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Meta-Analyses of Externalizing Disorders: Genetics or Prenatal Alcohol Exposure?

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Abstract

Background—Externalizing disorders are heritable precursors to alcohol dependence, common in children of alcoholics (COA), and in children with prenatal alcohol exposure (PAE). Pregnancies involving alcohol exposure sufficient to affect the fetus may involve women with genetic risk for alcohol dependence (AD). We hypothesized that known PAE will increase the odds of having an externalizing disorder compared to COA.

Methods—The odds ratios of three externalizing disorders [attention deficit hyperactivity (ADHD), conduct disorder (CD), and oppositional defiant disorder (ODD)] were obtained for two domains: (1) PAE and (2) COA, by estimating the logged odds ratios (LOR) for each study. Permutation tests were implemented to compare LORs for PAE vs COA studies within each disorder, including PAE vs an AD mother and PAE vs an AD father.

Results—In PAE studies, the odds of ADHD and CD were elevated. Rates of all three disorders were elevated in COA studies. Permutation tests revealed that the mean LOR for ADHD was significantly higher in PAE studies compared to: COA ($p=0.01$), AD mother ($p<0.05$) and AD father ($p=0.03$). No differences were found for ODD ($p=0.09$) or CD ($p=0.21$).

Conclusion—These results provide compelling evidence of an increased risk of ADHD in those with PAE beyond that due to parental alcohol dependence or a genetic liability, consistent with a unique etiology most likely due to direct alcohol exposure during prenatal development.

Keywords

externalizing disorders; ADHD; prenatal alcohol exposure; children of alcoholics; genetics

INTRODUCTION

Prenatal alcohol exposure (PAE) is associated with a vast array of adverse outcomes, including cognitive deficits, impaired executive function, altered sensory function, deficits in motor functions, mental retardation, and high comorbidities with disruptive behavioral

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disorders (Streissguth et al., 2004). The presence and severity of these effects can vary depending on the timing, frequency, and amount of alcohol exposure to the fetus (Fryer, McGee, Matt, Riley, & Mattson, 2007; Mattson, Crocker, & Nguyen, 2011; Streissguth, Sampson, & Barr, 1989). A recent meta-analysis of prevalence rates of PAE outcomes from around the world (identified as fetal alcohol spectrum disorders) reported a global prevalence of 22.8 per 1,000, with slightly higher rates in Canada (30.5) and the United States (33.5) (Roozen et al., 2016). The adverse effects of PAE are likely to become an even larger problem; the Center for Disease Control found the risk of an alcohol-exposed pregnancy in women of reproductive age to be 7.3%, with 3.3 million women at risk during a 1-month period (Green, McKnight-Eily, Tan, Mejia, & Denny, 2016).

Evidence from animal models and clinical studies confirm that PAE often results in some degree of insult to the developing fetal brain that can affect many neural systems (Patten, Fontaine, & Christie, 2014). In particular, the prefrontal cortex (PFC) is directly affected by prenatal alcohol exposure in humans (Moore, Migliorini, Infante, & Riley, 2014). Several animal model studies have also documented that fetal alcohol exposure damages the medial PFC, with effects including neuronal cell loss (Mihalick, Crandall, Langlois, Krienke, & Dube, 2001), reduction in dendritic branching and density (Hamilton, Whitcher, & Klintsova, 2010; Lawrence, Otero, & Kelly, 2012), and reduction of presynaptic proteins involved in synaptic transmission and implicated in cognitive function (Barr, Hofmann, Phillips, Weinberg, & Honer, 2005). The PFC is necessary in executive function tasks including regulation of attention to relevant stimuli and response inhibition (Talpos & Shoaib, 2015). Consistent with this, response inhibition and overall executive function are frequently compromised in individuals with PAE (Kodituwakku, 2007; Mattson et al., 2011). Impairment of executive functioning is associated with externalizing disorders including attention deficit hyperactive disorder (ADHD) (Sun & Buys, 2012), conduct disorder (CD) (Johnson, 2015), and oppositional defiant disorder (ODD) (Matthys, Vanderschuren, & Schutter, 2013).

ADHD is characterized by a continued pattern of hyperactivity/impulsivity, inattention, or both and involve problems that interfere with school or home functioning. CD is defined by opposition to authority and is associated in children and young adults with headstrong behavior and substance use, whereas ODD is characterized by a negative, angry mood and is associated with anxiety and emotional disorders (Rowe, Costello, Angold, Copeland, & Maughan, 2010). These externalizing disorders are more prevalent in individuals with PAE compared to those without prenatal exposure (Tsang, Lucas, Carmichael Olson, Pinto, & Elliott, 2016), with timing and amount of alcohol exposure moderating the degree of problems (May et al., 2013; Sayal et al., 2014). Estimates of these disorders in individuals with PAE, based on smaller studies, range from 38% to 95% (Burd, Klug, Martsolf, & Kerbeshian, 2003; Fryer et al., 2007; Popova et al., 2016). In addition a meta-analysis estimated the prevalence of “disturbances of activity and attention” to range from 24%–78% in PAE individuals (Popova et al., 2016), and results from a large cohort of more than 2,000 PAE individuals revealed that ADHD was the most prevalent comorbid disorder (41%), with ODD and CD having a prevalence of less than half that (~17%) (Bhatara, Loudenberg, & Ellis, 2006).

Although most women discontinue drinking once they discover they are pregnant, one study has shown that 27% of pregnant women continue to drink at some level throughout their pregnancy (Muggli et al., 2016). Women who have children with a fetal alcohol spectrum disorder drink more drinks per drinking day, consume more when they drink, and binge drink more than mothers of children who do not have a fetal alcohol spectrum disorder (May et al., 2014) and therefore are more likely to be alcohol dependent (AD) (Hill, Lowers, Locke-Wellman, & Shen, 2000; May et al., 2013). Due to assortative mating, there is a 3.4 times greater risk that the father is also AD (Tyrfingsson et al., 2010). This maternal, and likely paternal, alcohol dependence could be a key factor underlying the "link" between PAE and increased rates of externalizing disorders in PAE individuals, as these externalizing disorders are prevalent in children of alcoholics (COA) and in individuals with a family history of alcohol dependence and abuse (Kuperman, Schlosser, Lidral, & Reich, 1999; Waldron, Martin, & Heath, 2009). In particular, children of AD mothers are more likely to have externalizing disorders compared to children in families with no history of alcohol dependence (Hill, Locke, Lowers, & Connolly, 1999; Hill, Tessner, & McDermott, 2011).

These externalizing disorders are also heritable (Krueger et al., 2002), with heritability estimates highest for ADHD, ranging from 70–90%, (Brikell, Kuja-Halkola, & Larsson, 2015). Heritability of CD and ODD is slightly lower, ranging from 50–80% for CD (Porsch et al., 2016) and 61% for ODD (Coolidge, Thede, & Young, 2000). Thus, it is possible that these disorders were inherited from one or both parents. In summary, these externalizing disorders observed in PAE offspring could be due to (1) direct exposure to alcohol during fetal development, inherited factors associated with (2) alcohol dependence or (3) externalizing disorders in the mother or father, or some combination, or (4) a gene by environment interaction due to an AD mother consuming alcohol while pregnant (Figure 1).

The current study tested whether rates of externalizing disorders are higher in individuals with PAE than in COA. Six individual meta-analyses were performed: three estimating the effect sizes of ADHD, CD, and ODD in those with PAE compared to unexposed individuals, and another three estimating the effect sizes of the same disorders in COA compared to those with no family history of alcohol dependence. These analyses tested the hypotheses that rates of externalizing disorders are increased both in PAE and in COA. The novel analyses of this study were the subsequent comparisons of effect sizes between PAE and COA within each disorder, including a comparison of rates between PAE children (confirmed alcohol-exposed pregnancy) vs. offspring of (confirmed) AD mothers. These analyses tested the hypothesis that confirmed alcohol-exposed pregnancies increase the risk for externalizing disorders beyond that of heritable factors associated with confirmed maternal (or paternal) alcohol dependence. Notably, if the risk for an externalizing disorder is greater in PAE (maternal alcohol dependence likely but undocumented) than in COA (drinking during pregnancy likely but undocumented), it would provide compelling, novel evidence that the etiology of that disorder is attributable to the prenatal alcohol exposure.

METHODS

Eligibility Criteria

Descriptions of inclusion and exclusion criteria are provided in Table 1. To reduce potential bias of overlapping samples, if the same cohort was reported in more than one study, data from the study with the largest sample was included. When numbers were not presented, they were estimated from percentages, or obtained as cross-tabs from corresponding authors.

Studies based on twin samples included offspring of "control" monozygotic (MZ) twins (i.e., MZ mothers who did not drink while pregnant, MZ mothers who were not AD, MZ fathers who were not AD). A conservative approach to reduce genetic bias was taken and the data from these MZ categories were included in the control comparison groups.

Information Sources

Several databases were employed for the literature search, including PubMed, PsycINFO, and Web of Science. The corresponding author was contacted to request relevant information for studies presenting partial data. The literature search included all available articles published before January 1, 2017.

Search Strategy

All combinations of keywords included "childhood behavior* disorder", "disruptive behavior* disorder", "externalizing disorder", "attention deficit hyperactivity", "attention deficit", "attention deficit AND disruptive behavior", "conduct disorder", "oppositional defiant disorder" were included in a search using AND with the following keywords "gestation", "prenatal alcohol exposure", "fetal alcohol exposure", "fetal alcohol spectrum disorder", "fasd", "family history alcohol*", "familial alcohol", "sons of alcoholic", "children of alcoholic", "multi generation* alcohol*". Additional studies were identified through reference section reviews and automated email alerts from all searches.

Study and Sample Characteristics

Demographic data were recorded by the first author. All study and sample characteristics for the PAE and COA literature are provided in Tables S1 and S2, respectively. In summary, studies from the PAE domain compared children with prenatal alcohol exposure (defined in Table S1 for each study, when available) to children without evidence (either physical or from parental reports) of prenatal alcohol exposure as the control group. If an exposed group was not defined by the authors, we conservatively assigned individuals with *any* PAE to the exposed group, due to varied differences in details and thresholds regarding maternal alcohol consumption during pregnancy. Conversely, if the non-exposed group was not defined by the authors, we included individuals with no or unknown alcohol exposure. Studies from the COA domain compared children of an alcohol dependent parent to children without an alcohol dependent parent as the control group. Table S3 contains a list of all instrument abbreviations with the detailed names of each instrument. Two-sample t-tests were used to test for differences in quantitative demographic characteristics and chi-squared tests were used to compare categorical differences between the PAE and COA domains of literature.

Meta-analytic Procedure

Due to the inherent differences in the two domains of literature, simple counts were obtained to calculate one odds ratio (OR) for each study. The OR was chosen as the best effect size since both variables (parent information and disorder diagnosis) were dichotomous (Lipsey & Wilson, 2001). One advantage of using the OR is its equivalence across all studies, regardless of the literature domain (PAE vs COA), different covariates collected and utilized across studies, or type of sample (twin study vs ascertained sample). For each study, simple counts were entered into a 2 (prenatal alcohol exposure/AD parent = yes or no) × 2 (disorder diagnosis = yes or no) table in the "2 by 2 frequency table" option in the Practical Meta-Analysis Effect Size Calculator (David B. Wilson, Ph.D., George Mason University, http://www.campbellcollaboration.org/resources/effect_size_input.php). The website provided the OR, a 95% confidence interval (CI), natural log of the OR, and the variance of the natural log of the OR, among other statistics. Numbers for the 2×2 frequency table were based on (1) tables or counts in published studies, and (2) percentages or proportions reported.

The natural log of the OR (logged odds ratio, LOR) was used in the meta-analysis. The LOR has a normal distribution with a mean of 0, with LOR<0 indicating reduced odds and LOR>0 indicating increased odds (Lipsey & Wilson, 2001). Advantages of using the LOR include a symmetric distribution, with equal "weighting" on either side of 0, no recoding, and the ability to calculate the variance. An LOR=0 denotes equivalent odds, with symmetry around 0; therefore a 95% CI which includes 0 indicates lack of differences in odds between the two groups. This differs from the odds ratio which ranges between 0 and infinity, with 1 indicating a lack of differences in odds, and non-symmetry around 1. Both LOR and the converted OR (exp(LOR)) are provided in the Results, since most readers are familiar with interpreting the OR and its corresponding CI. The random effects model was used to estimate the overall effect size of the LOR. An analysis of variance (ANOVA) model implemented in SAS was used to test if percent male, race, mean age, or other demographic measures predicted the LOR within each domain, collapsing across disorders. The R package "meta" was used to calculate Q, I^2, ζ^2, the overall LOR based on the random effects model, and to plot the LORs for all studies (https://cran.r-project.org/web/packages/meta/index.html).

Comparison of the LOR from the Two Domains: Permutation Tests

When comparing the LORs between the two domains for each disorder, we did not want to make any assumptions about the distribution of the test statistic, or of the underlying population distributions, means or medians. Therefore the permutation test (Pitman, 1937) was implemented to estimate the true distribution of the test statistic under the null hypothesis that the mean LOR from the PAE literature is equal to the mean LOR from the COA literature.

The permutation test is based on the premise that by (1) shuffling the domain assignment (i.e., randomly assign the LOR to either PAE or COA), then (2) computing the test statistic based on the random assignment, and (3) repeating this process a very large number of times, the distribution of the test statistic under the null hypothesis (i.e., there is no difference in LOR between PAE and COA studies) is approximated. A frequency plot of the

test statistics from all permutations is created, and the permutation p-value is the area under the "curve" to the right of the test statistic computed from the actual data, i.e., permutation p-value = (# of permuted test statistic values to the right of the actual statistic)/total # of permutations.

Each permutation randomly assigned PAE and COA labels to the LORs, computed and recorded the test statistic, and then repeated this process 10,000 times to obtain one distribution of the test statistic under the null hypothesis. The test statistic based on the actual PAE and COA assignments was then compared to this null distribution to calculate the permutation p-value. This was repeated 10,000 times in order to construct a frequency distribution of 10,000 permutation p-values.

Three non-parametric permutation tests comparing means and medians were implemented: (1) the Fisher-Pitman permutation test which tests if two distributions have the same mean and variance, (2) the Independence Test which tests if the LOR is independent of group assignment (i.e., PAE or COA), and (3) the Savage Test, which tests if one distribution is larger than the other. The R package coin (**Co**nditional **In**ference Procedures in a Permutation Test Framework) was used to implement the permutations and computations (https://cran.r-project.org/web/packages/coin/index.html). The approximate distribution of the test statistic was estimated using Monte Carlo resampling, applying 10,000 permutations per test.

A distribution of p-values was estimated for each of the following null hypotheses, with the mean p-value reported for: (a) PAE = COA; (b) PAE = mother AD; (c) PAE = father AD; (d) PAE = unknown parent AD (i.e., no information about which parent was AD), and (e) mother AD = father AD. These distributions were estimated for ADHD and CD. Due to the small number of studies obtained for ODD, only p-value distributions for hypotheses (a) and (c) and (d) were estimated.

RESULTS

Study Demographics

A total of 407 abstracts were screened for the PAE literature, with 17 meeting inclusion criteria; 145 abstracts were screened for the COA, with 37 meeting criteria. Several studies were excluded because they used symptom count, latent class or factor analysis, severity scores, or some other quantitative measure of the behavioral disorders. Other studies were excluded because the comparison group was ascertained on a specific characteristic (e.g., PAE with ADHD vs ADHD alone), did not assess PAE or parental alcohol dependence, was ascertained on a broader substance dependence criteria, or had a small sample size (total N < 20). The final sample consisted of 24 ORs from 17 independent studies in the PAE domain, and 62 ORs from 32 independent studies in the COA domain, with several studies reporting on more than one disorder, or reporting on both maternal and paternal alcohol dependence (Tables S1 and S2).

The mean sample size did not differ between the two domains of literature (p=0.33; Table 2A). The COA participants were older than those in PAE studies (p=0.02) and were more

likely to be male (60% vs 46%, p=0.04). Subsequent analyses comparing age and percent male separately for each disorder revealed that for ADHD, COA individuals were older than PAE individuals (p=0.02; Table 2B) and higher percent male (p=0.04); there were no differences in age or percent male between PAE and COA studies for CD (all p>0.31) or ODD (all p>0.56). There was no association between the LOR and gender, race or age in PAE studies (all p>0.49) or in COA studies (all p>0.26).

The majority of COA studies ascertained based on having either parent with alcohol dependence (59%). Most of the remaining studies specifically included participants based on the father being AD (29%). Maternal alcohol consumption during pregnancy was primarily confirmed via clinical evaluations of the offspring (47%) or maternal interviews and questionnaires (40%) and the mother was rarely evaluated for alcohol dependence. PAE studies were more likely to assess maternal smoking or drug use during pregnancy (53%) compared to COA studies (13%; X2(1)=9.3, p=0.0023). Diagnosis of the externalizing disorder was made primarily using DSM-IV criteria in PAE studies (94%), whereas only 47% of COA studies used DSM-IV (X2(1)=9.9, p=0.0016). This is likely due to dates of the studies used in the meta-analysis: the earliest PAE study was from 2003, while 14 (44%) of the COA studies ranged from 1983 – 2002, and therefore primarily used DSM-III-R criteria (52%).

Meta-analytic Results

Attention Deficit Hyperactivity Disorder (ADHD)—Measures of homogeneity indicated heterogeneity of both PAE (Q=910, df=15, p<0.0001; I^2=98%) and COA studies (Q=103,928, df=25, p<0.0001; I^2=100%), with moderate between-study variability for PAE (ζ^2 =0.41) but low between-study variability for COA (ζ^2 =0.009) studies. The overall LOR computed from the random effects model for the PAE domain, shown as the red diamond at the bottom of Figure 2A, was 1.13 (95% CI = [0.77, 1.49]), indicating higher rates of ADHD in children with PAE compared to children without PAE (Q=910.56, df=15, p<0.001). The resulting odds ratio (derived from OR = exp(LOR)) and 95% CI was 3.10 [2.16, 4.44] for ADHD in children with PAE. The overall random effects LOR for COA literature, shown as the blue diamond at the bottom of Figure 2B, was 0.72 (95% CI = [0.66, 0.78]), also signifying higher rates of ADHD in COA compared to controls (Q=103,929, df=25, p<0.001). The odds ratio for COA = 2.05 (95% CI = [1.93, 2.18]).

As hypothesized, the mean LOR for PAE was significantly greater than the mean LOR for COA (p=0.01; Table 3A; Figure 3). Similarly, the mean LOR for PAE was significantly higher for all comparisons to the other parent of interest: PAE vs mother AD (p<0.05), PAE vs father AD (p<0.04), and PAE vs unknown parent AD (p<0.04). Conversely, the LOR based on the mother being AD was not significantly greater than the LOR based on the father being AD (p≥0.10).

Conduct Disorder (CD)—Measures of homogeneity again indicated heterogeneity of both PAE (Q=60, df=3, p<0.0001; I^2=95%) and COA studies (Q=3,211, df=25, p<0.0001; I^2=99%), with modest between-study variability for PAE (ζ^2 =0.28) but low between-study variability for COA (ζ^2 =0.08) studies. The overall LOR computed from the random effects

model for the PAE domain, shown as the red diamond at the bottom of Figure 2C, was 1.12 (95% CI = [0.48, 1.75]), Q=60, df=3, p<0.001), with an OR of 3.06 (95% CI = [1.62, 5.75]). The overall random effects LOR for COA literature, depicted as the blue diamond in Figure 2D, was 0.95 (95% CI = [0.83, 1.08], Q=1,816, df=25, p<0.001), with an OR of 2.59 (95% CI = [2.29, 2.94]). The mean LOR from the PAE domain was the same or higher than all other comparison groups (Figure 3); however, none of the differences was significant (all $p \geq 0.21$; Table 3B).

Oppositional Defiant Disorder (ODD)—As above, there was high heterogeneity of PAE (Q=164, df=3, p<0.0001; I^2=98%) and COA studies (Q=202, df=9, p<0.0001; I^2=96%), with lower between-study variability for PAE (ζ^2 =0.16). However, contrary to ADHD and CD, effect sizes for ODD yielded higher between-study variability for COA (ζ^2 =0.29) studies. The LOR from the random effects model across PAE studies was 0.38 (red diamond, Figure 2E) and the 95% CI included 0 [−0.05, 0.80], (OR=1.46; 95% CI=[0.95, 2.23]), indicating approximately equal odds. The LOR from COA studies was 0.93 and the CI did not include 0, (95% CI=[0.51, 1.36], Figure 2F), resulting in an odds ratio of 2.53 (95% CI=[1.63, 3.94]). Due to the limited number of studies, only a comparison of PAE vs: COA, father AD and unknown parent AD could be tested. As seen in Figure 3, the mean LOR for PAE studies was smaller than the mean LOR for COA studies, but did not reach significance ($p \geq 0.08$). All other comparisons were non-significant as well ($p \geq 0.15$; Table 3C).

DISCUSSION

This is the first meta-analysis reporting on rates of externalizing disorders in PAE and comparing these rates with those from a meta-analysis examining the same disorders in COA. Consistent with our hypothesis, the LOR was significantly higher for ADHD in PAE studies compared to the LOR for ADHD in COA. Importantly, the LOR was significantly higher even for the specific comparison of PAE studies compared to studies reporting on children with an AD mother, despite the fact that PAE studies did not exclude based on maternal alcohol dependence and COA studies did not exclude based on prenatal alcohol exposure. The LOR in studies reporting on offspring with an AD mother was not significantly higher than the LOR in studies reporting on offspring with an AD father, indicating that there is no evidence of increased risk of ADHD in offspring of AD mothers compared to AD fathers, despite the potential confound that most COA studies did not exclude based on likely maternal consumption during pregnancy. Contrary to our hypothesis, the comparisons of LORs for ODD revealed slightly higher LOR in COA studies compared to PAE studies, and no significant difference for CD.

This study presents important evidence of a unique etiology of ADHD in individuals prenatally exposed to alcohol. That the average LOR for ADHD in these studies was higher than the average LOR in studies of COA, and specifically, than in studies of mothers with AD, indicates that there is an insult above and beyond that attributable to a genetic liability inherited from an AD parent. This significant difference in risk of ADHD could provide empirical evidence to support the growing literature emphasizing cognitive and behavioral differences between children with a comorbid PAE and ADHD and children with ADHD but no PAE (Mattson et al., 2011; Mattson et al., 2013; O'Malley & Nanson, 2002).

Children with PAE have difficulty shifting and encoding, compared to ADHD individuals without prenatal alcohol exposure, who demonstrated difficulty in focusing and sustaining attention (Coles, 2001). This was confirmed in a meta-analysis comparing PAE children to those without PAE on a variety of measures of executive function, with the largest effect sizes found for set-shifting measures (Khoury, Milligan, & Girard, 2015). A different meta-analysis compared individuals with PAE to those with ADHD (without PAE) and found that the two groups have different cognitive profiles, including increased deficits in set-shifting and verbal fluency in PAE compared to ADHD. These authors also suggest different origins of ADHD diagnosis between the two groups (Kingdon, Cardoso, & McGrath, 2015). Glass and colleagues showed that children with PAE and ADHD were equally impaired at executive function tasks as exposed children without ADHD, whereas in the non-exposed sample, those with ADHD were more impaired than controls, suggesting that these executive function deficits in exposed children are due to different underlying mechanisms of impairment (Glass et al., 2013). A unique etiological origin of ADHD in those with PAE could also account for differential response to ADHD pharmaceutical treatment (Frankel, Paley, Marquardt, & O'Connor, 2006; Koren, 2015; Murawski, Moore, Thomas, & Riley, 2015; O'Malley, Koplin, & Dohner, 2000; Peadon & Elliott, 2010). This highlights an important distinction in individuals with a traditional ADHD diagnosis, i.e., differences in etiological origin are responsible for the differing ADHD characteristics in PAE individuals compared to ADHD characteristics in non-PAE individuals. The distinction in putative etiology and differential response to therapeutics may be underappreciated, given that most PAE studies do not ascertain whether the mother is alcohol dependent and most COA studies do not ascertain whether the alcohol-dependent mother drank while pregnant.

There were no significant differences between PAE and COA studies for CD and ODD. Although this lack of difference could be due to the smaller number of studies in the PAE domain, or to the more homogenous definition of "affected" for these disorders, it is likely that there is no difference in etiology between the two domains for either disorder, as there is an absence of literature comparing PAE vs non-exposed individuals. Malone and colleagues specifically addressed the effect of maternal alcohol dependence ***and*** alcohol consumption during pregnancy on rates of CD and ODD (Malone, McGue, & Iacono, 2010). They found that including measures of drinking during pregnancy did not change the results based on maternal alcohol dependence alone, indicating that PAE did not account for their initial association of maternal alcohol dependence on CD or ODD.

As expected, within each domain, the odds of having a disorder was higher compared to respective controls. Although the LOR for ODD was increased in PAE studies, the 95% confidence interval included 0. This result agrees with a meta-analysis showing the prevalence of ODD in those with PAE to be about 25%, but the 95% confidence interval of that study included 0 as well (Popova et al., 2016). The overall odds reported here of 3.10 for having ADHD in PAE children was higher than the reported odds ratio of 2.33 from a different meta-analysis examining rates of ADHD in PAE literature; it was however, within their reported confidence interval (95% CI = 1.18, 4.61) (Gronimus, Ridout, Sandberg, & Santosh, 2009).

The current study has several limitations. First, comorbidity between the disorders was not addressed. However, results from this study were based on the odds ratio, which is calculated from presence or absence of the disorder and not severity of the disorder. Therefore, comorbidity would not have skewed these results or affected conclusions. Second there was no method to directly compare rates of disorders between PAE and COA. The permutation tests presented are comparisons of the LOR estimated within each domain, which employed a different control group. Third, this meta-analysis sought to compare rates of the three disorders in PAE and COA literature, and the best effect size measure to compare two binary traits was an odds ratio (Lipsey & Wilson, 2001). Thus, it was impossible to include obvious environmental factors such as education, socio-economic status, parental relationship, stressful life events, and peer relationships which are known to mediate genetic influence in externalizing disorders (Hicks, South, Dirago, Iacono, & McGue, 2009). Parental diagnosis of the externalizing disorder was another factor for which it was impossible to covary. Thus, the inability to control for the genetic liability due to a parent having the disorder, or a parent being alcohol dependent, or both, was a confound of this study. The ability to control for age and gender could address the confound of older, predominantly male participants in some COA studies compared to PAE participants for those with ADHD. However, since rates of ADHD are higher in males than in females, this would potentially result in an over-estimate of ADHD in COA studies compared to PAE. Thus the significantly higher rates of ADHD in PAE compared to COA studies is a conservative result. Although differences in age between PAE and COA studies for ADHD may have resulted in different ADHD criteria being met in one group compared to the other group, or in different means of assessment of the disorder (parental vs personal report), the LORs employed were for ADHD diagnosis and not based on particular criteria, sub-diagnosis, or symptom count. Maternal illicit drug use during pregnancy was not accounted for in either domain; however, although illicit drug use was associated with attention problems, it was not associated with an increase in externalizing disorders in offspring (Irner, 2012). A substantial proportion (12%–43%) of mothers who drink while pregnant also smoke but there are mixed results demonstrating increased rates of disorders attributable to smoking (Han et al., 2015; Hill et al., 2000), or no significant increase in risk after covarying for other risk factors (Knopik et al., 2004; Mick, Biederman, Faraone, Sayer, & Kleinman, 2002). Slightly fewer than half of the PAE studies established maternal consumption during pregnancy via an interview requiring retrospective recall, which might be considered a weakness. However, one study has shown that maternal retrospective (14 years) recall of consumption during pregnancy was a better predictor of attention and externalizing behavior problems in their offspring than consumption amounts reported *during* the pregnancy (Hannigan et al., 2010).

A potential limitation of not statistically controlling for environmental effects is that many COA studies included in the meta-analysis ascertained their samples based on one of the parents having the disorder of interest. As described above, these disorders are more common in AD individuals and are heritable traits. Thus, we would expect a bias of increased rates of these disorders in the COA domain. This might account for the effect size of ODD in the COA literature being higher than in the PAE literature. However, this was not true for studies reporting on ADHD or CD. In addition, although the home environment may

be more detrimental in one domain compared to the other, the finding that overall rates of ADHD were higher in PAE, whereas ODD rates were higher in COA indicate that the home environment is not preferentially accounting for effects in one group compared to the other.

The strengths of this study include the comparison of effect sizes between two domains of literature using non-biased assumption-free statistical methods to provide a range of p-values. This study also highlights a major weakness of the two fields of research. Only 2 PAE studies ascertained whether or not the mother was AD, and did not exclude participants based on that information. Similarly, 5 COA studies assessed whether the mother drank while pregnant, yet only one excluded the participant if the mother drank more than a certain threshold while pregnant. This implies that noise and heterogeneity are introduced into the "control" samples in *both* domains. Very few studies have taken into account both the risk of alcohol dependence in mothers who drink while pregnant, and prenatal alcohol exposure in offspring of AD mothers (Cottencin, Nandrino, Karila, Mezerette, & Danel, 2009; Malone et al., 2010; O'Brien & Hill, 2014; Sharma & Hill, 2017). Three of these studies demonstrated that taking maternal alcohol dependence and consumption during pregnancy into consideration moderated the outcome phenotypes, indicating the necessity of controlling for both dependence and consumption.

In summary, this study compared the rates of three externalizing disorders within and between those with prenatal alcohol exposure and children of alcoholics and found that rates of ADHD were significantly higher in those with prenatal alcohol exposure compared to children of alcoholics, despite the fact that participants with *any* prenatal alcohol exposure were included in the PAE group. Furthermore, the rates of ADHD were higher in individuals whose mothers drank while pregnant compared to individuals with an AD mother, but there were no differences in rates between individuals with an AD mother compared to those with an AD father. These results provide compelling evidence of increased risk of ADHD in those with PAE above and beyond potential alcohol dependence in the mother. Taken together with the growing literature demonstrating specific differences between those with PAE compared to those with ADHD without exposure, and the lack of response of PAE individuals to typical pharmaceutical treatment to ADHD, this could imply that these traits in individuals prenatally exposed to alcohol are not a constellation of ADHD criteria in the traditional sense but rather arise from a unique etiology most likely due to direct alcohol exposure during prenatal development.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

Barr AM, Hofmann CE, Phillips AG, Weinberg J, Honer WG. Prenatal ethanol exposure in rats decreases levels of complexin proteins in the frontal cortex. Alcohol Clin Exp Res. 2005; 29(11): 1915–1920. [PubMed: 16340446]

Bhatara V, Loudenberg R, Ellis R. Association of attention deficit hyperactivity disorder and gestational alcohol exposure: an exploratory study. J Atten Disord. 2006; 9(3):515–522. DOI: 10.1177/1087054705283880 [PubMed: 16481668]

Brikell I, Kuja-Halkola R, Larsson H. Heritability of attention-deficit hyperactivity disorder in adults. Am J Med Genet B Neuropsychiatr Genet. 2015; doi: 10.1002/ajmg.b.32335

Burd L, Klug MG, Martsolf JT, Kerbeshian J. Fetal alcohol syndrome: neuropsychiatric phenomics. Neurotoxicol Teratol. 2003; 25(6):697–705. [PubMed: 14624969]

Coles CD. Fetal alcohol exposure and attention: moving beyond ADHD. Alcohol Res Health. 2001; 25(3):199–203. [PubMed: 11810958]

Coolidge FL, Thede LL, Young SE. Heritability and the comorbidity of attention deficit hyperactivity disorder with behavioral disorders and executive function deficits: a preliminary investigation. Dev Neuropsychol. 2000; 17(3):273–287. DOI: 10.1207/s15326942dn1703_1 [PubMed: 11056845]

Cottencin O, Nandrino JL, Karila L, Mezerette C, Danel T. A case-comparison study of executive functions in alcohol-dependent adults with maternal history of alcoholism. Eur Psychiatry. 2009; 24(3):195–200. DOI: 10.1016/j.eurpsy.2008.12.003 [PubMed: 19195848]

Frankel F, Paley B, Marquardt R, O'Connor M. Stimulants, neuroleptics, and children's friendship training for children with fetal alcohol spectrum disorders. J Child Adolesc Psychopharmacol. 2006; 16(6):777–789. DOI: 10.1089/cap.2006.16.777 [PubMed: 17201621]

Fryer SL, McGee CL, Matt GE, Riley EP, Mattson SN. Evaluation of psychopathological conditions in children with heavy prenatal alcohol exposure. Pediatrics. 2007; 119(3):e733–741. DOI: 10.1542/peds.2006-1606 [PubMed: 17332190]

Glass L, Ware AL, Crocker N, Deweese BN, Coles CD, Kable JA, May PA, Kalberg WO, Sowell ER, Jones KL, Riley EP, Mattson SN. Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD). Neuropsychological deficits associated with heavy prenatal alcohol exposure are not exacerbated by ADHD. Neuropsychology. 2013; 27(6):713–724. DOI: 10.1037/a0033994 [PubMed: 24040921]

Green PP, McKnight-Eily LR, Tan CH, Mejia R, Denny CH. Vital Signs: Alcohol-Exposed Pregnancies - United States, 2011–2013. MMWR Morb Mortal Wkly Rep. 2016; 65(4):91–97. DOI: 10.15585/mmwr.mm6504a6 [PubMed: 26845520]

Gronimus R, Ridout D, Sandberg S, Santosh P. Maternal alcohol consumption. London J Prim Care (Abingdon). 2009; 2(1):28–35.

Hamilton GF, Whitcher LT, Klintsova AY. Postnatal binge-like alcohol exposure decreases dendritic complexity while increasing the density of mature spines in mPFC Layer II/III pyramidal neurons. Synapse. 2010; 64(2):127–135. DOI: 10.1002/syn.20711 [PubMed: 19771589]

Han JY, Kwon HJ, Ha M, Paik KC, Lim MH, Gyu Lee S, Yoo SJ, Kim EJ. The effects of prenatal exposure to alcohol and environmental tobacco smoke on risk for ADHD: a large population-based study. Psychiatry Res. 2015; 225(1–2):164–168. DOI: 10.1016/j.psychres.2014.11.009 [PubMed: 25481018]

Hannigan JH, Chiodo LM, Sokol RJ, Janisse J, Ager JW, Greenwald MK, Delaney-Black V. A 14-year retrospective maternal report of alcohol consumption in pregnancy predicts pregnancy and teen outcomes. Alcohol. 2010; 44(7–8):583–594. DOI: 10.1016/j.alcohol.2009.03.003 [PubMed: 20036487]

Hicks BM, South SC, Dirago AC, Iacono WG, McGue M. Environmental adversity and increasing genetic risk for externalizing disorders. Arch Gen Psychiatry. 2009; 66(6):640–648. DOI: 10.1001/archgenpsychiatry.2008.554 [PubMed: 19487629]

Hill SY, Locke J, Lowers L, Connolly J. Psychopathology and achievement in children at high risk for developing alcoholism. J Am Acad Child Adolesc Psychiatry. 1999; 38(7):883–891. DOI: 10.1097/00004583-199907000-00019 [PubMed: 10405507]

Hill SY, Lowers L, Locke-Wellman J, Shen SA. Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. J Stud Alcohol. 2000; 61(5):661–668. [PubMed: 11022804]

Hill SY, Tessner KD, McDermott MD. Psychopathology in offspring from families of alcohol dependent female probands: a prospective study. J Psychiatr Res. 2011; 45(3):285–294. DOI: 10.1016/j.jpsychires.2010.08.005 [PubMed: 20801463]

Irner TB. Substance exposure in utero and developmental consequences in adolescence: a systematic review. Child Neuropsychol. 2012; 18(6):521–549. DOI: 10.1080/09297049.2011.628309 [PubMed: 22114955]

Johnson AC. Developmental pathways to attention-deficit/hyperactivity disorder and disruptive behavior disorders: Investigating the impact of the stress response on executive functioning. Clin Psychol Rev. 2015; 36:1–12. DOI: 10.1016/j.cpr.2014.12.001 [PubMed: 25590346]

Khoury JE, Milligan K, Girard TA. Executive Functioning in Children and Adolescents Prenatally Exposed to Alcohol: A Meta-Analytic Review. Neuropsychol Rev. 2015; 25(2):149–170. DOI: 10.1007/s11065-015-9289-6 [PubMed: 26037669]

Kingdon D, Cardoso C, McGrath JJ. Research Review: Executive function deficits in fetal alcohol spectrum disorders and attention-deficit/hyperactivity disorder - a meta-analysis. J Child Psychol Psychiatry. 2015; doi: 10.1111/jcpp.12451

Knopik VS, Heath AC, Madden PA, Bucholz KK, Slutske WS, Nelson EC, Statham D, Whitfield JB, Martin NG. Genetic effects on alcohol dependence risk: re-evaluating the importance of psychiatric and other heritable risk factors. Psychol Med. 2004; 34(8):1519–1530. [PubMed: 15724882]

Kodituwakku PW. Defining the behavioral phenotype in children with fetal alcohol spectrum disorders: a review. Neurosci Biobehav Rev. 2007; 31(2):192–201. DOI: 10.1016/j.neubiorev.2006.06.020 [PubMed: 16930704]

Koren G. Pharmacological treatment of disruptive behavior in children with fetal alcohol spectrum disorder. Paediatr Drugs. 2015; 17(3):179–184. DOI: 10.1007/s40272-015-0118-4 [PubMed: 25634057]

Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. J Abnorm Psychol. 2002; 111(3):411–424. [PubMed: 12150417]

Kuperman S, Schlosser SS, Lidral J, Reich W. Relationship of child psychopathology to parental alcoholism and antisocial personality disorder. J Am Acad Child Adolesc Psychiatry. 1999; 38(6):686–692. DOI: 10.1097/00004583-199906000-00015 [PubMed: 10361786]

Lawrence RC, Otero NK, Kelly SJ. Selective effects of perinatal ethanol exposure in medial prefrontal cortex and nucleus accumbens. Neurotoxicol Teratol. 2012; 34(1):128–135. DOI: 10.1016/j.ntt.2011.08.002 [PubMed: 21871563]

Lipsey, MW., Wilson, DB. Practical meta-analysis. Thousand Oaks, CA, US: Sage Publications, Inc; 2001.

Malone SM, McGue M, Iacono WG. Mothers' maximum drinks ever consumed in 24 hours predicts mental health problems in adolescent offspring. J Child Psychol Psychiatry. 2010; 51(9):1067–1075. DOI: 10.1111/j.1469-7610.2010.02219.x [PubMed: 20085606]

Matthys W, Vanderschuren LJ, Schutter DJ. The neurobiology of oppositional defiant disorder and conduct disorder: altered functioning in three mental domains. Dev Psychopathol. 2013; 25(1):193–207. DOI: 10.1017/s0954579412000272 [PubMed: 22800761]

Mattson SN, Crocker N, Nguyen TT. Fetal alcohol spectrum disorders: neuropsychological and behavioral features. Neuropsychol Rev. 2011; 21(2):81–101. DOI: 10.1007/s11065-011-9167-9 [PubMed: 21503685]

Mattson SN, Roesch SC, Glass L, Deweese BN, Coles CD, Kable JA, May PA, Kalberg WO, Sowell ER, Adnams CM, Jones KL, Riley EP. CIFASD. Further development of a neurobehavioral profile of fetal alcohol spectrum disorders. Alcohol Clin Exp Res. 2013; 37(3):517–528. DOI: 10.1111/j.1530-0277.2012.01952.x [PubMed: 22974253]

May PA, Baete A, Russo J, Elliott AJ, Blankenship J, Kalberg WO, Buckley D, Brooks M, Hasken J, Abdul-Rahman O, Adam MP, Robinson LK, Manning M, Hoyme HE. Prevalence and

characteristics of fetal alcohol spectrum disorders. Pediatrics. 2014; 134(5):855–866. DOI: 10.1542/peds.2013-3319 [PubMed: 25349310]

May PA, Blankenship J, Marais AS, Gossage JP, Kalberg WO, Joubert B, Cloete M, Barnard R, De Vries M, Hasken J, Robinson LK, Adnams CM, Buckley D, Manning M, Parry CD, Hoyme HE, Tabachnick B, Seedat S. Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): quantity, frequency, and timing of drinking. Drug Alcohol Depend. 2013; 133(2):502–512. DOI: 10.1016/j.drugalcdep.2013.07.013 [PubMed: 23932841]

Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S. Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. J Am Acad Child Adolesc Psychiatry. 2002; 41(4):378–385. DOI: 10.1097/00004583-200204000-00009 [PubMed: 11931593]

Mihalick SM, Crandall JE, Langlois JC, Krienke JD, Dube WV. Prenatal ethanol exposure, generalized learning impairment, and medial prefrontal cortical deficits in rats. Neurotoxicol Teratol. 2001; 23(5):453–462. [PubMed: 11711248]

Moore EM, Migliorini R, Infante MA, Riley EP. Fetal Alcohol Spectrum Disorders: Recent Neuroimaging Findings. Curr Dev Disord Rep. 2014; 1(3):161–172. DOI: 10.1007/s40474-014-0020-8 [PubMed: 25346882]

Muggli E, O'Leary C, Donath S, Orsini F, Forster D, Anderson PJ, Lewis S, Nagle C, Craig JM, Elliott E, Halliday J. "Did you ever drink more?" A detailed description of pregnant women's drinking patterns. BMC Public Health. 2016; 16:683.doi: 10.1186/s12889-016-3354-9 [PubMed: 27485120]

Murawski NJ, Moore EM, Thomas JD, Riley EP. Advances in Diagnosis and Treatment of Fetal Alcohol Spectrum Disorders: From Animal Models to Human Studies. Alcohol Res. 2015; 37(1):97–108. [PubMed: 26259091]

O'Brien JW, Hill SY. Effects of prenatal alcohol and cigarette exposure on offspring substance use in multiplex, alcohol-dependent families. Alcohol Clin Exp Res. 2014; 38(12):2952–2961. DOI: 10.1111/acer.12569 [PubMed: 25581650]

O'Malley KD, Koplin B, Dohner VA. Psychostimulant clinical response in fetal alcohol syndrome. Can J Psychiatry. 2000; 45(1):90–91. [PubMed: 10696504]

O'Malley KD, Nanson J. Clinical implications of a link between fetal alcohol spectrum disorder and attention-deficit hyperactivity disorder. Can J Psychiatry. 2002; 47(4):349–354. [PubMed: 12025433]

Patten AR, Fontaine CJ, Christie BR. A comparison of the different animal models of fetal alcohol spectrum disorders and their use in studying complex behaviors. Front Pediatr. 2014; 2:93.doi: 10.3389/fped.2014.00093 [PubMed: 25232537]

Peadon E, Elliott EJ. Distinguishing between attention-deficit hyperactivity and fetal alcohol spectrum disorders in children: clinical guidelines. Neuropsychiatric Disease and Treatment. 2010; 6:509–515. [PubMed: 20856914]

Pitman EJG. Significance Tests Which May be Applied to Samples From any Populations. Supplement to the Journal of the Royal Statistical Society. 1937; 4(1):119–130. DOI: 10.2307/2984124

Popova S, Lange S, Shield K, Mihic A, Chudley AE, Mukherjee RA, Bekmuradov D, Rehm J. Comorbidity of fetal alcohol spectrum disorder: a systematic review and meta-analysis. Lancet. 2016; 387(10022):978–987. DOI: 10.1016/s0140-6736(15)01345-8 [PubMed: 26777270]

Porsch RM, Middeldorp CM, Cherny SS, Krapohl E, van Beijsterveldt CE, Loukola A, Korhonen T, Pulkkinen L, Corley R, Rhee S, Kaprio J, Rose RR, Hewitt JK, Sham P, Plomin R, Boomsma DI, Bartels M. Longitudinal heritability of childhood aggression. Am J Med Genet B Neuropsychiatr Genet. 2016; doi: 10.1002/ajmg.b.32420

Roozen S, Peters GJ, Kok G, Townend D, Nijhuis J, Curfs L. Worldwide Prevalence of Fetal Alcohol Spectrum Disorders: A Systematic Literature Review Including Meta-Analysis. Alcohol Clin Exp Res. 2016; 40(1):18–32. DOI: 10.1111/acer.12939 [PubMed: 26727519]

Rowe R, Costello EJ, Angold A, Copeland WE, Maughan B. Developmental pathways in oppositional defiant disorder and conduct disorder. J Abnorm Psychol. 2010; 119(4):726–738. DOI: 10.1037/a0020798 [PubMed: 21090876]

Sayal K, Heron J, Draper E, Alati R, Lewis SJ, Fraser R, Barrow M, Golding J, Emond A, Davey Smith G, Gray R. Prenatal exposure to binge pattern of alcohol consumption: mental health and learning outcomes at age 11. Eur Child Adolesc Psychiatry. 2014; 23(10):891–899. DOI: 10.1007/s00787-014-0599-7 [PubMed: 25209690]

Sharma VK, Hill SY. Differentiating the Effects of Familial Risk for Alcohol Dependence and Prenatal Exposure to Alcohol on Offspring Brain Morphology. Alcohol Clin Exp Res. 2017; 41(2):312–322. DOI: 10.1111/acer.13289 [PubMed: 28084631]

Streissguth AP, Bookstein FL, Barr HM, Sampson PD, O'Malley K, Young JK. Risk factors for adverse life outcomes in fetal alcohol syndrome and fetal alcohol effects. J Dev Behav Pediatr. 2004; 25(4):228–238. [PubMed: 15308923]

Streissguth AP, Sampson PD, Barr HM. Neurobehavioral dose-response effects of prenatal alcohol exposure in humans from infancy to adulthood. Ann N Y Acad Sci. 1989; 562:145–158. [PubMed: 2742272]

Sun J, Buys N. Early executive function deficit in preterm children and its association with neurodevelopmental disorders in childhood: a literature review. Int J Adolesc Med Health. 2012; 24(4):291–299. DOI: 10.1515/ijamh.2012.042 [PubMed: 23183728]

Talpos J, Shoaib M. Executive function. Handb Exp Pharmacol. 2015; 228:191–213. DOI: 10.1007/978-3-319-16522-6_6 [PubMed: 25977083]

Tsang TW, Lucas BR, Carmichael Olson H, Pinto RZ, Elliott EJ. Prenatal Alcohol Exposure, FASD, and Child Behavior: A Meta-analysis. Pediatrics. 2016; 137(3):1–20. DOI: 10.1542/peds.2015-2542

Tyrfingsson T, Thorgeirsson TE, Geller F, Runarsdottir V, Hansdottir I, Bjornsdottir G, Wiste AK, Jonsdottir GA, Stefansson H, Gulcher JR, Oskarsson H, Gudbjartsson D, Stefansson K. Addictions and their familiality in Iceland. Ann N Y Acad Sci. 2010; 1187:208–217. DOI: 10.1111/j.1749-6632.2009.05151.x [PubMed: 20201855]

Waldron M, Martin NG, Heath AC. Parental alcoholism and offspring behavior problems: findings in Australian children of twins. Twin Res Hum Genet. 2009; 12(5):433–440. DOI: 10.1375/twin.12.5.433 [PubMed: 19803771]

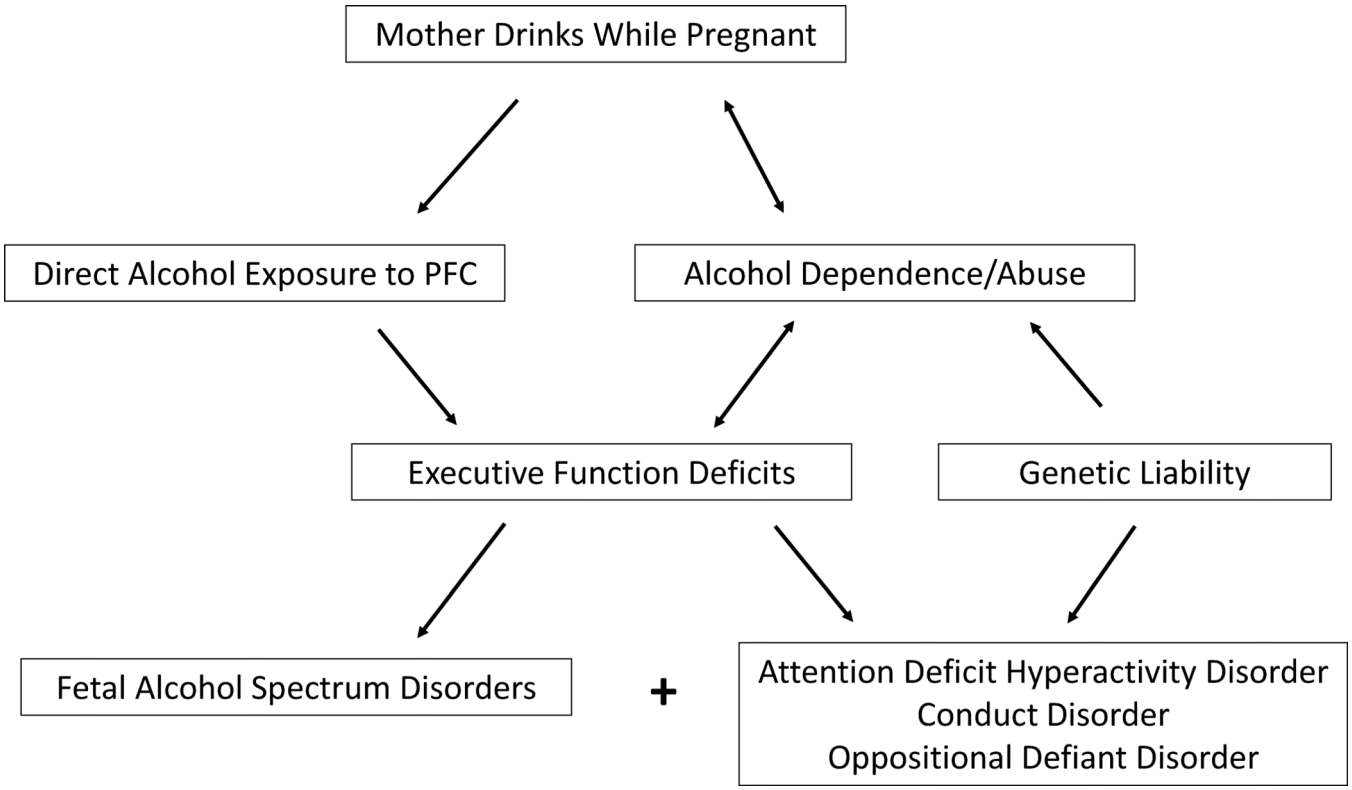
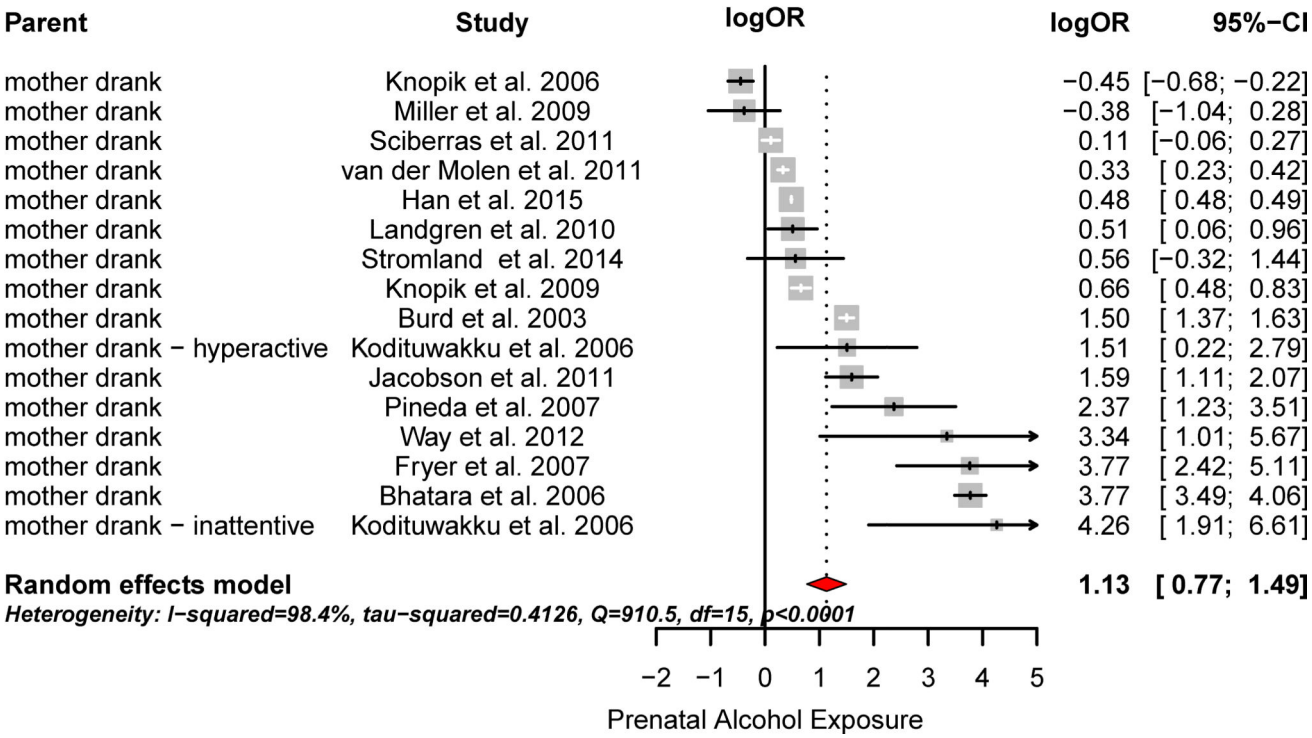


Figure 1.
Visualization of the dual burden of maternal alcohol consumption and alcohol dependence.

A



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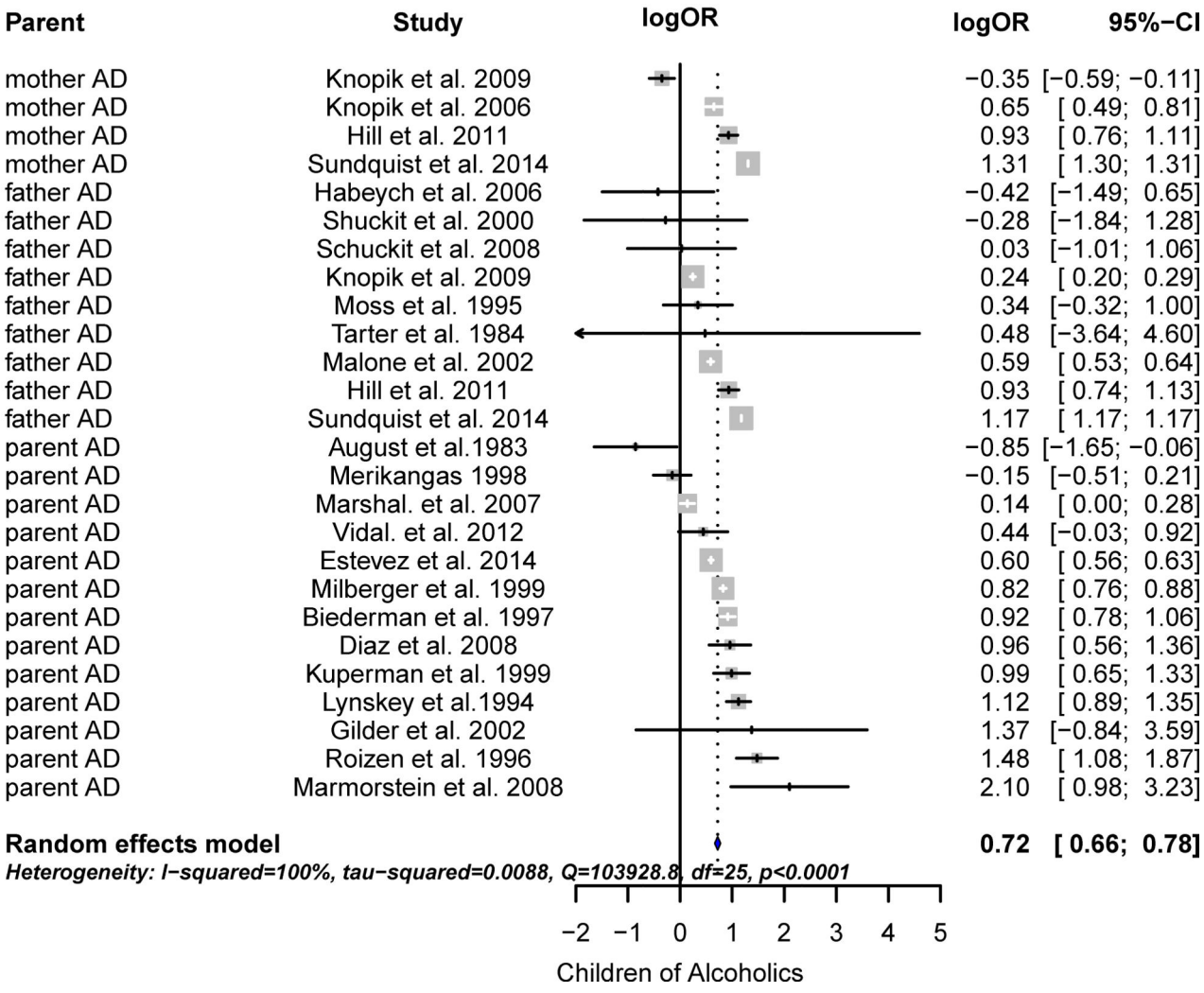

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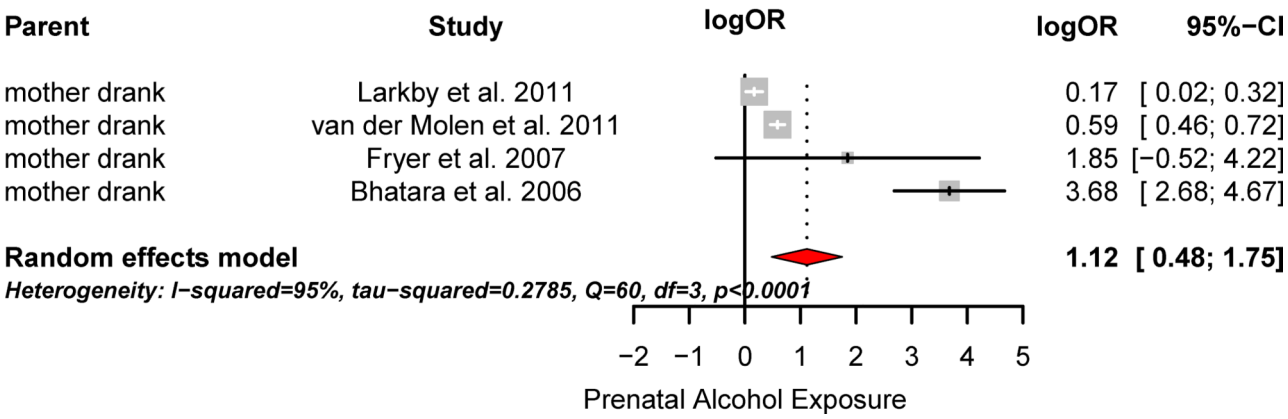

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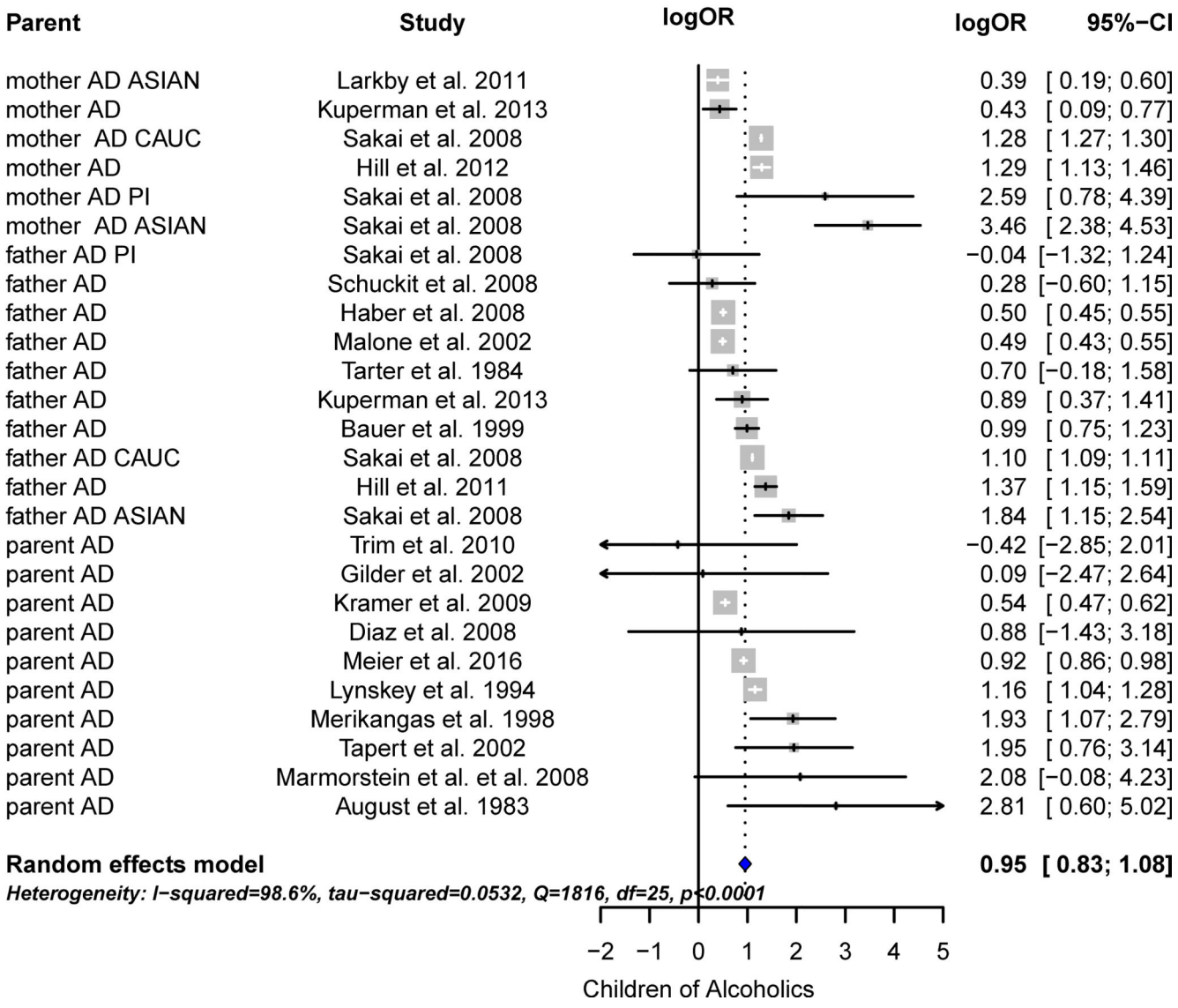

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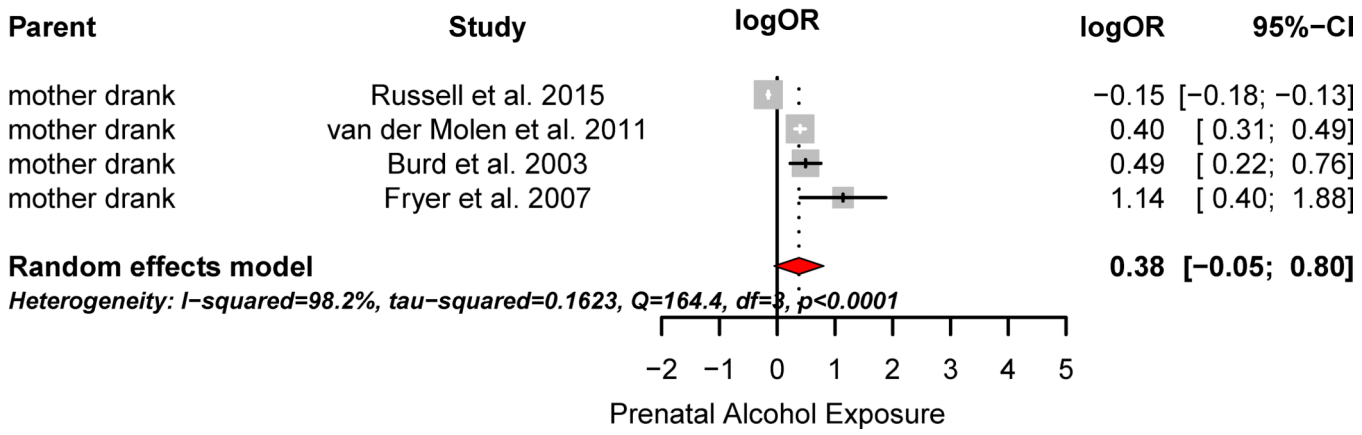

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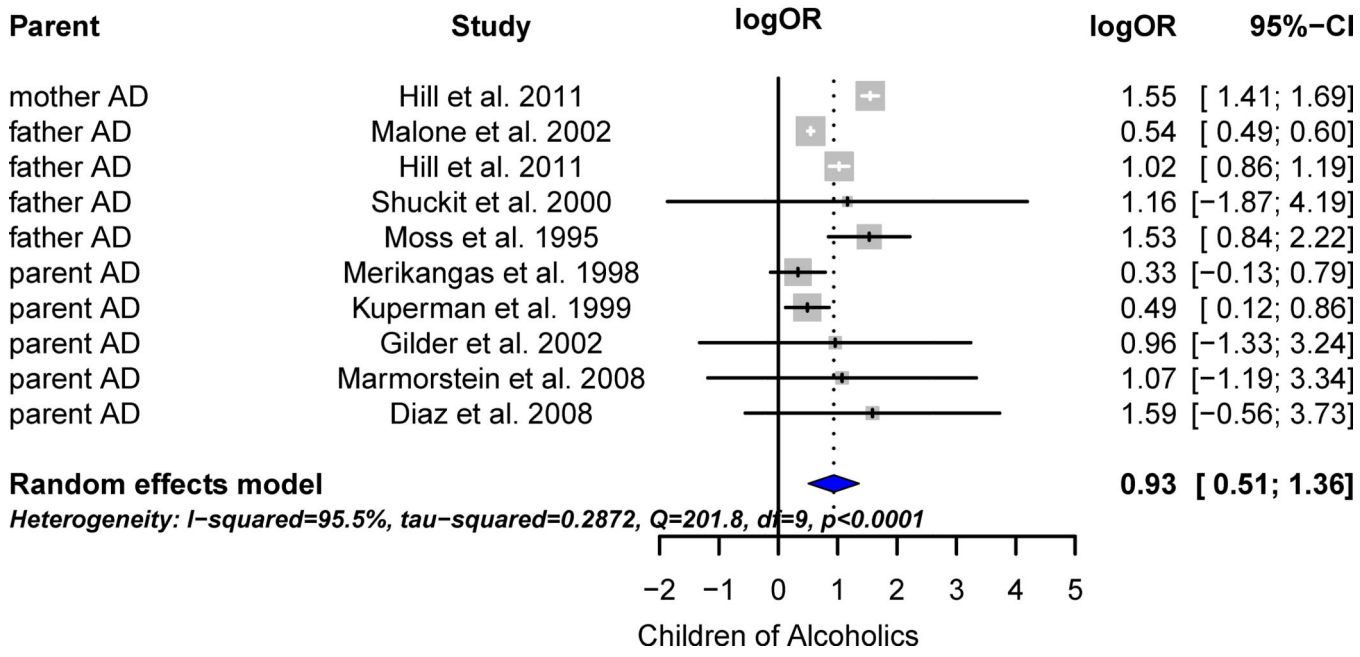

Figure 2.

Forest plots including heterogeneity and random effects LOR for attention deficit disorder for (A) PAE studies, and (B) COA studies; conduct disorder for (C) PAE studies and (D) COA studies; and oppositional defiant disorder for (E) PAE studies and (F) COA studies. Each square plots the natural log of the odds ratio calculated from the study (depicted as a plus sign in the center of the square), comparing the odds of having the disorder in alcohol-ascertained samples (prenatal alcohol exposure or children of alcoholics) compared to normal controls (non-exposed or families with no genetic loading for alcohol dependence). Size of the square indicates sample size, with larger squares reflecting larger samples. The 95% confidence interval of the log odds ratio is represented by bars on each side of the plus sign. For visualization purposes, white bars are used when the confidence interval lies completely within the square, and black bars are used when the confidence interval extends beyond the square. PAE = prenatal alcohol exposure, COA = children of alcoholics.

Figure 2A: Attention Deficit Hyperactivity Disorder Forest Plot of PAE Studies

Figure 2B: Attention Deficit Hyperactivity Disorder Forest Plot of COA Studies

Figure 2C: Conduct Disorder Forest Plot of PAE Studies

Figure 2D: Conduct Disorder Forest Plot of COA Studies; ASIAN = Asian sample, PI = Pacific Islander sample, CAUC = Caucasian sample

Figure 2E: Oppositional Defiant Disorder Forest Plot of PAE Studies
Figure 2F: Oppositional Defiant Disorder Forest Plot of COA Studies

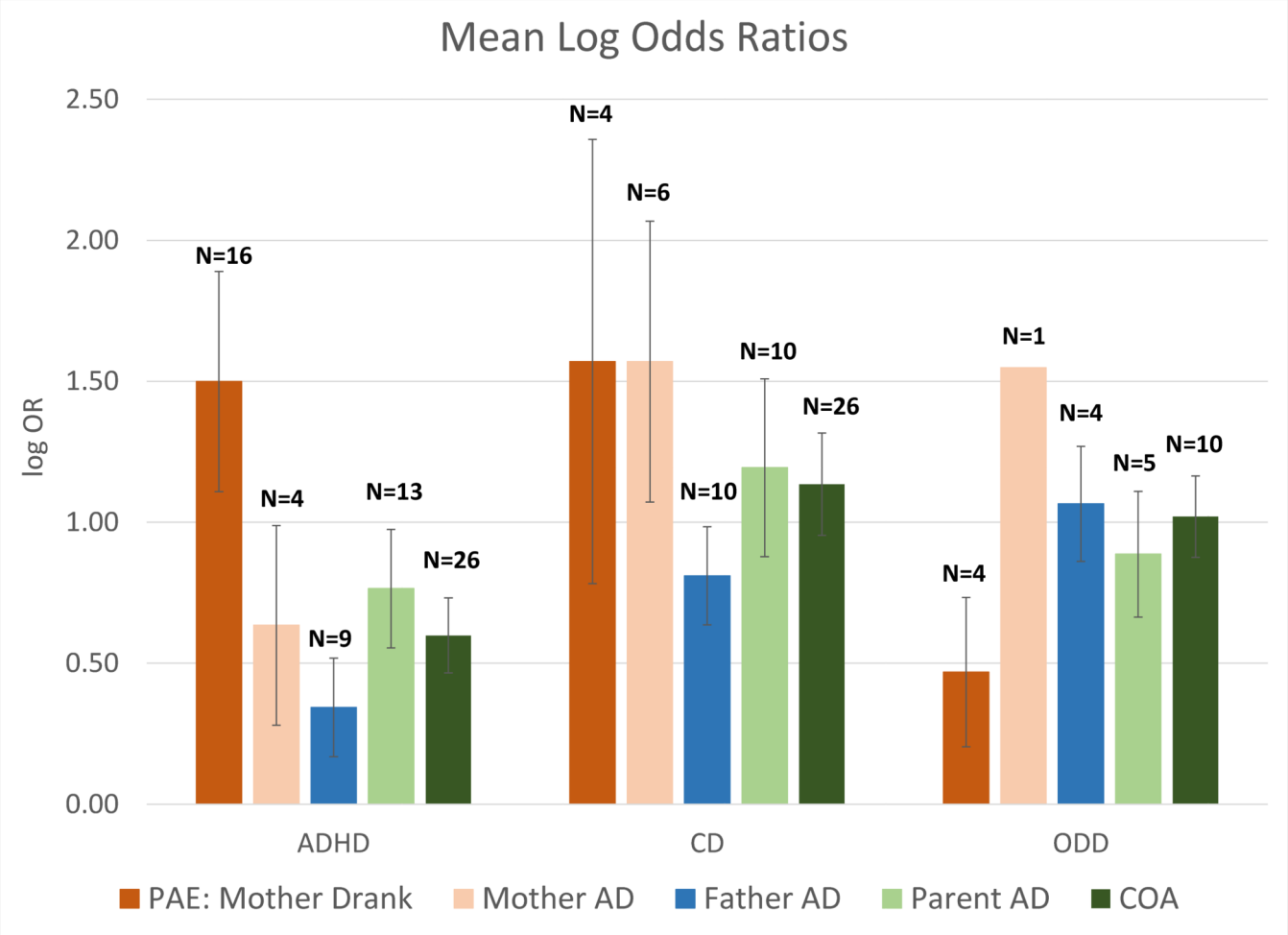

Figure 3.

Mean log odds ratios for each parent of interest within each domain and standard error bars. The number of studies used to compute the mean is provided above each bar. OR = odds ratio, ADHD = attention deficit hyperactivity disorder, CD = conduct disorder, ODD = oppositional defiance disorder, AD = alcohol dependence, PAE = prenatal alcohol exposure, COA = children of alcoholics, OR = odds ratio

Table 1

Inclusion and exclusion criteria.

Inclusion Criteria	**Exclusion Criteria**
English	Non-English
Published in peer-reviewed journal	Case-study, book chapter, dissertation
Human participants	Animal studies
Sample size > 20	Sample size ≤ 20
Control/comparison group included	Ascertained sample on the disorder (i.e., no control)
Used dichotomous affection status for disorder	Used symptom count, latent class, or anything other than a yes/no diagnosis
Used accepted interview methods or instrument to diagnose disorder	Did not report on disorder diagnosis or did not use accepted means of diagnosis
Verified maternal alcohol consumption	
Used accepted interview methods or instrument to diagnose alcohol dependence or alcohol abuse	Did not report on how diagnose of alcohol dependence or abuse was obtained, or ascertainment on substance other than alcohol

Table 2

Summary of demographic information for both domains of literature: (A) combined across all disorders, and (B) by disorder. P-values are reported for t-tests of difference in *mean* values between the two domains (i.e., not median, minimum, or maximum values). **Bolded** values represent significant ($p<0.05$) differences between PAE and COA studies. PAE = prenatal alcohol exposure, COA = children of alcoholics.

Table 2A: Demographic information across all disorders									
	Mean		Median		Minimum Value Reported		Maximum Value Reported		Difference in Mean Value PAE vs COA
	PAE	COA	PAE	COA	PAE	COA	PAE	COA	p-value
Age	11.5	15.3	10.8	15.3	6.2	6.0	19.7	32.0	**0.02**
Minimum Age	8.2	11.4	7.0	11	4.8	5	15.9	18	0.19
Maximum Age	15.2	20.0	15.3	18	7.2	12.0	24.7	43	**0.03**
% Male	45.6	60.5	53.1	52.0	0	1.4	59	100	**0.04**
Total N	2,031	248,340	529	428	44	41	19,940	7,904,130	0.33

Table 2B: Demographic information by disorder. SE = standard error									
	Attention Deficit Hyperactivity Disorder		Attention Deficit Hyperactivity Disorder	Conduct Disorder		Conduct Disorder	Oppositional Defiant Disorder		Oppositional Defiant Disorder
	PAE	COA	p-value	PAE	COA	p-value	PAE	COA	p-value
Mean Age (SE)	10.7 (1.1)	14.0 (0.8)	**0.02**	13.0 (1.8)	15.9 (1.3)	0.31	12.5 (1.7)	13.0 (0.9)	0.80
Mean % Male (SE)	48.5 (15.5)	65.2 (5.5)	**0.04**	40.8 (13.6)	52.0 (5.0)	0.37	40.4 (13.6)	50.3 (9.3)	0.56

Table 3

Summary of permutation p-values comparing logged odds ratio of prenatal alcohol exposure (PAE) studies and children of alcoholic (COA) studies for (A) attention deficit hyperactivity disorder, (B) conduct disorder, and (C) oppositional defiant disorder. P-values < 0.05 are bolded. AD = alcohol dependent.

Table 3A – Permutation p-values for attention deficit hyperactivity disorder

Comparison	Independent test p-value	Fisher-Pitman p-value	Savage p-value
PAE vs COA	**0.01**	**0.01**	**0.01**
Mother drank vs Mother AD	**0.04**	**0.05**	**0.04**
Mother drank vs Father AD	**0.04**	**0.03**	**0.03**
Mother drank vs Unknown parent AD	**0.04**	**0.03**	**0.02**
Mother AD vs Father AD	0.12	0.13	0.10

Table 3B – Permutation p-values for conduct disorder

Comparison	Independent test p-value	Fisher-Pitman p-value	Savage p-value
PAE vs COA	0.44	0.44	0.26
Mother drank vs Mother AD	0.32	0.36	0.31
Mother drank vs Father AD	0.32	0.33	0.21
Mother drank vs Unknown parent AD	0.72	0.73	0.51
Mother AD vs Father AD	0.33	0.31	0.27

Table 3C – Permutation p-values for oppositional defiant disorder

Comparison	Independent test p-value	Fisher-Pitman p-value	Savage p-value
PAE vs COA	0.09	0.09	0.18
Mother drank vs Mother AD	NA	NA	NA
Mother drank vs Father AD	0.26	0.22	0.34
Mother drank vs Unknown parent AD	0.18	0.15	0.39
Mother AD vs Father AD	NA	NA	NA