ADHD and the development of alcohol/substance problems

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Objectives

- I. Is early ADHD a risk factor for alcohol and substance use disorders (ASUD)?
- II. What "intermediate" factors may contribute to ASUD in youth with ADHD?
- III. Is stimulant medication associated with ASUD and related problems?
- IV. How prevalent is stimulant misuse in college students?

ADHD Outcomes

- Non-mental health care expenses (Barkley, 2002)
- Substandard academic achievement (Hinshaw, 1992)
- Poor social functioning (Lee et al., 2008)
- Eating pathology (Mikami et al., 2009)
- Driving risks and auto accidents (Barkley et al., 2003)
- Workplace competency (Barkley et al., 2007)

Resilience is also an outcome.

Alcohol and Substance Problems

- Dopamine neurotransmission is central to theories of ADHD and alcohol/substance use disorders (ASUD)
  - Stimulant medication reduces ADHD symptoms
  - Shared neural structures and circuits impaired in ADHD (human and non-human animals) (Groman et al., 2009)
- Shared risk factors and causal influences
  - ADHD and ASUD appear together families
  - Similar genetic influences on ADHD and ASUD (Iacono et al., 2009)

But what about development?

- ADHD symptoms as moderately stable with some remission
  - Inattention versus hyperactivity
  - Poor outcomes even when ADHD symptoms improve
- Early-onset alcohol/substance use predict worse outcomes?
  - Propensity matching: Odgers et al. (2008)
- Developmentally-sensitive changes in ADHD and ASUD
  - Social context: Pubertal onset, deviant peer influences, etc.

I. Is ADHD a risk factor for ASUD?

- Cross-sectional and prospective associations (Disney et al., 1999; Mannuzza et al., 1998
- Null (Boyle & Offord, 1991; DeSanctis et al., 2008)
- Complicating factors
  - "Censored" samples (Biederman et al., 2010; 6-18 years)
  - Clinic-referred vs. population- or school-based vs. other?
  - Inattention versus hyperactivity

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Prospective association of childhood attention-deficit/hyperactivity disorder (ADHD) and substance use and abuse/dependence: A meta-analytic review ☆

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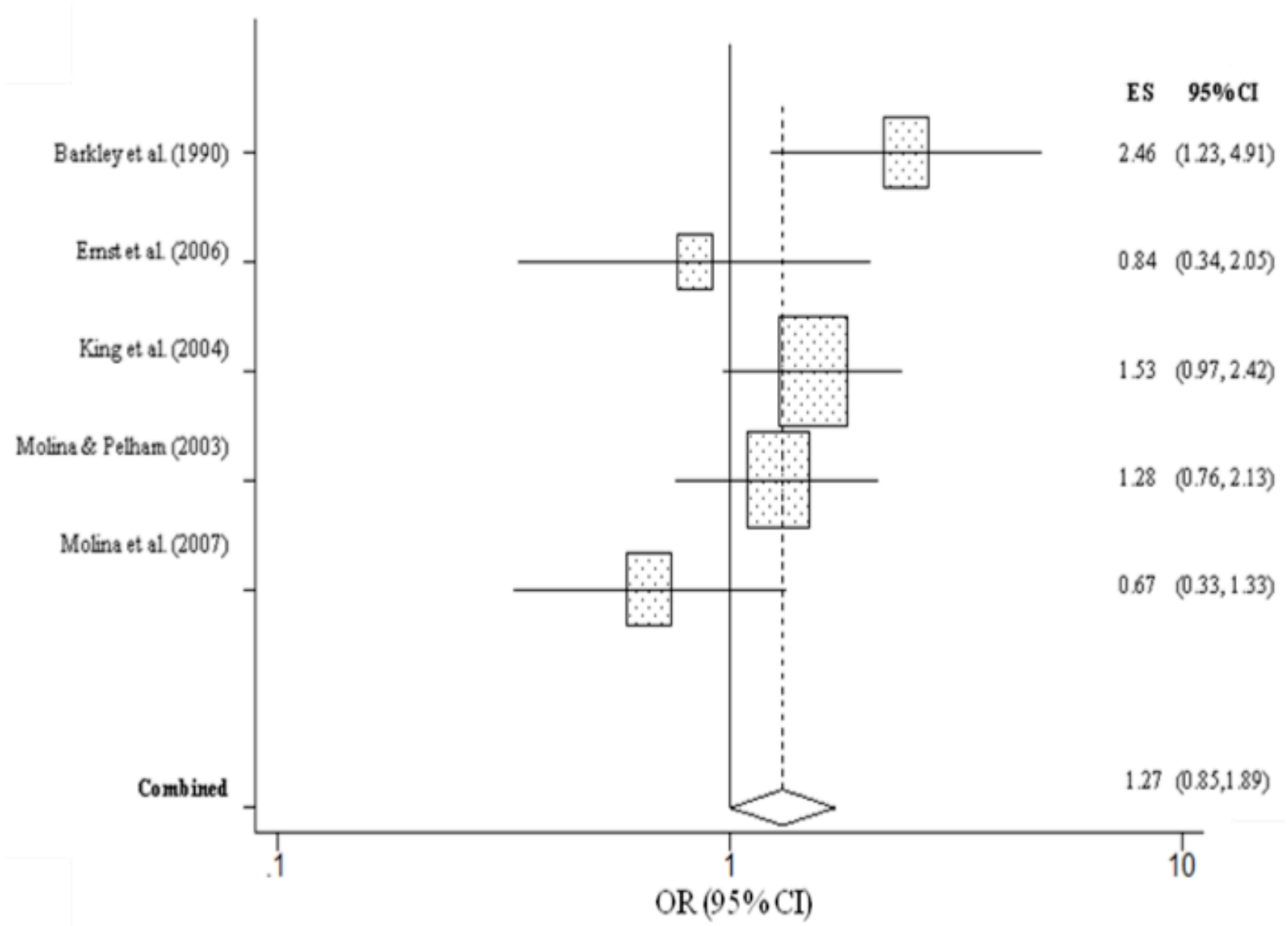
ABSTRACT

Given the clinical and public health significance of substance disorders and the need to identify their early risk factors, we examined the association of childhood attention-deficit/hyperactivity disorder (ADHD) with substance use (nicotine, alcohol, marijuana) and abuse/dependence outcomes (nicotine, alcohol, marijuana, cocaine, other). To strengthen a potential causal inference, we meta-analyzed longitudinal studies that prospectively followed children with and without ADHD into adolescence or adulthood. Children with ADHD were significantly more likely to have ever used nicotine and other substances, but not alcohol. Children with ADHD were also more likely to develop disorders of abuse/dependence for nicotine, alcohol, marijuana, cocaine, and other substances (i.e., unspecified). Sex, age, race, publication year, sample source, and version of the Diagnostic and Statistical Manual of Mental Disorders (DSM) used to diagnose ADHD did not significantly moderate the associations with substance outcomes that yielded heterogeneous effect sizes. These findings suggest that children with ADHD are significantly more likely to develop substance use disorders than children without ADHD and that this increased risk is robust to demographic and methodological differences that varied across the studies. Finally, few studies addressed ADHD and comorbid disruptive behavior disorders (DBD), thus preventing a formal meta-analytic review. However, we qualitatively summarize the results of these studies and conclude that comorbid DBD complicates inferences about the specificity of ADHD effects on substance use outcomes.

Figure 3. Lifetime alcohol use predicted from childhood ADHD



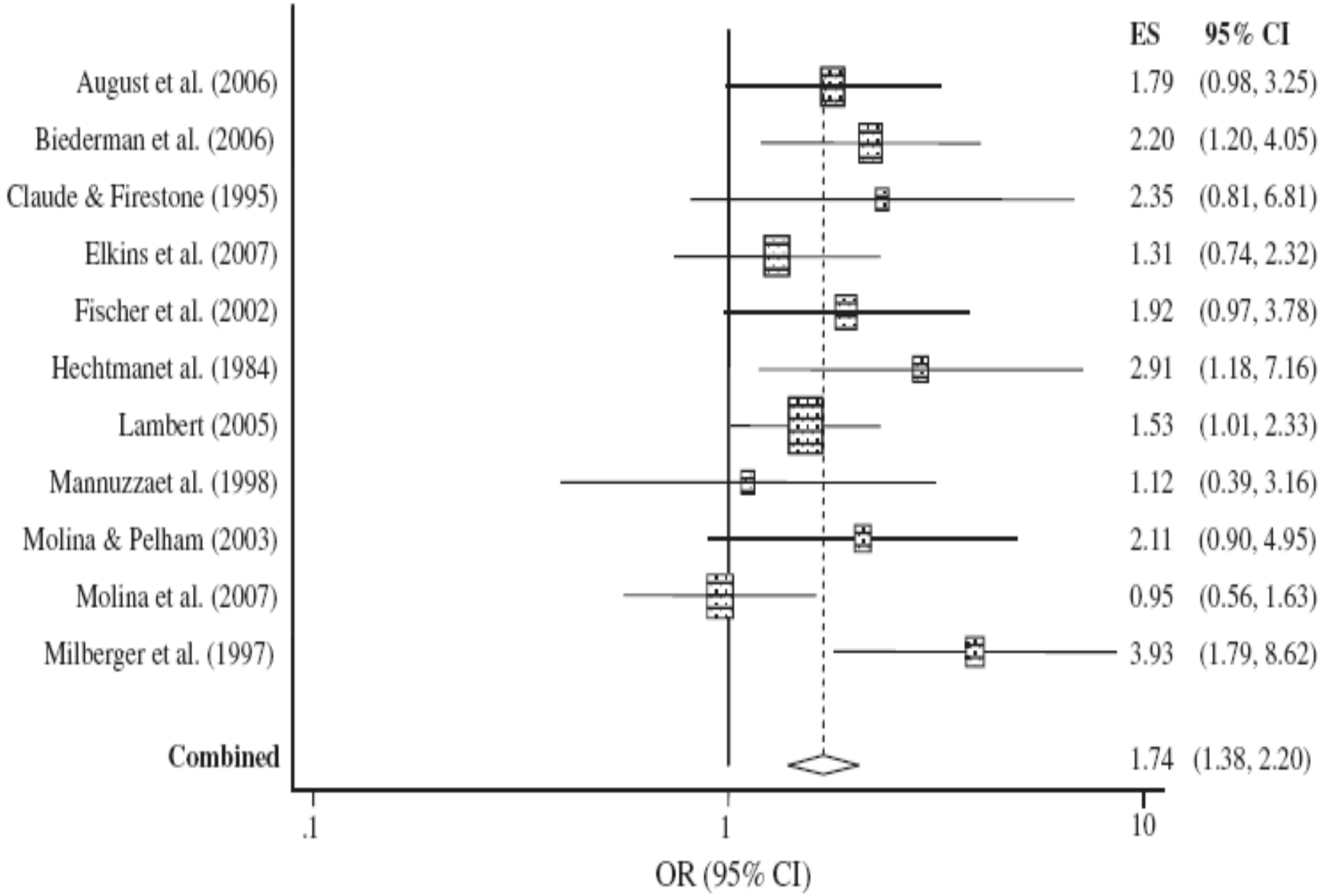


Fig. 4. Alcohol abuse or dependence predicted from childhood ADHD.

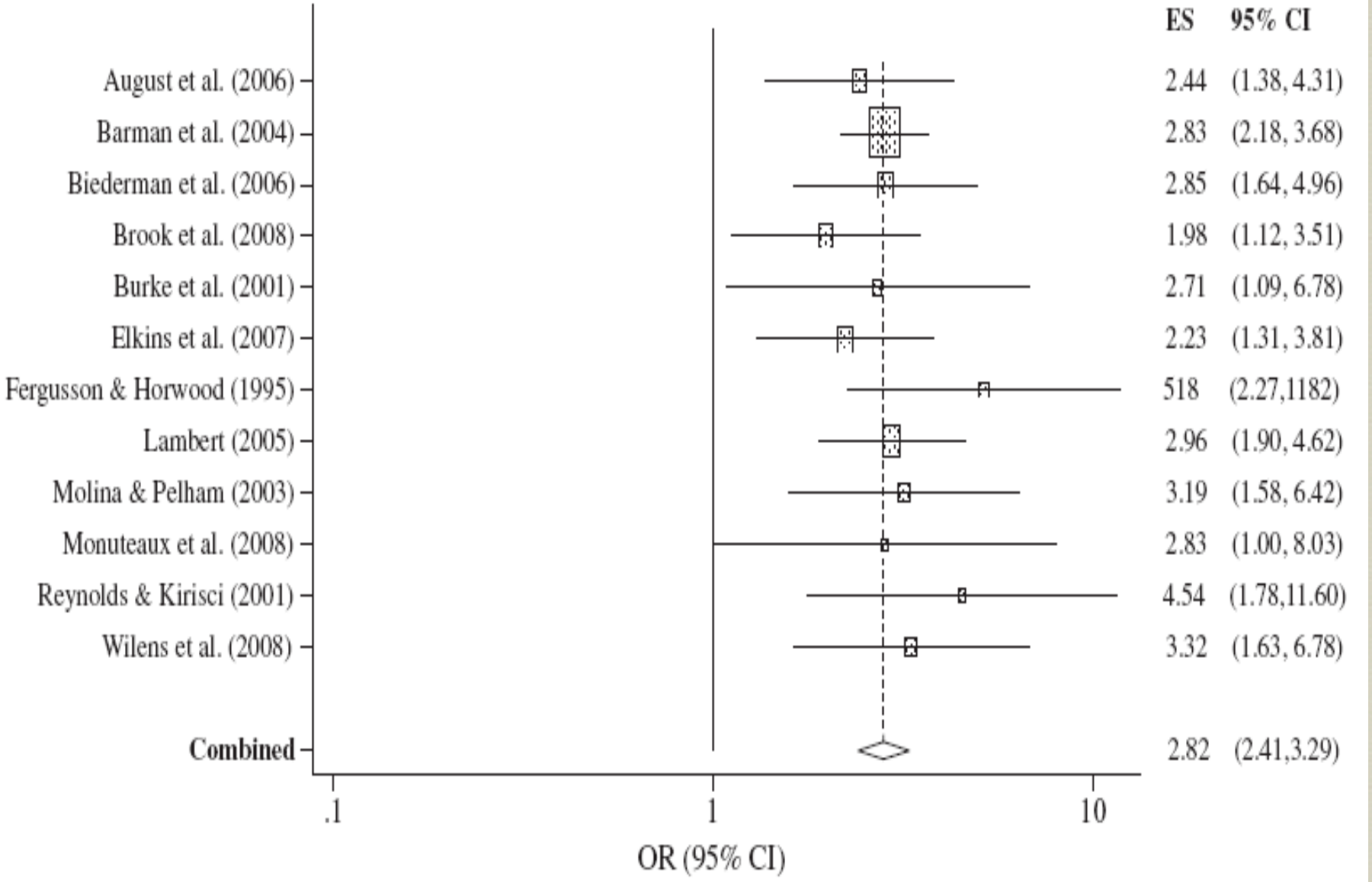


Fig. 2. Nicotine dependence predicted from childhood ADHD.

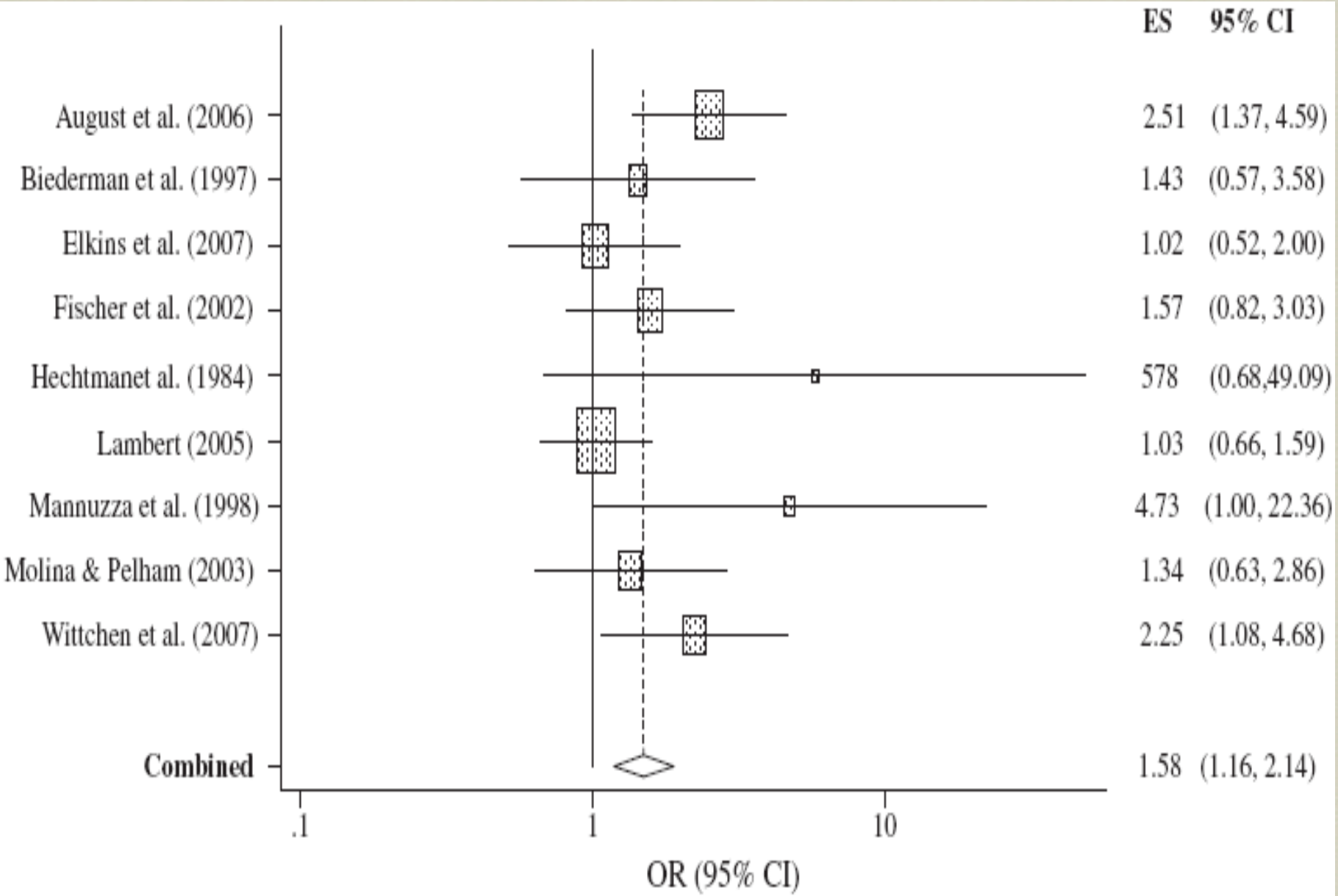


Fig. 6. Marijuana abuse or dependence predicted from childhood ADHD (excluding Gignac et al. (2005)).

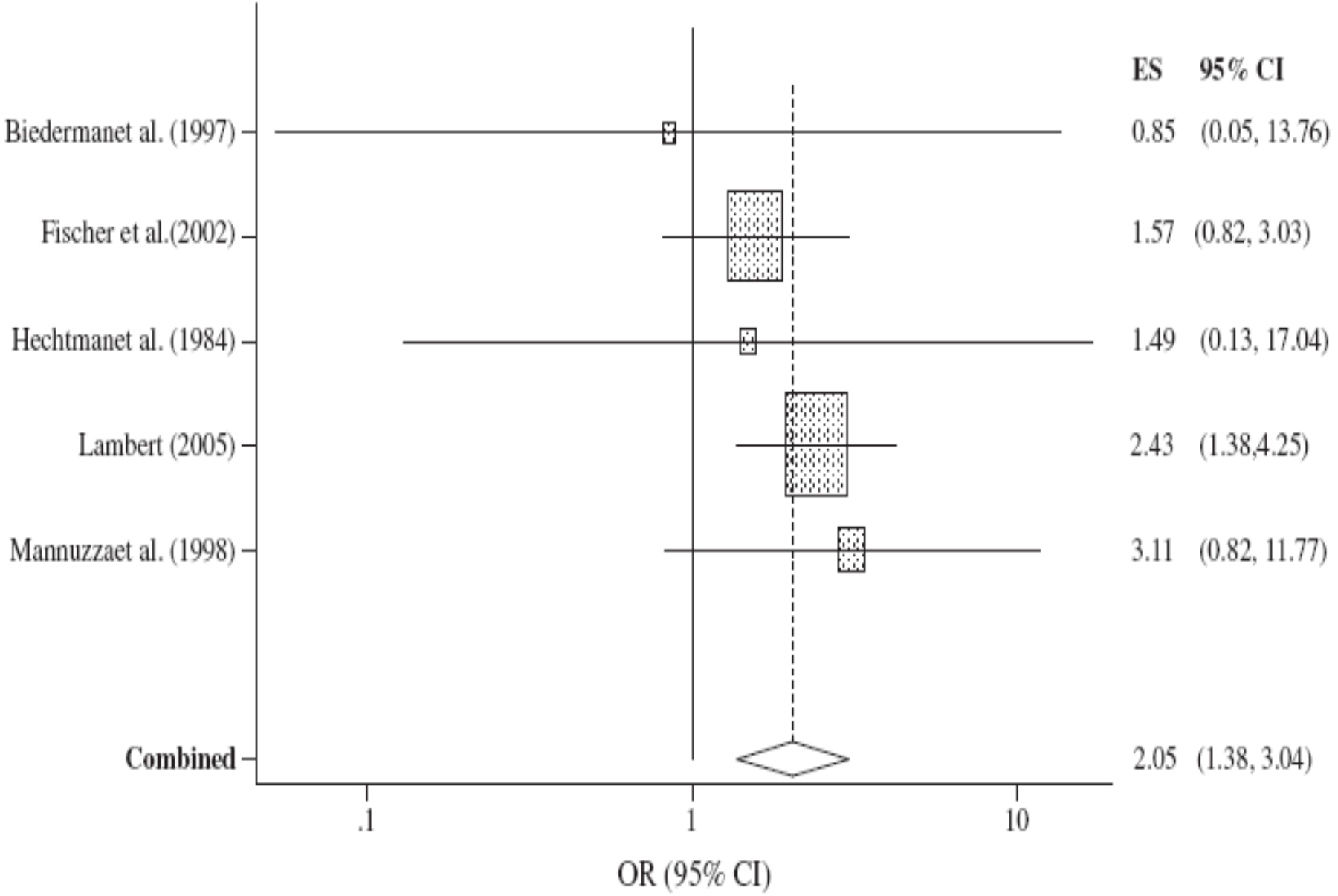


Fig. 7. Cocaine abuse or dependence predicted from childhood ADHD.

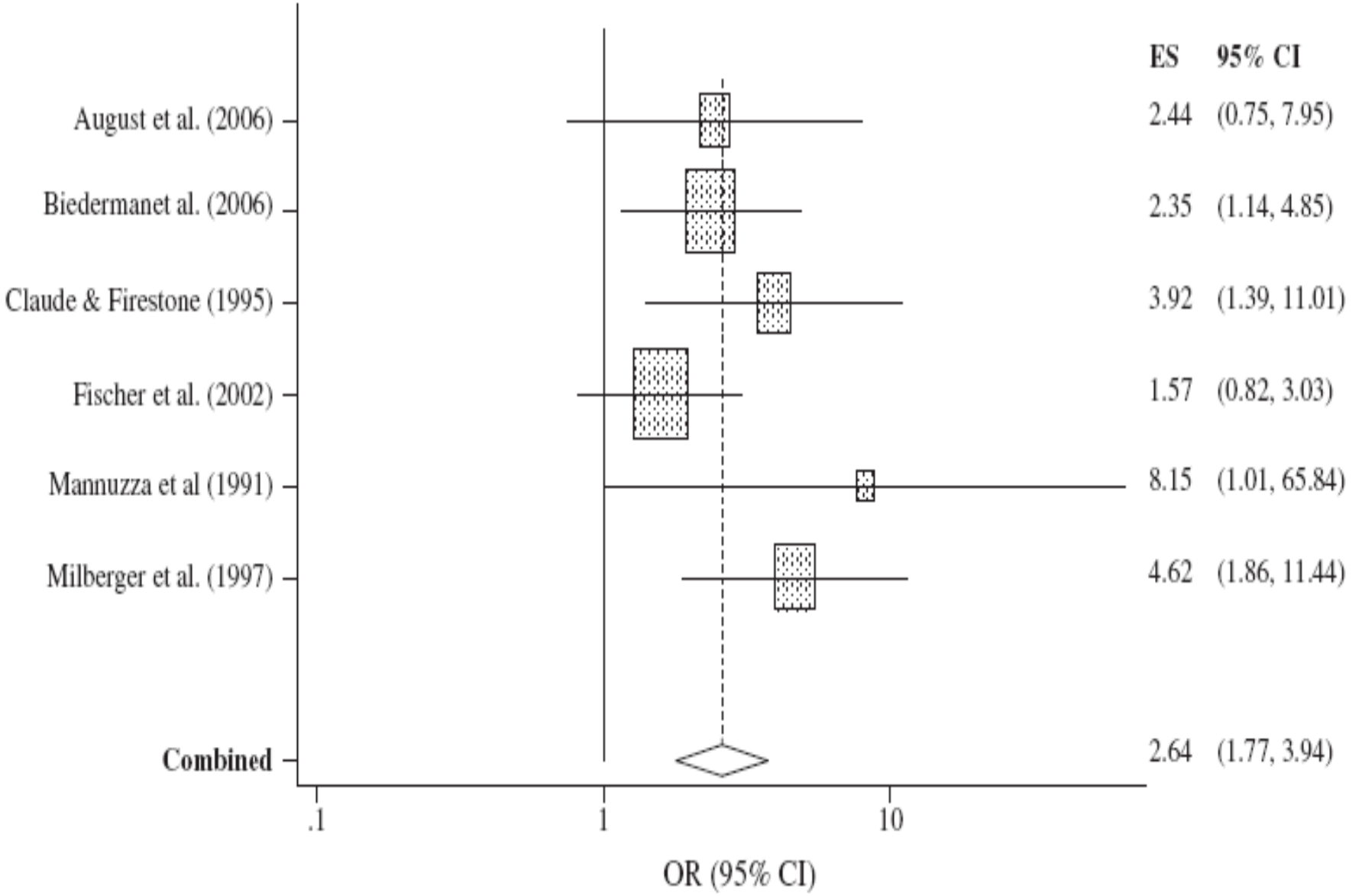


Fig. 8. Non-specific substance abuse or dependence predicted from childhood ADHD.

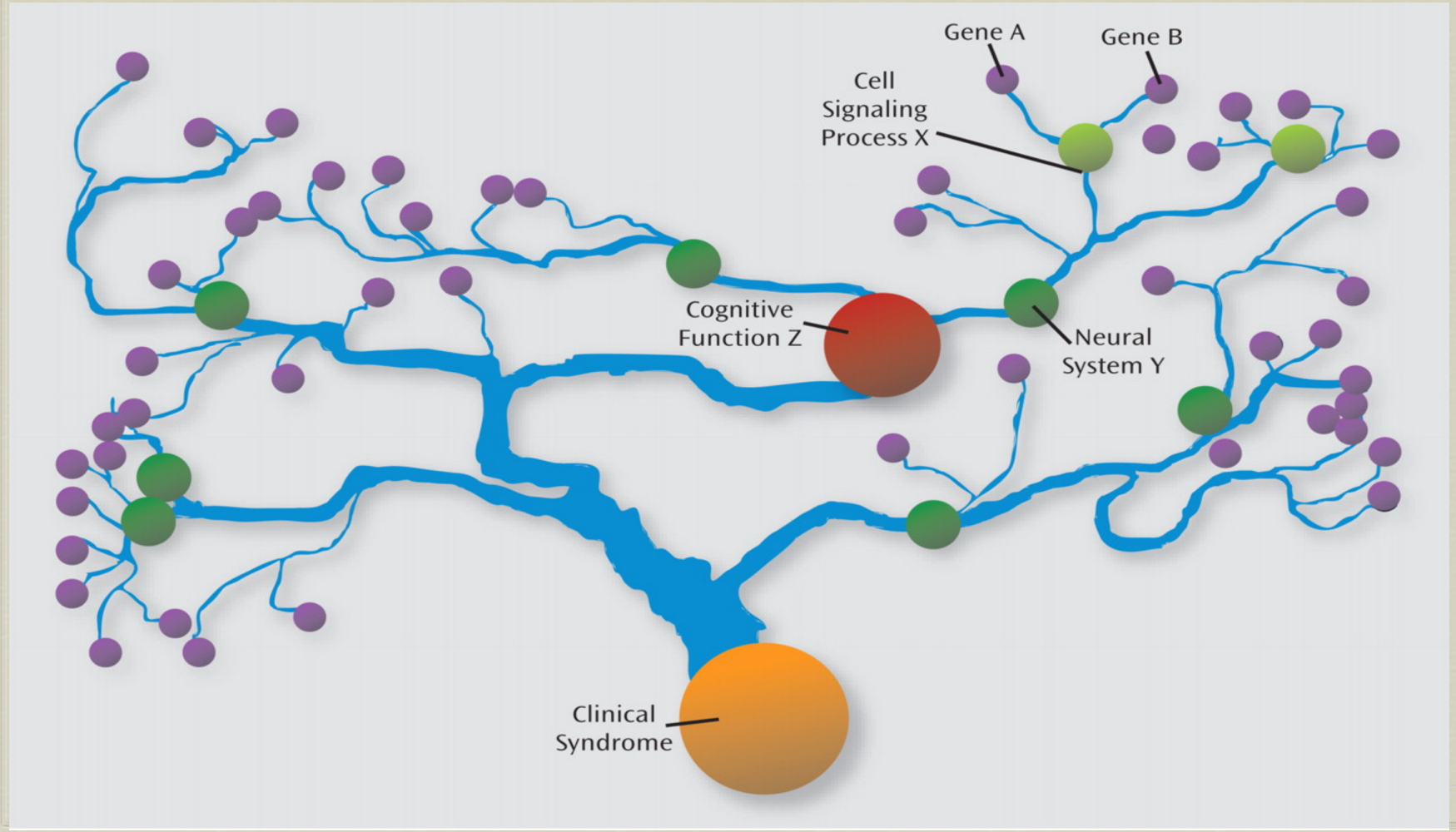
Objective 1: Summary

- Early ADHD is a potent risk factor in the development of later alcohol, nicotine, and substance use problems
  - Two independent meta-analyses (Charach et al., 2011)
- Remaining questions/challenges
  1. ADHD is correlated with other risk factors – specificity is elusive
     1. Conduct problems, executive functioning problems
  2. What are potential mechanisms or pathways TO ASUD?
     1. *How* does ADHD contribute to ASUD?

Objective 1: Clinical implications

- Delinquency and conduct disorder as a pathway to ASUD from early ADHD (Sibley et al., 2014; Molina et al., 2014)
  - Escalation in conduct problems predicted earlier/heavier engagement
- ADHD assessment and intervention must include multiple domains of functioning to prevent ASUD
  - Delinquency (e.g., truancy, theft)
  - Conduct disorder (e.g., aggression, property destruction)

Watershed Model (Cannon, 2010)



Objective 2: Alcohol Expectancies

- "…beliefs about the effects of consuming alcohol" (Donovan et al., 2009)
  - Evident prior to and predict explicit alcohol use (Zucker et al., 1995; Christiansen et al., 1989; Colder et al., 1997)
  - Critical period at 8-10 years-old (Hipwell et al., 2005)
- Positive expectancies: enhanced socialization, arousal, relaxation, mood
- Negative expectancies: sedating effect, impaired
- Development: positive AE increase and negative AE decrease beginning in middle-late childhood through adolescence

Alcohol Expectancies

- "There has been relatively little research, however, on the antecedents of alcohol expectancies" (Donovan et al., 2009)
  - Parent alcohol use, male sex, perceived peer alcohol use, school problems (Martino et al., 2006; Ouliette et al., 1999, Cumsille et al., 2000)
  - Acquired Preparedness Model: disinhibition predicts positive alcohol expectancies (Smith & Anderson, 2001)
  - Precursors to alcohol expectancies in school-age children?

ADHD and Alcohol Expectancies?

- Disinhibition is central to theories of ADHD and alcohol expectancies (Smith & Anderson 2001; Nigg, 2001)
- Parent alcohol and substance use predict offspring ADHD and externalizing problems (Marmorstein et al., 2009; Molina et al., 1997)
- Deviant peer affiliation mediated predictions of adolescent substance use from early ADHD (Marshal et al., 2003)
- Siblings of ADHD probands earlier onset and higher rates of substance use than siblings of controls (Milberger et al., 1997)

Does Childhood ADHD Predict Alcohol Expectancies?

- Baseline
  - 230 6-9 year-old children with and without DSM-IV ADHD
  - Structured diagnostic interviews, neuropsychological and academic achievement, analogues, observational
- Participants
  - Ethnically diverse; ADHD vs. non-ADHD youth comparable in age, sex, race-ethnicity, and family income; 91% retention, 8-11 years-old
- Two-year follow-up
  - Age 6-9 inattention vs. hyperactivity-impulsivity uniquely predict youth self-reported positive alcohol expectancies at ages 8-11, controlling for ODD and demographic factors

ADHD and Positive Expectancies

- ADHD is associated with deficient reward processing
  - Greater sensitivity to reward, more risky decisions, aversion to reward delay (e.g., von Rhein et al., 2015)
- Youth Alcohol Expectancies
  - Positive-social (e.g., happy, fun)*
  - Positive-wild/crazy (e.g., goofy)*
  - Negative-arousal (e.g., mad, sad)
  - Negative-sedated/impaired (e.g., sleepy)

Positive Social Expectancies

Predictor	Beta (β)	P-value
Step 1		
Age	-.01	.24**
Sex	.16	.07
Full Scale IQ	.07	.41
# ODD symptoms	-.12	.21
# CD symptoms	.04	.68
Step 2		
# baseline inattention sxs	-.05	.62
# baseline hyperactivity sxs	-.06	.60

Wild/crazy Alcohol Expectancies (Positive)

Predictor	Beta (β)	P-value
Step 1		
Age	-.06	.48
Sex	.15	< .09
Full Scale IQ	.07	.44
# ODD symptoms	-.08	.83
CD symptoms	-.09	.34
Step 2		
# Wave 1 inattention sxs	.00	.97
# Wave 1 hyperactivity sxs	.38	<.01**

Objective 2 Summary

- Age 8-11 Youth Alcohol Expectancies
  - Negative: unrelated to early ADHD, ODD, and CD
  - Positive Social: also unrelated to early ADHD, ODD, and CD
- Hyperactivity as precursor to positive wild/crazy alcohol expectancies
  - Controlling for age, sex, IQ, ODD, and CD
- Wave 3 follow-up (10-13 years) completed this year
  - Are positive alcohol expectancies a unique pathway FROM early ADHD to subsequent adolescent alcohol outcomes

Objective 3: Stimulant Medication and ASUD

- Methylphenidate (MPH) effectively treats ADHD (Greenhill et al., 2002; Swanson & Volkow, 2009)
- MPH side effects
  - Cardiovascular, height/weight, somatic (Rapport & Moffitt, 2002)
  - Sleep and appetite (Sonuga-Barke et al., 2009)
  - Decreased rate of physical growth (Swanson et al., 2007)

MPH & ASUD: Biological Plausibility

- DA neurotransmission central to theories of ADHD and SUD (Volkow et al., 2009)
- Rats: Increased consumption (Andersen et al., 2002; Brandon et al., 2001)
- Non-human primates: MPH unrelated to DAT or D2/D3 receptor availability, growth, or self-administered cocaine (Gill et al., 2012)

MPH and ASUD Risk: Human Studies

- Increased risk for SUD
  - Age of MPH tx predicted increased SUD (Mannuzza et al., 2008)
  - Lambert & Hartsough (1998)
- Decreased risk for SUD
  - Wilens et al. (2003) meta-analysis (n=6), Schoenfelder et al. (2013) (nicotine)
- Null association
  - Biederman et al. (2008), Barkley et al. (2003), Molina et al. (2013)
- Key question: is stimulant medication associated with altered risk for ASUD among (mostly) ADHD youth?

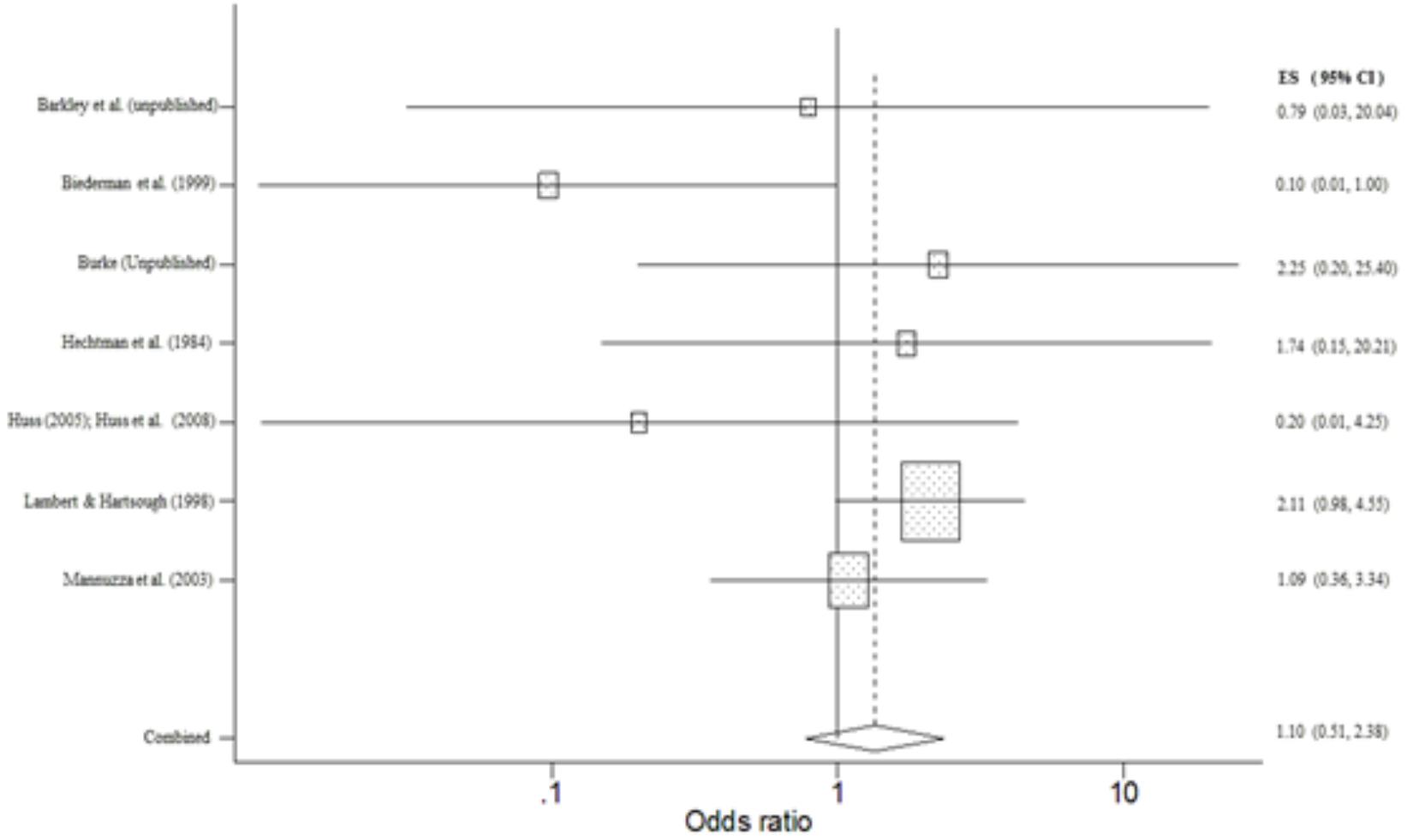
Inclusion Criteria

- I. Longitudinal design (i.e., medication tx preceded ASUD assessment)
- II. Dichotomous ADHD vs. non-ADHD*
- III. Dichotomous (+) abuse/dependence vs. (-)
- IV. Available data to calculate proportions or reported odds ratios
- V. Publication between 1980 and February 2012
- * 1 study of reading disorder vs. non-reading disorder (n = 239 medicated, n = 63 unmedicated)
- N = 2565 (mostly Caucasian boys); 60% medicated

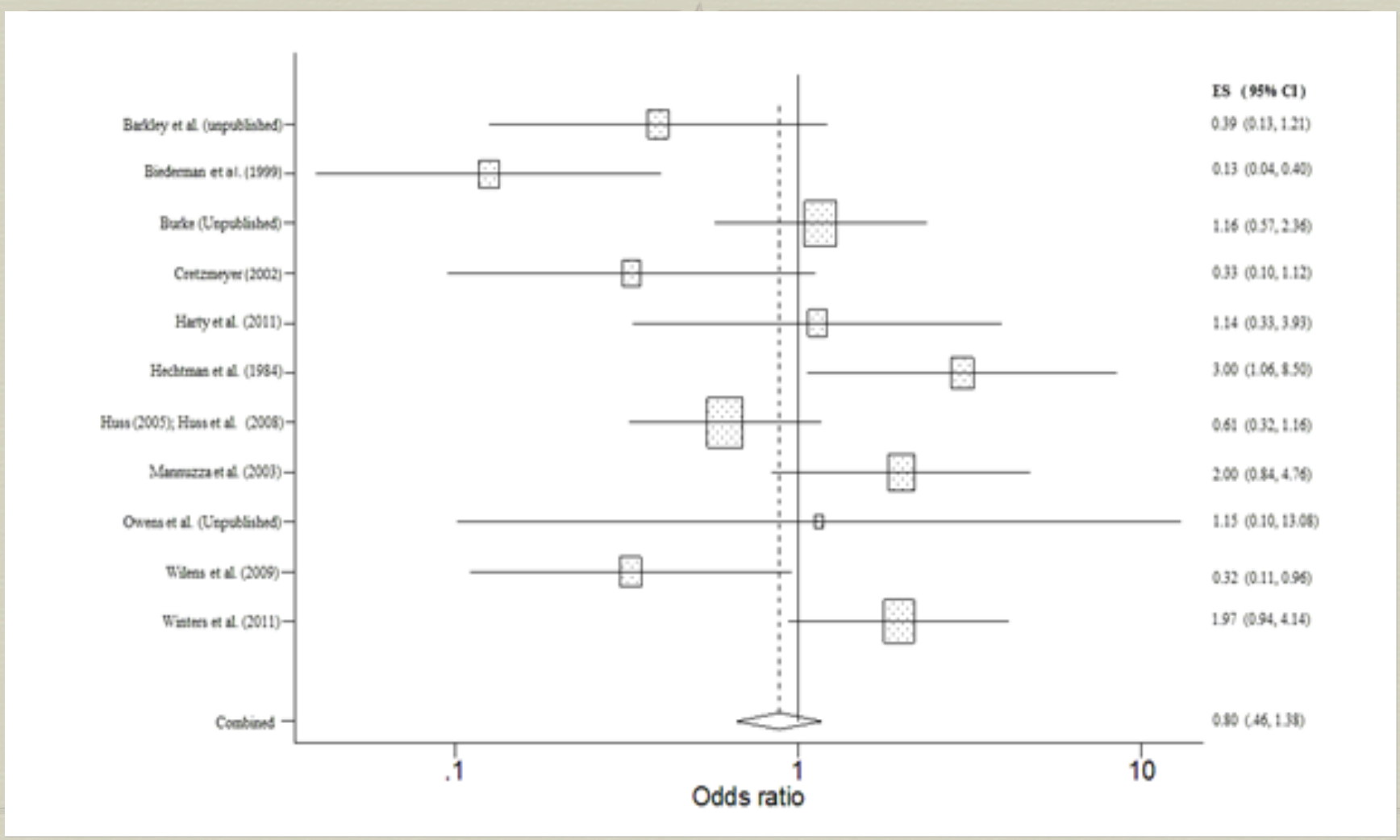
Objective

- To *meta-analyze* alcohol and substance abuse/ dependence (ASUD) outcomes among children with treated vs. untreated with MPH
  - Prioritize abuse/dependence given clinical significance
- Calculated odds ratios (OR)
  - Positive vs. negative stimulant history
  - Positive vs. negative ASUD outcome
- Random effects models with OR weighted by the inverse of the variance

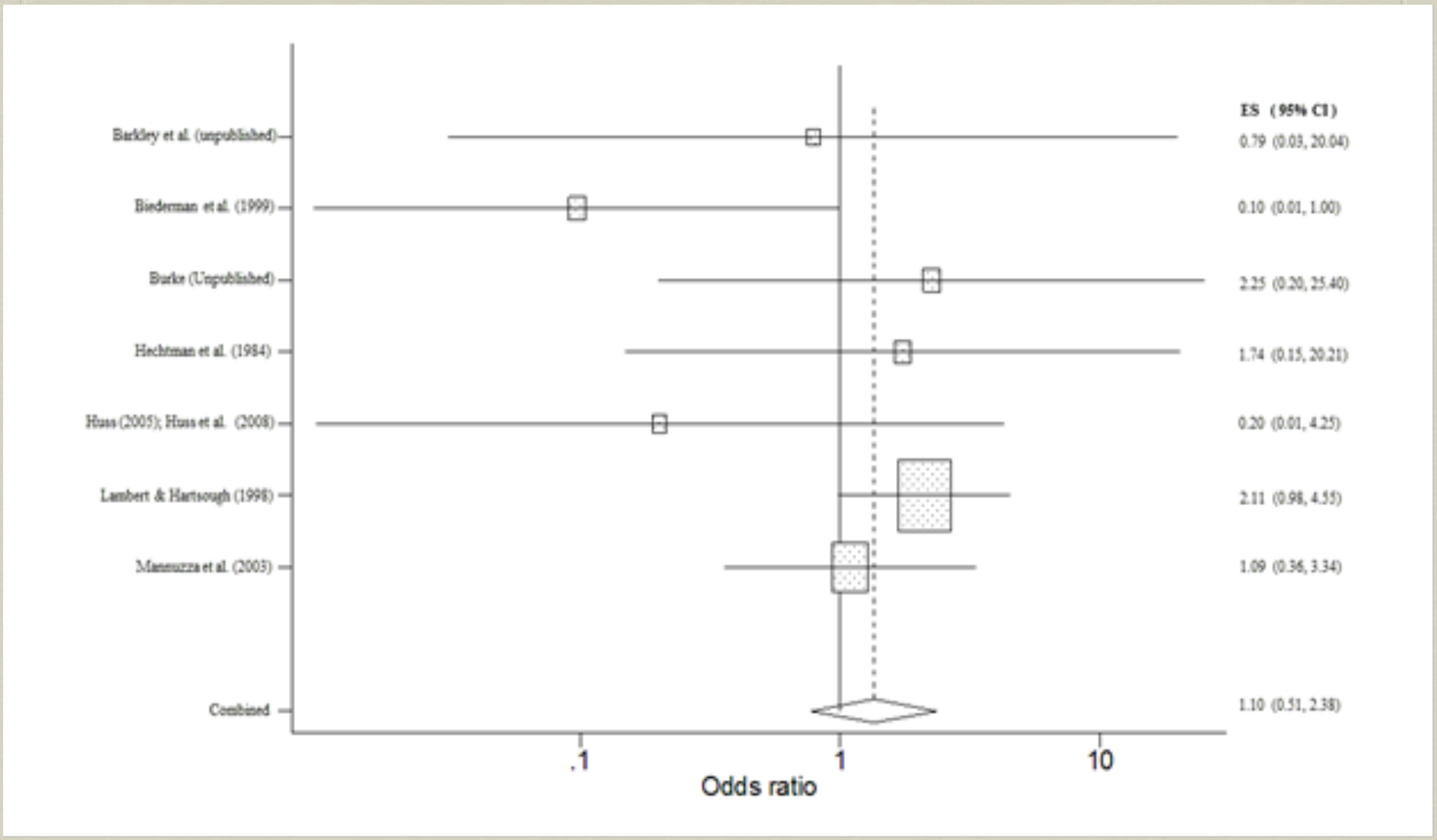
Nicotine Dependence



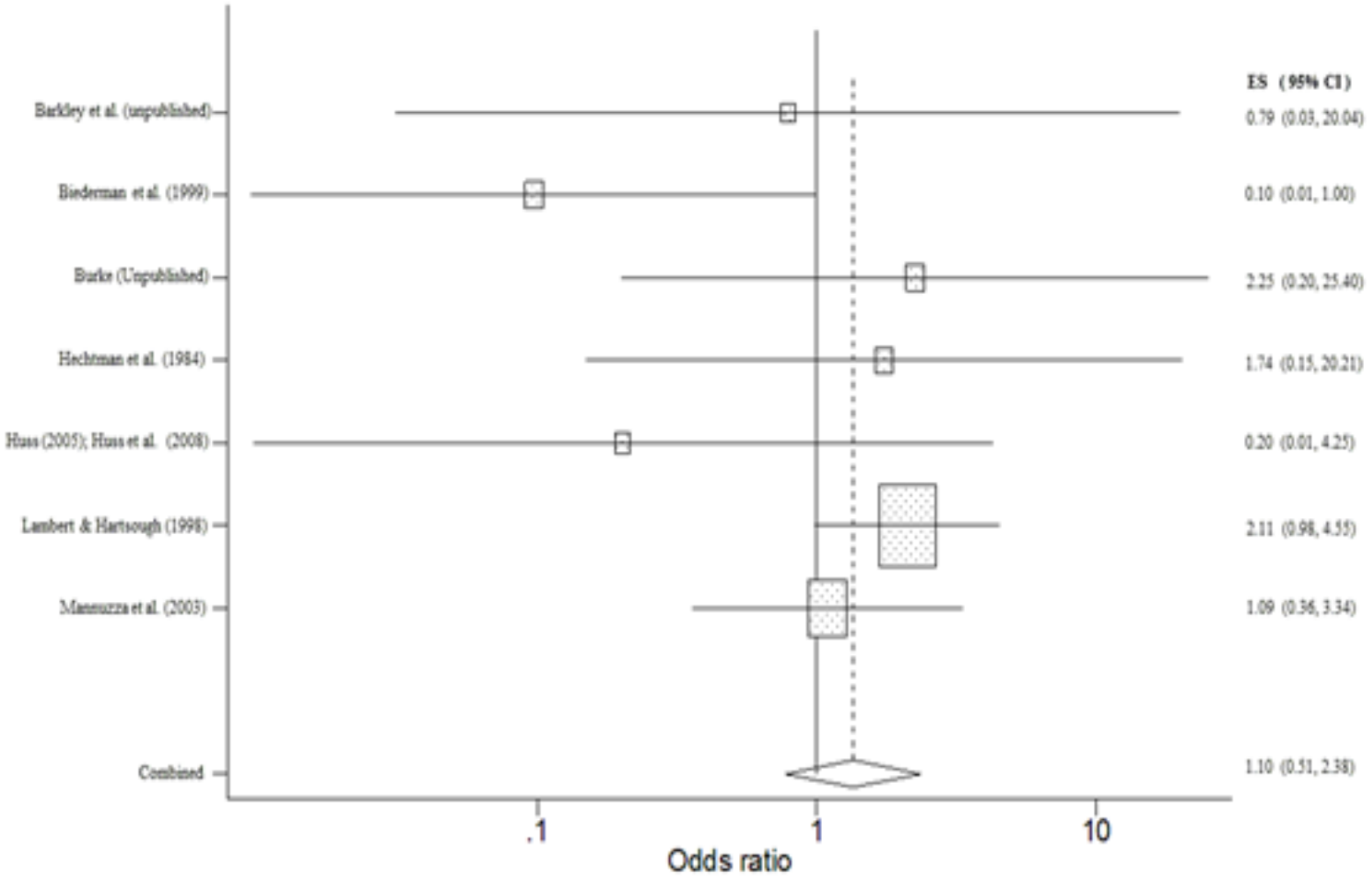
Alcohol Abuse/Dependence



Marijuana Abuse/Dependence



Cocaine Abuse/Dependence



Objective 3 Summary

- Youth treated with MPH were comparable to youth not treated with MPH on all ASUD outcomes (Humphreys et al., 2013)
- Remaining questions/challenges
  - MPH not randomly assigned
  - Intervention selection bias (Larzelere et al., 2004)
- Clinical care with stimulant medication
  - Medication holidays, changes in dosage, timing/onset
  - Careful & continuous measure of MPH administration

Objective 4: Misuse of Stimulant Medication in College Students

- Potential influences on misuse of stimulant medication in college students?
  - Easily available
  - Expectancies of improved academic functioning (not the same as objective improvement)
  - Increasing interest in adult ADHD

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Are Prescription Stimulants "Smart Pills"? The Epidemiology and Cognitive Neuroscience of Prescription Stimulant Use by Normal Healthy Individuals

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Use of prescription stimulants by normal healthy individuals to enhance cognition is said to be on the rise. Who is using these medications for cognitive enhancement, and how prevalent is this practice? Do prescription stimulants in fact enhance cognition for normal healthy people? We review the epidemiological and cognitive neuroscience literatures in search of answers to these questions. Epidemiological issues addressed include the prevalence of nonmedical stimulant use, user demographics, methods by which users obtain prescription stimulants, and motivations for use. Cognitive neuroscience issues addressed include the effects of prescription stimulants on learning and executive function, as well as the task and individual variables associated with these effects. Little is known about the prevalence of prescription stimulant use for cognitive enhancement outside of student populations. Among college students, estimates of use vary widely but, taken together, suggest that the practice is commonplace. The cognitive effects of stimulants on normal healthy people cannot yet be characterized definitively, despite the volume of research that has been carried out on these issues. Published evidence suggests that declarative memory can be improved by stimulants, with some evidence consistent with enhanced consolidation of memories. Effects on the executive functions of working memory and cognitive control are less reliable but have been found for at least some individuals on some tasks. In closing, we enumerate the many outstanding questions that remain to be addressed by future research and also identify obstacles facing this research.

Keywords: amphetamine, enhancement, neuroethics, psychopharmacology, stimulant

Prevalence of Misuse of Stimulant Medication in College Students

Misuse of Stimulant Medication Among College Students: A Comprehensive Review and Meta-analysis

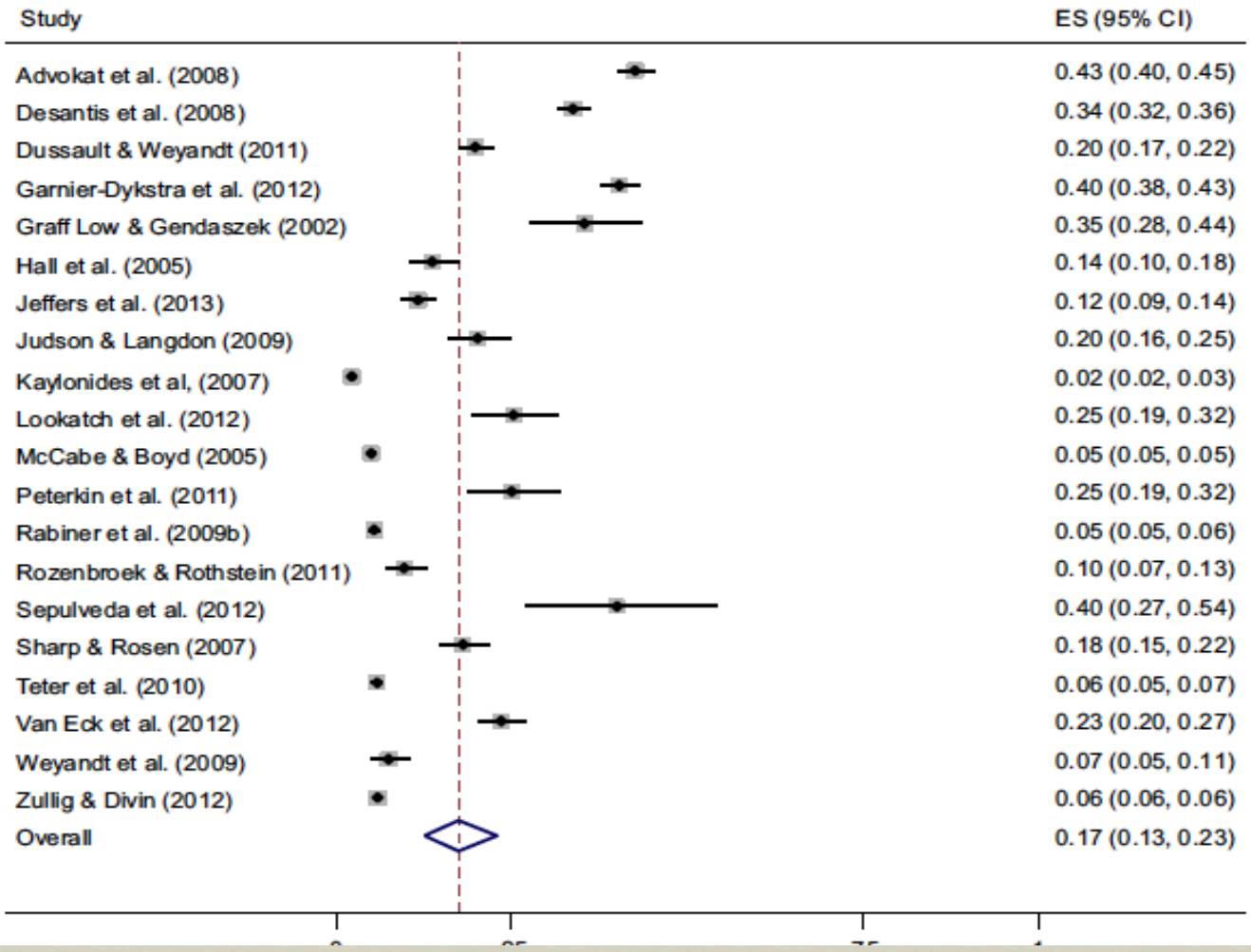
Kari Benson · Kate Flory · Kathryn L. Humphreys · Steve S. Lee

Abstract The misuse of stimulant medication among college students is a prevalent and growing problem. The purpose of this review and meta-analysis is to summarize the current research on rates and demographic and psychosocial correlates of stimulant medication misuse among college students, to provide methodological guidance and other ideas for future research, and to provide some preliminary suggestions for preventing and reducing misuse on college campuses. Random-effects meta-analysis found that the rate of stimulant medication misuse among college disorders requires further investigation, as do the reasons why students divert or misuse and whether policies on college campuses contribute to the high rates of misuse among students. Future research should also work to develop and implement effective prevention strategies for reducing the diversion and misuse of stimulant medication on college campuses.

Keywords Stimulant medication · Misuse · College students · Motives · Psychological correlates

Meta-Analysis of Misuse of Stimulant Medication in College Students

Fig. 1 Meta-analysis results for rates of stimulant medication misuse



Drilling down further

- What predicted higher rates of misuse?
  - Longitudinal studies yielded higher estimates of misuse
  - Studies with higher proportion of ADHD students
- Qualitative review
  - 40% bought meds from peers; 40% "given" by peers
  - 55% & 82% reported it was easy to get stimulant meds (Sharp & Rosen, 2007; DeSantis et al., 2008)
- Expectancy effects in substance use (e.g., alcohol consumption on 21st birthday)

Concluding Remarks

- Childhood ADHD is a risk factor for later ASUD
  - What are the *risk processes*? How does ADHD confer risk?
  - Social and familial impairments, conduct problems are key candidates
  - Positive alcohol expectancies?
- Medication management decision is complex
  - Later ASUD are unlikely iatrogenic side effect of stimulant medication (*may* be protective for nicotine problems; Schoenfelder et al., 2013)
  - Misuse of stimulant medication is prevalent yet distressingly little is known about motivation, severity, comorbidity, etc.

Shared pathways

- Peer and family problems explained the risk for depression from early ADHD (and inattention specifically)
- Replicated in two independent samples
- Remediating common pathways may reduced risk for multiple negative outcomes associated with ADHD

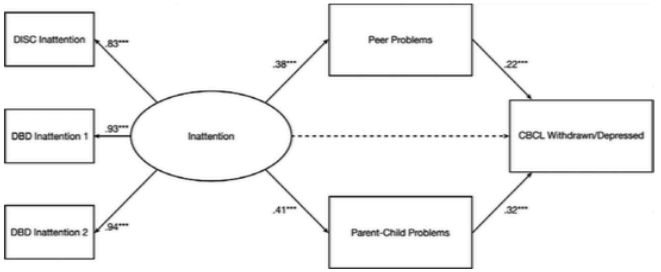


Figure 1. Model of the association of attention-deficit/hyperactivity disorder (ADHD) inattention with depression as mediated by peer rejection and parent–child problems (n = 229). DISC = Diagnostic Interview Schedule for Children; DBD = Disruptive Behavior Disorder Rating Scale; CBCL = Child Behavior Checklist. Standardized parameter estimations are shown; errors and covariances not shown. Nonsignificant paths are represented by dotted lines. *** $p < .001$.

Moderation by sex. Sex differences in the multiple mediation model were first examined by evaluating the difference in model between a model in which all paths were constrained to be equal across sex compared with a model in which all pathways were free to vary. Satorra–Bentler chi-square difference tests revealed no difference in model fit between the more restrictive and less restrictive models, χ^2_{diff} (7) = 3.57, p = .83. Second, there were no significant differences between boys and girls for any path coefficients or indirect effects.

Moderation by sex was then explored in the model in which ODD was included as a predictor. The Satorra-Bentler chi-square difference test revealed a marginally significant difference in model fit between the more restrictive and less restrictive models, χ^2_{diff} (11) = 17.92, p = .08. Specifically, ODD predicted pa

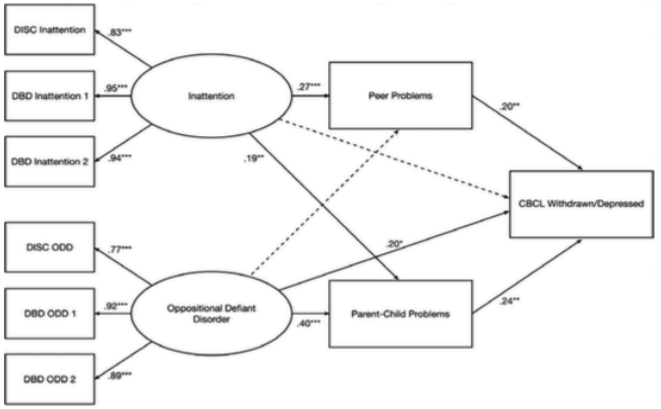


Figure 2. Model of the association of both attention-deficit/hyperactivity disorder (ADHD) inattention and oppositional defiant disorder with depression as mediated by peer rejection and parent–child problems (n = 229). DISC = Diagnostic Interview Schedule for Children; DBD = Disruptive Behavior Disorder Rating Scale; CBCL = Child Behavior Checklist. Standardized parameter estimations are shown; errors and covariances not shown. Nonsignificant paths are represented by dotted lines. * $p < .05$. ** $p < .01$. *** $p < .001$.