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Characteristics of the Symptoms of the Proposed ND-PAE Disorder in First Grade Children in a Community Sample

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Abstract

The proposed symptoms for Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) were evaluated in children who participated in the Collaboration on Fetal Alcohol Spectrum Disorders Prevalence study. Children “at-risk” for ND-PAE (n = 204) were contrasted to children with no prenatal alcohol exposure, alcohol-related dysmorphia or growth deficits (n = 908). Symptoms were defined based on neuropsychological testing using two diagnostic threshold levels (1.0 and 1.5 STD). Individuals at risk for ND-PAE had higher endorsement rates of the self-regulation and adaptive impairments at the 1.0 threshold and of the neurocognitive and self-regulation impairments at the 1.5 threshold. Endorsement of the disorder significantly differed at the 1.0 threshold. Receiver operating characteristic curve analysis indicated that having an IQ below 70 was not predictive of the diagnosis but modifications of the IQ criterion improved predictive validity. Discrimination validity was poor without documentation of PAE which continues to be a necessity for a diagnosis of ND-PAE.

Keywords

ND-PAE; Prenatal alcohol; Fetal alcohol; Psychiatric disorder; Children

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Conflict of interest The authors declare that they have no conflicts of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Introduction

Medical diagnoses focusing on the physical characteristics associated with prenatal alcohol exposure (PAE) have not been effective in capturing the neurobehavioral problems that are often the most serious outcomes of the exposure. Accordingly, the Diagnostic and Statistical Manual, 5th edition (DSM-5) of the American Psychiatric Association included in the Conditions for Further Study section, a disorder intended to capture the range of mental health and developmental problems associated with PAE, referred to as Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) [1]. The disorder can be diagnosed either in the presence or absence of the physical effects of PAE [i.e., a diagnosis of Fetal Alcohol Syndrome (FAS) or partial FAS (pFAS)]. It appears that alcohol-exposed individuals who do not meet full criteria for FAS are at higher risk than those who have been given a medical diagnosis of FAS/pFAS for a number of adverse life outcomes, including delinquency, school failure, and substance abuse problems [2]. Also, in a prospective cohort of individuals with PAE, those who had no alcohol-related physical effects were found to have more poorly developed adaptive life skills in adulthood [3] than those who had PAE with alcohol-related dysmorphia. The development of ND-PAE as a mental health diagnosis marks an important step in the appropriate identification and treatment of those individuals with behavioral and mental health problems associated with their PAE as recognition of the disorder may improve identification of their treatment needs [4].

Three symptom domains were proposed for ND-PAE: (1) neurocognitive, (2) self-regulation and (3) adaptive functioning. Within the neurocognitive domain are five potential symptom areas, including impairments in global intellectual functioning, executive functioning, learning, memory, or visual-spatial reasoning and within the self-regulation domain are three potential symptoms, including impairment in mood or behavioral regulation, attention deficits, or impairment in impulse control. One symptom needs to be endorsed within the neurocognitive and self-regulation domains, but the adaptive functioning domain (AF) requires two of four possible symptoms (impairments in communication, social skills, daily living skills, or motor functioning) of which endorsement of either communication or social impairments is needed (AF 2/4 criteria).

Evidence supporting the proposed symptoms used in the diagnostic formulation of ND-PAE was substantial [5], but additional taxometric research is needed for the condition to be recognized as a unique psychiatric disorder. Since the publication of the DSM-5, efforts have been made to establish the reliability and validity of the diagnosis. The interrater reliability in making the diagnosis of the disorder has been reported to be high, exceeding 0.90’s in published studies of archival clinical record reviews [6, 7]. To establish the validity of the disorder, assessments of the homogeneity of the symptoms, of the relative contribution of each of the proposed symptoms in identifying the severity of ND-PAE, and of each symptom’s capacity to differentiate those affected by PAE from typically developing children and individuals with other mental health or developmental disorders are also needed [8].

Convergent validity was evaluated in an archival study [9]. In contrasting those who met criteria for the ND-PAE diagnosis as compared to an Alcohol-Related Neurodevelopmental

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Disorder (ARND) categorization, 95% sensitivity and 75% specificity was found, and an 89.5% overall correct classification was obtained relative to ARND as defined by a designated cut-off using an ARND behavior checklist. Receiver operating characteristic curve analysis (ROC), which plots the true positive rate (sensitivity) against the false positive rate (false alarm rate or 1-specificity), resulted in an area under the curve (AUC) estimate of 90.1%, suggesting considerable convergence of these two methods of characterizing the behavioral effects of PAE.

A previous study [10] on the internal validity of ND-PAE symptoms using a small sample (n = 56) of children between the ages of 3 and 10 who were identified as having FAS or pFAS found a high degree of internal consistency among symptom endorsement. Most symptoms, with the exception of impulsiveness, contributed uniquely to the diagnostic formulation of ND-PAE. In this clinical sample, the number of endorsed ND-PAE symptoms was not related to the child's environment or placement experiences but was moderately related to the child's age, with younger children having fewer symptoms than older children. This study also found that the proposed 'two of four' criteria for adaptive symptoms was often completely redundant with endorsement of the disorder and therefore evaluated using an alternative criterion consisting of only one symptom in the adaptive functioning domain (AF 1 criterion) as an alternative approach to the diagnostic formulation. The AF 1 criterion resulted in less redundancy with the overall diagnosis endorsement than did the AF 2/4 criteria. Although the results of this study were promising, they are limited by the small sample size and the fact that the sample was a clinical sample who were enrolled in an intervention study. Further evidence was subsequently found in another clinical sample of children with an FASD [11] of adequate specificity (94.1%) but poor sensitivity (56.1%) when applying the criteria as proposed, and concerns were expressed regarding the restrictive nature of the AF 2/4 criteria.

The factorial validity of the ND-PAE symptoms was assessed in a small sample of clinical patients (n = 58) [11]. The authors concluded that ND-PAE had weak construct validity and was best explained by one principal component factor, consisting of predominantly neurocognitive and adaptive functioning domains, and three weaker factors that did not correspond to the suggested symptom domains. Only the factors consisting of learning and communication deficits differentiated those with FASD. The conclusions of this study, however, are severely limited by the small sample size and the number of identified dimensions as often these type of analyses are vulnerable to idiosyncratic features of their sample that do not generalize well [12]. Further evaluation in a larger cohort is needed to confirm these findings.

To evaluate the validity of the symptoms, additional research is needed with other individuals who have been impacted by PAE to establish the disorder's internal validity and discriminate validity with other populations. As the previous research has been done on relatively small cohorts of children seen in Fetal Alcohol Spectrum Disorders (FASD) diagnostic clinics, larger more diverse samples may further aid in our understanding of the characteristics of the symptoms associated with the disorder. The Collaboration on FASD Prevalence (CoFASP) was a large multisite consortium that focused on establishing the prevalence and characteristics of FASD among first grade children in diverse U.S.

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communities using active case ascertainment methodology [13]. Information obtained in the study included maternal alcohol consumption and other risk factors for FASD, the physical traits of children with FASD, and the neurobehavioral functioning of children with FASD, all of which were compared to children without PAE and alcohol-related dysmorphia in the same communities. These data can be used to map onto the proposed ND-PAE symptoms, enabling further investigation into the validity of the disorder and its associated symptoms. Using this cohort, individuals who were identified as being at risk for ND-PAE based on maternal drinking behavior during pregnancy or evidence of the physical characteristics of PAE were anticipated to have higher levels of endorsement of the symptoms, domains, and overall of ND-PAE diagnosis in comparison to a contrast sample with no PAE and no physical characteristics associated with PAE. In addition, the large cohort allowed for comparisons of the endorsement rates by sex. Estimates of the internal consistency of the symptoms and predictive validity of the symptoms relative to the diagnosis were also evaluated within the whole sample, by risk level, and by sex to evaluate potential biases. Finally, the characteristics of the underlying factor structure and symptom endorsement were also evaluated to assess the validity of the diagnostic symptoms.

Methods

Sample Recruitment and Selection

Description of the CoFASP Cohort—First grade children between 5 and 7 years of age were recruited from one of four U.S. sites between 2011 and 2015. At each site, approvals from local boards of education and administrators were granted and Institutional Review Board (IRB) approval was obtained by the academic institutions of the CoFASP's primary investigators (Christina D. Chambers, Phil A. May). All study related procedures were conducted in compliance with the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study. Federal Certificates of Confidentiality were also issued due to the sensitive nature of questions asked in the study. Participants were provided incentives for completing various aspects of the study and parents/caregivers were sent a summary report of their child's evaluations.

Participants underwent a tiered assessment process which is outlined in detail in a previous publication [13] to identify individuals who were impacted by PAE. Assessments were performed by study personnel who were blinded to the child's PAE history and the results of the other assessments. Participant's physical growth was measured, and they were examined for the presence or absence of the key features of FAS [14] using a standard checklist completed by a dysmorphologist or pediatric geneticist with expertise in alcohol-related dysmorphology. Neurodevelopmental testing was completed by school psychologists or trained psychometrists. Assessments were done in Spanish or English depending on the child's primary language. The tests were chosen to assess domains relevant to alcohol-related neurodevelopmental impairment, including cognition functioning, academic achievement, emotional and behavioral functioning, and adaptive skills.

A structured interview was used to assess the child's exposure to alcohol prenatally and was adapted for collecting collateral information from caregivers, relatives, and foster parents, when the biological mother was not available. The content of the interview covered the

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quantity and frequency of alcohol consumed prior to pregnancy and during each trimester with alcohol consumption reported by type of alcohol.

Children were excluded if they spoke neither English nor Spanish or were cognitively functioning at or below the moderately intellectually deficient range using standardized neurodevelopmental assessments. Children who had other diagnoses such as chromosomal anomalies, a known genetic syndrome, significant physical head trauma, or cerebral palsy were also excluded from participation.

Three sampling methods were used for the parent study. One sampling method, which was used in 2 of 8 samples, recruited a simple random sample of participants, and the other two methods used both random methods and oversampled children who may be developmentally compromised in an attempt to identify children who had an FASD. For the oversampling, children were selected if their height, weight, or occipitofrontal circumference was at or below the 25th percentile. In addition, for these two methods, children were also selected if there were developmental concerns. One method attempted to differentially select children whose teachers referred them or who had repeated the first grade, and the other differentially selected children based on the child repeating first grade or on parents' responses to the Parents Evaluation of Developmental Status (PEDS) [15]. The PEDS was developed for use in pediatricians' offices to flag children up to age eight years who require more comprehensive professional evaluations. Those children identified with at least two areas of "significant concern" (e.g., Cognition, Receptive and Expressive Language, Fine Motor, Gross Motor, School) were selected.

A total of 6639 children were screened, with data available on 3310 participants. For 1717 participants, data relevant to the ND-PAE symptoms were collected.

ND-PAE Risk and No ND-PAE Risk Sample—Based on the DSM-5 criteria, participants were defined as *at risk* for ND-PAE if their mothers reported drinking more than minimal amounts of alcohol during pregnancy, which was defined in the DSM-5 as an amount greater than 13 drinks per month or more than 2 drinks on any one occasion [1]. A positive history of PAE was also assumed if the child had a cluster of physical effects associated with PAE, including a history of growth delays as defined as less than or equal to the 10th percentile in body length or body weight at the time of enrollment in the study *and* positive indicators of alcohol-related dysmorphology. The latter was defined as having a minimum of 2 of 3 of the hallmark features of FAS (smooth philtrum, thin vermilion border of the upper lip, or palpebral fissure length ≤ 10th percentile) [14]. The comparison sample had none of the above-mentioned alcohol-related dysmorphia, had growth above the 10th percentile, and had mothers who denied any alcohol consumption in pregnancy. The comparison sample does not represent a contrast to typically developing children but rather a sample with a high base rate of mild learning or neurobehavioral impairment as a result of the original cohort's selection processes. From the 1717 potential participants, a total of 204 were identified as being at risk for ND-PAE (ND-PAE Risk) while 904 had no evidence of PAE (No ND-PAE Risk). The remaining 609 participants were excluded from this analysis as they did not meet criteria for either group.

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Assessments

Symptom Mapping—Neurobehavioral measures from standardized assessments collected in the CoFASP sample were mapped on to specific symptoms so that each symptom was characterized as being present or absent within each individual. The first symptom criterion established a clear cut-off of 2 standard deviation units on any measure of intellectual functioning, which corresponds to a standard score of 70 or below on most tests of intelligence, but the remaining symptoms were not as clearly defined. Two thresholds (1.0 and 1.5 standard deviation units (SD)) of clinical significance were analyzed separately as was done in a previous study of the internal validity of the ND-PAE symptoms [10], and the model using the proposed adaptive criteria (AF 2/4) and the model using only one adaptive symptom (AF 1) were contrasted at each of the thresholds, resulting in evaluation of four models for making the diagnosis.

Neurocognitive Domain Measures—The *Differential Ability Scales, 2nd edition* (DAS-II) [16], a nationally standardized measure of children's intellectual functioning, was administered to assess impairments in global intellectual functioning. Performances on specific processing tasks were aggregated into cluster scores of the child's verbal, nonverbal, and spatial cognitive skills, and then an index of the child's overall intellectual functioning (the General Cognitive Ability score, GCA) was generated. Scores of less than 70 were considered positive for endorsing impairment in global intellectual functioning as per the criteria specified in the DSM-5 [1]. To assess impairment in executive functioning skills, two subtests (*Inhibition* and *Speeded Naming*) from the *NEPSY-II* [17] were used. The *Inhibition* subtest assessed the child's ability to inhibit automatic responses in favor of novel responses and to switch between response types. *Speeded Naming* assessed the child's cognitive control needed to name arrays of colors, shapes, or letters and numbers quickly. To assess learning impairments, the *School Readiness Composite* (SRC) of the *Bracken Early Concept Scales Revised* [18] was used to assess overall academic learning, and three additional subtests from this test *(Direction/Position, Quantity, and Time/Sequence)* that are not part of the SRC were also used. In addition, the School Competence scale from the Child Behavior Checklist (CBCL) [19] and the Academic Performance and the Learning scales from the Teacher Report Form (TRF) were also used to assess learning impairments. The CBCL and the TRF are questionnaires designed to assess the child's emotional and behavioral functioning as well as the child's competence in their home life, school environment, and social functioning. The questionnaires include problem behaviors that are rated as "not true," "sometimes true," or "very true" by the reporter. Impairment in visual-spatial reasoning was assessed using the Nonverbal, Spatial and Special Nonverbal Composite scores from the DAS-II. Impairments in memory functioning were not assessed as part of the CoFASP neurodevelopmental battery in all the regions sampled and therefore could not be evaluated as part of this analysis.

Self-regulation Domain Measures—To assess impairment of mood and behavioral regulation symptoms, the Total Problems and the DSM Affective Problems scales from the CBCL and the TRF were used. Impairment in attention skills was assessed using the Attention and DSM ADHD scales from the CBCL and TRF. Finally, impulse control was assessed using the Rule Breaking subscale from the CBCL and TRF.

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Adaptive Functioning—To assess adaptive functioning, the Vineland Adaptive Behavior Scale, (VABS) [20] was used. The VABS allows parents to report adaptive functioning via a structured interview with modules in the following areas: communication, daily living skills, socialization, and motor skills. To assess deficits in adaptive communication, the VABS Communication score was used. To assess social impairment, the VABS Socialization score was used as well as the CBCL and TRF Social Problems scale. Impairment in independent living skills was assessed using the VABS Daily Living Skills and the TRF Adaptive Functioning score. Finally, adaptive motor functioning impairment was assessed using the VABS Motor Domain score, the Developmental Test of Visual Motor Integration (VMI) [21], which assesses graphomotor skills, and the NEPSY II Visual Motor Precision Combined score, which assesses graphomotor speed and accuracy.

Statistical Analysis

Rates of endorsement for symptoms, the three domains (neurocognitive, self-regulation, and adaptive functioning), and ND-PAE disorder were computed for the four methods of classification evaluated and were examined for sex effects. Endorsement of each of the symptoms was then related to the three domains and to the endorsement of the disorder. Cronbach's alpha, which is an index of internal consistency of symptoms, was computed. Principal components analysis was done to assess the factor structure of the symptoms using the various threshold levels proposed for making the diagnosis. Finally, receiver operating characteristic curves (ROC) were used to assess the contribution of each item and domain in the discrimination of the ND-PAE disorder within those classified as at risk or not.

Results

Sample Characteristics

Table 1 displays the characteristics of the sample. The participants were on average 7 years of age and predominantly Caucasian. Approximately one third were of Hispanic descent. The overall intellectual functioning, as assessed by the DAS-II, of both groups fell in the Average range [ND-PAE Risk: 99.9 (12.6) and No ND-PAE Risk: 101.3 (12.2)] and did not differ by group status. Significant differences were found in marital status with the ND-PAE Risk group having fewer parents who reported being married than did the No ND-PAE Risk group. In accordance with the selection criteria, the ND-PAE Risk group were more likely to report more than minimal levels of PAE and consisted of children who were more likely to have alcohol-related dysmorphology and were smaller in height, weight, and head circumference.

Endorsement Rates and Symptom Characteristics for Symptoms, Domains, and ND-PAE Disorder by Risk Status

Table 2 contains the percentage of participants who were endorsed for each of the criteria by cut off level. Using the AF 2/4 criteria, endorsement of the disorder for those identified as at risk occurred in 5.9% using the 1.5 SD and 24.5% using the 1.0 SD symptom threshold levels. Using the AF 1 criterion, endorsement of the disorder in the ND-PAE Risk group occurred in 16.2% using the 1.5 SD and 44.6% using the 1.0 SD cut-offs. Regardless of threshold level or endorsement model, those in the ND-PAE Risk group had higher rates of

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endorsement for the disorder, but only the 1.0 threshold levels were statistically significant from the No ND-PAE Risk group (44.6% vs. 28.7% for AF 1, $\chi^2 = 19.47$, $p < 0.0001$; 24.5% vs. 12.9% for AF 2/4, $\chi^2 = 17.70$, $p < 0.001$).

Relative to sex (see Supplementary Tables 1a and 1b), endorsement for overall diagnosis was higher for males at both cut-off levels when using the modified AF1 criteria (1.5 SD: 23.6% vs. 13.5%, $\chi^2 = 6.963$, $p < 0.008$; 1.0 SD: 52.7 vs 32.4, $\chi^2 = 15.87$, $p < 0.0001$) and was higher in the 1.0 cut-off level for the AF 2/4 model (32.7% vs 16.7%, $\chi^2 = 14.28$, $p < 0.0001$). Only a trend was found for higher endorsement for ND-PAE Risk males relative to No ND-PAE Risk males in the 1.5 cut-off level (9.1% vs 4.6%, $\chi^2 = 5.13$, $p < 0.061$). For females, higher rates of endorsement for overall ND-PAE diagnosis were obtained on the modified AF1 ND-PAE diagnosis (35.1% vs 24.9%, $\chi^2 = 4.101$, $p < 0.043$) but only a trend was found in the 2/4 AF model at the 1.0 cut-off level (14.9% vs.8.9%, $\chi^2 = 3.11$, $p < 0.078$).

Relative to specific symptoms, the neurocognitive domain symptoms only differed in the area of executive functioning at the 1.5 SD cut-off level and learning at the 1.0 SD cut-off level, but this is not surprising given the differential recruitment of children who were identified by either their teachers or parents as having developmental concerns. Relative to sex, symptoms of the neurocognitive domain only had group differences in males on the symptom of executive functioning (EF) deficits at the 1.5 SD cut-off level and learning impairment at the 1.0 SD cut-off level where those with ND-PAE Risk had higher rates of endorsement (EF: 1.5 SD: 44.5% vs 31.9%, $\chi^2 = 6.24$, $p < 0.013$; Learning: 1.0 SD: 63.6% vs 52.0%, $\chi^2 = 4.88$, $p < 0.027$). No group differences were found in the neurocognitive symptoms of females at either cut-off level. Endorsement of impairment in global intellectual functioning was low across the entire sample at a rate of 0% in the ND-PAE Risk sample and 1.0% of the No ND-PAE Risk sample, which is not above the rate expected from sampling from a normal distribution of intelligence scores (2%). Impairment in visual-spatial reasoning was also relatively low (4.9% at the 1.5 SD cut-off and 17.1% at the 1.0 SD cut-off) within the ND-PAE Risk sample and did not deviate from expectations based on sampling within a normal distribution of ability level (7% at a 1.5 SD cut-off level and 16% at the 1.0 SD cut-off level).

All of the self-regulation symptoms, with the exception of impulsiveness at the 1.5 cut-off level and the domain endorsement, varied by group status for both cutoff levels (mood/behavior regulation: 1.0 SD: 49.0% vs 35.4%, $\chi^2 = 13.084$, $p < 0.0001$; 1.5 SD: 28.9% vs. 17.3%, ($\chi^2 = 14.397$, $p < 0.0001$); attention: (1.0 SD: 49.5% vs 34.0%, $\chi^2 = 17.240$, $p < 0.0001$; 1.5 SD: 30.9% vs. 20.2%, ($\chi^2 = 11.128$, $p < 0.001$); impulsiveness: (1.0 SD: 30.9% vs 19.7%, $\chi^2 = 12.262$, $p < 0.0001$; 1.5 SD: 14.7% vs. 10.0%, $\chi^2 = 3.769$, $p < 0.052$); self-regulation domain: (1.0 SD: 58.3% vs. 48.1%, $\chi^2 = 7.013$, $p < 0.0001$; 1.5 SD: 41.2% vs. 28.1%, $\chi^2 = 13.474$, $p < 0.0001$). ND-PAE Risk males had significantly higher rates of endorsement for all self-regulation symptoms at both cut-off levels (mood/behavior regulation: (1.0 SD: 58.25% vs 38.9%, ($\chi^2 = 13.48$, $p < 0.0001$; 1.5 SD: 39.1% vs. 20.9%, ($\chi^2 = 15.88$, $p < 0.0001$); attention: (1.0 SD: 56.4% vs 37.0%, ($\chi^2 = 13.853$, $p < 0.0001$; 1.5 SD: 35.5% vs. 23.7%, ($\chi^2 = 6.32$, $p < 0.012$); impulsiveness: (1.0 SD: 40.0% vs 23.0%, ($\chi^2 = 13.163$, $p < 0.0001$; 1.5 SD: 18.2% vs. 10.0%, $\chi^2 = 5.762$, $p < 0.016$) as well as

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endorsement for the overall domain (1.0 SD: 67.3% vs. 52.8%, $\chi^2 = 7.51$, $p < 0.0001$; 1.5 SD: 49.1% vs. 32.5%, $\chi^2 = 10.692$, $p < 0.001$) but females only differed on the attention impairment at both cut-off values (1.0 SD: 41.5% vs 31.0%, $\chi^2 = 3.91$, $p < 0.048$; 1.5 SD: 25.5% vs. 16.5%, $\chi^2 = 4.31$, $p < 0.038$).

For the adaptive behavioral symptoms, group differences were found on adaptive social impairment at the 1.0 SD level cut-off (29.4% vs 17.2%; $\chi^2 = 16.00$, $p < 0.0001$) and in both cut-off values in motor functioning (1.0 SD: 33.3% vs 18.8, $\chi^2 = 20.84\%$, $p < 0.0001$); 1.5 SD: 9.8% vs 4.6%, ($\chi^2 = 8.48$, $p < 0.004$). Overall adaptive domain endorsement varied as a function of group status at both cut-off values for the AF 1 model (1.0 SD: 64.2% vs 49.9%, ($\chi^2 = 13.61$, $p < 0.0001$); 1.5 SD: 30.9% vs 23.8%, ($\chi^2 = 4.46$, $p < 0.035$) but only in the 1.0 SD cut-off level for the AF 2/4 model (27.0% vs 16.3%, ($\chi^2 = 12.74$, $p < 0.0001$). Impairment in adaptive communication deficits was also not endorsed at a rate higher than expected relative to chance (6.4% at the 1.5 SD cut-off level and 14.2% at the 1.0 SD cut-off level). Males did not differ in adaptive daily living skills but had higher rates of endorsement on each of the other three adaptive symptoms in all areas but Social Impairment at the 1.5 SD cut-off level (communication:1.0 SD: (21.8% vs 13.8%; $\chi^2 = 4.36$, $p < 0.037$); 1.5 SD: (10.9% vs 5.1%; $\chi^2 = 5.22$, $p < 0.022$); social: 1.0 SD: 35.5% vs. 19.6%, $\chi^2 = 12.80$, $p < 0.0001$; motor: (1.0 SD: 40.0% vs 20.7%, $\chi^2 = 18.02$, $p < 0.0001$); 1.5 SD: 14.5% vs 5.4%, ($\chi^2 = 10.99$, $p < 0.001$), and the overall adaptive domain (AF 1 model: (1.0 SD: 69.1% vs 53.9%, ($\chi^2 = 8.34$, $p < 0.004$); 1.5 SD: 38.2% vs 27.2%, ($\chi^2 = 5.13$, $p < 0.024$); AF 2/4 model: 1.0 SD: 36.4% vs 21.1%, $\chi^2 = 11.347$, $p < 0.001$). Females only differed in endorsement on adaptive motor impairment with higher rates in the ND-PAE Risk group in contrast to the No ND-PAE Risk group in the 1.0 cut-off model (25.5% vs 16.9%, $\chi^2 = 3.83$, $p < 0.050$) and in the overall endorsement of AF in the AF1 model at the 1.0 cut-off level (58.5% vs. 45.9%, $\chi^2 = 4.97$, $p < 0.026$).

Internal Consistency by Risk Status and Sex

Using the entire sample, the overall internal consistency of symptom endorsement resulted in a Cronbach's alpha of 0.72 for the cut-off value of 1.5 SD and 0.76 for the cut-off value of 1.0 SD. Rates were comparable across sexes with rates at the 1.0 SD cut-off level being 0.76 for males and 0.73 for females and at the 1.5 SD cut-off level, being 0.73 for males and 0.70 for females. Relative to group status, the No ND-PAE Risk group had rates of 0.74 at the 1.0 SD level and 0.73 at the 1.5 SD level and ND-PAE risk group had rates of 0.79 at the 1.0 SD threshold and 0.70 at the 1.5 SD threshold. These results suggest a fairly uniform latent trait of neurodevelopmental compromise across the entire group, sex, and ND-PAE risk status.

Principal Component Analysis (PCA) of Symptoms

Principal component analysis (PCA) was done on the 11 symptoms at each of the cut-off levels. A Promax rotation was performed on the factors as this rotation estimates underlying factor structures while allowing for correlation between factors, which is to be expected with these symptoms. Using the entire sample (n = 1112), the 11 symptoms had sufficient redundancy to be described by a few factors (1.0 STD: Kaiser–Meyer–Olkin Measure of Sampling Adequacy (KMO) = 0.810, Bartlett's Test of Sphericity χ^2 (55) = 2530.045, $p < 0.0001$; 1.5 STD: KMO = 0.795, Bartlett's Test of Sphericity χ^2 (55) = 2278.216, p

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< 0.0001). For each cut-off level, a two factor solution was derived with factors being correlated (1.0 STD: r = 0.323; 1.5 STD: r = 0.304). Factor one had eigenvalues of 3.547, accounting 32.2% of the variance, at the 1.0 cut-off level and 3.336, accounting for 30.3% of the variance, at the 1.5 cut-off level. Factor 2 eigenvalues were 1.619, accounting for 14.7% of the variance, at the 1.0 cut-off level and 1.654, accounting for 15.0% of the variance, at the 1.5 cut-off level. At both cut-off levels, Factor 1 loaded highly (< 0.500) on all self-regulation symptoms, adaptive social skills, and adaptive independent living skills. For Factor 2, both models included overall IQ, visual-spatial functioning, adaptive communication and adaptive motor skills. In the 1.0 cut-off threshold, learning impairment was above the 0.500 threshold but it was just below that in the 1.5 cut-off level (0.485).

Receiver Operating Characteristic (ROC) Curve Analysis

ROC was used to analyze the predictive accuracy of symptoms of ND-PAE relative to the diagnosis. ROC involves graphically representing the discriminatory power of the variables to predict endorsement of the disorder by determining the AUC associated with each of the 11 symptom curves. Values range between 0 and 1 with chance level of prediction at 0.5. Table 3 has the AUC values for each symptom. Having an IQ below 70 was not a unique contributor to the diagnosis in any of the models. Relative to the whole sample, the remaining symptoms contributed significantly to the diagnosis. Within the 1.0 SD level of endorsement, each of the remaining symptoms also significantly contributed regardless of the model used to formulate the diagnosis when looking across the entire sample with the exception of visual-spatial impairment. The contribution of the visual spatial deficits was no longer significant in the ND-PAE risk group at both cut-off levels and was not predictive at the 1.5 SD level cut-off level in the AF 1 model for the No ND-PAE Risk group. Executive functioning deficits were not contributing to the diagnosis in the ND-PAE Risk group using the AF 2/4 criteria at the 1.5 SD level of symptom severity. Adaptive motor skills deficits were not significant the ND-PAE Risk group for both the AF 1 and AF 2/4 models of diagnosis at the 1.5 SD cut-off level.

ROC analysis of domain endorsement (see Table 4) indicated good (0.80–0.90) to excellent prediction (> 0.90) from the self-regulation and adaptive functioning domains but poor (< 0.70) prediction for the neurocognitive impairment domain in the 1.0 SD level and good prediction at the 1.5 SD level, reflecting a lack of predictive utility for the neurocognitive domain within the sample at the lower threshold.

ROC analysis of domain prediction to ND-PAE risk status resulted in poor prediction for all four models evaluated. For the 1.5 SD threshold level, AUC values were as follows: neurocognitive 0.545 ($p < 0.046$), self-regulation 0.565 ($p < 0.003$), AF 2/4 adaptive 0.512 (ns) and AF 1 adaptive 0.535 (ns). For the 1.0 SD threshold, AUC values were as follows: neurocognitive 0.532 (ns), self-regulation 0.551 ($p < 0.022$), AF 2/4 adaptive 0.553 ($p < 0.017$), and AF 1 0.571 ($p < 0.001$).

Modification of the Threshold for IQ

Based on the results of the study, the IQ variable was recoded so that endorsement of the symptom was based on given thresholds, 1.0 and 1.5 SD, which were used for the other

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variables. At the 1.0 SD level, 14.6% of those in the ND-Risk group received endorsement as compared to 9.4% of the No ND-PAE Risk group ($\chi^2 = 4.436$, $p < 0.035$). At the 1.5 SD level, 4.9% of the ND-PAE Risk group were endorsed as compared to 3.3% of the No ND-PAE Risk group (ns). The internal consistency of the symptoms of the whole sample was 0.77 for the 1.0 SD level and 0.74 for the 1.5 SD level. AUC values for the prediction of the diagnosis for the modified definition of global impairment were significant for each model at both cut-off levels (1.0 SD, AF 1: 0.578, $p < 0.0001$; AF 2/4: 0.627, $p < 0.0001$ and 1.5 SD, AF 1: 0.555, $p < 0.047$; AF 2/4: 0.675, $p < 0.0001$), reflecting improved predictive validity by lowering the threshold needed for symptom endorsement of intellectual impairment.

Discussion

The study examined the validity of the symptoms for the newly proposed ND-PAE, a mental health disorder diagnosis developed to capture the neurobehavioral sequalae associated with PAE. The sample used in the current study was considerably larger than the previous validity studies conducted with clinic samples [9–11]. It was drawn from first grade children who were deemed at risk for ND-PAE based on their mother's report of her drinking during pregnancy and/or based on their physical characteristics but who had not been defined as having a neurobehavioral or medical disorder, and therefore reflected the less affected end of the spectrum of neurobehavioral impact. The larger community sample used in this study afforded an opportunity to evaluate its discriminant validity relative to a contrast group that had a high base rate of mild neurobehavioral impairment. Two criteria levels for symptoms, 1.5 and 1.0 SD, were evaluated and the impact of using one symptom from the adaptive functioning domain or the recommended AF 2/4 criteria was also evaluated.

The rate of endorsement of symptoms for those identified as at risk for ND-PAE in this community sample was dramatically less than in the previous studies of clinically-referred children diagnosed with FAS/pFAS [10, 11]. For overall endorsement using the AF 1 criterion at both cut-off levels, over 80% of a clinical sample of children with an FASD met criteria for ND-PAE [10], while in the current sample only 16.2% met criteria at the higher threshold level and 44.6% at the lower threshold level. The comparison is equally dramatic using the AF 2/4 criteria. The differential rate of endorsement is not surprising in that the individuals in this sample had not been referred for mental health care, so the degree of symptomatology would not be expected to be as high. Despite sampling from the lower end of neurobehavioral impact, the internal consistency of the symptom endorsement in this study was in the acceptable range (0.70–0.80) regardless of the cut-off level used and was comparable to that seen in previous clinical studies [10, 11].

The rate of endorsement of specific ND-PAE symptoms (i.e. general cognitive deficits, visual-spatial deficits, and adaptive communication deficits) did not exceed chance levels in this at-risk sample, which is more problematic as one would expect a higher rate of occurrence based on the PAE history of the sample if the proposed symptoms are a cohesive index of alcohol-related neurodevelopmental impairment. Although one may posit that the low rate of endorsement is simply an artifact of the sample who were recruited as part of an epidemiological study rather than from a clinic where care had been sought for the child's

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neurobehavioral problems, this explanation is not adequate. Both this study and the previous study on the internal validity of the symptoms [10] indicated that intellectual impairment was not endorsed at comparable rates to the other areas of impairment within the respective samples.

As the average level of intelligence often reported for individuals with a history of PAE is typically in the borderline range [22], a different threshold value (i.e. 1.5 or 1.0 SD) was evaluated to determine if this change would improve the rate of endorsement of this symptom among those affected by PAE and the cohesion of this symptom with other ND-PAE symptoms. At the lower threshold level, group differences were found in rates of endorsement of the global cognitive impairment symptom relative to ND-PAE risk status with those in the ND-PAE Risk group having higher rates of endorsement than those in the No ND-PAE Risk group. Minimal improvements were found in the internal consistency of the symptoms after the modifications for both cut-off levels but the revised symptom endorsement was able to predict uniquely to the ND-PAE diagnosis at each level for both models (AF 1 and AF 2/4) evaluated, suggesting that the proposed criterion used for endorsing intellectual impairment is too restrictive and should be modified to improve the cohesiveness of the symptoms. Given that those who have intellectual impairment at a level of 2 SD units below the population mean and associated adaptive behavioral deficits would meet criteria for one of the existing DSM-5 codes for intellectual deficiency [23], its inclusion as a symptom in the ND-PAE diagnostic formulation seems unnecessary and therefore, should be modified or removed to improve the internal consistency and cohesion of symptoms related to this disorder.

In the previous study [10] endorsement of visual-spatial deficits and adaptive communication deficits exceeded chance levels and uniquely predicted to making the ND-PAE diagnosis. The previous study had multiple measures of visual spatial functioning, and it is possible that the differences in the results of the two studies may be simply that having more methods of assessment led to greater sensitivity. Adaptive communication deficits also did not exceed chance level in the current sample, but the current study primarily used the same instrument as was used in the prior study, suggesting that at this end of the FASD spectrum, these deficits are not part of the signature of PAE and that a greater severity of PAE impact is needed before these adaptive communication deficits manifest. In contrast, the impulsiveness symptom did not contribute uniquely to endorsement for the ND-PAE disorder in the previous sample of children recruited from a clinical context [10] but did differentiate ND-PAE risk status in this study with those identified as being in the ND-PAE Risk group having higher rates of endorsement relative to those identified as not being at risk. These results suggests that impulsiveness may be redundant with other self-regulation symptoms in those with higher levels of symptom expression but may be important in differentiating those who are less affected.

The convergence of symptoms from the three domains seemed to improve the differentiation of participants in the ND-PAE risk group from the No ND-PAE Risk sample, but in no case did the symptoms reach levels of discrimination that would be required to identify children in the absence of confirmed maternal alcohol consumption. This is a major limitation of the disorder’s criteria as this information is not readily available in all cases. Efforts to

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identify biomarkers of exposure [24] are underway and may someday improve our capacity to identify those who are alcohol-affected. Additional work is also needed in clarifying the alcohol dosage level and timing of the dose needed for symptom expression [25].

Discrimination of symptoms was stronger for males than females in this cohort. Males identified as at risk had greater endorsement of the overall diagnosis in all but the most restrictive model applied to the symptoms (AF 2/4 at 1.5 cutoff) where only a trend was found. In addition, seven of the 11 specific symptoms significantly differed by group status for males at the 1.0 level and 6 of 11 at the 1.5 cut-off level. Females at risk, in contrast, differed only on the least restrictive diagnostic model (AF 1 at the 1.0 cut-off), suggesting that the proposed symptoms as defined by the neurobehavioral battery used in this study may not be adequately capturing symptom expression in females. In addition only 2 symptoms significantly differed for females at the 1.0 level and 1 at the 1.5 level. Sex differences are not frequently studied in FASD [26, 27] and the results from this study suggest that more attention should be given to how alcohol-related neurobehavioral deficits may manifest as a function of biological sex. This should not be unexpected for this disorder given that other psychiatric conditions also have variable expression as a function of biological sex [28–30].

The principal components analysis done in this study resulted in two main factors, neurocognitive and self-regulation, with adaptive symptoms being parsed between the two factors. This is different than what was obtained previously but the previous study used a much smaller sample size and was comprised of clinically-referred children. Sample size can have a huge impact on these type of analyses and often larger sample sizes (~ 300) are needed to approximate true population congruence [31] so it is possible that that this larger cohort provides a better representation of the underlying factor structure of the symptoms. The nature of subjects should also be considered in that it is possible that the response surface of symptom expression may vary as a function of severity of symptom expression. In other words, individuals who are affected sufficiently by PAE that their caregivers' sought clinical care may have different underlying relationships between the symptoms than do a cohort of children recruited from a first grade classrooms. This would imply that the symptoms may converge onto one factor as symptom severity increases. PCA in larger cohorts of clinically-referred children would be needed to further clarify this.

The assessment of memory impairment was not included in this analysis and has been identified by many as being a key component of alcohol-related neurodevelopmental deficits [32, 33]. The omission of the symptom may have altered the outcomes related to identification of neurocognitive impairment and overall diagnosis and estimates of internal stability and convergence with other symptoms. Future studies are encouraged to include all of the symptoms when possible to avoid this limitation.

This study assessed the characteristics of ND-PAE symptoms using an existing database and scores obtained on standardized measures and suggested that, in doing so, the signature of PAE can be identified, even in a community sample. The findings support but do not model directly onto the clinical context where the ND-PAE diagnosis would be used. This distinction is made because the threshold levels employed in this study do not define the

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clinical significance of a symptom as would be used when making a clinical diagnosis of a disorder. In the clinical situation, endorsement of symptoms are based on identified real world impairment and result from the clinician evaluating existing records, interviews and standardized measures. The environment in which an individual functions also contributes to the extent to which a given level of impairment results in clinically significant levels of dysfunction and emotional distress; thus, a given cut-off level on a standardized measure is not sufficient to make a mental health diagnosis. As such, this study only approximates the internal consistency and validity of the disorder.

Early recognition of those impacted by PAE is of great importance to initiate appropriate habilitative care to take advantage of the neural plasticity of the developing brain [34]. ND-PAE is a disorder that can aid in the identification of prenatal alcohol-related brain impairment as it does not rely on recognition of the physical effects of PAE in making the diagnosis and opens up the identification of those affected to various mental health providers to help with meeting their treatment needs [5]. Although some modifications may be needed in the level of intellectual impairment needed for endorsement and in the adaptive criteria to minimize the false rejection of individuals impacted by PAE [7], the proposed symptoms occur at higher base rates in individuals with a history of PAE relative to a sample with a high base rate of other neurobehavioral impairment and have good internal consistency across male and female children.

Summary

The validity of the proposed Neurobehavioral Disorder Associated with Prenatal Alcohol Exposure (ND-PAE) was evaluated in first graders who were part of the Collaboration on Fetal Alcohol Spectrum Disorders Prevalence study. Children were defined as “at-risk” for ND-PAE based on their mother’s drinking history during pregnancy or if the child had the physical effects of prenatal alcohol exposure (PAE). A contrast group who had a high rate of mild neurobehavioral impairment but no PAE, alcohol-related dysmorphia or growth deficits were also recruited. Participants were given a neuropsychological battery to define symptom endorsement at two diagnostic threshold levels, 1.0 and 1.5 STD. Individuals identified as at risk for ND-PAE had higher rates of endorsement of the self-regulation and adaptive domain deficits at the lower symptom threshold level and of the neurocognitive and self-regulation domain deficits at the higher threshold level relative the contrast group. Endorsement of the overall disorder significantly differed between group at only the lower threshold level in this non-clinically referred sample. Overall internal consistency ranged from 0.72 at the higher symptom threshold level to 0.76 at the lower level. Receiver operating characteristic curve analysis indicated that having an IQ below 70 was not predictive of the diagnosis but modifications of the IQ criterion resulted in improved predictive validity. Although the symptom domains significantly contributed to differentiating ND-PAE risk status, the discrimination level was poor. Symptoms of ND-PAE demonstrated acceptable levels of internal consistency and higher prevalence rates in alcohol-exposed individuals relative to a contrast group but documentation of PAE is necessary for making the diagnosis.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Sample characteristics by ND-PAE status

	ND-PAE risk n = 204	No ND-PAE risk n = 908
Age of child (years)	7.0 (.54)	7.0 (.49)
Sex n (% female)	94 (46.1)	449 (49.4)
Gestational age (weeks)	38.5 (2.6)	38.8 (2.3)
Race, number n (%)		
White	157 (84.9)	749 (83.8)
Black	5 (2.7)	49 (5.5)
Asian or Pacific Islander	11 (5.9)	47 (5.3)
Native American/Alaska Native	3 (1.6)	16 (1.8)
Mixed/other	9 (4.9)	33 (3.7)
Hispanic ethnicity, number n (%)	67 (36.2)	273 (30.6)
Maternal marital status, number n (%)		
Married	100 (54.6)****	630 (70.7)
Widowed	3 (1.6)	4 (0.4)
Divorced	20 (10.9)	54 (6.1)
Separated	8 (4.4)	35 (3.9)
Single	37 (20.2)	73 (8.2)
Unmarried, living with partner	15 (8.2)	95 (10.7)
Estimated current household income, n (%)		
0–9999	13 (7.6)	37 (4.4)
10,000–14,999	12 (7.0)	42 (5.0)
15,000–19,999	16 (9.3)	61 (7.3)
20,000–24,999	14 (8.1)	73 (8.8)
25,000–34,999	16 (9.3)	89 (10.7)
35,000–49,999	20 (11.6)	96 (11.5)
50,000–74,999	23 (13.4)	137 (16.4)
≥ 75,000	58 (33.7)	299 (35.9)
Consumed risky levels of alcohol, n (%)	130 (79.3)****	0 (0)
Dysmorphology present, n (%)	101 (49.8)****	0 (0)
Growth deficit in height and/or weight, n (%)	88 (44.2)****	0 (0)
Current mean height percentile	37.0 (30.8)****	58.2 (25.5)
Current mean weight percentile	40.3 (31.1)****	61.8 (25.4)
Current mean occipitofrontal circumference	43.4 (31.1)****	55.9 (30.3)
DAS[a] general conceptual ability score mean	99.9 (12.6)	101.3 (12.2)

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

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Table 2

ND-PAE symptom and domain endorsement by cut-off values used on standardized measures

		ND-PAE risk		No risk	
Domain	**Specific symptom**	**% Positive endorsement (1.0 SD)**	**% Positive endorsement (1.5 SD)**	**% Positive endorsement (1.0 SD)**	**% Positive endorsement (1.5 SD)**
Neurocognitive	Global intellectual functioning	0	0	1.0	1.0
Neurocognitive	Executive functioning	60.3	39.2	56.2	29.2**
Neurocognitive	Impairment in learning	59.3	29.9	49.5*	26.5
Neurocognitive	Impairment in visual-spatial reasoning	17.3	4.9	14.2	3.2
Self-regulation	Impairment in mood and behavioral regulation	49.0	28.9	35.4****	17.3****
Self-regulation	Attention deficit	49.5	30.9	34.0****	20.2***
Self-regulation	Impairment in impulse control	30.9	14.7	19.7****	9.9 [T]
Adaptive functioning	Adaptive communication deficit	14.2	6.4	10.6 [T]	3.7 [T]
Adaptive functioning	Adaptive social impairment	29.4	10.3	17.2****	8.1
Adaptive functioning	Adaptive impairment in daily living	37.7	16.2	33.3	15.0
Adaptive functioning	Adaptive motor impairment	33.3	9.8	18.8****	4.6**
Overall domain and diagnostic endorsement					
Neurocognitive	1 Symptom	77.9	51.0	71.6 [T]	42.1*
Self-Regulation	1 Symptom	58.3	41.2	48.1**	28.1****
Adaptive functioning	2 of 4 symptom	27.0	7.4	16.3***	4.7
ND-PAE diagnosis	3 Symptoms (Neurocognitive, Self-Regulation, AF 2 of 4)	24.5	5.9	12.9****	3.4 [T]
Modified AF criteria					
Adaptive functioning	1 Symptom	64.2	30.9	49 9****	23.8*
ND-PAE diagnosis	3 Symptoms (neurocognitive, self-regulation, AF 1)	44.6	16.2	28.7****	12.0

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Table 3

Area under the curve values for ND-PAE symptoms in predicting the ND-PAE diagnosis

Group	Model	1.0 Threshold cut-off level											1.5
		IQ below 70	Executive functioning	Teaming	Visual spatial	Mood and irritability	Attention problems	Impulsiveness	Adaptive communication	Adaptive social Skills	Adaptive living Skills	Adaptive motor	IQ be 70
Overall	AF1	0.510	**0.646**	**0.758**	**0.578**	**0.816**	**0.821**	**0.690**	**0.631**	**0.721**	**0.752**	**0.672**	0.5
	AF 2/4	0.516	**0.624**	**0.749**	**0.597**	**0.807**	**0.802**	**0.704**	**0.757**	**0.879**	**0.723**	**0.716**	0.5
No risk	AF1	0.513	**0.661**	**0.749**	**0.586**	**0.807**	**0.810**	**0.675**	**0.634**	**0.712**	**0.765**	**0.652**	0.5
	AJF 2/4	0.552	**0.631**	**0.756**	**0.601**	**0.799**	**0.798**	**0.694**	**0.768**	**0.876**	**0.736**	**0.712**	0.5
ND-	AF 1	0.500	**0.597**	**0.785**	0.549	**0.844**	**0.846**	**0.731**	**0.622**	**0.741**	**0.718**	**0.718**	0.5
PAE risk	AF 2/4	0.500	**0.604**	**0.722**	0.584	**0.819**	**0.791**	**0.714**	**0.734**	**0.878**	**0.689**	**0.703**	0.5

Significant effects are in bold

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Table 4

Area under the curve values for ND-PAE symptom domains for prediction to ND-PAE diagnosis

Group	Model	1.0 Threshold cut-off level			1.5 Threshold cut-off level		
		Neurocognitive	Self-regulation	Adaptive	Neurocognitive	Self-regulation	Adaptive
Overall sample	AF 1	0.699	0.866	0.847	0.823	0.898	0.929
	AF 2/4	0.660	0.794	0.981	0.793	0.863	0.993
No risk	AF 1	0.699	0.864	0.851	0.829	0.909	0.933
	AF 2/4	0.663	0.798	0.980	0.800	0.872	0.993
ND-PAE risk	AF 1	0.699	0.876	0.823	0.792	0.851	0.912
	AF 2/4	0.646	0.776	0.984	0.760	0.813	0.992