Meta-Analysis of the Association Between Birth Weight and ADHD

Aspen Makkar[1*], Ryan A. Manning[1*], Michael Vargas[1], Arielle Plavnick[1], Olivia Einbund[1], Valerie S. Knopik, PhD[2], & Taylor F. Smith, PhD[1,2]

1. Department of Psychology and Child Development, California Polytechnic State University, San Luis Obispo, CA USA
2. Division of Behavioral Genetics, Rhode Island Hospital; DPHB, Brown University, Providence, RI USA

* Denotes co-first authors

Introduction

- Lower birth weight is among the strongest identified risk factors for Attention-Deficit/ Hyperactivity Disorder (ADHD)
- However, the strength of association between lower birth weight and ADHD varies across studies
- Therefore, there is a critical need to identify factors that contribute to variability in the association between lower birth weight and ADHD

Objectives

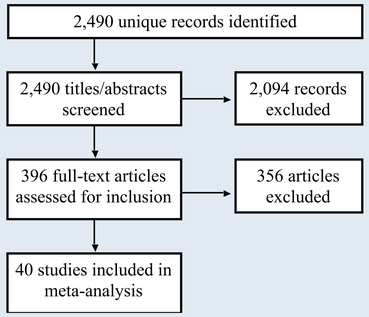
- Meta-analysis examining the strength of the association between lower birth weight and ADHD across studies
- Examine sample and methodological factors which influence the relationship between lower birth weight and ADHD

Methods

- **Databases:** PubMed, EBSCO, Science Direct, and Web of Science
- **Search terms:** (ADHD OR Hyperkinetic OR "attention deficit" OR inattentiv* OR hyperactiv* OR impulsiv*) AND ("Birth Weight" OR birthweight OR LBW OR IUGR OR SGA OR growth restrict* OR "fetal growth" OR "Intrauterine Growth" OR "Gestational age" OR Prematur*)
- **Review Process:** Abstract review, full-text review, and data extraction was completed independently by two co-authors.
- **Inclusion Criteria:**
  1. Prospective study (case-control or cohort) with individuals born with lower birth weight (<3000g) and/or lower gestational age
  2. Measure of birth weight
  3. ADHD diagnostic status, ADHD symptom severity OR inattention and hyperactivity-impulsivity behavioral measure
  4. Sufficient data to calculate effect size between birth weight and ADHD risk
- **Exclusion Criteria:** Overlapping samples, non-English language publication, family-based design, retrospective study, and biased control sample

Study Selection

Figure 1. Flow of information through meta-analytic review (adapted from Moher et al., 2009)



Meta-Analysis

- Random-effects meta-analysis
  - Cohen's *d* and relative risk (*RR)* were calculated for each sample and converted into odds ratio (*OR*)
  - Mixed-effects meta-regression analyses (unrestricted maximum likelihood) examined the influence of moderating factors
- *Q and* I^2 assessed between-study heterogeneity
- Publication bias assessed with Egger's test and visual inspection of funnel plot
- All analyses conducted with CMA.V2

Results

- A total of 40 studies and 54 independent samples were included in the meta-analysis.
- Across all samples the **pooled *OR* = 2.15 (1.83-2.51; p<.01).** Effect sizes were also examined based on severity of lower birth weight (see Table 1).
- There was significant variability in the strength of association between lower birth weight and ADHD across studies (*Q = 273.98;* df = 53; *p* <.01; I^2 = *80.66*).
- Egger's test for publication bias was significant (*t = 6.05, p < .01),* suggesting the presence of positive publication bias (see Figure 4).

Results (continued)

Table 1. Pooled effect sizes for lower birth weight and ADHD

		Cohen's *d*		
Birth weight	*n*	*d*	CI	*p*
All Studies	20	0.96	0.57-1.35	<.001*
<1000	3	2.04	1.15-2.93	<.001*
<1500	7	0.87	0.30-1.45	.003*
<2000	0	-	-	-
<2500	0	-	-	-
2500-3000	0	-	-	-
		Relative Risk		
Birth weight	*n*	*RR*	CI	*p*
All Studies	34	2.27	1.87-2.77	<.001*
<1000	6	2.31	1.2-4.12	.005*
<1500	8	2.32	1.71-3.13	<.001*
<2000	3	1.53	1.29-1.81	<.001*
<2500	7	3.03	1.47-6.22	0.003*
2500-3000	2	1.29	0.79-2.09	0.3
		Odds Ratio		
Birth weight	*n*	*OR*	CI	*p*
All Studies	54	2.15	1.83-2.51	<.001*
<1000	9	2.51	1.68-3.75	<.001*
<1500	15	2.16	1.63-2.88	<.001*
<2000	3	1.59	1.32-1.90	<.001*
<2500	7	3.45	1.59-7.44	0.001*
2500-3000	2	1.31	0.79-2.16	0.3

Note. Birth weight classification based on sample inclusion criteria. *All studies* also includes samples selected based on lower gestational age (but were also of lower birth weight).

Table 2. Meta-regression of log *OR* on sample level moderators

Moderator	γ_1	SE	z	df	*p*
Birth year	0.02	0.01	1.73	40	0.08
Age at assessment (years)	0.01	0.02	0.35	46	0.72
Gender index	0.94	0.31	3.02	35	<.01*
Birth weight (case *M*)	-4.3E-04	2.7E-04	-1.55	36	0.12
Gestational age (case *M*)	-0.11	0.05	-2.44	34	0.01*
ADHD measurement type	0.16	0.11	1.52	52	0.13

Note. γ_1= meta-regression coefficient. Gender index = (male cases/female cases)/ (male controls/female controls). ADHD measurement coding: 1= a single rating scale to 4=a structured diagnostic interview and rating scale.

Figure 2. Study log *OR* on mean gestational age for cases

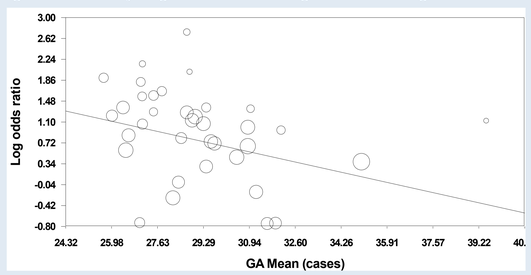
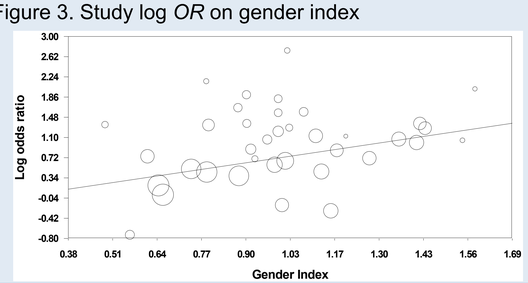
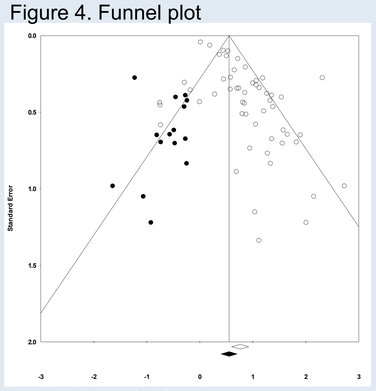


Figure 3. Study log *OR* on gender index



Results (continued)

Figure 4. Funnel plot



Note. X-axis is log *OR*. Open dots represent observed studies. Filled dots represent imputed missing studies

Discussion

- The pooled ***OR* = 2.15**, suggesting that lower birth weight is associated with a 2.15 fold increase in the odds of developing ADHD (or high levels of ADHD symptoms).
- Across samples there is a dose-response relationship between lower gestational age (but not birth weight) and the association between birth weight and ADHD
- Failing to match cases and controls (i.e., on gender) and publication bias likely inflated the association between lower birth weight and ADHD.
- **Limitations**
  - Heterogeneous sample inclusion criteria
  - Gestational age confound
  - Publication bias
- **Future Directions**
  - Examine the influence of multiple gestation on the association between birth weight and ADHD
  - Investigate non-shared environmental factors that underlie the relationship between lower birth weight and ADHD risk (Groen-Blokhuis et al., 2011; Ficks et al., 2013; Peterson et al., 2015)
  - Progress towards the development of preventative interventions for ADHD in individuals exposed to prenatal risk