Parent-Rated Oppositional ODD Symptoms (DBD)	3.8 (0.2)	-
Parent-Rated Negative Emotionality	25.0 (0.5)	-
Parent-Rated ADHD Symptoms (DBD)	20.5 (1.1)	-
Parent-Rated Internalizing T-Score (CBCL)	53.8 (0.9)	-
Parent-Rated Total Anxiety & Depression T-Score (RCADS)	-	46.8 (0.8)
Youth-Rated Total Anxiety & Depression T-Score (RCADS)	-	43.3 (0.9)
Parent-Rated CD Symptoms (DBD)	1.7 (0.2)	1.1 (0.1)
Youth-Rated ASB	-	3.6 (0.4)
Parent-Rated Psychopathic Traits	4.9 (0.3)	4.5 (0.3)
Youth-Rated Lifetime Sips of Alcohol	-	5.7 (1.1)
Parent- & Interviewer Rated Functional Impairment (CGAS)	70.4 (1.2)	-
Parent-Rated Functional Impairment (BFIS)	-	2.0 (0.3)

Notes. Data include means and standard deviations unless otherwise noted. ODD = oppositional defiant disorder; DISC = Diagnostic Interview Schedule for Children-IV; ADHD = Attention-deficit/hyperactivity disorder; Anxiety Disorder = generalized anxiety disorder, social anxiety disorder, and/or specific phobia; Depressive Disorder = major depressive disorder and/or dysthymia; CD = conduct disorder; Symptoms = 0-3 rating x number of symptoms; DBD = Disruptive Behavior Disorder Rating Scale; CBCL = Child Behavior Checklist; RCADS = Revised Children's Anxiety & Depression Scale; ASB = Antisocial Behavior; CGAS = Children's Global Assessment Scale; BFIS = Barkley Functional Impairment Scale

Table 2. ODD Confirmatory Factor Analysis Results

Symptoms	Irritable Factor	Oppositional Factor
Often loses temper	.80	
Is often spiteful or vindictive	.76	
Is often angry and resentful	.76	
Is often touchy or easily annoyed by others	.76	
Often actively defies or refuses to comply with adults' requests or rules		.83
Often argues with adults	.30	.78
Often deliberately annoys people		.68
Often blames others for his/her own mistakes or misbehavior		.41
Eigenvalues	2.51	1.92
Proportion of variance	.31	.24
Cumulative proportion of variance	.31	.55

Note. Factor loadings, eigenvalues, and explanations of variance are based on exploratory factor analysis with promax rotation with eight parent-rated ODD symptoms according to the DBD at Wave 1. Factor loading of $d < .30$ were suppressed.

Table 3. Bivariate Correlations Among Key Study Variables (N = 145)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Wave 1 Parent-Rated Irritable ODD Symptoms	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2. Wave 1 Parent- Rated Oppositional ODD Symptoms	.70*	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3. Wave 1 Parent- Rated Negative Emotionality	.71*	.72*	-	-	-	-	-	-	-	-	-	-	-	-	-
4. Wave 1 Parent-Rated ADHD Symptoms	.51*	.67*	.56*	-	-	-	-	-	-	-	-	-	-	-	-
5. Wave 1 Parent-Rated Internalizing T-Score (CBCL)	.43*	.40*	.51*	.42*	-	-	-	-	-	-	-	-	-	-	-
6. Wave 3 Parent-Rated Total Anxiety & Depression T-Score (RCADS)	.26*	.18	.27*	.26*	.45*	-	-	-	-	-	-	-	-	-	-
7. Wave 3 Youth-Rated Total Anxiety & Depression T-Score (RCADS)	.11	.05	.11	.18*	.19*	.45*	-	-	-	-	-	-	-	-	-
8. Wave 1 Parent-Rated CD	.69*	.65*	.50*	.55*	.29*	.10	.04	-	-	-	-	-	-	-	-
9. Wave 3 Parent-Rated CD	.25*	.29*	.19*	.34*	.24*	.21*	.14	.43*	-	-	-	-	-	-	-
10. Wave 3 Youth-Rated ASB	.11	.10	.13	.25*	.07	.06	.19*	.02	.19*	-	-	-	-	-	-
11. Wave 1 Parent-Rated Psychopathic Traits	.57*	.67*	.57*	.62*	.36*	.18*	.12	.70*	.46*	.19*	-	-	-	-	-
12. Wave 3 Parent-Rated Psychopathic Traits	.43*	.47*	.40*	.49*	.33*	.22*	.09	.53*	.65*	.10	.74*	-	-	-	-
13. Wave 3 Youth-Rated Lifetime Sips of Alcohol	-.01	.07	-.02	-.02	-.07	-.23*	<.01	-.15	.07	.33*	.02	-.02	-	-	-
14. Wave 1 Parent- & Interviewer-Rated Functional Impairment (CGAS)	-.50*	-.60*	-.54*	-.72*	-.47*	-.27*	-.16	-.46*	-.34*	-.27*	-.46*	-.37*	.06	-	-
15. Wave 3 Parent-Rated Functional Impairment (BFIS)	.28*	.30*	.22*	.43*	.24*	.31*	.17	.32*	.36*	.18	.50*	.55*	.05	-.38*	-

Note: ODD = oppositional defiant disorder; ADHD = Attention-deficit/hyperactivity disorder; Symptoms = 0-3 rating x number of symptoms; CBCL = Child Behavior Checklist; RCADS = Revised Children's Anxiety & Depression Scale; CD = conduct disorder; ODD, ADHD, and CD Symptoms are all based-on parent reports according to the Disruptive Behavior Disorders Rating Scale; ASB = antisocial behavior; CGAS = Children's Global Assessment Scale (note that high numbers indicate better functioning); BFIS = Barkley Functional Impairment Scale (note that high number indicate worse functioning); * $p < .05$.

Table 4. Predictions of Parent-Rated Anxiety and Depression

Wave 3 Dependent Variable	Baseline Predictors	*β*	*SE*	*p*
Total Anxiety & Depression	Irritable ODD	.61	.51	.23
(*n* = 142)	Oppositional ODD*	-1.12	.36	< .001
	Negative Emotionality	.17	.20	.39
	ADHD*	.13	.06	.04
	Internalizing Problems*	.32	.07	< .001
Total Anxiety	Irritable ODD	.71	.52	.17
(*n* = 142)	Oppositional ODD*	-1.12	.37	< .01
	Negative Emotionality	.16	.21	.46
	ADHD	.06	.06	.37
	Internalizing Problems*	.31	.07	< .001
Depression	Irritable ODD	.05	.42	.90
(*n* = 142)	Oppositional ODD*	-.98	.44	.03
	Negative Emotionality	.16	.19	.41
	ADHD*	.31	.07	< .001
	Internalizing Problems*	.28	.07	< .001

Note. ODD = oppositional defiant disorder. ADHD = attention-deficit/hyperactivity disorder. *B* = parameter estimate; *SE* = standard error, and *p* = p-value. * p < .05.

Table 5. Predictions of Parent-Rated Anxiety Subscales

Wave 3 Dependent Variable	Baseline Predictors	*β*	*SE*	*p*
Separation Anxiety	Irritable ODD	.67	.47	.15
(*n* = 142)	Oppositional ODD*	-1.56	.46	< .001
	Negative Emotionality	.25	.23	.27
	ADHD	.13	.08	.10
	Internalizing Problems*	.19	.08	.01
Generalized Anxiety	Irritable ODD	.28	.50	.58
(*n* = 142)	Oppositional ODD	-.81	.44	.07
	Negative Emotionality	.30	.23	.18
	ADHD	.04	.08	.62
	Internalizing Problems*	.24	.07	< .01
Panic	Irritable ODD	.41	.48	.40
(*n* = 142)	Oppositional ODD*	-.84	.33	.01
	Negative Emotionality	-.03	.21	.88
	ADHD	.07	.07	.28
	Internalizing Problems*	.29	.08	< .001
Social Phobia	Irritable ODD	.43	.51	.40
(*n* = 142)	Oppositional ODD	-.48	.38	.20
	Negative Emotionality	.09	.22	.69
	ADHD	-.01	.06	.89
	Internalizing Problems*	.28	.08	< .001
Obsessions/Compulsions	Irritable ODD*	.85	.43	.04
(*n* = 142)	Oppositional ODD*	-.91	.34	< .01
	Negative Emotionality	.11	.17	.51
	ADHD	.02	.05	.65
	Internalizing Problems*	.13	.06	.03

Note. ODD = oppositional defiant disorder. ADHD = attention-deficit/hyperactivity disorder. *B* = parameter estimate; *SE* = standard error, and *p* = p-value. * p < .05.

Table 6. Predictions of Youth-Rated Anxiety and Depression

Wave 3 Dependent Variable	Baseline Predictors	*β*	*SE*	*p*
Total Anxiety & Depression	Irritable ODD	.36	.47	.44
(*n* = 142)	Oppositional ODD*	-1.18	.56	.04
	Negative Emotionality	.06	.27	.83
	ADHD*	.19	.09	.04
	Internalizing Problems	.16	.10	.10
Depression	Irritable ODD	-.08	.53	.88
(*n* = 142)	Oppositional ODD	-.82	.55	.14
	Negative Emotionality	-.09	.24	.71
	ADHD*	.26	.09	< .01
	Internalizing Problems*	.22	.09	.01

Note. ODD = oppositional defiant disorder. ADHD = attention-deficit/hyperactivity disorder. *B* = parameter estimate; *SE* = standard error, and *p* = p-value. * p < .05.

Table 7. Predictions of Externalizing Problems

Wave 3 Dependent Variable	Baseline Predictors	*β*	*SE*	*p*
Parent-Rated Conduct Disorder	Irritable ODD	-.01	.06	.90
(*n* = 145)	Oppositional ODD	.03	.05	.56
	Negative Emotionality	-.02	.03	.50
	ADHD*	.02	.01	.03
	Parent-Rated Conduct Disorder*	.11	.04	.02
Parent-Rated Psychopathic Traits	Irritable ODD	.01	.03	.82
(*n* = 137)	Oppositional ODD	-.02	.03	.47
	Negative Emotionality	-.01	.01	.96
	ADHD	.01	.01	.08
	Parent-Rated Psychopathic Traits*	.15	.02	< .001

Note. ODD = oppositional defiant disorder. ADHD = attention-deficit/hyperactivity disorder. *B* = parameter estimate in logits; *SE* = standard error, and *p* = p-value. * p < .05.

Table 8. Predictions of Functional Impairment

Wave 3 Dependent Variable	Baseline Predictors	*β*	*SE*	*p*
Parent-Rated Impairment (BFIS)	Irritable ODD	.08	.06	.21
(*n* = 134)	Oppositional ODD	-.06	.06	.33
	Negative Emotionality	-.03	.03	.36
	ADHD*	.04	.01	< .01
	Parent/Interviewer-Rated* Impairment (CGAS)	-.02	.01	.03

Note. BFIS = Barkley Functional Impairment Scale. ODD = oppositional defiant disorder. ADHD = attention-deficit/hyperactivity disorder. CGAS = Children's Global Assessment Scale. *B* = parameter estimate in logits; *SE* = standard error, and *p* = p-value. * p < .05.

Study III: Reactive Aggression Mediates Predictions of Youth Antisocial Behavior from Irritable ODD

Abstract

Objective: Oppositional defiant disorder (ODD) consists of separable dimensions (e.g., irritable and oppositional dimensions) and although some pathways underlying predictions of later antisocial behavior (ASB) from ODD overall have been elucidated, little is known about the pathways mediating predictions from separable irritable versus oppositional facets. The aim of the present study was to test reactive and proactive aggression as simultaneous, temporally-ordered mediators of predictions of multi-informant rated ASB (i.e., youth-reported ASB and parent-rated conduct disorder (CD) symptoms) from irritable ODD symptoms and oppositional ODD symptoms in a sample of school-age youth followed prospectively.

Method: 134 ethnically-diverse youth (69.4% male; 54.5% Caucasian; 50.0% with ADHD at baseline; mean age 7.9 years at baseline; mean age 10.1 years at Wave 2; mean age 12.5 years at Wave 3) were followed prospectively from childhood to early adolescence. A multiple mediator macro with bootstrapping tested the mediational roles of reactive and proactive aggression.

Results: Individual differences in Wave 2 reactive aggression significantly mediated the prediction of Wave 3 youth-rated ASB from baseline irritable ODD. Wave 1 irritable ODD positively predicted Wave 2 reactive aggression in all prediction models. No other mediated effects were observed.

Conclusions: Given reactive aggression's unique mediation of youth ASB in predictions from irritable ODD, youth with early irritable ODD may benefit from interventions targeting improvements in emotion regulation skills to prevent the development of reactive aggression and

subsequent ASB. Moreover, irritability may constitute a transdiagnostic factor that requires further assessment with respect to correlates, outcomes, and causal mechanisms.
Keywords: ODD; Irritability; Oppositionality; Aggression; Antisocial behavior

Reactive Aggression Mediates Predictions of Youth Antisocial Behavior from Irritable ODD

Historically, ODD was conceptualized unidimensionally (Bauermeister, 1992; Burns, Boe, Walsh, Sommers-Flanagan, & Teegarden, 2001; Burns & Patterson, 2000; Pelham, Gnagy, Greenslade, & Milich, 1992). However, efforts to improve the nosology of mental disorders for DSM-5 (American Psychiatric Association, 2013; Pardini, Frick, & Moffitt, 2010) reported that ODD consisted of separable dimensions: some ODD symptoms (e.g., "often angry or resentful") differentially loaded onto an irritable or affective dimension, which predicted internalizing (e.g., anxiety, depression) *and* externalizing problems. Other ODD symptoms (e.g., "often argues with adults") loaded onto an oppositional/defiant dimension that was more specifically associated with CD and related ASB (Burke, 2012; Burke, Rowe, & Boylan, 2014; Burke, Hipwell, & Loeber, 2010; Drabick & Gadow, 2012; Rowe, Costello, Angold, Copeland, & Maughan, 2010; Stringaris & Goodman, 2009a, 2009b). This evidence is reflected in DSM-5's (American Psychiatric Association, 2013; Hawes, 2014) criteria for ODD, with separate "angry/irritable mood," "argumentative/defiant behavior," and "vindictiveness" typologies. Given this heterogeneity, examining the potential utility of separable ODD dimensions in clinical decision-making and treatment response is a vital next step for the field (Wakschlag et al., 2015).

Although there is considerable evidence on potential pathways underlying predictions of later ASB from ODD overall, little is known about predictions from separable irritable versus oppositional facets, including identifying mediating pathways and processes. That is, to improve causal models of psychopathology and to accelerate innovations in intervention (MacKinnon, 2015; Rose, Holmbeck, Coakley, & Franks, 2004), elucidation of potential mechanisms underlying predictions of later psychopathology and impairment from irritable and oppositional ODD dimensions is necessary. Theoretical formulations suggest that models of risk processes in

ODD should be examined specifically with respect to aggression subtypes (Bubier & Drabick, 2009; Drabick, Ollendick, & Bubier, 2010). Reactive aggression and proactive aggression constitute potentially important mediators underlying predictions of later ASB from irritable and oppositional ODD, respectively. Reactive aggression is retaliatory or in response to provocation, typically in the presence of negative affective states (Miller & Lynam, 2006), whereas proactive aggression is organized and goal-oriented without requiring provocation (Raine et al., 2006; Vitaro, Gendreau, Tremblay, & Oligny, 1998). ODD is highly associated with reactive and proactive aggression (Becker, Luebbe, Fite, Greening, & Stoppelbein, 2013; Waschbusch & Willoughby, 1998). Similar to irritable ODD, reactive aggression is positively associated with negative emotionality, neuroticism, irritability, negative affect (Miller & Lynam, 2006; Raine et al., 2006; Vitaro, Barker, Boivin, Brendgen, & Tremblay, 2006), as well as internalizing problems (Bubier & Drabick, 2009; Marsee, Weems, & Taylor, 2008; Scarpa, Haiden, & Tanaka, 2010). Like oppositional ODD, proactive aggression is positively associated with intentional rule-breaking and defiance, and is specifically associated with ASB outcomes including serious violent offending and high psychopathic traits (Fite, Raine, Stouhthamer-Loeber, Loeber, & Pardini, 2009; Raine et al., 2006). Reflecting their empirical separability (Hubbard, McAuliffe, Morrow, & Romano, 2010), reactive and proactive aggression each uniquely predict ASB (Fite et al., 2009). Thus, reactive aggression is a plausible mediator in predictions of significant ASB from irritable ODD, whereas proactive aggression may similarly mediate predictions from oppositional ODD.

Meta-analytic data suggest that reactive and proactive aggression are correlated, but separable (Polman, Orobio de Castro, Koops, van Boxtel, & Merk, 2007) with respect to genetic influences, stability estimates (Baker, Raine, Liu, & Jacobson, 2008; Bezdijan, Raine, Tuvblad,

& Baker, 2011; Tuvblad, Raine, Zheng, & Baker, 2009), and autonomic arousal (Scarpa et al., 2010; Scarpa & Raine, 1997). Similarly, neurobiologically, impaired ventromedial prefrontal cortex (Blair, 2009) and low neural serotenergic functioning (van Honk, Harmon-Jones, Morgan, & Schutterk, 2010) are relatively specific to the etiology of reactive aggression. Given that reactive and proactive aggression are separable but correlated, their potential explanatory roles underlying emergent ASB should be accounted for simultaneously. By employing multiple mediation, the current study tested the collective and potentially unique (i.e., controlling for their inter-correlation) meditational roles of reactive and proactive aggression with respect to predictions of self-reported ASB and parent-rated CD from irritable and oppositional ODD.

Carefully examining reactive and proactive aggression as mediators from irritable and oppositional ODD to later ASB has important clinical implications for youth with externalizing problems. Parent training is considered the standard treatment for youth with early conduct problems, including ODD (e.g., Furlong et al., 2013; Michelson, Davenport, Dretzke, Barlow, & Day, 2013). However, interventions for reactive aggression focus on increasing emotion regulation skills, coping skills for negative emotions, and social skills, while also promoting positive peer relationships to prevent development of internalizing disorders (Fite et al., 2009; Marsee & Frick, 2007; Merk, Orobio de Castro, Koops, & Mathys, 2005). In contrast, children with primary proactive aggression may benefit from problem solving skills training to evaluate the consequences of behavior (Fite et al., 2009), reward/punishment contingencies (Smithmeyer, Hubbard, & Simmons, 2010; Vitello & Stoff, 1997), and developing alternative behaviors to attain goals typically attained via aggression (Day, Bream, & Pal, 1992; Merk et al., 2005). Accordingly, if mediational models find reliable associations between irritable ODD and reactive

aggression and/or oppositional ODD and proactive aggression, it would suggest specific treatment targets to prevent enduring ASB for youth depending on their clinical presentation.

The aim of the present study was to test reactive and proactive aggression as simultaneous mediators of predictions of multi-informant rated ASB (i.e., youth-reported ASB and parent-rated CD symptoms) from irritable ODD symptoms and oppositional ODD symptoms. We hypothesized that Wave 2 reactive aggression would uniquely mediate (i.e., controlling for proactive aggression) predictions of Wave 3 ASB and CD symptoms from Wave1 irritable ODD symptoms, controlling for Wave1 ADHD and oppositional ODD symptoms, as well as key demographic variables. Additionally, we hypothesized that Wave 2 proactive aggression, independent of Wave 2 reactive aggression, would uniquely mediate predictions of Wave 3 ASB and CD symptoms from Wave 1 oppositional ODD symptoms, controlling for Wave 1 ADHD and irritable ODD symptoms, as well as demographic factors.

Method

Participants

Participants were 223 ethnically-diverse children (67% male; 50.7% Caucasian; 8.5% Black; 10.8% Hispanic; 3.6% Asian; 21.9% mixed; 4.5% other or declined) children with (52%) and without ADHD (48%). There were no diagnostic group differences with respect to age, sex, race-ethnicity, or socioeconomic status among youth with and without ADHD. Subjects were 5- to 10-years-old (M = 7.9 years, SD = 1.2 years) at baseline (i.e., Wave 1), 7- to 13-years-old (M = 10.2 years, SD = 1.3 years) at their two- to three- year follow-up (i.e., Wave 2), and 9 to 15-years-old (M = 12.6 years, SD = 1.3 years) at the Wave 3 follow-up. Approximately 88% of the original sample was assessed at Wave 2 and 78% of the original sample (i.e., n = 174) participated at all three waves. Expectedly, the sample size varied across measures and waves:

for specific Wave 3 outcomes, the N varied from n = 104 for predictions of Wave 3 youth-rated ASB to N = 134 for predictions of Wave 3 parent-rated CD symptoms. Table 1 includes demographic characteristics for the participants with complete data across all three waves in the present study (i.e., N = 134).

At baseline, participants were recruited from the community (e.g., advertisements in local schools) as well as referrals from pediatricians and local mental health service providers in a large metropolitan city in the Western United States. Participants were required to live with at least one biological parent at least half-time, be enrolled in school full-time, and be fluent in English. Participants with a Full Scale IQ less than 70, an autism spectrum disorder (including if it was suspected and not formally assessed), seizure, or neurological disorder were excluded from participation. Non-ADHD comparison children who met diagnostic criteria for mental disorders other than ADHD were included in the study to avoid exaggerating diagnostic group differences. All participants were recruited, screened, and assessed using identical procedures.

Procedures

At baseline, interested families completed an initial telephone screen to determine their study eligibility based on the inclusionary and exclusionary criteria listed above. Rating scales were mailed to eligible families and they were subsequently invited for in-person laboratory-based assessments. After parental consent and child assent was obtained, clinical psychology doctoral students and/or bachelor of arts-level trained staff assessed children's academic achievement, cognitive ability, and socio-emotional functioning while a second member of the research staff concurrently interviewed parents about their child's psychopathology. All interviewers were initially blind to the child's diagnostic status, but the blind could not always be preserved given the extensive information gathered about the child. Parents (85% mothers at

Wave 1, 88% at Wave 2, and 84% at Wave 3) were asked to rate each child based on his or her unmedicated behavior. Parents were administered the Diagnostic Interview Schedule for Children, 4th edition (DISC-IV; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000), a fully structured diagnostic interview including questions on DSM-IV criteria including age of onset and functional impairment. All *diagnostic* information for the sample, including ADHD proband status (i.e., ADHD versus non-ADHD comparison) and psychopathology (e.g., ODD, CD) outcomes, were ascertained via the DISC-IV. Additional disorder and/or construct-specific measures were also administered. Thus, diagnostic and impairment outcomes were assessed with the DISC-IV *and* through additional comprehensive measures. The majority of participants were evaluated unmedicated during the assessment (i.e., 94%, 89%, and 92% of children at Wave 1, Wave 2, and Wave 3, respectively).

Approximately two years after the initial assessment, families were invited to participate in a follow-up laboratory assessment (i.e., Wave 2). Consisting of highly similar assessment procedures to those at Wave 1, relevant domains at Wave 2 included youth psychopathology, functional impairment, academic achievement, as well as family functioning. There were no demographic or diagnostic differences (i.e., age, sex, ethnicity, family income, baseline ADHD diagnostic status, baseline ODD diagnostic status, and baseline CD status) between participants at Wave 1 and 2 versus non-participants at Wave 2. A Wave 3 assessment was completed approximately two to three years after Wave 2, once again consisting of parallel assessment domains, but with developmentally-appropriate modification and expansions (e.g., alcohol and substance use interviews). There were no demographic or diagnostic status (i.e., age, sex, ethnicity, family income, baseline ADHD status, baseline ODD status, and baseline CD status)

differences between families that participated at all three waves of the study versus those who did not participate at Wave 3. All study procedures for all waves were approved by the IRB.

Measures

ODD, ADHD, and CD symptoms. ODD, ADHD, and CD symptoms were assessed at every wave by parents with the Disruptive Behavior Disorders Rating Scale (DBD; Pelham et al., 1992). The DBD is an evidence-based assessment measure of ADHD, ODD, and CD symptoms with excellent psychometric properties (Lahey et al., 2004; Pelham, Fabiano, & Massetti, 2005; Shemmassian & Lee, 2016). The measure consists of 8 ODD items (e.g., "often argues with adults" and "often loses temper"), 18 ADHD items (e.g., "often fidgets with hands or feet or squirms in seat"), and 15 CD items (e.g., "has been physically cruel to people" and "has deliberately destroyed others' property.") All items were rated as being present "not at all," "just a little", "pretty much," or "very much." To maximize variance because disruptive behavior problems are often infrequent in young children, we examined ODD, ADHD, and CD symptoms dimensionally (i.e., 0-3 range for each item summed across the 8, 18, and 15 total items, respectively). 216 participants completed the DBD at Wave 1 (Cronbach alphas of .89 for ODD, .96 for ADHD, and .67 for CD). 152 of those participants had complete DBD data at Wave 3 (Cronbach alphas of .88 for ODD, .95 for ADHD, and .54 for CD).

Wave 1 ODD dimensions. Irritable and oppositional ODD dimensions were calculated with confirmatory factor analysis using the Wave 1 DBD (see Table 2 for factor loadings; consistent with prior factor analyses in this sample- McKenzie & Lee, 2014) which yielded results similar to those in other samples that have demonstrated that ODD is best characterized as two separate dimensions (Lavigne, Bryant, Hopkins, & Gouze, 2015). Irritable ODD consisted of "is often spiteful or vindictive," "is often angry and resentful," "is often touchy or easily annoyed

by others," and "often loses his/her temper." Oppositional ODD is composed of "often argues with adults," "often blames others for his/her mistakes or behavior," "often actively defies or refuses to comply with adults' requests or rules," and "often deliberately annoys people." The Cronbach alpha is .84 for the irritable dimension and .81 for the oppositional dimension.

Reactive and proactive aggression. The Reactive-Proactive Aggression Questionnaire (RPQ; Raine et al., 2006) was administered separately to parents and youth at Wave 2. The RPQ is a 23-item questionnaire of reactive aggression (i.e., retaliatory; in response to provocation) and proactive aggression (i.e., instrumental, organized). The reactive aggression subscale consists of 11 items (e.g., "gets angry or mad when they don't get their way") and the proactive aggression subscale consists of 12 items (e.g., "uses force to get others to do what they want," "damages or breaks things for fun"). The RPQ is psychometrically sound with evidence of cross-cultural generalizability (Fossati et al., 2009; Fung, Raine, & Gao, 2009; Raine et al., 2006).[6]

Given the clinical utility of multi-informant ratings of reactive and proactive aggression (Ollendick, Jarrett, Wolff, & Scarpa, 2009) and to reduce Type I error associated with multiple tests, we combined separate parent and youth self-reports of reactive and proactive aggression. Given concern that parents may underreport relevant behaviors due to lack of insight into the motivation for their child's aggression (Baker et al., 2008), the maximum rating between the child and parent was selected (e.g., if a child rated himself a 1 and a parent rated him a 0, 1 was selected) for each item, and then the combined ratings were summed to calculate the reactive and proactive aggression subscales (Cronbach alphas of .83 and .80 respectively).

[6] To ensure that reactive and proactive aggression items did not share significant variance or symptom overlap with ODD items, we conducted an exploratory factor analysis that included parent-ratings of all Wave 2 reactive aggression, Wave 2 proactive aggression, and Wave 1 ODD items. Results indicated that all ODD items were separable from reactive and proactive aggression items.

Self-reported ASB. Youth completed the 32-item Self-Reported Antisocial Behavior (SRA; Loeber, Stouthamer-Loeber, Van Kammen, & Farrington, 1989) semi-structured interview of ASB and delinquency (e.g., theft, aggression, vandalism, substance use) at Wave 3. One item was excluded (i.e., "How many times in the past 6 months have you sniffed glue?") from analyses because none of the study participants endorsed it. The frequency of behaviors were rated as "never," "once," "twice," or "more often," in the past 6 months and coded 0-3, respectively. We utilized the sum of all item ratings to estimate ASB (possible range = 0 to 93), which had a Cronbach alpha of .71; 118 participants completed the full SRA at Wave 3. See Table 3 for correlation table.

Data Analytic Procedures

We examined whether individual differences in Wave 2 combined parent- and youth-rated reactive aggression and proactive aggression mediated separate predictions of Wave 3 youth-reported ASB and Wave 3 parent-rated CD symptoms from Wave 1 parent-rated irritable and oppositional ODD dimensions. Notably, all key constructs (i.e., independent variables, mediators, dependent variables) were temporally-ordered across the three waves, a necessary but rarely satisfied requirement for causal mediation (Kraemer, Stice, Kazdin, Offord, Kupfer, 2001). A multiple mediator macro with bootstrapping (i.e., a non-parametric re-sampling procedure that repeatedly samples from a dataset *k* number of times and empirically estimates a sampling distribution of the indirect effect of mediators) was employed (Preacher & Hayes, 2008) using the PROCESS macro in SPSS 24.0, which deletes missing data listwise as it requires complete data and does not accommodate imputed data. Note that the sample size used in the present analyses (n = 104 to 134) exceeds the required sample size (n = 71) to adequately power (i.e., .8 power) product-of-coefficients tests of mediation using bootstrap methods for path

coefficients with medium effects (Fritz & Mackinnon, 2007). Bootstrapping is robust to non-normal data (Preacher & Hayes, 2008), a key advantage with psychopathology data. Also, because the distribution is non-symmetrical, the betas for the indirect effect, divided by the standard error are not equivalent to traditional *t* statistics. Multiple mediation is superior to traditional mediation because it concurrently accounts for variance due to more than one mediator (Hayes, 2013; Preacher & Hayes, 2008; Zhao et al., 2010). Unlike traditional mediation theories, mediation does not require a significant association between the independent variable and dependent variable. Rather, mediation follows a "stage sequence" framework in which the independent variable initially affects the mediator, which then affects the dependent variable (Collins, Graham, & Flaherty, 1998). Therefore, a significant direct effect of the independent variable on the dependent variable is not required for significant mediation (Zhao et al., 2010).

First, Wave 1 *irritable* ODD symptoms were entered as an independent variable, controlling for Wave 1 ADHD and oppositional ODD symptoms; Wave 2 reactive and proactive aggression were entered as simultaneous mediators in predictions of Wave 3 *youth-reported* ASB. Next, in a separate model, Wave 1 *oppositional* ODD symptoms were entered as an independent variable, controlling for Wave 1 ADHD and irritable ODD symptoms to improve model specificity, with Wave 2 reactive and proactive aggression entered as simultaneous mediators in predictions of Wave 3 *youth-reported* ASB. These exact models were then reproduced to predict Wave 3 *parent-rated* CD symptoms. Given that sex was significantly correlated with parent and youth combined ratings of proactive aggression ($r\ (143) = .17$, $p = .04$) and that Wave 1 family income correlated significantly with Wave 3 youth-reported ASB ($\chi^2(120) = 150.96$, $p = .03$) and Wave 3 parent-rated CD symptoms ($\chi^2(72) = 115.79$, $p < .001$), sex and family income were controlled in all models.

Results

Predictions of Youth-Reported ASB from Irritable and Oppositional ODD: Mediation by Reactive and Proactive Aggression

We evaluated whether Wave 2 parent- and youth-combined ratings of reactive and proactive aggression mediated the prediction of Wave 3 youth-rated ASB from Wave 1 parent-rated irritable ODD, controlling for Wave 1 parent-rated oppositional ODD, Wave 1 parent-rated ADHD, youth sex, and family income (Model 1). Regression-based path coefficients generated by the PROCESS macro for this multiple mediation model are presented in Figure 1. There was no significant total effect (i.e., excluding the mediators from the model) or direct effect (i.e., including Wave 2 reactive and proactive aggression as mediators in the model) of Wave 1 irritable ODD on Wave 3 youth-rated ASB, but Wave 1 irritable ODD was positively associated with Wave 2 reactive aggression (β = .42, *SE* = .18, p = .02). The total indirect effect (i.e., point estimate difference between the total effect and direct effect through the two mediators) did not statistically differ from zero; however, consistent with our hypothesis, Wave 2 reactive aggression mediated the prediction of Wave 3 self-rated ASB from Wave 1 irritable ODD (CI: .01 to .31; see Table 4). Specifically, baseline irritable ODD positively predicted reactive aggression two years later, which in turn was positively associated with Wave 3 youth-rated ASB.

In a highly similar model, we examined whether Wave 2 parent- and youth-combined ratings of reactive and proactive aggression mediated the prediction of Wave 3 youth-rated ASB from Wave 1 parent-rated *oppositional* ODD, controlling for Wave 1 parent-rated *irritable* ODD, Wave 1 parent-rated ADHD, youth sex, and family income (Model 2; see Figure 2 and Table 4). There was no significant total effect or direct effect of Wave 1 oppositional ODD on Wave 3

youth-rated ASB, but consistent with the model described above, Wave 1 irritable ODD was positively associated with Wave 2 reactive aggression (β = .42, *SE* = .18, p = .02). However, there were no significant specific indirect effects of Wave 2 reactive aggression or proactive aggression in this model, nor a significant total indirect effect. To summarize, Wave 2 reactive aggression mediated predictions of Wave 3 youth-rated ASB from Wave 1 *irritable ODD*, with control of key demographic and diagnostic variables, as well as above and beyond concurrent proactive aggression, which did not mediate the prediction of Wave 3 youth-rated ASB from Wave 1 irritable ODD. Neither reactive or proactive aggression mediated the prediction of Wave 3 youth-rated ASB from Wave 1 *oppositional* ODD when accounting for pertinent demographic and diagnostic variables.

Prediction of Wave 3 Parent-Rated CD: Mediation by Reactive and Proactive Aggression

Next, we tested whether Wave 2 parent- and youth-combined ratings of reactive and proactive aggression mediated the prediction of Wave 3 *parent-rated CD* from Wave 1 parent-rated irritable ODD, controlling for Wave 1 parent-rated oppositional ODD, Wave 1 parent-rated ADHD, youth sex, and family income (Model 3; see Figure 3 and Table 4). There was no significant total effect or direct effect of Wave 1 irritable ODD on Wave 3 parent-rated CD; similarly, there were no significant specific indirect effects of Wave 2 reactive aggression or proactive aggression in this model, nor a total indirect effect. However, Wave 1 irritable ODD significantly predicted Wave 2 reactive aggression (β = .48, *SE* = .18, $p < .01$) and Wave 1 ADHD positively predicted Wave 2 proactive aggression (β = .08, *SE* = .03, $p < .01$).

Finally, we evaluated whether Wave 2 parent- and youth-combined ratings of reactive and proactive aggression mediated the prediction of Wave 3 parent-rated CD from Wave 1 parent-rated *oppositional* ODD, controlling for Wave 1 parent-rated *irritable* ODD, Wave 1

parent-rated ADHD, youth sex, and family income (Model 4; see Figure 4 and Table 4). There was not a significant total effect or direct effect of Wave 1 oppositional ODD on Wave 3 parent-rated CD. There were no significant specific indirect effects of Wave 2 reactive aggression or proactive aggression in this model, nor a total indirect effect. Once again, Wave 1 irritable ODD was significantly and positively associated with Wave 2 reactive aggression (β = .48, *SE* = .18, p < .01) and Wave 1 ADHD significantly and positively predicted Wave 2 proactive aggression (β = .08, *SE* = .03, p < .01). Thus, neither reactive or proactive aggression mediated predictions of Wave 3 parent-rated CD from either Wave 1 irritable *or* oppositional ODD while accounting for key demographic and diagnostic variables.

Discussion

To review, we evaluated whether individual differences in Wave 2 combined parent- and youth-rated reactive aggression and proactive aggression mediated separate predictions of Wave 3 youth-reported ASB and Wave 3 parent-rated CD symptoms from Wave 1 parent-rated irritable and oppositional ODD dimensions, controlling for pertinent clinical and demographic variables. In a sample of children followed prospectively into early adolescence, affording temporal ordering of predictors, mediators, and outcomes, Wave 2 reactive aggression significantly mediated predictions of Wave 3 youth-rated ASB from Wave 1 *irritable* ODD, even with control of concurrent proactive aggression as well as Wave 1 ADHD, oppositional ODD, youth sex, and family income. However, proactive aggression did not mediate predictions of youth-rated ASB. Neither Wave 2 reactive nor proactive aggression mediated predictions of Wave 3 youth-rated ASB from Wave 1 oppositional ODD. Similarly, neither Wave 2 reactive nor proactive aggression mediated predictions of Wave 3 parent-rated CD from either Wave 1

irritable ODD or oppositional ODD. Notably, Wave 1 irritable ODD predicted Wave 2 reactive aggression in all models.

Although the irritable/negative affective dimension of ODD predicts both internalizing and externalizing problems (e.g., Burke, 2012; Burke et al., 2010; Drabick & Gadow, 2012; Stringaris & Goodman, 2009a, 2009b), there is little research on the developmental progression from irritable ODD to later psychopathology (see Kessel et al., 2016 for an exception). Preliminary results from the current study implicate the role of reactive aggression, subsequent to elevated irritable ODD symptoms, in the development of subsequent ASB. These findings add to a growing body of evidence that irritable ODD is associated with key components of reactive aggression (e.g., negative affect, emotional reactivity) as well as externalizing behavior. Thus, the irritability component of ODD may relate transdiagnostically to multiple dimensions of psychopathology and their comorbidity, reflecting multifinality and shared etiological and pathophysiological processes (Kessel et al., 2016; Kring, 2008; Nolen-Hoeksema & Watkins, 2011). For example, the general psychopathology factor, which predicts individual dimensions of psychopathology and their covariation, may consist of negative emotionality, a construct related to irritability (Caspi et al., 2014; Tackett et al., 2013; Laceulle, Vollebergh, & Ormel, 2015). Moreover, multiple dimensions of psychopathology respond similarly to the same interventions, suggesting that a transdiagnostic approach has treatment utility (Caspi et al. 2014; Craske, 2012; Farchione et al., 2012). Given that irritability is a symptom of more than twelve internalizing *and* externalizing disorders (e.g., disruptive mood dysregulation disorder, bipolar disorder, generalized anxiety disorder, ODD, antisocial personality disorder), irritability is a compelling transdiagnostic factor (Althoff, 2018). Future research and intervention would benefit from more consistent measurement approaches, as well as meta-analytic reviews of its genetic, neurological,

and psychophysiological correlates (see Althoff, 2018 for more information on the ENIGMA irritability consortium that has these important aims; see Stringaris et al., 2012 for a potential solution for more consistently measuring irritability).

These preliminary findings that irritable ODD predicted the development of reactive aggression and subsequent ASB highlight the importance of delivering interventions to address irritability, putatively enhancing emotion regulation, and thereby preventing antisocial outcomes. A recent randomized controlled trial tested whether a cognitive behavioral therapy-based treatment with an emphasis on improving emotion regulation skills (i.e., the Stop Now and Plan (SNAP) Program) reduced irritability relative to a treatment as usual group among preadolescent boys; there was a significant indirect effect such that improved emotion regulation skills were associated with substantial and significant reductions in irritability (Derella, Johnston, Loeber, & Burke, 2017). In the same sample, intervention produced improvements in emotion regulation skills, prosocial behavior, and reductions in parental stress, which partially mediated improvements in child aggression; additionally, improved emotion regulation skills partially mediated anxiety and depression outcomes (Burke & Loeber, 2015). These findings suggest that interventions that specifically improve emotion regulation (e.g., dialectical behavior therapy (DBT) and mindfulness approaches) are critical to reducing irritability and aggression. One study found that a modified DBT skills training program for oppositional and defiant adolescents (i.e., 32 participants, 85% male) significantly reduced self-reported externalizing symptoms, internalizing symptoms, and depression, as well as caregiver-reported reductions in negative behaviors as well as increased positive behaviors (Nelson-Gray et al., 2006). Future intervention studies that test the effectiveness of treatments to reduce childhood irritability and aggression must include more girls, compare multiple effective treatments (e.g., emotion regulation skills

training approach vs. parent management training approach vs. combined treatment), and consider transdiagnostic treatment of irritability (see Sukhodolsky, et al., 2016).

To date, there is limited research on pharmacotherapy for treatment of irritability specifically, as well as ODD-related irritability. There is considerable pharmacological evidence on reductions on autism-related irritability (e.g., Elbe & Lalani, 2012 review) and emerging evidence for disruptive mood dysregulation disorder-related irritability (Tourian et al., 2015). Additionally, there is pharmacotherapy treatment of diagnoses comorbid with ODD, but not ODD itself (Ghosh, Ray, & Basu, 2017; Steiner & Remsing, 2007). In a systematic review of its effectiveness for the treatment of irritability and related behavioral phenotypes, antidepressant medication had a small effect on irritability and related symptoms, but samples were highly heterogeneous and only two specifically assessed irritability (Kim & Boylan, 2016). Although psychosocial-based interventions are the most efficacious interventions for ODD (Ghosh et al., 2017; Steiner & Remsing, 2007), the field must clarify the role of pharmacotherapy for irritability and ODD specifically.

Several study limitations should be considered when evaluating findings from the current study. First, the internal consistency of Wave 3 CD symptoms was modest, which likely reflects that participants in this sample were not fully into adolescence, when more variance would be expected. Additionally, only parent-reported CD was collected at Wave 3. Because covert behaviors may not be observed by or communicated with parents, supplemental informants, including youth themselves, are important in measurements of CD and ASB, especially during the transition to adolescence (Loeber, Burke, Lahey, Winters, & Zera, 2000). Note that at Wave 3 of this study, there was more variability and higher mean ratings of pre-adolescent self-reported ASB (including delinquency and substance use) relative to parent ratings of Wave 3

CD. Parents' lack of knowledge regarding some of their children's covert ASB and the low internal consistency of Wave 3 parent-rated CD may help explain why there were not significant findings with respect to mediation models predicting Wave 3 CD. Finally, the current sample was predominately male, preventing evaluation of whether mechanisms underlying the development from irritable and oppositional ODD to antisocial outcomes differed by sex. Given the relative absence of knowledge about ODD dimensions in girls (see Burke, et al., 2010 and Hipwell et al., 2011 for exceptions), we await future studies that expand mechanistic research on this population.

In summary, we observed that individual differences in reactive aggression significantly mediated the prediction of youth-rated ASB from irritable ODD. Specifically, baseline irritable ODD positively predicted reactive aggression two years later, which in turn positively predicted Wave 3 youth-rated ASB. Wave 1 irritable ODD positively predicted Wave 2 reactive aggression in all of the models we tested. These findings underscore the importance of conceptualizing irritability as a transdiagnostic factor and further refining the definition and measurement of youth irritability. Our results suggest that youth with early irritable ODD would benefit from interventions targeting improvements in emotion regulation skills to better prevent the progression to reactive aggression and ASB. The field would benefit from further mechanistic research related to the development of ODD dimensions and innovations with respect to treatment of youth irritability.

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Table 1. Descriptive Statistics of Key Variables

Variable	Wave 1	Wave 2	Wave 3
Age (years)	7.9 (1.1)	10.1 (1.2)	12.5 (1.2)
Sex (% Male)	69.4%	69.4%	69.4%
Race (% Caucasian)	54.5%	54.5%	54.5%
Household Income (% <$70k/yr)	24.6%	-	-
% ODD Diagnosis (DISC)	29.1%	16.4%	12.7%
% ADHD Diagnosis (DISC)	50.0%	41.0%	28.4%
% CD Diagnosis (DISC)	2.2%	0.7%	0.7%
Irritable ODD Symptoms (DBD)	2.4 (2.5)	-	-
Oppositional ODD Symptoms (DBD)	3.9 (2.7)	-	-
ADHD Symptoms (DBD)	20.4 (13.7)	-	-
Reactive Aggression	-	9.0 (4.0)	-
Proactive Aggression	-	2.0 (2.9)	-
Antisocial Behavior	-	-	4.1 (4.1)
CD Symptoms (DBD)	-	-	1.1 (1.5)

Notes. Data presented are for the n = 134 participants subset included in the present study's analyses. Demographic and diagnostic data for the sample were included for all waves, and variables used at only particular waves are specified for only those respective waves. Data include means and standard deviations unless otherwise indicated as percentages. ODD = oppositional defiant disorder; DISC = Diagnostic Interview Schedule for Children-IV; ADHD = Attention-deficit/hyperactivity disorder; CD = conduct disorder; Symptoms = 0-3 rating x number of symptoms; DBD = Disruptive Behavior Disorder Rating Scale. All ADHD, ODD, and CD information is based on parent reports-only. Reactive aggression and proactive were based on combined parent and youth reports. Antisocial behavior was youth-reported.

Table 2. ODD Confirmatory Factor Analysis Results

Symptoms	Irritable Factor	Oppositional Factor
Often loses temper	.80	
Is often spiteful or vindictive	.76	
Is often angry and resentful	.76	
Is often touchy or easily annoyed by others	.76	
Often actively defies or refuses to comply with adults' requests or rules		.83
Often argues with adults	.30	.78
Often deliberately annoys people		.68
Often blames others for his/her own mistakes or misbehavior		.41
Eigenvalues	2.51	1.92
Proportion of variance	.31	.24
Cumulative proportion of variance	.31	.55

Note. Factor loadings, eigenvalues, and explanations of variance are based on exploratory factor analysis with promax rotation with eight parent-rated ODD symptoms according to the DBD at Wave 1. Factor loading of $d < .30$ were suppressed.

Table 3. Bivariate Correlations Among Key Study Variables

	1	2	3	4	5	6	7	8
1. Wave 1 Irritable ODD Symptoms	-	-	-	-	-	-	-	-
2. Wave 1 Oppositional ODD Symptoms	.70**	-	-	-	-	-	-	-
3. Wave 1 ADHD Symptoms	.51**	.67**	-	-	-	-	-	-
4. Sex	.15	.15	.09	-	-	-	-	-
5. Wave 2 Reactive Aggression	.37**	.30**	.23**	.07	-	-	-	-
6. Wave 2 Proactive Aggression	.20*	.25**	.37**	.19*	.51**	-	-	-
7. Wave 3 Youth-Rated Antisocial Behavior	.09	.10	.21*	.16	.30**	.35**	-	-
8. Wave 3 CD Symptoms	.27**	.29**	.30**	.01	.18*	.20*	.22*	-

Note: ODD = oppositional defiant disorder; ADHD = Attention-deficit/hyperactivity disorder; Symptoms = 0-3 rating x number of symptoms; CD = conduct disorder; ODD, ADHD, and CD Symptoms are all based-on parent reports according to the Disruptive Behavior Disorders Rating Scale. Wave 2 reactive and proactive aggression are based on parent- and child-combined ratings.

* $p < .05$; ** $p < .01$

Table 4. Prediction of Wave 3 ASB & CD from Wave 1 ODD Dimensions: Mediation by Wave 2 Reactive and Proactive Aggression

	Predictor: Wave 1 Irritable ODD				Predictor: Wave 1 Oppositional ODD			
			95% BC Bootstrap CI				95% BC Bootstrap CI	
	Point est.	SE	Lower	Upper	Point est.	SE	Lower	Upper
Outcome: Wave 3 Youth-Reported ASB								
Reactive Aggression	**.10**	**.07**	**.01**	**.31**	.01	.05	-.06	.16
Proactive Aggression	.02	.05	-.06	.17	.02	.05	-.06	.16
Total	.11	.10	-.05	.32	.03	.08	-.11	.23
Outcome: Wave 3 Parent-Reported CD								
Reactive Aggression	.01	.02	-.03	.06	<.01	.01	-.01	.03
Proactive Aggression	<.01	.01	-.02	.03	-.56	.36	-.04	.02
Total	.01	.02	-.04	.06	-.01	.02	-.04	.03

Note: ODD = oppositional defiant disorder; BC Bootstrap CI = bias corrected confidence interval; Point est. = point estimate of the indirect effect; SE = standard error; ASB = antisocial behavior; CD = conduct disorder. All models controlled for Wave 1 parent-rated ADHD, youth sex, and family income. For models where Wave 1 parent-rated irritable ODD was a predictor, Wave 1 parent-rated oppositional ODD was controlled for as a covariate. Similarly, in models where Wave 1 parent-rated oppositional ODD was a predictor, Wave 1 parent-rated irritable ODD was controlled for as a covariate. Bold indicates a statistically significant indirect effect.

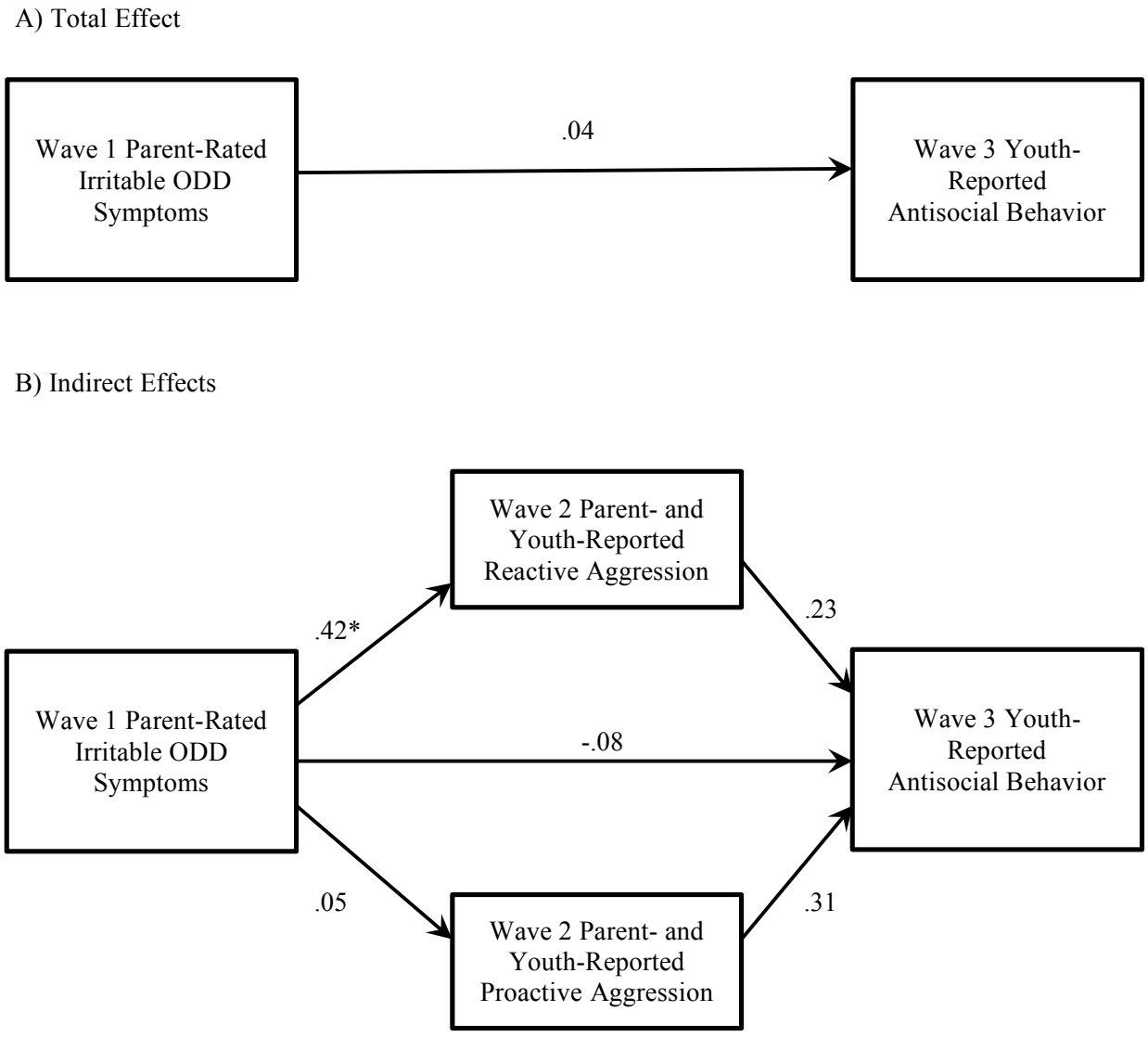


Figure 1. Model 1 Results: The prediction of Wave 3 youth-reported ASB from Wave 1 parent-rated irritable ODD symptoms by Wave 2 parent- and youth-combined ratings of reactive aggression and proactive aggression, controlling for W1 parent-rated ADHD and oppositional ODD symptoms, youth sex, and family income. *Note:* Numbers shown reflect unstandardized beta coefficients. *$p < .05$.

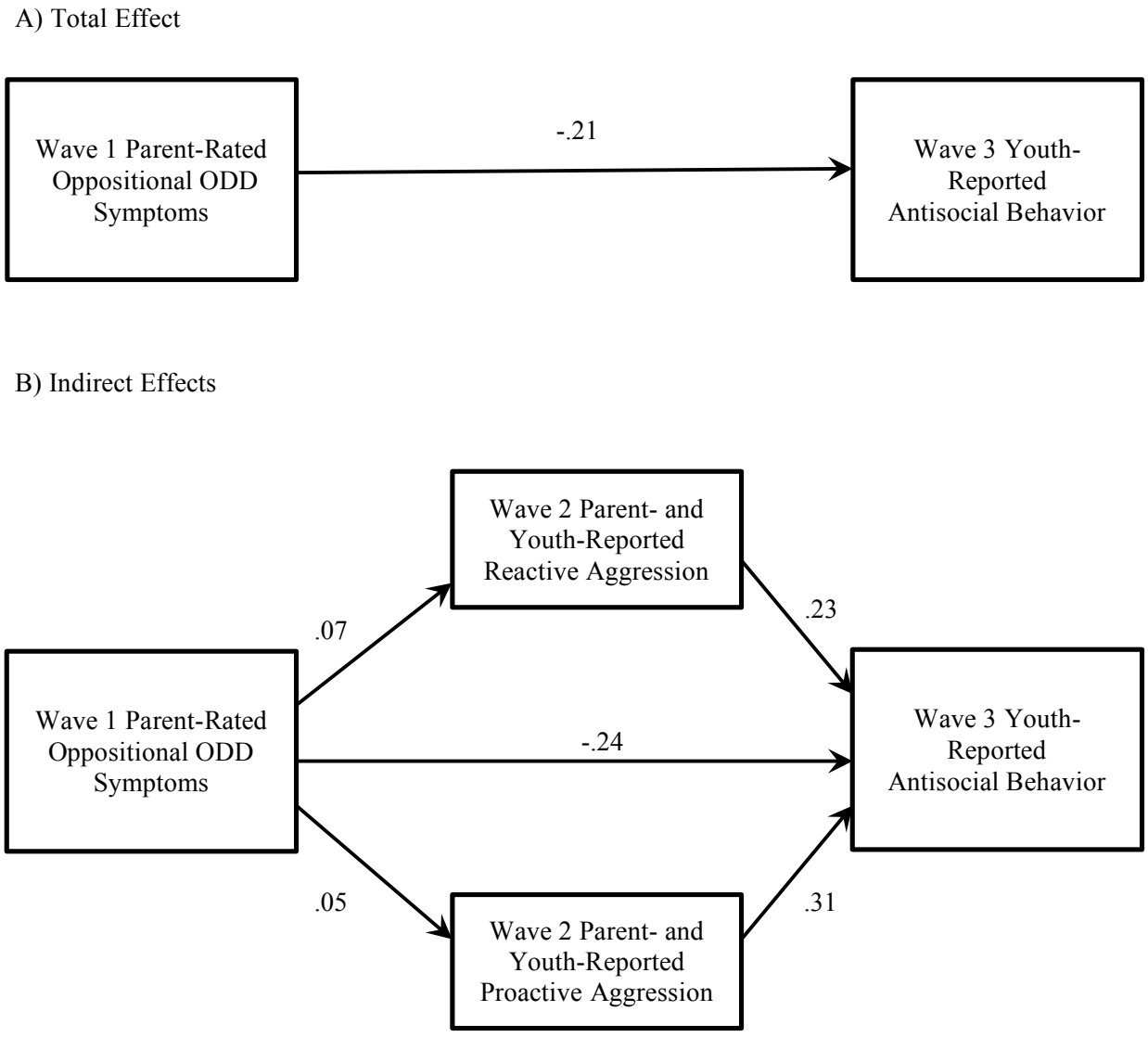


Figure 2. Model 2 Results: The prediction of Wave 3 youth-reported ASB from Wave 1 parent-rated oppositional ODD symptoms by Wave 2 parent- and youth-combined ratings of reactive aggression and proactive aggression, controlling for W1 parent-rated ADHD and irritable ODD symptoms, youth sex, and family income. *Note:* Numbers shown reflect unstandardized beta coefficients. *p < .05.

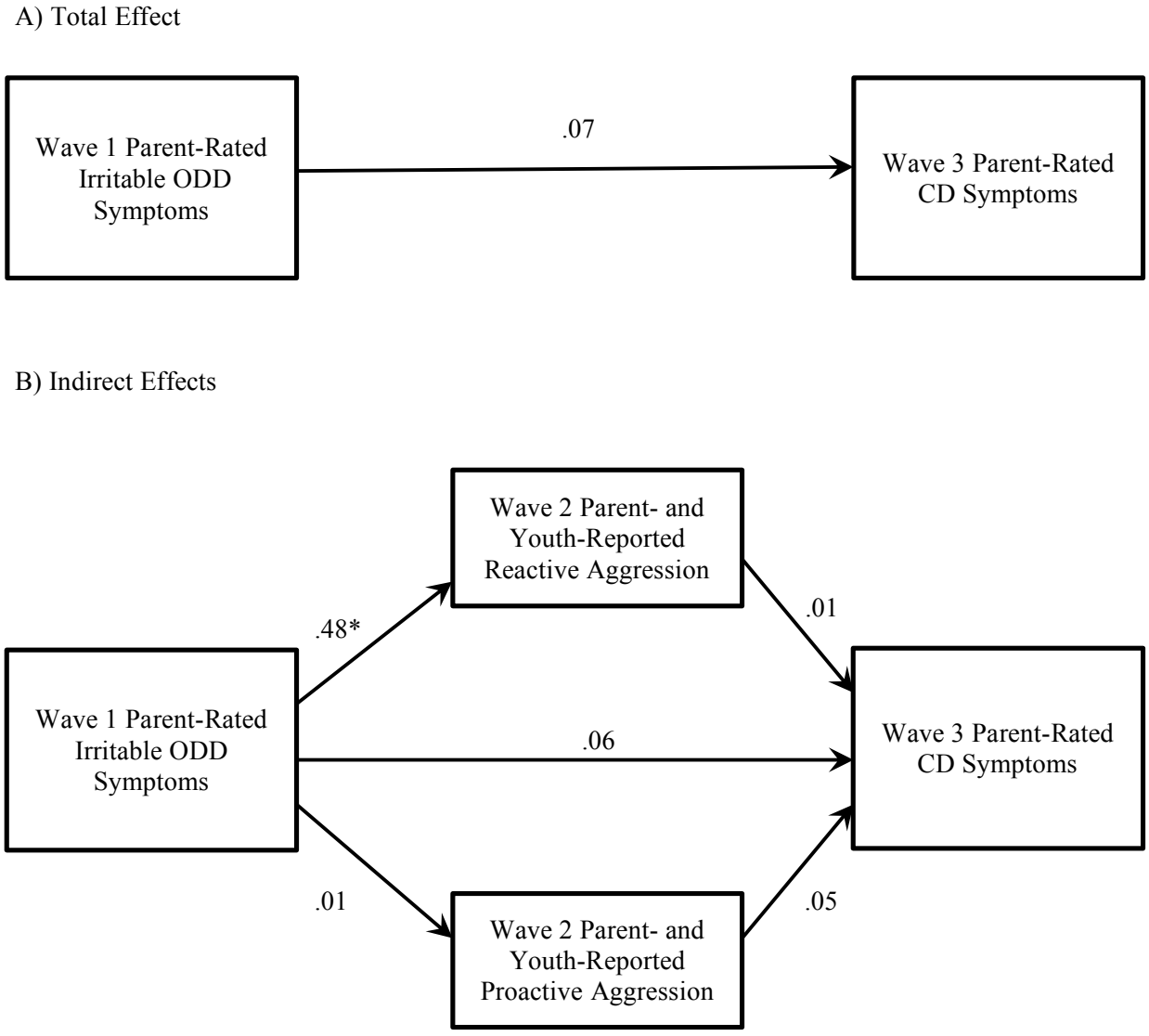
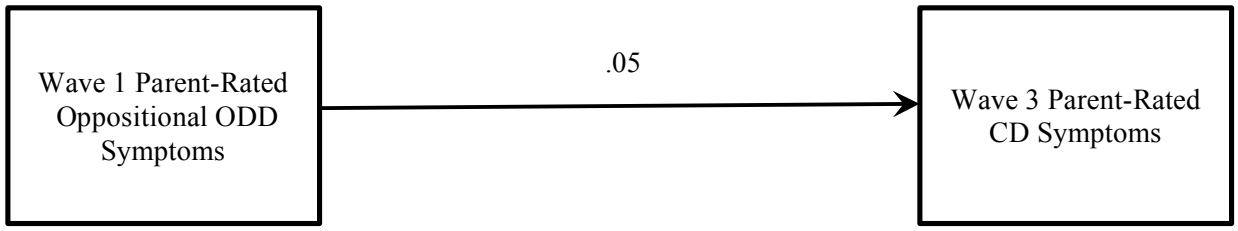


Figure 3. Model 3 Results: The prediction of Wave 3 parent-rated CD symptoms from Wave 1 parent-rated irritable ODD symptoms by Wave 2 parent- and youth-combined ratings of reactive aggression and proactive aggression, controlling for W1 parent-rated ADHD and oppositional ODD symptoms, youth sex, and family income. *Note:* Numbers shown reflect unstandardized beta coefficients. *p < .05.

A) Total Effect



B) Indirect Effects

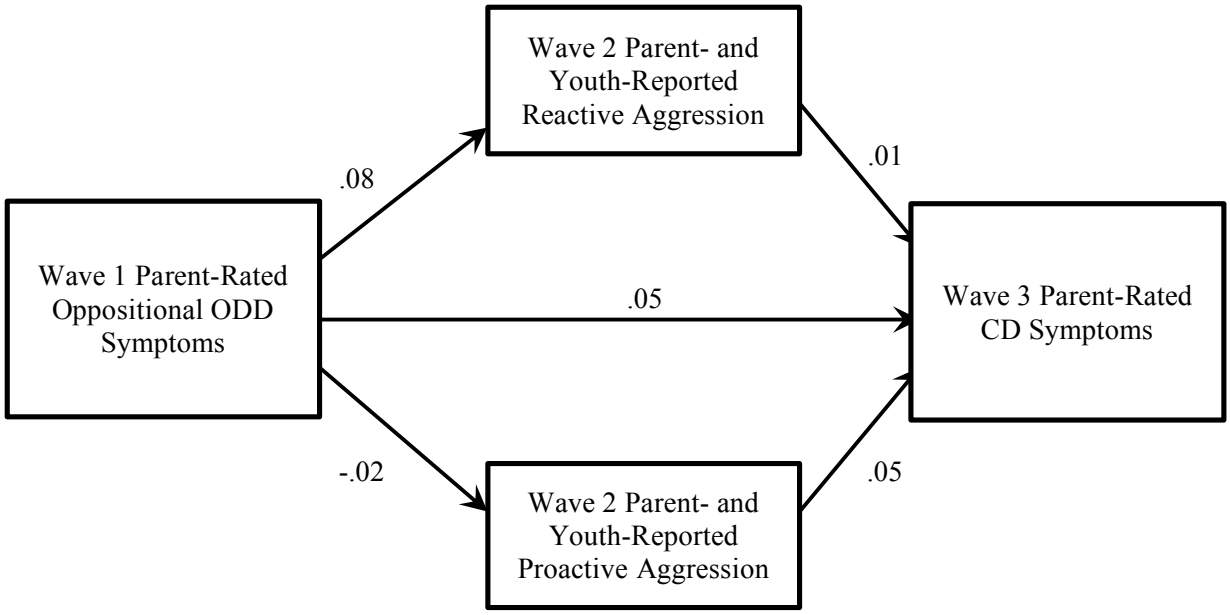


Figure 4. Model 4 Results: The prediction of Wave 3 parent-rated CD symptoms from Wave 1 parent-rated oppositional ODD symptoms by Wave 2 parent- and youth-combined ratings of reactive aggression and proactive aggression, controlling for W1 parent-rated ADHD and irritable ODD symptoms, youth sex, and family income. *Note:* Numbers shown reflect unstandardized beta coefficients. *p < .05.

Conclusions

Oppositional defiant disorder (ODD) was first codified as a disorder in DSM-III, theorized as a precursor to conduct disorder (CD), and intended to identify youth at greatest risk for the development of subsequent CD. ODD continued to be conceptualized as a disruptive behavior disorder in subsequent versions of the DSM through 2000, with relatively minor changes made with respect to symptoms and diagnostic criteria over time. In the development of DSM-5, there was a paradigm shift wherein etiological and dimensional approaches to diagnostic classification were emphasized relative to purely categorical approaches. Reflecting this shift, a small literature emerged highlighting that ODD consisted of separable dimensions: a dimension reflecting irritability/negative affect indicated risk for both internalizing and externalizing outcomes and an oppositional/behavioral dimension was more specifically associated with enduring externalizing problems (see Pardini, Frick, & Moffitt, 2010 for a more detailed history). ODD was included in the *Disruptive, Impulse-Control, and Conduct Disorders* section in DSM-5, but it was updated to include separate symptom clusters: Angry/Irritable Mood, Argumentative/Defiant Behavior, and Vindictiveness. Despite ODD remaining in a section primarily devoted to externalizing disorders, some authors argued that ODD may be better conceptualized as an emotion regulation disorder (Cavanagh, Quinn, Duncan, Graham, & Balbuena, 2014). Notably, persistent concerns remain about the legitimacy of ODD, the potential to pathologize developmentally normative behavior, and ultimately whether DSM-5 ODD symptom dimensions have clinical and scientific utility (Frick & Nigg, 2012; Pardini et al., 2010). The historical context outlined above motivated this dissertation to address limitations in the field and clarify prospective outcomes among youth with ODD, the validity and utility of ODD dimensions, and possible mechanisms underlying the development of putative ODD

dimensions to later psychopathology. These aims were targeted at improving the nosological and nomological basis of ODD.

Study I utilized meta-analytic methods to determine the prevalence of multiple psychopathology outcomes among youth studied in longitudinal, prospective studies. Among 1137 youth with ODD from 17 prospective, longitudinal studies, 13% developed a subsequent anxiety disorder, 5% developed depressive disorders, and 21% developed subsequent CD or antisocial personality disorder (ASPD). Relative to epidemiologically-based 12-month prevalence rates, these preliminary findings suggest that individuals with ODD had lower prevalence rates of anxiety disorders, comparable rates of depressive disorders, and higher rates of CD/ASPD. Meta-regression revealed that older participants at baseline had elevated rates of later depression, and higher psychotropic medication use at baseline yielded higher rates of later depression and CD/ASPD. These findings demonstrate both heterotypic and homotypic continuity among youth with ODD, but provide more robust evidence of ODD being a precursor to CD. Moreover, these results are more consistent with ODD being conceptualized as an externalizing disorder rather than an emotion regulation disorder. It is important to highlight that nearly all of the samples included in the analyses oversampled for attention-deficit/hyperactivity disorder (ADHD) or externalizing problems. Thus, these data may not reflect patterns based on samples enriched for internalizing problems, for example. This underscores the importance of studying internalizing and externalizing disorders simultaneously, especially in the context of the Research Domain Criteria (RDoC) initiative (Insel et al., 2010).

Although Study I consisted of important limitations, particularly with respect to specificity (e.g., developmental sensitivity, accounting for ODD dimensions, consideration of comorbidity and temperamental constructs related to ODD), Study II addressed many of these

shortcomings with use of a sample of well-ascertained children studied prospectively into early adolescence. Study II tested the predictive validity of irritable and oppositional ODD dimensions with respect to psychopathology outcomes (i.e., anxiety, depression, CD) and other negative outcomes (i.e., antisocial behavior [ASB], psychopathic traits, alcohol use, and functional impairment), with control of baseline negative emotionality, ADHD symptoms, and baseline levels of outcomes in each respective model. Oppositional ODD only *inversely* predicted separate parent and youth ratings of anxiety and depression, and irritable ODD predicted parent-rated obsessions and compulsions only. That is, we found limited evidence of the predictive validity of irritable and oppositional ODD dimensions when we conservatively controlled for baseline negative emotionality, ADHD, and relevant baseline levels of outcomes. Thus, separable ODD dimensions should be interpreted cautiously, particularly without consideration of other developmentally-sensitive childhood risk factors such as early ADHD and psychopathology.

Study III tested reactive and proactive aggression as simultaneous mediators of predictions of multi-informant rated ASB (i.e., youth-reported ASB and parent-rated CD symptoms) from irritable ODD symptoms and oppositional ODD symptoms. Once again, we adopted a developmentally-informed approach and utilized a sample of children followed prospectively into early adolescence, and utilized temporally ordered predictors, mediators, and outcomes. The key finding in Study III was that Wave 2 reactive aggression significantly mediated predictions of Wave 3 youth-rated ASB from Wave 1 *irritable* ODD when there was statistical control of concurrent proactive aggression as well as Wave 1 ADHD, oppositional ODD, youth sex, and family income. Additionally, Wave 1 irritable ODD predicted Wave 2 reactive aggression in all models that were tested. These preliminary findings that irritable ODD

predicted the development of reactive aggression and subsequent ASB underscore the importance of delivering interventions to address irritability and enhance emotion regulation in youth to prevent antisocial outcomes, rather than solely taking an approach that uses parent training to treat ODD. Study III identified one developmental pathway through which individuals with irritable ODD develop ASB, but more mechanistic work related to ODD dimensions to address principles of equifinality and multifinality are needed.

Collectively, these results suggest: (1) consistent with prior research, ODD is a precursor to CD and more strongly associated with externalizing outcomes relative to internalizing outcomes, (2) ODD dimensions should be interpreted cautiously without consideration of other developmentally-sensitive risk factors for psychopathology, and (3) irritable ODD confers risk for the development of reactive aggression and subsequent ASB, and therefore prevention and intervention efforts should go beyond utilizing parent training techniques and also prioritize teaching vulnerable youth emotion regulation skills. Together, these results also suggest that formal codification of ODD symptoms into separable dimensions may have been premature and additional work testing ODD as an emotion regulation disorder is warranted given lingering concerns about the validity and utility of ODD dimensions. Clinically, these results also indicate a need to consider whether ODD is primary or secondary to other dimensions of psychopathology (e.g., are ODD symptoms exhibited alone, a manifestation of emotion dysregulation due to trauma, or a result of anxiety-related distress or avoidance?), which has key implications for assessment and intervention approaches.

Expanding beyond these studies, there is utility in considering the role of ODD and its dimensions as transdiagnostic factors (Kessel et al., 2016; Kring, 2008; Nolen-Hoeksema & Watkins, 2011) or as indicators of a general psychopathology factor (Caspi et al., 2014; Tackett

et al., 2013; Laceulle, Vollebergh, & Ormel, 2015). In particular, given that irritability is a central feature of over a dozen internalizing and externalizing disorders, there is a compelling need to consistently measure pediatric irritability and to elucidate the role of irritability with respect to the development of psychopathology. For example, it is unclear what level of irritability should be considered normative versus clinically significant. Furthermore, improved understanding of irritability may also lend well to developing a transdiagnostic treatment of irritability similar to how there are now transdiagnostic treatments to treat emotional disorders (Craske, 2012; Farchione et al., 2012; Sukhodolsky, et al., 2016). Stringaris et al. (2012) proposed the Affective Reactivity Index (ARI) as an improved measure to assess pediatric irritability and negative affect that can quickly and efficiently be utilized in both clinical and research settings with just seven items (Stringaris et al., 2012). However, the items on the ARI are very similar to one another and are essentially the same as irritable ODD symptoms with items including: "easily annoyed by others," "often loses his/her temper," "stays angry for a long time," "is angry for most of the time," "gets angry frequently," and "loses temper easily." Thus, the ARI is an imperfect solution for improving measurement of pediatric irritability. Moreover, delineating the nomological network of ODD and irritability is needed: for example, it is pertinent to consider the association of irritability with respect to genetic, psychophysiological, and neurobiological correlates (see Althoff, 2018 for more information on the ENIGMA irritability consortium that is working on these aims).

In summary, these results suggest that the precise nature of ODD as a risk factor for subsequent psychopathology must be qualified by key considerations (e.g., considering co-occurring risk factors, specific psychopathology outcomes explored) and that ODD dimensions should be interpreted with caution, while also elucidating one potential pathway in the

development from irritable ODD to subsequent ASB. Future research should prioritize studying ODD along with internalizing disorders, externalizing disorders, relevant transdiagnostic factors, and the general psychopathology factor with developmentally-informed methods. Focusing on these areas will help to elucidate areas for intervention of ODD and prevention of persistent psychopathology, to ultimately reduce the individual and societal costs that result from them.

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