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# Measurement of neurodevelopmental effects of prenatal alcohol exposure in Ukrainian preschool children

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## Abstract

Effects of prenatal alcohol exposure (PAE) are rarely measured in preschool children due to relative insensitivity of assessment methods at this age. To examine the potential of a nonverbal battery in early identification of cognitive problems in alcohol-exposed children, 291 prospectively identified Ukrainian children were evaluated using a test battery focusing on early executive functioning (EF) and visuospatial skills, areas of cognitive development particularly sensitive to PAE in older children. Tests included the Differential Ability Scales, 2nd Edition (DAS-2) and several NEPSY/NEPSY-II subtests, standardized in the United States. Others were adapted from commonly used non-standardized neuropsychological measures of EF (Preschool Spatial Span, Imitation Hand Game, A not B, Delayed Attention, Subject Ordered Pointing). Children in two sites in Ukraine, Rivne and Khmelnitsky, were tested at 3 ½−4 ½ years to identify effects of PAE. Although most children performed within the average range, Alcohol-Exposed preschoolers had lower scores on DAS-II Summary Scores as well as on specific subtests. To evaluate the effects of alcohol dose during the pre-pregnancy recognition period and during midgestation

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of pregnancy, generalized linear regression models were used controlling for demographic and individual variables. In addition to DAS-II variables, measures reflecting sustained attention, working memory and ability to shift cognitive set were impacted by alcohol dose. Early executive function appears to subsume these performance differences. In conclusion, findings indicate that the effects of PAE can be identified in the preschool period and reliably measured using tests assessing nonverbal and spatial skills supported by executive functioning.

## Keywords

Prenatal alcohol exposure (PAE); Fetal Alcohol Spectrum Disorder (FASD); preschool assessment; executive function (EF)

Neurodevelopmental effects of prenatal alcohol exposure (PAE) have been studied extensively in older children, particularly in school-aged children and adolescents, where PAE can affect overall cognitive functioning as well as executive functioning (EF; i.e., planning, organization, and memory; Kable, O'Connor et al., 2016). There is also evidence, particularly from longitudinal exposure studies, that there may be more effect on visual-spatial functions (or simultaneous processing) than verbal (sequential) processing (Coles et al., 2002; Kable, Coles, Jones et al., 2016). In contrast, there is relatively little information about the assessment of prenatal alcohol effects in preschool children. To some extent, this lacunae in our understanding of the impact of this teratogen on development results from lack of access to young children, many of whom are not identified as needing clinical referral until they are older. However, it can also be attributed to insensitivity of measures in the preschool period to what are believed to be the most salient effects of alcohol exposure (Espy et al., 1999). The result is often that clinicians do not attempt to evaluate children of this age for the cognitive effects of PAE (Cook et al., 2016). Alternatively, expecting that assessment of FASD is not possible before early school age, they may attribute observed effects to other factors.

Studies of children in this age range have contributed to this perception since reported findings are ambiguous as was noted in a recent review (Subramoney et al., 2018). Some differences can be attributed to measuring different types of samples, that is, clinical versus exposure cohorts. For example, in a clinical sample, Fuglestad et al. (2015) examined EF in preschool children with FASD (average age 4.1 to 4.7 yrs). The sample included 39 children diagnosed with FASD at a University Clinic and 51 age-matched community controls. Those with FASD performed more poorly than controls on an EF card-sorting task, the Executive Function Scale of Early Childhood, (Carlson & Schaefer, 2012) and on a modification of the Delay of Gratification task (Mischel et al., 1989) but FASD diagnostic groups (i.e. Fetal alcohol syndrome [FAS], partial FAS [pFAS], and Alcohol Related Neurodevelopmental Disorder [ARND]) did not differ from each other. Since these diagnostic groups should reflect the severity of impact of exposure, it might be expected that there would be a dose-response curve evident. However, the study reported that there was a moderate to high correlation between ability and test results and ability scores were significantly lower in the FASD group [control group mean was 114 on the Differential Ability Scales, 2nd Edition (DAS-II; Elliot, 2007), while the mean developmental score for the FASD group was 85 on

the Mullen Scales of Early Learning (Mullen, 1995)]. This pattern of results cannot rule out the possibility that the small effects that were noted were the result of factors associated with clinical referral rather than FASD. In addition, the difference between tests used to measure ability level creates a systematic bias that may have affected interpretation. In a contrasting example, a retrospective study of clinically-referred children in this age range with PAE who did or did not have a FASD diagnosis, found that those who were so diagnosed demonstrated more significant deficits on a range of tests although both groups differed from the average based on test norms (Hanlon-Dearman et al., 2020), suggesting that outcomes might reflect diagnostic severity

In research with exposure samples in which preschool children were identified in the perinatal period and followed longitudinally, results are also mixed. Such studies do not select subjects from clinical populations but rather based on knowledge about maternal alcohol use, and most such studies report that effects are dependent on the amount of alcohol exposure. In their seminal study, Streissguth et al. (1984) reported significantly lower ability scores in 4-year-olds with alcohol exposure although both this group and controls were in the average range. Effects were also reported for attention on a vigilance (sustained attention) task. The authors noted that there were dose/response patterns with the most heavily exposed most affected. Cluver et al. (2019) examined cognitive and neurocognitive outcomes in a prospective cohort in South Africa. Both the groups exposed to alcohol and the nonexposed contrast group were from the same disadvantaged population and this design allowed control of socioeconomic status (SES). Children were 4 years of age and were assessed with the Kaufman Assessment Battery for Children, 2nd Ed (K-ABC-II; Kaufman & Kaufman, 2004) and the NEPSY-II (Korkman et al., 2007). Use of the K-ABC-II was designed to measure how children processed different kinds of information as it includes separate scales of Sequential and Simultaneous processing, while minimizing reliance on verbal instruction and response. Results indicated that there were no overall significant differences in general mental processing ability; however, on the Simultaneous Scale, the children with the most heavy exposure (Very Heavy PAE) had lower scores than children in the SES-matched control group. No differences in sequential processing were observed overall although the Word Order subtest was lower in the very heavy PAE group. On the NEPSY-II, no differences were observed in attention/executive function, memory and learning or visuospatial functioning while the Very Heavy PAE group was lower on two subtests, Speeded Naming and Hand Position, a measure of visual short-term memory. In a Danish sample, assessed at 3 ½ (Olsen, 1994) and 5 years (Falgreen Eriksen et al., 2012), no differences were found for children of moderately drinking women versus controls although heavier drinking was related to lower verbal scores on the Wechsler Preschool and Primary Scales of Intelligence-revised (WIPPSI-R; Wechsler, 1989). The UK Millennium Cohort Study (Kelly et al., 2009) found that, at 3-years of age, the children of both abstaining and heavily drinking women performed less well than children of light drinkers suggesting the results reflect social differences rather than effects of a teratogen. Finally, Noland et al. (2003) examined the cognitive performance of 4-year-old children in Cleveland with a focus on executive functioning. The study examined effects of prenatal exposure to alcohol, tobacco and marijuana finding that alcohol exposure was related to impaired ability on the

WPPSI-R and on a measure of inhibition (Tapping Inhibition) confirming that both general ability and EF are impacted by alcohol exposure.

The studies reviewed here suggest that both social factors and exposure level may contribute to identification of effects during this age range. The design of the studies reviewed also suggest that group differences (i.e. alcohol group versus non exposed contrast group) are not commonly found and occurred only when the most heavily exposed groups were isolated. There is also limited information about the measures that are most effective in identifying alcohol effects at this age.

To provide more information about the effect of PAE during the preschool period, we evaluated Ukrainian children who were followed from prenatal identification. Using this well-characterized sample it was possible to identify those with PAE and examine specific cognitive outcomes both across exposure groups and as a function of prenatal dosage both before the pregnancy was recognized and in mid-gestation. Through examination of this cohort, areas that were specifically affected by alcohol exposure, if any, could be identified and serve as a guide for future screening in this age group. We were also able to control for SES and other factors that might influence outcomes. In addition, by comparing results obtained using group differences versus those obtained using information about alcohol dose while controlling for covariates (i.e., partial correlation), comparison with previous research is possible.

It was hypothesized that in comparison to an unexposed contrast group, those with alcohol exposure would demonstrate specific deficits in nonverbal ability as well as in early executive function and visual/motor processing consistent with previous research (Castillo Castejón et al., 2019; Enns & Taylor, 2018; Fuglestad et al., 2015). Further, we hypothesized that outcomes on measures of executive function and attention would be sensitive to higher doses of alcohol both during the pre-recognition period and in midgestation.

## Methods

### Study design

This cohort study (Chambers et al., 2014) originally recruited 686 women of whom half drank alcohol at moderate to heavy levels, and half were controls reporting low drinking levels or abstaining. Recruitment was done at two sites in Ukraine affiliated with OMNINet, a network of educational and research sites focused on the prevention of birth defects. In the original study, half of the women within each of the two exposure groups (high/moderately exposed and low/unexposed) were assigned randomly to receive a daily MVM supplement (over-the-counter prenatal vitamin, Theravit®), and half to standard of care (prenatal vitamins recommended). Half of the MVM-supplemented group also received a daily dose of 750 mg of supplemental choline. When infants were born, information was collected from medical records and direct examination on growth, physical features associated with prenatal alcohol exposure, and other factors affecting development. A subsample of mothers/children ($N$ = 291) were followed into the preschool period drawn from those ($N$ = 341) who had participated in follow-up at 6 and/or 12 months. Of these, alcohol use by 40 women was suspected but not confirmed by self-report and they were

not eligible for the current study. Thus, 93.6% of the 301 eligible in the preschool period are included here; however, not all measures were completed by all participants as some children did not complete individual tests. The overall study was approved through the institutional review boards at the University of California San Diego and Lviv Medical University in Ukraine.

## Study participants

Women were recruited at their first prenatal visit (on average at 19 weeks gestation) at the *Rivne Regional Medical Diagnostic Center* and the *Khmelnitsky Perinatal Center* in Ukraine. From 2007 to 2012, staff screened more than 13,000 pregnant women and 94% reported drinking at some time while 45% reporting drinking since they became pregnant. Further, 33% continued to drink in pregnancy, and 9% drank in a binge pattern of at least 4–5 drinks per occasion (Chambers et al., 2014). Women who reported at least weekly binge-drinking episodes (5+ drinks), at least five episodes of 3–4 standard drinks or at least 10 episodes of 1–2 standard drinks either in the month around conception or the most recent month of pregnancy, were invited to participate in the study, and gave informed consent both for participation and for their deidentified data to be used in scientific reports. Those reporting use were provided with information on the risks of alcohol consumption during pregnancy. The next nondrinking woman meeting comparison subject screening criteria (defined as no binge episodes, minimal or no alcohol in the month around conception, and no drinking in the most recent month of pregnancy) was recruited as a control.

## Assessment of maternal alcohol use

During the enrollment interview, *w*omen reporting any lifetime drinking were asked to report the number, volume, and type of alcoholic drinks consumed on a day by day basis in a typical week before pregnancy recognition and in the most recent 2 weeks using a time-line follow back method (Sobell et al., 2001). Quantity and frequency of alcohol consumption in responses to these questions was summarized in two ways: 1) the average number of standard drinks per day over the period for which the mother was reporting as a reflection of the overall quantity of alcohol consumed (drinks/day), and 2) the average number of standard drinks per day for only the days in which the mother reported any alcohol consumed (drinks/drinking day), as a reflection of heavier episodic or binge drinking during the time period covered by the maternal report. Reported drinking was converted to a standard of absolute ounces of alcohol (oz/AA) per time period using a factor of two. That is, two standard drinks were equivalent to one ounce of absolute alcohol.

## Demographic and outcome measures

Demographic information was obtained during the initial interview and included family (e.g. maternal and paternal age) and pregnancy characteristics (e.g. parity, that is, number of children). Hollingshead (2011) social class ratings were calculated later from education and occupational information. In addition, information was captured on health-related activities like tobacco use. At delivery, information was obtained about infants gestational age (GA), in weeks, as well as infant growth (Birthweight, Length, and Head Circumference). When children were 3 ½ to 4 ½ years of age, families who had participated at an earlier follow-up were invited to return to the recruitment sites and children assessed using the test battery

in Table 1. A single psychologist at each test site was trained by investigators and was responsible for child assessment. Recruitment and monitoring of group status were carried out by other staff members to restrict psychologists' information about alcohol exposure. Periodic review of test administration and scoring was carried out in person and via recordings.

**Preschool battery (Table 1)—**In working with this Ukrainian cohort, we wanted to design a test battery that could be used in a non-English speaking environment while discriminating effects of alcohol. Focus was on nonverbal assessment of cognitive functioning both because of the language differences and because this area of development appears to be more affected by prenatal exposure (Coles et al., 2002; Paolozza et al., 2014). Specific criteria for test selection were the following: 1) Capable of detecting effects of PAE; 2) Developmentally appropriate for use with preschool children; 3) Flexible enough for use in a non-English speaking cohort; 4) Cross-culturally relevant. Based on previous research on effects of PAE (Falgreen Eriksen et al., 2012; Kable, O'Connor et al., 2016; Subramoney et al., 2018), we targeted the following content areas for inclusion in the battery: General ability, visual/spatial processing, and aspects of executive functioning that could be measured in the preschool period. These included sustained attention and the ability to inhibit appropriately (impulse control) that are considered to be characteristic of attention deficit, hyperactivity disorder, as well as working memory, ability to reverse set, and memory. Some tasks selected included a cognitive control aspect. That is, the child had to internalize and apply a rule in selecting a response. In some cases, appropriate tests were available commercially although they had been standardized in the United States. For instance, we used the Nonverbal and Spatial portions of the DAS-II (Elliot, 2007). Performance of these subtests does not rely on a knowledge of English and instructions can be given by the examiner in the child's native language. Similarly, we selected the Visual Attention subtest from the NEPSY (Korkman et al., 1998) and the Statue and Speeded Naming subtests from the NEPSY-II (Korkman et al., 2007) as well as the Attention Sustained subtest from the Leiter-3 (Roid et al., 2013) to measure aspects of sustained attention and impulse control (e.g. Statue). The Visual Attention subtest from the first edition of the NEPSY was used despite having older norms because this subtest is not included in the NEPSY-II and we wanted to include a sustained attention task at both the beginning and the end of the battery. Finally, where no tests were available, we adapted measures that are commonly used by neuropsychologists for older individuals. We adapted these tests based on the developmental limitations of preschool children (e.g. spatial span, a measure of visual short term memory, and subject ordered pointing, a memory task that requires the child to retain knowledge of items previously identified). To adapt the spatial span task, for instance, the number of blocks in a Corsi-Block-type array (Berch et al., 1998) was reduced. In the subject ordered pointing task (Gillett, 2007), culturally appropriate pictures were substituted for the designs used for adults. All instructions and scoring material were translated into Ukrainian for use by local psychologists. Ukrainian examiners were trained on all materials by the authors.

### Data analysis

Data collected on-site in Ukraine were entered into databases by local study staff and transmitted electronically to the University of California San Diego, La Jolla, California and Emory University, Atlanta, Georgia. Databases were compiled subsequently to address specific research outcomes. Data from this study are available to researchers through an application process from the Collaborative Initiative for Fetal Alcohol Spectrum Disorders (CIFASD; https://cifasd.org/data-sharing/). In the preschool follow up, 291 children were tested whose alcohol exposure could be confirmed. Due to their age, some children were unable to complete all items in the battery and, for that reason, the number participating in a particular test is given in the tables below. To compare alcohol groups and effects of MVM, for categorical and ordinal data, chi square analyses were used. For the analysis of demographic data with continuous variables, and for test outcomes, two factor multivariate analyses were used. However, since the focus of this paper was the impact on alcohol exposure on test outcome, after an initial analysis was done that included the MVM intervention and no differences were found as the result of this factor, data were collapsed over this variable and presented as a single factor, two group study focusing on alcohol effects.

Generalized Linear Regression (GLR) was used to measure the relationship between the daily dose of PAE, before pregnancy recognition and in mid-gestation, and performance on child cognitive measures. Test Battery outcomes were the Responses predicted while the following variables were considered as covariates in the individual models: Micronutrient Supplementation, Data Collection Site, Cigarette Use, Hollingshead SES, Maternal Age, Paternal Age, Parity, Gestational Age at Birth, Child Sex, and Child Age. These variables were selected because they were related to either alcohol use or to child outcomes. To determine specific covariates for individual analyses, a preliminary model was calculated and any covariate with a relationship achieving a significance level of .10 with a particular outcome was used as a covariate in the final GLR model. The Variance Inflation Factor (VIF) was calculated when regressions were done to assure that collinearity was not affecting results.

## Results

### Demographic information

As noted in Table 2, there were few differences among groups although the fathers of children with alcohol exposure were older than those of unexposed children. SES was significantly lower in families of women using alcohol and such women were more likely to be smokers. The majority of the mothers reported drinking in a “moderate” range (with approximately 1.38 drinks a day on average in the drinking group during the pre-recognition period and 1.26 drinks per day mid-gestation). When Infant characteristics were measured, those exposed to alcohol were significantly lower in gestational age, birth weight and birth length (Table 3).

## Child cognitive outcomes

Table 4 shows the group effects of alcohol exposure as measured by the DAS-II (Elliot, 2007). While all the scores are within the average range, significant group differences related to alcohol exposure were noted in the following subtests, Pattern Construction and Picture Similarities, and the following summary scores, Spatial Standard Score and the Nonverbal Composite Score.

Table 5 shows measures of sustained attention none of which demonstrate group differences related to alcohol group status. Table 6 shows measures of Executive Function and Memory. With the exception of Speeded Naming, none of these measures show effects of alcohol group.

## Effect of alcohol dose on outcomes

Evaluation of outcomes by group may obscure effects of dose and may not take into account the contribution of potential confounding factors like SES and cigarette smoking to outcomes.

To evaluate these effects, we used generalized linear regression models to estimate the degree of relationships between the alcohol variables, Ounces of Absolute Alcohol per day (oz.AA/day) both before pregnancy recognition and mid-gestation, with test outcomes. Potentially confounding variables that demonstrated significant correlations with either measure of alcohol exposures or that were related to outcome variables were included in these models when appropriate. These factors were: MVM group, site of data collection, child sex and age, maternal age, paternal age, family SES, gestational age, parity and cigarette use in pregnancy. The goal was to identify tests that were *sensitive to the effects of higher levels of prenatal alcohol exposure* and to identify the period of exposure when this occurred. The results are shown in Table 7 and there are a number of significant relationships even with potentially confounding factors controlled. Higher alcohol exposure before pregnancy recognition is associated with Nonverbal Processing and Spatial Processing on the DAS-II, and with the Picture Similarities and Copying subtests. Significant relationships were also noted with Visual Attention (Leiter), Visual short-term memory (Hand Game Identical and Reversed) and a measure of executive functioning, set shifting (Delayed Alternation Task). Higher alcohol exposure in midgestation is associated with the DAS-II Nonverbal Reasoning standard score, as well as the Nonverbal and Spatial Composites, and with the Matrices subtest. In addition, differences were noted on spatial working memory (Corsi Blocks Forward) and a measure of set shifting (Hand Game, Reversed).

Based on these results a principal components factor analysis was calculated using all of the non-DAS-II measures to identify any patterns that might represent particular cognitive functions. This analysis yielded a 4 factor solution accounting for 54.41% of the variance. The initial factor (16.65%) appeared to represent executive functioning and was found to correlate significantly with pre-recognition alcohol use ($r = -.198$, $p < .01$) and mid-gestation alcohol use ($r = -.191$, $p < .01$). Tests loading on this factor at greater than .50 included Corsi Blocks Forward, Draw-a-Line Slowly, Hand Game Imitative, Hand Game,

Conflict, AB Game Total Correct, AB Game Perseveration Errors, Delayed Alternation Total and number of Errors, and Subject Oriented Pointing. Other factors, including Factor 2 that represented Sustained Attention (13.17%), did not correlate with alcohol exposure. A further GLR model was calculated using the EF factor score as the Predictor finding that both periods of alcohol use are significantly related to this EF indicator. These outcomes are also shown in Table 7.

## Discussion

The limited literature on the effects of PAE on cognitive performance among preschool children presents a mixed picture. Analyses of longitudinal exposure samples that compare groups of children find that only the most heavily exposed groups demonstrate effects and these studies have sometimes been used to suggest that moderate alcohol is not a risk factor (Kelly et al., 2009; Olsen, 1994). Studies that select samples from clinical population are more likely to find that all those diagnosed with FASD are cognitively affected (Fuglestad et al., 2015). In addition, there is limited evidence to provide guidance about the most appropriate measures to use to identify specific outcomes associated with PAE in this age group.

The current study employs a cohort identified based on maternal report of their own drinking and followed longitudinally and allowed ascertainment of socioeconomic status as well as other factors, like smoking, that allowed some control over potentially confounding factors.

Results demonstrate again that, when groups identified as part of exposure samples are compared, alcohol-exposed children score similarly to controls. However, in this sample, there are significant group differences on the Summary scores on the DAS-II that are measurable while not placing children in a clinically impaired range. In addition, it is apparent that some of the measures used are sensitive to alcohol dose effects rather than to group status. This finding provides support for the idea that the differences noted are, in fact, the effect of alcohol exposure rather than other, unmeasured covariates associated with alcohol group status. These measures include the DAS-II Nonverbal Summary Scores as well as a number of the subtests. Other measures that demonstrated effects were the Leiter Sustained Attention task, Spatial Span and the Hand Game/Identical (both Visual Short-Term Memory tasks), and tests that require the cognitive flexibility associated with set shifting and reversal shift (e.g., the Hand Game/Reversed; Delayed Alternation). These tests are early indicators of potential problems in executive functioning and, therefore, consistent with the results of research in older children (Kable, O'Connor et al., 2016; Khoury et al., 2015). The impact on early executive function is further emphasized by the factor analysis and the relationship between this factor and alcohol exposure at both periods of pregnancy.

In the last decade, there has been substantial interest in the early measurement of EF (e.g. Wiebe et al., 2011) with a general agreement that very early EF functions are undifferentiated (Morra et al., 2018). However, In the preschool period, several processes have been identified as emerging that contribute to early EF including working memory, inhibition or the ability to suppress inappropriate responses, and set shifting or cognitive flexibility. (Morra et al., 2018). In older individuals, working memory and set shifting have

been found repeatedly to be impacted by prenatal alcohol exposure (Coles et al., 1997) and to be related to structure (Riley et al., 2004) and function (Kable, Coles, Mattson et al., 2020) of frontal lobes. It is interesting then to see in the current study, that it is tests that measure these functions that are identified as alcohol affected and that load on the factor that we have called “executive functioning”. This results supports the assumption that the deficits observed in older children, particularly those in clinical settings, are likely to be the result of the teratogenic exposure to alcohol rather than just the effects of negative caregiving environments. In addition, these results suggest that problems in these areas, that are so likely to have a long term effect on behavior and academic function, can be identified early in life. The opportunity for timely identification of delays in EF development may allow more effective early intervention efforts.

It is notable that despite the repeated reports in the clinical literature association with attention deficit, hyperactivity disorder (Coles et al., 1997), as well as our understanding of early EF, some of those tests that required the ability to inhibit impulsive response (e.g., NEPSY statue) do not reflect alcohol effects in this sample. However, this is consistent with previous studies (Kable & Coles, 2017) and suggests the need for more research on impulsivity in this group of children. Other tasks, that have been identified previously as reflecting alcohol effects (i.e., Speeded Naming) or memory/executive function (i.e., Subject Order Pointing) appear to be influenced by other factors. For instance, when we examined Speeded Naming using the GLR model, cigarette smoking during pregnancy was the significant contributor to performance on this task while there was no effect of alcohol. It may be that cigarette use, which is highly associated with alcohol use in pregnancy, accounts for the previously observed relationships. These findings illustrate the importance of studies that allow the discrimination of alcohol effects from those that arise from exposure to other drugs and nonoptimal caregiving environments that can also be influential on processes that contribute to EF (Vrantsidis et al., 2019)

While not the focus of the current report, it is notable that we did not observe effects of the MVM intervention in pregnancy either directly or in interaction with alcohol at this follow-up. This observation is in contrast to findings reported when these children were younger (Coles et al., 2015; Kable, Coles, Jones et al., 2016). It may be that the benefits associated with the nutritional intervention are not persistent or that they cannot be observed in the areas of functioning that were measured here.

This study has both strengths and weaknesses. This follow-up to a larger study allowed careful measurement of prenatal alcohol exposure as well control for numerous factors that might also affect development. In addition, because of the location in Ukraine where stigma associated with alcohol use was less than in the United States, we may have been able to document maternal use more accurately. However, there are certainly limitations in the current study. Due to the research setting, we could not employ measures of verbal function so that aspect of child development remains unexplored in this cohort. Although we attempted to control for a number of factors associated with prenatal alcohol exposure, like SES, smoking, parental age and perinatal factors, it is possible that some remain unmeasured. Generalizability is limited as this Ukrainian cohort may not reflect the characteristics of women and children in other settings. In addition, child educational

experiences, that might be expected to affect some of these test outcomes, may differ as well due to national differences in educational requirements (Shyyan et al., 2018). (However, the preschool enrollment rate and starting age for schooling are the same in both countries, Ukraine vs United States Education Stats Compared (nationmaster.com)).

Despite these limitations, these results suggest that it is possible to identify specific alcohol-effects in preschool children and that the areas identified are consistent with those that have been observed elsewhere and in different age groups. Early indicators of executive function were particularly sensitive to alcohol effects. Measures employing nonverbal and visual tasks appear to be indicative to alcohol effects and therefore may be good choices in working with children of this age in the future.

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**Table 1.**

Measures in the test battery and functions assessed.

| Test Measure | Function Assessed |
|---|---|
| DAS-II[a] Nonverbal Reasoning Standard Score | Summary of Nonverbal Processing |
| DAS-II Nonverbal Composite | Nonverbal Processing Ability/Problem Solving |
| Matrices | |
| Picture Similarities | |
| DAS-II Spatial Composite | Spatial Processing Ability |
| Pattern Construction | |
| Copying | |
| "Corsi Block" Task | Spatial Span (Spatial Short Term Memory) |
| Forward | Spatial Working Memory |
| Backward | Spatial Working memory and EF |
| Leiter[b] Attention Sustained Subtest Total Scaled Score | Sustained Attention, Control of Impulsivity |
| NEPSY[c] Visual Attention Subtest | Sustained Attention, Control of Impulsivity |
| NEPSY[d] Statue | Self-Regulation, Motor Control |
| NEPSY[d] Speeded Naming | Executive Function, Verbal Fluidity |
| Draw-A-Line Slowly | Impulse Control |
| Hand Game | *Visual Short Term Memory/Motor Control* |
| Identical | Visual short term memory |
| Reversed/Conflict | Visual short term memory and EF (Switch) |
| AB Game (total Correct) | Executive Function |
| AB Game (Perseverative Errors) | Inability to "switch", Executive Function |
| Delayed Alternation (total Correct) | Executive Function/Impulse Control |
| Delayed Alternation (total Errors) | Inability to "switch", Executive Function |
| Subject Ordered Pointing | Executive Function/Memory |

[a]Differntial Ability Scales, 2nd Edition, (DAS-II) (Elliot, 2007).

[b]Leiter International Performance Scale, Third Edition (Roid et al., 2013).

[c]NEPSY (Korkman et al., 1998).

[d]NEPSY II (Korkman et al., 2007).

Other measures were adapted for use in preschool children in Ukraine from non-standardized neuropsychological tests.

**Table 2.**

Demographic characteristics of women at recruitment ($N = 291$).

| Characteristic | No Alcohol Exposure ($n = 178$) | Alcohol Exposure ($n = 113$) | Statistic | $p$-value |
|---|---|---|---|---|
| Maternal Age Years: *M (SD)* | 26.62 (4.30) | 26.95 (6.10) | $F_{(1,290)} = 0.280$ | .597, ns |
| Paternal Age Years: *M (SD)* | 28.76 (4.94) | 30.99 (7.61) | $F_{(1,289)} = 9.19$ | .003 |
| SES *M (SD)* | 41.37(11.67) | 34.96 (11.21) | $F_{(1,286)} = 21.30$ | .000 |
| Parity *M (SD)* | 0.66 (0.84) | 0.71 (0.98) | $F_{(1,290)} = 0.64$ | .638, ns |
| Alcohol (oz) Prerecognition Daily *M (SD)* | 0.002 (0.014) | 0.693 (0.781) | $F_{(1,289)} = 139.13$ | .000 |
| Alcohol (oz) 1st Trimester Daily *M (SD)* | 0.000 (0.006) | 0.637 (1.08) | $F_{(1,290)} = 61.91$ | .000 |
| Smoking pregnancy (%) | 3.4% | 35.8% | $X^2_{(1)} = 52.72$ | .000 |
| Maternal Audit Score *M (SD)* ($N = 285$) | 1.53 (2.18) | 6.79 (4.49) | $F_{(1,284)} = 174.49$ | .000 |
| Maternal TWEAK Score *M (SD)* ($N = 274$) | 0.04 (0.28) | 2.24 (1.53) | $F_{(1,269)} = 322.76$ | .000 |

**Table 3.**

Child characteristics as a function of prenatal alcohol exposure. ($N$ = 291).

| Characteristic | No Alcohol Exposure ($n$ = 178) | Alcohol Exposure ($n$ = 113) | Statistic | p-value |
|---|---|---|---|---|
| Age of Child/yr *M (SD)* at Follow-Up | 3.93 (0.31) | 4.02 (0.42) | $F_{(1,282)} = 4.46$ | .036 |
| Sex of child: % Male | 54.5% | 48.7% | $X^2_{(1)} = 0.33$ | ns |
| Gestational Age: wks *M (SD)* | 39.64 (1.34) | 39.12 (1.93) | $F_{(1,290)} = 7.15$ | $p < .008$ |
| Birthweight *M (SD)* | 3398.14 (438.42) | 3225.29 (560.67) | $F_{(1,290)} = 8.62$ | $p < .004$ |
| Birth Length (cm) *M (SD)* | 52.02 (2.06) | 51.30 (2.98) | $F_{(1,290)} = 5.86$ | $p < .016$ |
| Birth Head Circumference (cm) *M (SD)* | 34.62 (1.51) | 34.21 (1.77) | $F_{(1,290)} = 4.48$ | $p = .035$ |

**Table 4.**

Child outcomes: scores on differential ability scales[a], nonverbal scales as a function of alcohol exposure: (*N* = 288).

| Characteristic | No Alcohol Exposure (*n* = 175) | Alcohol Exposure (*n* = 113) | Statistic | *p*-value |
|---|---|---|---|---|
| DAS-II[a] | (*n* = 174) | (*n* = 112) | $F_{(1,285)} = 13.69$ | .000 |
| Pattern Construction T Score *M (SD)* (*n* = 286) | 56.87 (8.66) | 52.61 (10.72) | | |
| DAS-II[a] | (*n* = 174) | (*n* = 109) | $F_{(1,281)} = 1.16$ | .282, ns |
| Matrices T Score *M (SD)* (*n* = 282) | 45.07 (10.29) | 43.66 (11.31) | | |
| DAS-II[a] | (*n* = 175) | (*n* = 112) | $F_{(1,286)} = 6.32$ | .012 |
| Picture Similarities T Score *M (SD)* (*n* = 287) | 48.97 (9.34) | 45.74(12.14) | | |
| DAS-II[a] | (*n* = 173) | (*n* = 108) | $F_{(1,279)} = 3.10$ | .079, ns |
| Copying T Score *M (SD)* (*n* = 281) | 51.90 (7.77) | 50.12 (8.96) | | |
| DAS-II[a] | (*n* = 175) | (*n* = 112) | $F_{(1,285)} = 2.69$ | .10 |
| Nonverbal Reasoning Standard Score *M (SD)* | 94.17 (14.57) | 91.08 (16.93) | | |
| DAS-II[a] | (*n* = 119) | (*n* = 74) | $F_{(1,191)} = 7.46$ | .007 |
| Spatial Standard Score *M (SD)* (*n* = 193) | 106.73 (12.14) | 101.24 (15.61) | | |
| DAS-II[a] | (*n* = 173) | (*n* = 108) | $F_{(1,279)} = 6.29$ | .013 |
| Nonverbal Composite Standard Score *M (SD)* (*n* = 281) | 100.93 (13.19) | 96.44 (16.67) | | |

[a]Differential Ability Scales, 2nd Edition (Elliot, 2007).

Individual ANOVA rather than Multivariate analysis was used to avoid subject loss. Some children were not able to complete individual subtests. The DAS-II Spatial Standard score cannot be computed on the Lower Preschool Form of the test.

**Table 5.**

Outcomes for measures of sustained attention (Leiter[a] and NEPSY[b] visual attention sustained scores).

| | No Alcohol Exposure | Alcohol Exposure | Statistic | *p*-Value |
|---|---|---|---|---|
| Leiter Attention Sustained Scaled Score *M (SD)* | (*n* = 168)<br>10.68 (2.47) | (*n* = 109)<br>10.14 (2.43) | $F_{(1,275)} = 3.22$ | .074 |
| Leiter Attention Sustained Total Correct Scaled Score *M (SD)* | 11.01 (2.6) | 10.53 (2.69) | $F_{(1,275)} = 2.18$ | .141, ns |
| Leiter Attention Sustained Errors Scaled Score *M (SD)* | 8.96 (2.79) | 9.12 (2.81) | $F_{(1,275)} = 0.21$ | .663, ns |
| NEPSY Visual Attention Scaled Score *M (SD)* (*n* = 273) | (*n* = 165)<br>11.47(2.43) | (*n* = 108)<br>10.98 (2.55) | $F_{(1,271)} = 2.50$ | .115, ns |

[a]Leiter International Performance Scale, Third Edition (Roid et al., 2013); Multivariate Analysis of scores (N = 277).

[b]NEPSY (Korkman et al., 1998).

**Table 6.**

Child outcomes: scores on neurobehavioral tests as a function of alcohol group status (Individual test *N*'s shown below).

| Characteristic | No Alcohol Exposure | Alcohol Exposure | Statistic | p-value |
|---|---|---|---|---|
| "Corsi Blocks"[a] Forward Total *M (SD)* | (*n* = 100) 16.71 (5.48) | (*n* = 69) 16.57 (5.56) | $F_{(1,167)}$ = .028 | .867, ns |
| "Corsi Blocks"[a] Forward Span *M (SD)* | 2.49 (1.09) | 2.49 (1.00) | $F_{(1,167)}$ = .005 | .942, ns |
| "Corsi Blocks"[a] Backward Total *M (SD)* | 3.22 (3.64) | 2.91 (3.27) | $F_{(1,167)}$ = .315 | .575, ns |
| "Corsi Blocks"[a] Backward Span *M (SD)* | 1.03 (1.07) | 1.02 (1.03) | $F_{(1,167)}$ = .009 | .924, ns |
| Draw-A-Line[b] Slowly, 1st line *M (SD)* | (*n* = 169) 10.04 (7.14) | (*n* = 109) 10.52 (7.33) | $F_{(1,276)}$ = .303 | .583, ns |
| Draw-A-Line[b] Slowly, 2nd line *M (SD)* | 10.54 (6.77) | 10.97 (6.89) | $F_{(1,276)}$ = 2.68 | .605, ns |
| NEPSY Statue Scaled Score *M (SD)* (*N* = 226) | (*n* = 138) 10.71 (2.58) | (*n* = 88) 10.01 (2.79) | $F_{(1,224)}$ = 3.69 | .056 |
| Hand Game Correct *M (SD)* (*N* = 259) | (*n* = 158) 13.23 (3.13) | (*n* = 101) 12.80 (3.63) | $F_{(1,257)}$ = 103 | .310, ns |
| Hand Game Reversed Correct *M (SD)* | 9.93 (6.07) | 9.06 (6.32) | $F_{(1,257)}$ = 1.23 | .269, ns |
| AB Game[c] *M (SD)* (N = 284) | (*n* = 174) 8.33 (1.98) | (*n* = 111) 8.19 (2.12) | $F_{(1,283)}$ = .341 | .560, ns |
| Total Correct | | | | |
| Consecutive Correct | 6.98 (2.97) | 6.54 (2.94) | $F_{(1,283)}$ = 148 | .226, ns |
| Perseveration Errors | 0.59 (1.37) | 0.64 (1.61) | $F_{(1,283)}$ = .071 | .790, ns |
| Longest run of Errors | 0.55 (1.27) | 0.55 (1.41) | $F_{(1,283)}$ = .000 | .982, ns |
| Delayed Alternation[d] *M (SD)* (*N* = 274) | (*n* = 169) 12.24 (3.88) | (*n* = 106) 11.82 (4.46) | $F_{(1,273)}$ = .687 | .408, ns |
| Total Correct | | | | |
| Consecutive Correct | 6.21 (4.69) | 6.21 (5.47) | $F_{(1,273)}$ = .000 | .993, ns |
| Total Errors | 3.14 (3.16) | 3.79 (3.73) | $F_{(1,273)}$ = 2.45 | .12 |
| Longest run of Errors[5] | 1.88 (2.18) | 2.24 (2.51) | $F_{(1,273)}$ = 1.34 | .248, ns |
| Subject Ordered Pointing (SOP)[e] *M (SD)* Total Correct Trials | (*n* = 168) 2.82 (1.86) | (*n* = 108) 2.63 (2.12) | $F_{(1,274)}$ = .589 | .444, ns |
| Highest Number | 4.51 (2.29) | 4.19 (2.69) | $F_{(1,270)}$ = 1.12 | .291, ns |
| NEPSY Speeded Naming Scaled Score *M (SD)* (*N* = 214) | (*n* = 132) 9.92 (2.62) | (*n* = 82) 8.18 (2.88) | $F_{(1,212)}$ = 20.72 | .000 |

[a]Multivariate Analysis of Variance for all "Corsi Block" items, (*N* = 169).

[b]Multivariate Analysis used for Draw-A-Line Slowly items (*N* = 278).

[c]Multivariate Analysis of Variance for all AB Game items, (*N* = 284).

[d]Multivariate Analysis of Variance for all Delayed Alternation items, (*N* = 274).

[e]Multivariate Analysis of Variance for SOP, (*N* = 275).

**Table 7.**

Generalized linear regression outcomes[a] for measures included in preschool battery: ounces of absolute alcohol, pre-recognition and mid-gestation.

| Test Measure | Beta (β) | | Wald $X^2$ | | | Significance Level | | VIF (Highest)[e] | |
|---|---|---|---|---|---|---|---|---|---|
| **Period of Pregnancy Exposure** | **Pre** | **Mid** | **Pre** | **Mid** | **df** | **Pre** | **Mid** | **Pre** | **Mid** |
| DAS-II[b] Nonverbal Reasoning Standard Score | −2.50 | −7.75 | 2.87 | 4.79 | 1 | .09 | *.029* | 1.16 | 1.16 |
| DAS-II Nonverbal Composite | −3.05 | −8.09 | 4.54 | 6.37 | 1 | *.033* | *.012* | 1.18 | 1.17 |
| Matrices | −.957 | −7.17 | 0.80 | 9.48 | 1 | .370 | *.002* | 1.04 | 1.00 |
| Picture Similarities | −2.34 | −3.67 | 4.88 | 2.36 | 1 | *.027* | .124 | 1.18 | 1.22 |
| DAS-II Spatial Composite | −2.84 | −6.93 | 3.87 | 5.11 | 1 | *.049* | *.024* | 1.08 | 1.01 |
| Pattern Construction | −1.73 | −3.83 | 3.36 | 3.27 | 1 | .067 | .07 | 1.16 | 1.15 |
| Copying | −2.03 | −3.13 | 6.02 | 2.65 | 1 | *.014* | .104 | 1.04 | 1.00 |
| “Corsi Block” Task Forward | −1.51 | −3.13 | 5.634 | 4.71 | 1 | *.018* | *.03* | 1.46 | 1.19 |
| “Corsi Block” Task Backward | −.117 | .308 | .127 | .178 | 1 | .722 | .673 | 1.49 | 1.18 |
| Leiter[c] Attention Sustained Subtest | −.599 | −.651 | 5.93 | 1.37 | 1 | *.015* | .242 | 1.17 | 1.12 |
| NEPSY[d] Visual Attention Subtest | −.082 | −.636 | .123 | .662 | 1 | .726 | .416 | 1.06 | 1.04 |
| NEPSY Statue | .030 | −668 | .007 | .227 | 1 | .933 | .562 | 1.01 | 1.03 |
| NEPSY Speeded Naming | −.246 | −3.18 | .150 | 1.91 | 1 | .698 | .167 | 1.14 | 1.13 |
| Draw-A-Line Slowly | −.987 | −1.05 | 2.25 | .399 | 1 | .133 | .528 | 1.04 | 1.00 |
| Hand Game Identical | −1.24 | −.633 | 14.68 | .682 | 1 | *.000* | .409 | 1.00 | 1.03 |
| Hand Game Reversed/Conflict | −2.06 | −4.06 | 11.41 | 8.84 | 1 | *.001* | *.003* | 1.17 | 1.19 |
| AB Game (total Correct) | −.484 | −.864 | 5.11 | 3.32 | 1 | *.024* | .068 | 1.05 | 1.08 |
| AB Game (Perseverative Errors) | .225 | .078 | 2.29 | .052 | 1 | .130 | .820 | 1.06 | 1.03 |
| Delayed Alternation (total Correct) | −.888 | −1.36 | 3.77 | 2.18 | 1 | *.052* | .140 | 1.01 | 1.03 |
| Delayed Alternation (total Errors) | .862 | .692 | 5.67 | .891 | 1 | *.017* | .345 | 1.01 | 1.03 |
| Subject Ordered Pointing | −.186 | −.376 | .934 | .757 | 1 | .334 | .384 | 1.16 | 1.18 |
| Executive Function Factor | −.334 | −.466 | 13.19 | 4.91 | 1 | *.000* | *.027* | 1.17 | 1.21 |

[a]Tested as covariates were: Testing site, smoking, maternal age, paternal age, child sex, child age, gestational age, MVM, SES, and parity. These factors were significantly correlated with either alcohol use, the outcome variable or both. Initial GLR models were calculated including alcohol exposure measure and potential covariates and only those factors that were significant at p = .10 or less were include in regression models. Only Alcohol outcomes are shown here but other information is available from the authors.

[b]Differntial Ability Scales, 2nd Edition, (DAS-II) (Elliot, 2007).

[c]Leiter reference (Roid et al., 2013).

[d]NEPSY references, (Korkman et al., 1998, 2007); Other measures were adapted for use in preschool children in Ukraine from non-standardized neuropsychological tests.

[e]The highest value for the Variance Inflation Factors (VIF) among the variables included in the regression is given here. VIF is a measure of collinearity and scores less than 10 are considered to demonstrate acceptable degree of independence among variables.