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4 MATERNAL ALCOHOL USE DURING PREGNANCY AND OFFSPRING ADHD: A PROSPECTIVE SIBLING

5 CONTROL STUDY

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28

29 **Abstract**

30 **Background**

31 Maternal alcohol use during pregnancy has repeatedly been associated with development of ADHD in  
32 the offspring. It is, however not known whether this reflects a direct casual intra-uterine effect or a non-  
33 causal relationship due to confounding. We used three different approaches to control for measured and  
34 unmeasured confounding; statistical adjustment for covariates, negative control comparison against  
35 maternal pre-pregnancy alcohol use, and comparison among differentially exposed siblings.

36 **Methods**

37 The sample comprised 114 247 children (34 283 siblings) from 94 907 mothers, recruited to the  
38 Norwegian Mother and Child Birth Cohort Study between 1999 and 2008. Self-reported measurements  
39 of alcohol use were obtained in week 30 during the pregnancy. Mothers rated offspring ADHD symptoms  
40 at 5 years on two measures. Clinical ADHD diagnoses were obtained from the Norwegian Patient  
41 Registry.

42 **Results**

43 We found an overall positive association between maternal alcohol use during pregnancy and offspring  
44 ADHD symptoms, which was only marginally attenuated after inclusion of measured covariates. Both the  
45 negative control and sibling comparison analysis further attenuated the estimated association, but it  
46 remained greater than zero ( $\beta = .017$ , 95% CI = .005 - .030). No association was found between maternal  
47 alcohol use during pregnancy and offspring ADHD diagnosis.

48 **Conclusions**

49 For offspring ADHD symptoms we found a weak, but possibly causal association with maternal alcohol  
50 use during pregnancy, while no such effect was observed for clinical ADHD diagnosis.

51 **Keywords**

52 ADHD symptoms, ADHD diagnosis, prenatal alcohol exposure, negative control, sibling control, MoBa  
53 cohort study

54 **Key messages**

- 55 ● This study investigated the potential causal relationship between maternal alcohol use during  
56 pregnancy and offspring ADHD.
- 57 ● Controlling for confounding using observed covariates, a negative control and sibling comparison, we  
58 found an association for ADHD symptoms. No association was found for clinical diagnoses.
- 59 ● The results are consistent with a weak, causal effect of maternal alcohol use during pregnancy on  
60 offspring ADHD.

61

62 **Introduction**

63 Attention deficit hyperactivity disorder (ADHD), characterized by inattention and/or hyperactivity-  
64 impulsivity, is the most common behavioral disorder in childhood, manifest at an early age, and affects  
65 approximately 5% of children worldwide (1, 2).

66 Some women continue to drink after becoming pregnant (3), and ADHD is highly comorbid with fetal  
67 alcohol spectrum disorders (4). A positive association between maternal alcohol use during pregnancy  
68 and symptoms of ADHD in children has been reported in several studies (5, 6), including a meta-analysis  
69 (7).

70 Due to the large timespan between pregnancy and the development of child ADHD symptoms,  
71 prospective data collection is essential to ensure validity of measurements. In a prospective Danish birth  
72 cohort sample, comprising 1628 mothers and children, no association between attention deficits in  
73 children was found when mothers abstaining from alcohol were compared to mothers with low to  
74 moderate consumption. However, when abstaining mothers were compared to mothers consuming  
75 more than 8 drinks a week, a weak association was found (8). In a population based cohort of 604 eight-  
76 year-old children assessed for ADHD both by clinical diagnosis and ratings scales (9), an association  
77 between maternal alcohol use during pregnancy and ADHD was found, but disappeared after adjustment  
78 for measured covariates.

79 These studies are limited with respect to inferences regarding causal effects. An observed association  
80 might be spurious, caused by unmeasured familial factors common to both mothers and children (10).  
81 For instance, twin and family studies report high heritability estimates for both ADHD (11-13) and alcohol  
82 use disorders (14, 15), and that the genetic risk factors are partly overlapping (16-18). Familial factors are  
83 therefore likely to confound estimates of the association, and must be addressed in order to make valid

84 causal inferences. Additionally, the inconsistencies in results across studies might indicate that the effect  
85 of alcohol on ADHD is small, requiring large samples to be reliably identified.

86 The aims of this study are twofold. First we investigate whether maternal alcohol use during pregnancy is  
87 related to offspring ADHD, and second, we investigate if such an association is likely to reflect a causal  
88 effect. Integration of several methods and consensus of results would provide stronger support for  
89 causal inference. We apply three different approaches in order to control for confounding variables.  
90 First, we statistically adjust for measured covariates previously shown to be related to ADHD. Second, we  
91 use maternal alcohol use before pregnancy as a negative control comparison. Third, we utilize a quasi-  
92 experimental sibling comparison design, controlling for unmeasured family-varying variables.

## 93 **Methods**

### 94 **Sample**

95 The study is based on data from The Norwegian Mother and Child Cohort Study (MoBa), a large  
96 prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public  
97 Health (19). Participants were recruited from 1999 to 2008. The women consented to participation in  
98 41% of the pregnancies. The cohort includes approximately 114 500 children and 95 200 mothers.  
99 Version 9 of the quality-assured MoBa data files, released for research in December 2015, was used for  
100 the analyses. Written informed consent was obtained from all participants upon recruitment. The MoBa  
101 study has been granted a license from the Norwegian Data Inspectorate, and the current study was  
102 approved by the Regional Committee for Medical Research Ethics. Clinical ADHD diagnoses from the  
103 Norwegian Patient Registry (NPR) were linked with the MoBa cohort. Since 2008 NPR has collected data  
104 on diagnosis from all hospitals and outpatient clinics in Norway.

105 Table 1 here

### 106 **Measurements of offspring ADHD**

107 Symptoms of ADHD at 5-years of age were assessed by maternal report using the revised Conner's  
108 Parent Rating Scale (CPRS-R) (20) included in the MoBa questionnaire. The scale consists of 12 four-point  
109 items which were summed to a score ranging from 12 to 48 (see table 2 for description of key variables).  
110 ADHD symptoms were also assessed using the DSM-oriented ADHD scale of The Child Behavior Checklist  
111 (CBCL) (21). This included 6 three-point items summed to a score ranging from 6 to 18. Both measures  
112 were standardized to zero mean and unit variance prior analyses.

113 Children diagnosed with an ICD-10-diagnosis of Hyperkinetic disorder (HKD; F90.0, F90.1, F90.8, or F90.9)  
114 in the NPR between 2008 and 2014 were identified as having ADHD, corresponding to 2250 cases. HKD  
115 requires the combination of inattentive and hyperactive symptoms, and may therefore be regarded as a  
116 subtype of DSM-5 ADHD (22). In comparison to ADHD, HKD is characterized more by  
117 neurodevelopmental alterations in language and motor development (23). Age of onset for diagnosis  
118 ranged from 5 to 15 years. The prevalence of HKD in the sample was approximately 2%, with an  
119 estimated life-time prevalence of 4% at age 13.

#### 120 **Measurements of maternal alcohol use**

121 In MoBa, alcohol use was measured using the Alcohol Use Disorder Identification Test Consumption  
122 (AUDIT-C) (24), designed to identify harmful patterns of usage. The scale consists of 3 five-point items  
123 measuring drinking frequency, quantity and binge drinking, summed to a score ranging from 0 to 12. The  
124 questionnaire was administered around week 30 in pregnancy and mothers reported on their use pre-  
125 pregnancy and during the first trimester. Both measurements were standardized to zero mean and unit  
126 variance prior to analysis.

#### 127 **Additional covariates**

128 Variables previously shown to be related to ADHD were adjusted for in the analysis (9, 25) and included  
129 parental education and income, maternal smoking during pregnancy, children's birth order and  
130 children's gender.

### 131 **Statistical analysis**

132 To facilitate comparisons across analyses of ADHD symptoms, we restricted the sample to mothers with  
133 two or more birth records in MoBa, comprising 16 407 mothers and 34 283 children. Symptoms were  
134 modelled using linear multilevel regression models with random intercepts for mothers, allowing for  
135 residual correlations (familial dependence) in responses of siblings. The two outcome measures were  
136 analyzed separately. All parameter estimates are reported as standardized regression coefficients ( $\beta$ )  
137 with 95% confidence intervals (CI).

138 First, a crude estimate of the association with the outcome measures was obtained by including  
139 maternal alcohol use during pregnancy as a fixed effect in the models. In the next step we adjusted for  
140 measured covariates. We then used maternal alcohol use before the pregnancy as a negative control  
141 comparison. Maternal alcohol use before pregnancy is likely to be influenced by many of the same  
142 unmeasured variables as maternal alcohol use during pregnancy, but is not expected to have any direct  
143 causal influence on offspring ADHD. Differences in these estimates can then, at least partially, be  
144 attributed to causal effects of maternal alcohol use during pregnancy (26). We estimated the difference  
145 after fitting regression models including both variables, in addition to the control-variables. Lastly, our  
146 most stringent control for confounding was obtained by comparing siblings differentially exposed to  
147 alcohol during pregnancy. By decomposing the effect of maternal alcohol use during pregnancy into a  
148 within-mother effect and a between-mother effect, all mother specific covariates are held constant,  
149 thereby implicitly controlling the within effect for confounding variables at the mother level (27).  
150 Estimates were obtained by adjusting alcohol use during pregnancy for each mothers average alcohol  
151 use (sample means) across all pregnancies in addition to the control-variables.

152 We tested whether effect sizes associated with the two ADHD symptom measures were different, and if  
153 effect sizes associated with the negative control and sibling comparisons were different from those only  
154 adjusted for the measured covariates. Estimates were obtained fitting a main-effects model using  
155 weighted least squares, weighting the effect sizes by their precision.

156 We investigated the relationship between maternal alcohol use during pregnancy and ADHD diagnosis in  
157 the complete sample, using Cox proportional-hazards model with children’s age in months as the time  
158 metric. Results are presented as hazard ratios (HR) with 95% CI. We used a robust variance estimator to  
159 account for correlations in responses of siblings. First, we estimated the crude association between  
160 maternal alcohol use during pregnancy and ADHD diagnosis, and next we adjusted for measured  
161 covariates.

162 For all analyses partially missing observations were imputed using a multiple imputation procedure  
163 based on 20 independent chained-equations. Diagnosis and symptoms data were imputed separately. To  
164 accommodate clustering of responses within families, family means of the outcome variables were  
165 included in the imputation models.

166 All analyses were conducted using Stata 14 (28).

## 167 **Results**

### 168 **Descriptives**

169 Distributions of characteristics for the full sample and the restricted sibling sample are presented in table  
170 1. Summary statistics for key variables are presented in table 2. There was no indication of discrepancies  
171 between the samples for neither of the statistics. Acceptable reliability estimates were found for all  
172 scales, although AUDIT-C before pregnancy was slightly lower.

173 (Table 2 here)

174 **ADHD symptoms**

175 Without adjusting for any of the covariates (Model 1), we found maternal alcohol use during pregnancy  
176 to be associated with offspring symptoms of ADHD assessed via both CBCL ( $\beta = .051$ , 95% CI = .035 -  
177 .067) and CPRS-R ( $\beta = .065$ , 95% CI = .051 - .079).

178 After inclusion of measured covariates (Model 2), parameter estimates were attenuated, but still  
179 significantly different from zero for both CBCL ( $\beta = .040$ , 95% CI = .024 - .055) and CPRS-R ( $\beta = .054$ , 95%  
180 CI = .039 - .068).

181 Adjusted for covariates, maternal alcohol use before pregnancy was associated with ADHD symptoms  
182 assessed by the CBCL ( $\beta = .046$ , 95% CI = .029 - .063) and CPRS-R ( $\beta = .037$ , 95% CI = .022 - .051). For  
183 CBCL the effect was further reduced after subtracting the effect of maternal alcohol use before  
184 pregnancy (Model 3) and no longer statistically different from zero ( $\beta = -.005$ , 95% CI = -.031 - .020). The  
185 estimate for CPRS-R were further attenuated ( $\beta = .029$ , 95% CI = .006 - .052), but remained greater than  
186 zero.

187 Last, we estimated the sibling-comparison models, adjusting for the covariates (Model 4). Parameter  
188 estimates were reduced for both CBCL ( $\beta = .011$ , 95% CI = -.002 - .024) and CPRS-R ( $\beta = .017$ , 95% CI =  
189 .005 - .030). Maternal alcohol use during pregnancy was still associated with symptoms of ADHD as  
190 measured by CPRS-R, but not as measured by CBCL.

191 (Figure 1 here)

192 Averaged over the models, effect sizes associated with the CPRS-R scale were significantly larger than  
193 those associated with the CBCL scale. Furthermore, the effect sizes estimated under Model 3 and 4 were  
194 significantly lower than those estimated under Model 2, averaged over the outcome measures (see table  
195 3).

196

(Table 3 here)

197 **ADHD diagnosis**

198 We found no relationship between maternal alcohol consumption during pregnancy and offspring ADHD  
199 diagnosis based on the crude model without any covariates (HR = .98, 95% CI = .93 - 1.03). Adjustment  
200 for the measured covariates did not substantially change parameter estimates (HR = .97, 95% CI = .93 -  
201 1.01).

202 **Discussion**

203 We aimed to investigate the causal relationship between maternal alcohol use during pregnancy and  
204 offspring ADHD, using different non-experimental methodological approaches to control for  
205 confounding. Our analyses revealed four main findings. First, ADHD symptoms measured by the CPRS-R  
206 scale were associated with maternal alcohol use during pregnancy even under our most stringent  
207 control, indicating a possible causal effect. Second, the effect sizes were systematically different across  
208 the two symptom measures and the clinical diagnoses. Third, unmeasured variables appear to confound  
209 the association. Fourth, the estimated effect sizes was small. We discuss these findings in turn.

210 **Causal effect**

211 We found a positive association between maternal alcohol use during pregnancy and offspring ADHD  
212 symptoms that remained after controlling for the covariates. This pattern replicated across both ADHD  
213 symptom measures. Although the results conform to others findings (5, 6) and suggest that maternal  
214 alcohol use during pregnancy is related to ADHD, the approach is not very informative about the  
215 potential causal nature of the association. Because it is not clear which covariates are critical to adjust  
216 for, it is likely that this approach will omit important variables from the analysis.

217 Comparing maternal pre-pregnancy and alcohol use during pregnancy, we observed stronger  
218 associations for alcohol use during pregnancy for CPRS-R, but not CBCL. It seems that, at least for CPRS-R,

219 there is an association between maternal alcohol use during pregnancy and ADHD symptoms that cannot  
220 be attributed to factors influencing alcohol use both pre-pregnancy and during pregnancy.

221 The sibling comparison analysis showed a similar pattern of results; we found an effect only for CPRS-R.  
222 This design is powerful in that it allowed us to estimate the associations free from unmeasured familial  
223 risk factors that could bias the associations and distort inferences. Because siblings share many  
224 important aspects of social and household characteristics, the design excludes a wide set of potential  
225 confounding variables. Importantly, maternal genetic liability towards alcohol use is also constant across  
226 pregnancies, consequently excluding genetic confounding as a source of bias (29).

227 These results are consistent with maternal alcohol consumption during pregnancy exerting a causal  
228 effect on offspring ADHD symptoms. Convergence of results from the negative control and sibling  
229 comparison strengthens our inferences.

### 230 **Different measures of ADHD**

231 Effect sizes were consistently larger when ADHD symptoms were assessed by the CPRS-R scale rather  
232 than the CBCL scale (Figure 1). Because the two scales include different items, with the CPRS-R scale  
233 comprising more items related to inattention, they may capture somewhat different aspects of ADHD  
234 symptomology. However, as CPRS-R includes twice as many items as the CBCL scale, and thereby may be  
235 measured with higher reliability, the differences in effect sizes may also be explained by differential  
236 influences of measurement error.

237 Unlike for offspring ADHD symptoms, we found no association between maternal alcohol use during  
238 pregnancy and offspring ADHD diagnosis. As the number of children with an ADHD diagnosis by necessity  
239 will be smaller than children showing symptoms of ADHD, the statistical power and the possibility of  
240 detecting weak effects will be reduced. In the present study, the problem may be exaggerated as close to

241 90% of the children were 11 years or younger, and the lifetime diagnosis of ADHD may be  
242 underestimated. It will therefore be important to repeat the study as children grow older.

### 243 **Unmeasured confounding**

244 Our results suggest that the measured covariates do not adequately adjust for confounding and that  
245 unobserved familial factors contribute to the association. This is supported by the significant drop in  
246 effect size from Model 2 to Model 3 and Model 4 in the summary analysis. In line with our results,  
247 D’Onofrio et al. (30), using CBCL, found that familial factors influenced the association between prenatal  
248 alcohol exposure and attention/impulsivity problems. These results highlight the importance of  
249 methodological designs that control for confounding beyond traditional statistical adjustment.

250 The genetic resemblance between mothers and offspring is a factor that is controlled in the sibling  
251 comparison design. Results from two previous studies (18, 31) suggest that shared genes play a major  
252 role in determining the co-occurrence between maternal alcohol use during pregnancy and offspring  
253 ADHD. These studies therefore offer an explanation for the reduced associations we observed in the  
254 sibling comparison analysis.

### 255 **Effect size**

256 Our estimated effect sizes are small, even without adjustments. For example, a standard deviation  
257 increase on AUDIT-C is associated with an average of 8% of a standard deviation increase on CPRS-R  
258 across pregnancies. Given the nature of this association, we expect its magnitude to be small. If maternal  
259 alcohol use during pregnancy was a key determinant in explaining why some children develop ADHD, it  
260 would probably be well established and there would be less inconsistent findings in the literature. A  
261 plausible explanation is that several studies are under-powered for studying effects of this magnitude  
262 (32). For instance, a meta-analysis found that the odds of children prenatally exposed to alcohol having  
263 ADHD were 2.3 times greater than children not exposed (7). However, the 95% CI ranged from 1.2 to 4.6,

264 reflecting large uncertainty. For comparison, we dichotomized the CPRS-R variable at the 95th  
265 percentile, roughly corresponding to the population rate of ADHD in children (2), and the AUDIT-C  
266 measure during pregnancy at suggested cut-off (24), and obtained an estimated odds-ratio of 1.4. Given  
267 the large sample investigated in the current study, estimates are more likely to reflect the magnitude of  
268 true population effects. Consequently, our results suggest that maternal alcohol use during pregnancy is  
269 involved in development of ADHD symptoms, but that it only plays a minor role among several other risk  
270 factors.

### 271 **Strengths and limitations**

272 There are several strengths in this study: First, validity of measurement is enhanced due to prospective  
273 data collection; second, we utilize several methodological approaches to control for confounding  
274 variables; third, our large sample size provides sufficient statistical power to identify small associations;  
275 and fourth, comparison of associations across different measures enhances the validity of our  
276 conclusions.

277 There are also limitations in our design. First, siblings are not identical. They experience different  
278 environmental exposures beyond the stable family environment. We statistically adjusted for several  
279 potential intra-familial confounding variables, including maternal smoking during pregnancy, which  
280 repeatedly have been shown to be associated with ADHD (9, 25), but we have probably not been able to  
281 include all variables of relevance. Second, we have investigated average effects across families. There  
282 might be important moderators that determine the effect of maternal alcohol consumption, such as  
283 genetic factors (i.e., gene-environment interactions). Third, our analyses of symptoms were restricted to  
284 ADHD levels at 5 years of age, hence symptoms may have not yet manifested due to later age of onset or  
285 parental recognition. Although this would lead to an underestimation of the association, this problem is  
286 reduced by considering ADHD symptom levels on a continuum. Even if children at this age have not yet  
287 reached clinical thresholds for a diagnosis, they are still likely to exhibit increased symptom levels.

288 Fourth, given the social stigma associated with alcohol use during pregnancy it is possible, but unclear  
289 whether or to what extent, this is underreported. Underreporting would be problematic if it leads to  
290 “floor effects” which might bias estimates of associations. However, AUDIT-C have been shown to  
291 perform equally well in a sample of pregnant women as in samples from the general population (33). We  
292 did not have sufficient information to evaluate this in the current study.

### 293 **Implications and conclusions**

294 We found a positive association between maternal alcohol use during pregnancy and offspring ADHD  
295 symptoms. When studying probability of ADHD diagnosis, we were not able to demonstrate a  
296 comparable effect. Taken together, the association between maternal alcohol use during pregnancy and  
297 ADHD symptoms appears to be confounded by familial factors that bias the association upwards if not  
298 accounted for. Maternal alcohol use during pregnancy represents a small and potentially causal risk of  
299 developing ADHD symptoms, and may thereby be of importance for understanding the etiology of  
300 ADHD. Given the weak associations found in the present study as well as in other studies of the same  
301 phenomena, the effectiveness of preventive efforts aimed at reducing ADHD on an individual level, is  
302 debatable. However, for large scale public health interventions even weak causal effects may be of great  
303 importance – for global health as well as for social economic parameters.

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390

391

392 **Tables**

393 **Table 1.** Distributions of children and parent characteristics for the selected sibling sample and the full  
 394 sample.

	Sibling sample	Full sample
Male children	52%	51%
Highest education mother		
Below high school	5%	8%
High school	24%	28%
Above high school	71%	64%
Highest education father		
Below high school	8%	11%
High school	36%	38%
Above high school	55%	51%
Income mother		
<150 NOK	16%	18%
150-300 NOK	46%	45%
300-500 NOK	32%	32%
>500 NOK	5%	5%
Income father		
<150 NOK	6%	7%
150-300 NOK	26%	27%
300-500 NOK	50%	49%
>500 NOK	17%	17%
Parity		
1 <sup>st</sup>	37%	44%

2 <sup>nd</sup>	45%	36%
3 <sup>rd</sup>	15%	16%
4 <sup>th</sup>	3%	3%
5 <sup>th</sup>	1%	1%
Maternal smoking pregnancy		
Never	94%	91%
Sometimes	2%	3%
Daily	4%	6%

395

396 **Table 2.** Summary statistics of ADHD symptoms and maternal alcohol use from the selected sibling  
397 sample and the full sample (parentheses).

Measurement	M	SD	Alpha	r
ADHD symptoms				
CPRS-R	16.0 (16.4)	4.3 (4.6)	.87 (.88)	
CBCL	8.3 (8.6)	2.1 (2.2)	.73 (.74)	.64 (.65)
Maternal alcohol use				
AUDIT-C before pregnancy	3.2 (3.4)	2.1 (2.1)	.66 (.66)	
AUDIT-C during pregnancy	.63 (.70)	1.3 (1.4)	.73 (.76)	.38 (.38)

398 M: mean; SD: standard deviation; Alpha: Cronbach's alpha; r: Pearson's correlation coefficient between  
399 ADHD scales and between measures of alcohol usage.

400

401 **Table 3.** Results from comparing effect sizes associated with ADHD symptoms across models.

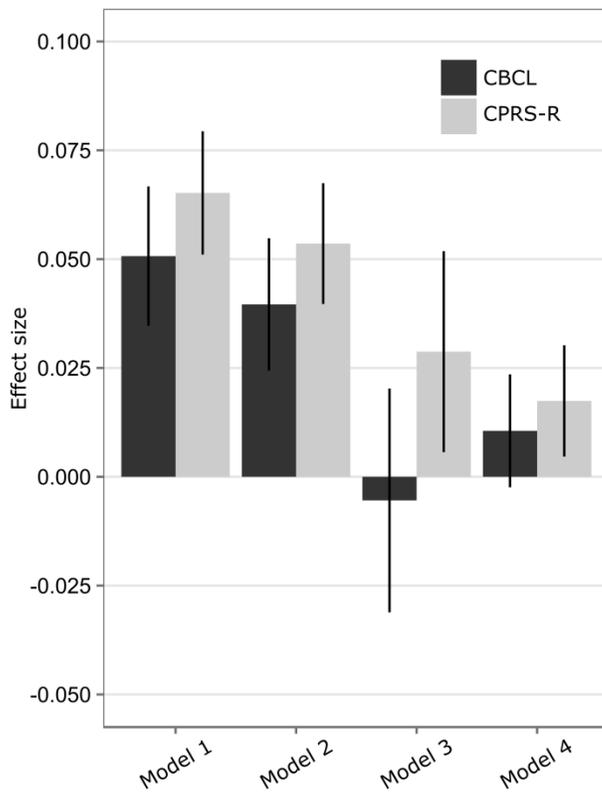
Contrast	Estimate	SE	Z	P-value
Constant	.040	.006	6.335	.000
CPRS-R > CBCL	.013	.007	2.046	.041
Model 3 > Model 2	-.034	.010	-3.315	.001

Model 4 > Model 2                    -.033                    .007                    -4.667                    .000

402 Regression coefficients are listed under the column titled estimate. The inequality symbol > describes the  
 403 estimated contrast. I.e., CPRS-R > CBCL means that the estimate represents how much larger the effect  
 404 size associated with CPRS-R is compared to CBCL. Actual effect sizes are presented in the result section.

405 **Figures**

406 **Figure 1.** Association between maternal alcohol use during pregnancy and the two measures of ADHD  
 407 symptoms. Bars represent standardized regression coefficients with 95% CI. Model 1, crude association;  
 408 Model 2, association adjusted for measured covariates; Model 3, difference between maternal alcohol  
 409 use during pregnancy and before pregnancy, adjusted for measured covariates; Model 4, association  
 410 estimated from sibling comparison, adjusted for measured covariates.



411