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Birth Outcomes, Lifetime Alcohol Dependence and Cognition in Middle Adulthood

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Abstract

Prenatal exposure to alcohol is associated with cognitive abnormalities that persist throughout the lifespan and are also often a focus of studies examining cognitive outcomes associated with excessive alcohol use by an individual. This study examined the effect of birth outcomes consistent with fetal alcohol exposure on associations between lifetime alcohol dependence and cognition in middle adulthood. The sample was comprised of 315 adult adoptees ranging in age from 31 to 64 years (*SD* = 7.20). Facial morphology, pre-morbid cognition, and current cognition were assessed. Birth parent behaviors and birth outcomes (e.g., birthweight, gestational age) were obtained from adoption agency records. Lifetime alcohol dependence was determined from the Semi-Structured Assessment of the Genetics of Alcoholism – II. Univariate associations showed significantly poorer pre-morbid and current cognition when birth parent problems, short palpebral fissures, and thin upper lips were present. Lifetime alcohol dependence was associated with lower perceptional organization, processing speed and working memory. Multivariate analyses demonstrated continued significance suggesting unique contributions of each to cognition. Evaluating the possible role of fetal alcohol exposure within studies on alcoholism can only further improve the treatment and prevention of alcohol-related problems by isolating those cognitive outcomes uniquely attributable to an individual's consumption of alcohol.

Keywords: Fetal alcohol exposure; Alcohol dependence; Cognition; Facial morphology

Introduction

Intra-uterine exposure to alcohol may be an important confound when examining cognitive outcomes associated with individual alcohol misuse. Direct associations between prenatal alcohol exposure and poor cognition are well-established and essential to the diagnosis of fetal alcohol syndrome and related spectrum disorders [1-6]. Indirect effects of prenatal alcohol exposure on cognition can also be inferred due to deficits in fetal growth attributed to alcohol exposure found in some [7-10], but not all studies [11] and transmission of co-morbid personality characteristics of alcoholic parents (e.g., externalizing behavior problems) that may manifest in offspring [12-16] and subsequently influence cognition [17]. Despite the potential for confounding, research into the effect of alcohol problems on cognition typically do not take into account consequences of prenatal exposure to alcohol. This study evaluates measures of facial morphology, birth outcomes, and parent behaviors as possible confounds in the study of alcohol-related cognitive deficits in adulthood.

Data from the Iowa Adoption Studies (IAS), which originally examined genetic and environmental influences on adult substance use and antisocial behaviors among adopted-away offspring [18], was used to test confounding. Alcohol use disorders have shown substantial transmission across generations in this sample [12,13,19-21]. Most recently, the IAS conducted a study designed to examine associations between substance use and cognition in middle age [22-24]. The heightened risk of known and unknown prenatal exposure among children of alcoholics places constraints on interpreting problems associated with offspring alcohol use since those individuals are at higher risk of being exposed to alcohol *in-utero*. Therefore, in order to approximate effects attributable to possible alcohol exposure, a measure of facial morphology was included in the follow-up. Measures of birth weight and length, head circumference, and birth parent problem behaviors (e.g., alcoholism and antisocial behaviors) were also included. Available standardized school achievement scores were collected from centralized state records for third through eighth grades and a standardized cognitive assessment was completed. Facial morphology, cognition, and lifetime alcohol dependence were measured concurrently when the subjects were in middle to late adulthood (age range 34-64). The supplemental measures available in this study will inform future studies of potentially important confounders to the association between alcohol dependence and current cognition. The University of Iowa Institutional Review Board approved the study. Written informed consent was collected from all participants.

Materials and Methods

Description of Sample

The IAS was originally designed to examine gene x environment interactions and substance use problems and antisocial behaviors using an adoption paradigm [see 18 for a description of methodology]. The most recent follow-up was designed to test associations between lifetime substance misuse (e.g., abuse or dependence) and adult cognitive functioning, while controlling for baseline cognitive performance and health problems [22-25]. Substance use histories, psychiatric and health problems, and a cognitive assessment were completed for a sub-sample of adoptees with available school achievement data (n = 330). Average household income at the time of recruitment was $40,000 to $49,999 per year. Subjects were predominantly White, non-Hispanic (N = 311, 94%) with the remainder of the participants African American, non-Hispanic (N = 7,

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2%), African American, Hispanic ($N = 2$, ~1%), Caucasian, Hispanic ($N = 8$, 2%), or mixed race ($N = 2$, ~1%).

Procedure

After providing written informed consent to participate in this study, participants completed a thorough cognitive assessment described elsewhere [22]. Briefly, assessments typically occurred in the home (or a private location) and began in the morning. Health histories and Axis I diagnoses, including lifetime substance abuse/dependence, were collected using the Semi-Structured Assessment of the Genetics of Alcoholism [SSAGA-II, 26] either at the conclusion of the cognitive assessment or by phone. The complete assessment, including the SSAGA-II, was completed in approximately 8 hours. This study also utilized the facial morphology protocol of the University of Washington Fetal Alcohol Syndrome Diagnostic and Prevention Network [27]. Digital photos were taken at the time of the cognitive assessment using guidelines put forth by the UW FAS-DPN protocol. All methods were approved by the Internal Review Board of the University of Iowa College of Medicine, Iowa City.

Measures

Birth parent behaviors: The original sampling scheme is described in detail by Yates et al. [18]. Briefly, agency records (e.g., adoption agency, hospitals) were reviewed for indicators of birth parent alcohol problems and antisocial behaviors. Birth parent alcohol problems were considered present when adoption agency records indicated a history of treatment for alcoholism or when a birth parent was noted to have drinking behavior leading to social or other problems, even if apparently untreated. The presence of birth parent antisocial behaviors was based on incarceration or placement in a state training school as a juvenile (or both). Non-incarcerated birth parents were designated antisocial when adoption agency records indicated one or more DSM antisocial symptoms. An overall indicator of any alcohol problems or antisocial behaviors among birth mothers or birth fathers was constructed for these analyses due to the high degree of overlap between alcohol and antisocial problems, and assortative mating between alcoholic mothers and fathers [28,29]. Furthermore, underreporting of alcohol use during pregnancy is a well-known limitation to studies on *in-utero* alcohol exposure [30]; a limitation that may be exaggerated among mothers placing their children up for adoption thereby providing further justification for combining indices of maternal and paternal behaviors. Of the 120 birth parents with problem behaviors, 42 had alcohol and antisocial behaviors, 50 had problems with alcohol only, and 28 had problems with antisocial behaviors only.

Birth outcomes: Information about birth weight and length, gestational age, and head circumference was collected from adoption agency records when available. Facial measurements were collected using facial photographs taken at the time of interview. The three outstanding features for FAS facial morphology include a small palpebral fissure length, a flat philtrum and a thin upper lip. These features were evaluated using subject photographs taken via the procedure recommended by the University of Washington FAS DPN Training Manual [27]. Frontal, ¾ view and lateral pictures were taken with a digital camera (5.0 mega pixel resolution) at the time of the subject interview. Images were transferred to computer and two research staff independently rated each subject once.

Using the Fetal Alcohol Syndrome Facial Photographic Analysis Software [27], mean palpebral fissure length (in mm) was computer generated from tracings of the participants palpebral fissure. The computer program also computed corresponding z-scores for PF length using normed growth charts [31]. Upper lip circularity was traced and each rater ranked philtrum depth and lip thinness according to the 5 point guide for those features. Race appropriate guides were used (e.g., Caucasian or African American). The ABC codes used for the 4-digit facial ranking were created from the computer generated mean palpebral fissure z-score, the circularity from the lip trace, and the 5-point Likert rating for the ¾ view for the philtrum rating. The computer program then utilized the three ABC codes (MPF, philtrum and upper lip thinness) to construct a 4-digit Diagnostic Rank for severity of FAS facial features: 4 = Severe, 3=Moderate, 2=Mild and 1=None. For a description of the different ABC combinations corresponding to each of the 4-digit diagnostic rankings see Astley and Clarren [32]. Photographic ratings were saved and uploaded to the study's central database for analysis.

Intra-class correlations were used to calculate rater agreement for the continuous facial measures and weighted kappas were used for categorical measures. Agreement was good for the internal measures of scale ($r = 0.997$, 95% CI = 0.996, 0.998) and the z-scores corresponding to mean palpebral fissure length ($r = 0.854$, 95% CI = 0.818, 0.883); adequate agreement was found for lip circularity ($r = 0.757$, 95% CI = 0.697, 0.805). Poor to moderate agreement was found for the categorical measures ranking the mean palpebral fissure (weighted $\kappa = 0.399$, 95% = 0.327, 0.471), philtrum smoothness (weighted $\kappa = 0.516$, 95% = 0.439, 0.592), lip circularity (weighted $\kappa = 0.516$, 95% = 0.447, 0.586), and the 4-digit facial code (weighted $\kappa = 0.441$, 95% = 0.360, 0.522). Therefore, analyses were limited to the continuous measures for mean palpebral fissure length and upper lip circularity.

Neurocognitive measures: Index scores for verbal comprehension, perceptual organization, and processing speed from the Weschler Adult Intelligence Scale III [WAIS-III, 33] and the three memory indices (e.g., general memory, immediate memory, and working memory) from the Weschler Memory Scales III [WMS-III, 34] were examined in this report. All tests were administered by a trained research assistant, double scored and reviewed by a neuropsychologist.

In addition to the WAIS-III and WMS-III, school achievement test scores from elementary school were also available for study participants. The Iowa Test of Basic Skills (ITBS) school achievement data were collected from the centralized state records office (1999-2003). The ITBS [35] is a standardized school achievement test battery administered in Iowa classrooms by school districts from 3rd through 8th grade. The average number of years of school data per subject was 4.82 (SD = 1.24, Min, Max = 2, 6) with 95% of the sample having 3 or more years of data. Achievement scores are reported as state-dependent percentile ranks for each year administered. The composite scores from each available year were averaged to create an overall summary score which has been shown to strongly predict IQ in middle adulthood [25].

Lifetime alcohol dependence: The Semi-Structured Assessment for the Genetics of Alcoholism [36] was used to diagnose lifetime alcohol dependence. DSM-IV dependence on alcohol was considered present if the subject endorsed three or more of the following symptoms within the same 12-month period: 1) tolerance defined as an increased need in quantity to achieve the same effect or diminished effect of the same amount, 2) withdrawal or avoidance of withdrawal by using substance, 3) amount of substance taken was more than intended, 4) efforts to cut down are unsuccessful, 5) considerable time is spent to obtain the substance, 6) important activities are reduced because

of substance use, 7) use of substance continues despite physical and psychological problems. The average age of onset of regular drinking (i.e., at least one a month for 6 months) was 19 years (SD = 4.42) and 24 years (SD = 5.33) for onset of alcohol dependence.

Statistical analysis

Spearman correlations were used to measure associations between facial morphology ratings, birth weight, and cognition. The Mann-Whitney U test statistic was used to test significance of group comparisons for adoptee alcohol dependence and birth parent problem behaviors. Multiple linear regression was used to examine multivariate predictors (e.g., birth parent problems, adoptee alcohol dependence, mean palpebral fissure length, upper lip circularity, and birth weight) of adoptee cognition.

Results

Nearly 10 percent of the adoptees had a lifetime diagnosis of alcohol dependence (Table 1) and over a third had a birth parent with alcohol and/or antisocial problem behaviors. Nearly 10 percent of the adoptees were low birthweight (<2500 grams). Head circumference data was only available on 98 subjects and correlated 0.30 (p=.002) with mean palpebral fissure length. Index scores for the WAIS-III and WMS-III and performance on the ITBS were slightly above average for the total sample.

Birth parent problems was not significantly associated with birth weight or any facial morphology measures; however, verbal comprehension (z = -3.62, p < .001), general memory (z = -2.50, p = .02), and pre-morbid cognition (ITBS) (z = -2.58, p = .01) were significantly lower among adoptees having a birth parent with behavior problems compared to controls (Table 2).

Birth weight was not significantly associated with any measure of cognition (Table 3). Longer MPFL measurements were significantly associated with higher scores on verbal comprehension (p < .001), perceptional organization (p < .001), and working memory (p < .001). Thinner upper lips (higher circularity) was associated with slower processing speed (p < .05).

	Total N	*N or M*	*% or SD*
Lifetime Alcohol Dependence Diagnosis	315	28	8.90
Birth Parent Problem Behaviors	315	120	38.10
Birth Weight			
LBW (<2,500 grams)	315	29	9.60
Gestational Age (weeks)	200	39.54	1.85
Head Circumference (inches)	87	13.62	0.88
Birth length (inches)	278	19.87	1.16
MPFL	315	-0.93	1.48
Circularity	315	77.40	30.86
WAIS-III			
Verbal Comprehension	315	104.28	14.21
Perceptual Organization	315	106.32	13.88
Processing Speed	314	111.34	13.74
WMS-III			
General Memory	314	107.70	15.17
Immediate Memory	314	106.56	15.73
Working Memory	314	107.48	16.91
Pre-morbid Cognition (ITBS)	294	57.10	26.08

Note. WAIS-III = Weschler Adult Intelligence Scales. WMS-III = Weschler Memory Scales. ITBS = Iowa Test of Basic Skills.

Table 1: Descriptive Statistics for Study Variables.

Adoptees reporting lifetime alcohol dependence had significantly thinner upper lips (larger circularity) (z = -2.19, p = .03); significantly lower scores were found for perceptual organization (z = -2.01 p = .05), processing speed (z = -2.55, p = .02), and working memory (z = -2.05, p = .04) (Table 4). Verbal comprehension (p=.07), general memory (z = -1.95, p = .06), immediate memory (p=.07), and pre-morbid cognition (ITBS) (p=.06) were also lower, but not significantly, among subjects with a lifetime diagnosis.

Multivariate linear regression

Results from the linear regression are presented in (Table 5). Lower pre-morbid cognition (ITBS) and lower index scores for verbal comprehension were found when the birth parent had an alcohol or antisocial behavior problem, the adoptee had a lifetime diagnosis of alcohol dependence, and when average MPFL was shorter. Higher index scores for perceptual organization were significantly associated with longer average MPFLs, and the presence of a lifetime diagnosis of alcohol dependence significantly predicted lower processing speed. Lower scores for general memory performance were found in the presence of birth parent problems and adoptee alcohol dependence, whereas poorer working memory performance was associated with alcohol dependence and shorter average MPFL. Upper lip circularity and birth weight were not significantly associated with cognition.

Discussion

In this paper, we examined the influence of birth outcomes, facial morphology, and birth parent problems on the association between lifetime alcohol dependence and cognition in middle adulthood. Non-significant associations were found between birth parent problems and adoptee birth outcomes (e.g., birth weight and length, head circumference, gestational age) and measures of facial morphology. Verbal comprehension, general memory, and ITBS school achievement scores were significantly lower when birth parent problems were present. The measures of facial morphology were the only birth outcomes significantly associated with cognition with non-normative values (e.g., short palpebral fissures, thin upper lips) associated with poorer performance. Lifetime alcohol dependence was associated with lower perceptional organization, processing speed and working memory. The multivariate analyses demonstrated continued significance for birth parent problems, alcohol dependence, and palpebral fissure length suggesting unique contributions of each to cognition.

There are several limitations to this study. Since all of our study participants were adopted, the majority of the data on possible fetal alcohol exposure was collected from information documented in the adoption agency records; information that was primarily ascertained from the birth mother. Because the initial studies originated over several decades and across several adoption agencies, the degree and rigor of screening for maternal alcohol use was most likely variable. Furthermore, the age of some of our subjects predates the emergence of FAS as a formal clinical diagnosis (adoptees were born between 1942 and 1977), and adoption agencies were less comprehensive in their collection of parental mental health histories at that time. Consequently, we only had documented prenatal alcohol exposure for 6 mothers, which precluded systematic examination of known intrauterine exposure on the tested associations. Due to possible incomplete information in the adoption agency records, we combined mother and father behavior problems. Therefore, it is difficult to separate maternal and paternal effects [37-39]. Furthermore, information about the amount and duration of possible

	Adoptee Lifetime Alcohol Dependence					
	Absent			*Present*		
Birth Outcomes	*N*	*M*	*SD*	*N*	*M*	*SD*
Birth Weight (grams)	277	3215.62	553.85	26	3332.76	516.72
Gestational Age (weeks)	181	39.55	1.88	19	39.47	1.58
Head Circumference (inches)	89	13.65	0.79	9	13.32	0.57
Birth length (inches)	254	19.88	1.18	24	19.78	0.90
Facial Measures						
Mean Palpebral Fissure Length (z-score)	287	-0.96	1.49	28	-0.61	1.34
Upper Lip Circularity*	287	76.89	31.52	28	82.60	22.89
WAIS-III Index Scores						
Verbal Comprehension	287	104.64	14.01	28	100.54	15.97
Perceptual Organization*	287	106.74	13.71	28	102.11	15.21
Processing Speed**	287	112.01	13.49	28	104.50	14.60
WMS-III Index Scores						
General Memory Index*	286	108.20	15.06	28	102.57	15.65
Immediate Memory Index	286	106.98	15.77	28	102.29	14.87
Working Memory Index*	286	107.91	16.65	28	103.14	19.14
Pre-morbid Cognition (ITBS)	271	58.00	25.67	23	46.53	29.11

Note. WAIS-III = Weschler Adult Intelligence Scale, 3rd Edition. WMS-III = Weschler Memory Scales, 3rd Edition. ITBS = Iowa Tests of Basic Skills.
Significant Mann-Whitney U differences (* $p < .05$, ** $p < .01$, *** $p < .001$).

Table 2: Study Variables by Adoptee Lifetime Alcohol Dependence.

	Birth Parent Problems					
	Absent			*Present*		
Birth Outcomes	*N*	*M*	*SD*	*N*	*M*	*SD*
Birth Weight (grams)	189	3227.12	537.29	114	3223.27	575.24
Gestational Age (weeks)	126	39.49	1.76	74	39.64	2.00
Head Circumference (inches)	63	13.71	0.88	35	13.46	0.51
Birth length (inches)	178	19.88	1.25	100	19.84	0.99
Facial Measures						
Mean Palpebral Fissure Length (z-score)	195	-0.85	1.53	120	-1.07	1.39
Upper Lip Circularity	195	76.29	31.06	120	79.20	30.59
WAIS-III Index Scores						
Verbal Comprehension***	195	106.39	14.44	120	100.84	13.19
Perceptual Organization	195	106.74	13.66	120	105.64	14.27
Processing Speed	195	111.85	13.36	120	110.51	14.35
WMS-III Index Scores						
General Memory Index**	194	107.97	14.23	120	104.27	17.71
Immediate Memory Index	194	109.55	13.44	120	104.71	17.25
Working Memory Index	194	108.37	15.09	120	106.04	19.47
Pre-morbid cognition (ITBS)**	183	60.17	25.29	111	52.04	26.68

Note. WAIS-III = Weschler Adult Intelligence Scale, 3rd Edition. WMS-III = Weschler Memory Scales, 3rd Edition. ITBS = Iowa Tests of Basic Skills.
Significant Mann-Whitney U differences (* $p < .05$, ** $p < .01$, *** $p < .001$).

Table 3: Study Variables by Birth Parent Problems.

in-utero exposure to alcohol was unknown. Finally, our sample was comprised of adults raised in adoptive homes, which eliminates environmental influences (i.e., living with an alcoholic parent) that might exacerbate the effects of prenatal alcohol exposure on later adjustment and result in attenuated associations compared to those typically published.

Despite the limitations of our study, our findings support including measures of facial morphology and parental behavior problems in studies examining future cognitive correlates of alcohol misuse even though the included measures were not identified as confounders. The inclusion of biologically sensitive data in the examination of negative effects of excessive alcohol consumption will allow greater delineation of alcohol-specific effects of individual use after removing effects due to inherent psychological and physiological characteristics. It is suggested by these data that individuals with alcoholic or antisocial parentage are at a cognitive disadvantage that may be manifest early in life (grades 3-8 in these data). These findings provide a possible biological (i.e., genetic) explanation for the observed link between externalizing behaviors and cognitive performance among alcohol-dependent individuals [17]. The associations between palpebral fissure length and cognition implicate possible structural or functional neurological deficits. In a recent study, Lyons-Jones et al [40] presented analyses suggesting that short palpebral fissures reflect a defect in forebrain development, which is consistent with the observed cognitive associations. The association

	Birth Outcomes				FAS DPN Facial Measurements	
Cognitive Outcomes	Birth Weight	Gestational Age	Head Circumference	Birth Length	MPFL	Circularity
WAIS-III						
Verbal Comprehension	.02	-.00	.10	.03	.21***	.06
Perceptual Organization	.10	.08	.05	.07	.22***	.03
Processing Speed	.01	.03	.05	-.04	-.02	-.14*
WMS-III						
General Memory	.01	.06	-.03	.01	.07	.06
Immediate Memory	-.01	.02	-.03	-.02	.04	.04
Working Memory	.06	.02	.03	.03	.15**	.00
Pre-morbid cognition (ITBS)	-.00	-.05	-.03	-.00	.11	-.00

Note. FAS ratings and 4-Digit code are the average between the two coders. WAIS-III = Weschler Adult Intelligence Scale, 3rd Edition. FSIQ = Full Scale IQ. VIQ = Verbal IQ. PIQ = Performance IQ. WMS-III = Weschler Memory Scales, 3rd Edition. ITBS = Iowa Tests of Basic Skills. FAS = Fetal Alcohol Syndrome. FAS DPN = Fetal Alcohol Detection and Prevention Network.
* $p < .05$. ** $p < .01$. *** $p < .001$.

Table 4: Spearman Correlations between FAS DPN Facial Measures and Clinical Outcomes.

			WAIS-III						WMS-III					
	Pre-morbid cognition (ITBS)		Verbal Comprehension		Perceptual Organization		Processing Speed		Immediate Memory		General Memory		Working Memory	
Predictors	*β(SE)*	*p*	*β(SE)*	*p*	*β(SE)*	*p*	*β(SE)*	*p*	*β(SE)*	*p*	*β(SE)*	*p*	*β(SE)*	*p*
Birth Parent Problems	**-2.12**	**.035**	**-3.21**	**.001**	-0.21	.836	-0.62	.537	-1.53	.127	**-2.65**	**.009**	-0.28	.780
Alcohol Dependence	**-2.13**	**.034**	**-2.49**	**.013**	-1.73	.085	**-2.35**	**.019**	-1.38	.168	**-2.22**	**.027**	**-2.10**	**.037**
MPFL	**2.56**	**.011**	**4.03**	**.000**	**2.61**	**.009**	-.21	.837	0.31	.760	0.94	.347	**2.33**	**.020**
Circularity	-0.82	.411	0.91	.362	0.19	.853	-1.88	.062	-0.51	.610	1.21	.227	-0.43	.665
Birth Weight	-0.69	.492	-1.22	.225	1.72	.087	-0.10	.919	-0.18	.861	0.03	.975	0.65	.517

Note. MPFL = mean palpebral fissure length. ITBS = Iowa Test of Basic Skills. WAIS-III = Weschler Adult Intelligence Scale. WMS = Weschler Memory Scales. *B* = standardized regression coefficient. *SE* = standard error. P = p-value.

Table 5: Multiple linear regression predicting adult cognition.

between palpebral fissure length and pre-morbid cognition further suggests that the possible forebrain deficits may manifest prior to the onset of alcohol use. Finally, the lack of association between parental behaviors is not surprising given the imprecise assessment of alcohol exposure and observed absence of effects found among mothers reporting light-to-moderate alcohol consumption in pregnancy [11].

Our suggested inclusion of facial morphology measures is consistent with recommendations of evaluation for fetal alcohol exposure within the clinical setting even when full diagnostic criteria are not met [41]. It is our recommendation that continuous (or quantitative) measures of facial morphology be used in populations with unknown fetal alcohol exposure since facial abnormalities may be less obvious or partially manifest in less well-defined samples [42-45]. Evaluatingthe possible role of fetal alcohol exposure within studies on alcoholism can only further improve the treatment and prevention of alcohol-related problems by isolating those cognitive outcomes uniquely attributable to an individual's consumption of alcohol. Based on these findings, we believe histories of alcohol (and other behavioral) problems within the family of origin could be used as an additional resource for identifying individuals who may have been exposed to alcohol prenatally [46,47] and deserve further evaluation.

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