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RESEARCH ARTICLE

Prenatal alcohol exposure and cognition at midlife: Evidence of fluid cognition deficits in two cohorts

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Abstract

Background: Prenatal alcohol exposure (PAE) impacts cognition in childhood and early adulthood. Here we evaluate the cognitive abilities of middle-aged adults with and without a history of PAE.

Methods: Participants ($N = 200$) were recruited from longitudinal cohorts in the Atlanta and Seattle metropolitan areas and completed measures comprising the National Institutes of Health Toolbox's Fluid Cognition Composite.

Results: We found that individuals with PAE had lower Fluid Cognition Summary scores and lower Dimensional Change Card Sort and Flanker task subtest scores than non-PAE controls, after accounting for both potentially confounding demographic variables using propensity scores and the effects of study site. When we evaluated the effects of PAE with and without dysmorphic physical features, we found that middle-aged adults in both groups had lower fluid cognition scores than non-PAE controls. However, only the presence of PAE with dysmorphic features was associated with lower performance on the Dimensional Change Card Sort Test and Flanker tasks.

Conclusion: While all participants with PAE had lower fluid cognition, those with PAE and dysmorphic features also exhibited specific deficits in their performance on measures of inhibition, attention, and cognitive flexibility. Thus, PAE is associated with ongoing cognitive deficits in middle adulthood, which can be observed most clearly among individuals with dysmorphic features.

KEYWORDS
adult, cognition, lifespan, middle-age, prenatal alcohol exposure

INTRODUCTION

Prenatal alcohol exposure is known to be associated with negative outcomes, including a wide range of cognitive deficits. Studies have found that children with a history of PAE show deficits across many cognitive domains (Mattson et al., 2011, 2019). These domains include lower overall intellectual ability (Mattson et al., 2011), sustained attention (Lee et al., 2004; Mattson et al., 2006), inhibitory control (Connor et al., 2000; Gerhold et al., 2017; Mattson et al., 1999), cognitive flexibility (Coles et al., 1997; McGee et al., 2008), processing speed (Burden et al., 2005), working memory (Green et al., 2009; Kodituwakku et al., 1995), as well as learning and memory (Coles et al., 2010; Vaurio et al., 2011). Relative to their peers, young adults with PAE continue to exhibit cognitive impairment on measures of intellectual ability (Streissguth et al., 1991), visual and auditory attention (Connor et al., 1999), verbal and nonverbal memory (Coles et al., 2010, 2011), and measures tapping executive functions (i.e., working memory, planning, and set-shifting; Rangmar et al., 2015).

Children with PAE also exhibit alterations in normative brain development, including reduced volume size across cortical and

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subcortical structures (Moore & Xia, 2022). Furthermore, several studies have found that these changes in brain volume are associated with performance on cognitive tasks. Hippocampal volume has been found to correlate with verbal and spatial memory (Willoughby et al., 2008), caudate volume with measures of cognitive control and verbal memory (Fryer et al., 2012), and smaller basal ganglia with lower IQ scores (Roussotte et al., 2012).

Thus far, there have been no studies of cognition in middle adulthood among people with PAE. In their review, Moore and Riley (2015) suggested that smaller brain volumes in children with PAE may reflect a "developmental delay," (for application of this framework to other developmental disorders, see: Chawner et al., 2017; Fisch et al., 1996; Hoogenhout & Malcolm-Smith, 2014; Kinsbourne, 1973), raising the possibility that affected individuals may "catch up" in some domains as they mature. This *developmental delay hypothesis* reflects a conception of development that assumes neurological impairment in a population is associated with developmental delays rather than persistent deficits. According to this viewpoint, older adults with PAE should exhibit equivalent ability to non-PAE controls in some or all cognitive domains most characteristic of PAE, presumably associated with the many factors in the postnatal environment that can lead to relative improvements in affected individuals. In contrast, the *developmental deficit hypothesis* provides an alternative prediction that there will be persistent and measurable deficits associated with PAE's early insult.

Studies evaluating long-term outcomes in individuals with other neurodevelopmental disorders tend to be consistent with the developmental deficit hypothesis. They find that intellectual ability tends to remain stable into middle age in some developmental disorders (i.e., remaining lower than that of typically developing adults), such as autism spectrum disorder (ASD) (Magiati et al., 2014) and Williams syndrome (Sauna-Aho et al., 2019; Searcy et al., 2004). Studies of these populations evaluating lifespan trajectories in cognitive domains beyond intellectual ability have been somewhat limited. A review of cognitive deficit domains among middle-aged and older adults with ASD is mixed (Tse et al., 2022), as some studies show worse performance in the ASD group, a minority show superior performance in the ASD group, and some show equivalent performance. Individuals with Williams syndrome have been found to show persistent impairment on measures tapping inhibition and attention, cognitive flexibility, and processing speed (Condy et al., 2022). Individuals with Down syndrome exhibit an earlier onset of physical aging and have higher rates of age-related cognitive decline in the form of dementia (Esbensen, 2010). Intellectual ability in adults with Down syndrome is lower than in typically developing adults, but the ability to quickly and flexibly solve novel problems (i.e., fluid intelligence) declines at a similar rate in both groups, while the application of accumulated knowledge (i.e., crystallized intelligence) decreases faster in Down syndrome (Carr, 2005). In attention-deficit/hyperactivity disorder (ADHD), there is limited evidence suggesting differences in intellectual ability may normalize in middle age (Hong et al., 2022), but individuals continue to exhibit a variety of cognitive deficits in other domains (Mostert et al., 2015; Mowinckel et al., 2015).

Prenatal alcohol represents a brain insult in utero, but the lifespan impact of this insult is not well known. The only available research is with young adults with confirmed PAE, and while that work suggests neurocognitive impairment persists into early adulthood (Coles et al., 2010, 2011; Connor et al., 1999, 2000; Streissguth et al., 1991), catching up may still be possible. Thus, there is a need for studies to evaluate individuals beyond their third decade of life to evaluate whether the *developmental delay* hypothesis remains viable and to understand the nature of those deficits that persist. Here we evaluate the cognitive ability of middle-aged adults with and without PAE using the National Institutes of Health (NIH) Toolbox, a standardized measure of cognitive functioning for use with individuals throughout the lifespan, to assess aspects of fluid cognition. We selected this domain because previous studies have shown that children with PAE exhibit deficits in fluid intelligence and related domains (e.g., executive functions; Briana Lees et al., 2020; Connor et al., 2000; Kodituwakku et al., 2011; Mattson et al., 2019). If the *developmental delay* hypothesis is true, we would expect the performance of individuals with and without PAE to be equivalent. Conversely, if the *developmental deficit* hypothesis is correct, we would expect adults with a history of PAE to demonstrate lower performance than those without such a history.

METHODS

Participants

Participants were recruited from two longitudinal research programs in Atlanta (Coles et al., 1985, 2002; Lynch et al., 2017) and Seattle (Streissguth et al., 1985, 1991, 1996) that are following individuals with a history of prenatal alcohol exposure as well as contrast groups of unexposed individuals. Recruitment at both sites targeted a subset of the original cohorts (target n at each site = 120), but enrollment was hampered by the COVID-19 pandemic. The Atlanta cohort was predominantly African American, consisting of 427 individuals between the ages 32 and 40, of whom 97 took part in the current study. The Seattle cohort was predominantly White and American Indian, comprising 475 individuals aged 29–64, of whom 103 took part in the current study.

The Atlanta cohort were children of women receiving prenatal care at a large, inner-city hospital that served a predominantly Black population of low socioeconomic class. All women applying for prenatal care between 1981 and 1986 were screened for alcohol use, and mothers were recruited for the study if they denied drinking any alcohol or if they reported drinking at least 1 ounce of absolute alcohol per occasion at least once a week. Participants were interviewed again a week later to obtain additional information, including detailed information regarding alcohol consumption. Following the family's recruitment and postpartum assessment of medical, behavioral, and dysmorphic outcomes (Coles et al., 1985, 1987), participants were reassessed in childhood (Coles et al., 1997), adolescence (Coles et al., 2002), and early adulthood (Lynch et al., 2015). Members of this cohort were not formally evaluated for diagnoses along the fetal

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TABLE 1 Demographic variables—Atlanta sample.

	Mean (SD) or %	Control ($n = 41$)	PAE ($n = 56$)	p	% missing
Age	36.49 (1.83)	37.02 (1.31)	36.11 (2.06)	<0.01; Control > PAE	0
Sex (% female)	69.1	68.3	69.6	ns	0
Income (Hollingshead Index)	3.68 (1.41)	3.85 (1.51)	3.77 (1.36)	ns	21.9
Occupation (Hollingshead Index)	3.31 (2.03)	3.90 (2.17)	2.88 (1.83)	<0.05; Control > PAE	0
Education (Hollingshead Index)	4.37 (1.33)	4.46 (1.36)	4.30 (1.32)	ns	0
Race					
American Indian	0.0	0.0	0.0	ns	0
Black	92.8	85.4	98.2	<0.05; PAE > control	0
White	6.2	12.2	1.8	<0.05 Control > PAE	0
Multiracial	1.0	2.4	0.0	ns	0
Hispanic/Latino	0.0	0.0	0.0	ns	0
Marital status					
Never married	54.6	46.3	60.7	ns	0
Living with partner	11.3	12.2	10.7	ns	0
Married	19.6	22.0	17.9	ns	0
Separated	3.1	7.3	0.0	<0.05 PAE > Control	0
Divorced	10.3	12.2	8.9	ns	0
Widowed	1.0	0.0	1.8	ns	0
Dysmorphic features	24.7	0	42.9	<0.001 PAE > Control	0

alcohol spectrum. However, they were previously assessed for dysmorphic features, which are present in a sizable minority within the sample (Table 1). Although the presence of such physical features does confer a diagnosis of FAS, these are more commonly found in infants with high levels of PAE (Bandoli et al., 2020). Furthermore, their presence is associated with worse cognitive outcomes in infancy (Bandoli et al., 2019) and early childhood (Bandoli et al., 2022), as well as worse physical outcomes in later life (Kable et al., 2023).

Most members of the Seattle cohort were referred as children to the University of Washington for clinical evaluation between 1973 and 1995 and recruited for participation in research studies when PAE was ascertained. Clinical referrals were predominantly due to cognitive and/or behavioral problems along with known or suspected PAE. Several reports have documented the cognitive and physical sequalae (among other characteristics) of PAE in members of this cohort beginning in childhood and continuing to adulthood (Streissguth et al., 1985, 1991, 1996). A substantial minority of children with a history of PAE from this cohort were diagnosed with fetal alcohol syndrome (FAS; Table 2). Notably, while children in both cohorts were assessed for dysmorphia, this assessment was not uniform across sites. Members of the Atlanta cohort were assessed using a weighted checklist, while the Seattle cohort evaluation was done using an unweighted checklist (Sampson et al., 1997). Both groups can be characterized as having alcohol-related dysmorphic features or not. Most members of the control group were recruited during the same time frame as the PAE groups and chosen to be similar to the PAE participants in age, sex, and race. In some cases, control participants were unexposed, nonbiological siblings of alcohol-affected individuals. To the extent that some contemporaneously recruited controls had moved away and were unable to participate, additional controls were recruited from the greater Seattle area. These more recently recruited controls were screened to ascertain that they were reasonably certain that their biological mother did not consume alcohol to any significant extent while pregnant.

Study records and commercially available databases that identified current addresses, phone numbers, and other information were used to obtain participant contact information. Eligible participants who could be reached were informed by mail, phone, or email of the opportunity to participate. Informed consent was carried out in person or remotely using REDCap (Research Electronic Data Capture), a HIPAA-compliant secure web application for building and managing online surveys and databases approved for use by the internal review boards at Emory University School of Medicine and the University of Washington. Participants who took part in the study completed the NIH Toolbox as part of an in-person research visit.

Measures

Participants completed a demographic survey, including self-reported income, occupation, education, race, ethnicity, and marital

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TABLE 2 Demographic variables—Seattle cohort.

	Mean (SD) or %	Control ($n = 31$)	PAE ($n = 72$)	p	% missing
Age	40.88 (8.65)	39.90 (8.79)	41.31 (8.62)	ns	0
Sex (% female)	45.6	51.6	43.1	ns	0
Income (Hollingshead Index)	4.03 (1.76)	5.77 (0.62)	3.24 (1.50)	<0.001; Control > PAE	3.9
Occupation (Hollingshead Index)	4.33 (2.64)	6.81 (2.04)	3.28 (2.10)	<0.001; Control > PAE	1
Education (Hollingshead Index)	5.12 (1.64)	6.84 (1.07)	4.39 (1.22)	<0.001; Control > PAE	1
Race					
American Indian	9.7	6.5	11.1	ns	0
Black	4.9	6.5	4.2	ns	0
White	70.9	80.6	66.7	ns	0
Multiracial	14.6	6.5	18.1	ns	0
Hispanic/Latino	5.8	9.7	4.2	ns	4
Marital status					
Never married	40.8	16.1	51.4	<0.001; PAE > Control	0
Living with partner	15.5	16.1	15.3	ns	0
Married	33.0	58.1	22.2	<0.001; PAE > Control	0
Separated	3.1	0.0	0.0	ns	0
Divorced	10.7	9.7	11.1	ns	0
Widowed	0.0	0.0	0.0	ns	0
Fetal alcohol syndrome (FAS)	29.1	0	41.7	<0.001; PAE > Control	0

status. Education and occupation were recoded into a set of discrete categories using the Hollingshead Index (Hollingshead, 2011). Information about PAE and the presence of dysmorphic features was collected during prior study visits.

Participants were also administered the set of subtests from the NIH Toolbox Cognition Battery (Weintraub et al., 2013) administered on an iPad. The Toolbox was administered by trained postdoctoral residents and graduate-level students in psychology.

Fluid cognition composite score

Performance on the NIH Toolbox subtests was used to derive a Fluid Cognition Composite Score (Akshoomoff et al., 2013). The Fluid Cognition standard score, with a mean of 100 and a standard deviation of 15, is thought to provide a global assessment of an individual's efficiency in learning and processing novel information. Fluid abilities are thought to be particularly vulnerable to disruptions in biological processes, including aging and disorders that affect the brain, and are less reliant on past experiences (Akshoomoff et al., 2013). These abilities are contrasted with crystallized intelligence, which is believed to reflect the accumulation of knowledge and experience and therefore declines with age at a slower rate than fluid intelligence. Subtests used to derive the Fluid Cognition Composite Score are listed below. Raw scores for the subtests and composite score were converted into age-adjusted standard scores, with a mean of 100 and a standard deviation of 15.

Dimensional change card Sort test (DCCS)

The DCCS is used to evaluate cognitive flexibility. Participants viewed two target pictures that varied in terms of shape and color. Participants were asked to match a series of test pictures to the target pictures according to one of these dimensions. On "Switch" trials, participants were required to change the dimension being matched (e.g., matching shapes on color, then on shape, and then on color again). Scoring was computed using a combination of accuracy and response times, with raw values ranging from 0 to10.

Flanker inhibitory control and attention (flanker)

The Flanker is a measure of attention and inhibitory control. Participants viewed a row of arrows and were instructed to indicate the direction the middle arrow was pointing. On congruent trials, the middle arrow pointed in the same direction as the surrounding arrows, and on incongruent trials, the middle arrow pointed in the opposite direction as the surrounding arrows. Scores were derived an integration of accuracy and response times, with raw values ranging from 010.

List sorting working memory test (list sorting)

The list sorting task is used to assess working memory. Participants were presented with pictures of different foods and animals

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displayed with accompanying audio recordings and written text (e.g., "elephant"). Participants were first asked to recall the items in size order from smallest to largest within a single dimension (either a list of animals or foods). Participants were then presented with lists containing both categories and to asked recall the food items that followed the animals (both in size order). Performance was scored by summing the number of correct responses on all lists and ranged from 0 to 26.

Picture sequence memory test (PSMT)

The PSMT was used to assess episodic memory. Participants were presented with a series of illustrations of objects and activities in a particular order. These illustrations were then shuffled, and participants were asked to place them in the correct order. Scoring was computed by converting the number of correctly placed adjacent pairs for trials 1 and 2 to a theta score, which ranges from 0 to 1.

Pattern comparison processing speed test (pattern comparison)

The pattern comparison is a measure of processing speed. Participants viewed a series of pictures, presented two at a time, and were asked to indicate if they were the same or not. Participants were given 85 s to respond to as many items as possible (up to a maximum of 130). Scores ranged from 0 to 130, reflecting the number of items answered correctly.

Analyses

Participants were permitted to refuse to answer any question they did not want to answer and to stop completing any cognitive test they did not want to finish. Fewer than 25% of participants did not answer all of the demographic questions, and fewer than 5% did not complete a cognitive test. To account for missing data (Tables 1 and 2), we conducted multiple imputation (Graham et al., 2007) of missing demographic and cognitive test scores using all available demographic variables with the MICE software package in R (Van Buuren & Groothuis-Oudshoorn, 2011). Multiple imputation is recommended for handling missing relative to listwise deletion because it reduces bias resulting from nonrandom patterns of missingness, preserves statistical power, and allows important characteristics of the sample to be preserved (Graham, 2009). Although there can be concern when imputing data that contains systematic patterns of nonrandom missingness, data imputation is relatively minimal and allows all available data to be utilized rather than relying on reports from participants with complete data.

We used two complementary approaches to control for potential variance associated with differences in site and demographic factors: propensity scores and multilevel modeling. Propensity scores are defined (Rosenbaum & Rubin, 1983) as the probability of treatment assignment (or group membership) conditional on observed covariates: $e_i = Pr(Z_i = 1|X_i)$. These scores reflect an individual's likelihood of membership in a particular group (e.g., PAE or control) given a set of covariates. Propensity scores are helpful when individuals cannot be randomly assigned to a group, as is the case here.

Propensity scores in this study were derived by regressing demographic variables on PAE status. Our use of propensity scores allowed us to account for a large number of important covariates without the additional complications arising from incorporating a large number of predictors within a regression (e.g., collinearity; Austin, 2011).

Given the differences across sites in demographic characteristics (Tables 1 and 2) and to account for the nested structure of our data (i.e., participants nested within sites), we calculated participants' propensity scores within a multilevel framework using the lme4 (Bates, Machler, Bolker, & Walker, 2015) and lmerTest (Kuznetsova, Brockhoff, & Christensen, 2017) packages in R (version 4.2.1). Given differences across cohorts in the recruitment of participants and assessment of PAE, we formally evaluated whether PAE was similarly associated with demographic characteristics and cognitive outcomes at each site. We hypothesized that the relationship between demographic variables and PAE would be unlikely to differ across sites (e.g., the relationship between income and PAE would be similar in both sites, while the mean values of these might vary across sites). In other words, we hypothesized the best model would be one in which intercept, but not slope, varied as a random effect for site. We were able to fit our hypothesized model but also evaluated a series of models in which we included random slopes and random intercepts. All models in which random slopes were included (i.e., models in which the relationship between demographic variables and PAE differed by site) resulted in a singular model fit, suggesting the inclusion of random slopes resulted in overfitting. Consequently, we selected our initial model (Barr et al., 2013).

We then conducted a series of multilevel regression models in which we predicted age-adjusted scores from the NIH Toolbox using PAE and our previously derived propensity scores while accounting for the hierarchical nature of the data (individuals nested within city). Again, we hypothesized that the relationship between PAE and propensity scores with our cognitive outcomes would be best described by a model with only random intercepts. Again, we were able to fit our hypothesized model, but the inclusion of random slopes in our model resulted in a singular model fit, eliminating our concern about interactions between site and PAE or propensity scores and leading us again to select our initial model.

We first evaluated the unconditional means model, in which we only regressed our outcomes on site using the following formula: Cognitive Outcome ~1 + (1|Site), with 1|Site representing the effect of site. We then derived the Intraclass Correlation Coefficient (ICC), which provides an estimate of the variance that can be attributed to the site for each outcome (Table 5). Of these, the Fluid Cognition

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Score ICC was the largest, indicating that 14.6% of the overall variance in this measure was attributable to between-site variation, whereas 85.4% was attributable to within-site variation. The ICC values for the individual subtest scores varied and ranged between 4.3% and 13.5%. Thus, we found evidence of significant cross-site variance supporting our modeling choice.

We first evaluated the hypothesis that PAE continues to be associated with deficits in fluid cognitive abilities in middle adulthood. We conducted a series of multilevel analyses in which we regressed PAE (defined as the presence or absence of any level of PAE) and the propensity score on each of the scores for the cognitive tasks (Fluid Cognition, DCCS, Flanker, List Sorting, PSMT, and Pattern Comparison). Models were specified in the following template: Cognitive Outcome ~ PAE Status + Propensity Score + (1|Site).

Next, we also evaluated the possibility that the association between PAE and cognitive ability will differ among individuals with and without dysmorphology (Bandoli et al., 2019, 2022). To test this possibility, we divided the alcohol-exposed individuals into those with dysmorphology (*PAE+*: Yes/No) and those without dysmorphology (*PAE−*: Yes/No). We created propensity scores for PAE+ and PAE− and then again regressed each one of the outcome measures on PAE+, PAE− and both propensity scores. These models were specified as follows: Cognitive Outcome ~ (PAE+) + (PAE−) + (Propensity Score for PAE+) + (Propensity Score for PAE−) + (1|Site).

RESULTS

The demographic characteristics of participants are shown in Tables 1 and 2. Although, similar in most respects, we found participants with PAE were lower on the Hollingshead classification of perceived job status across sites. In the Atlanta cohort, control group members were more likely to be White, less likely to be Black (although both groups were predominantly Black at 85.4% and 98.2%, respectively), and had lower rates of being separated from a partner than the PAE group. In Seattle, the control group had higher income and more education, was more likely to be currently married, and was less likely to have never been married relative to the PAE group.

Descriptive statistics for the cognitive scores in each cohort can be seen in Tables 3 and 4. Prenatal alcohol exposure (Yes or No) was associated with lower Fluid Cognition, DCCS, and Flanker scores after accounting for co-occurring demographic variables (all $p < 0.01$; Table 6). Other subtests did not show such effects. In this set of models, propensity scores predicted performance on all measures (all $p < 0.05$).

When we evaluated the presence (PAE+) or absence (PAE−) of dysmorphic features (Table 7), we found participant's PAE was associated with lower Fluid Cognition scores regardless of dysmorphology. However, only the presence of PAE with dysmorphia (PAE+) was also associated with significantly lower performance on the DCCS and Flanker tasks (both $p < 0.01$). In the second set of models, propensity scores for PAE+, but not PAE−, predicted task

TABLE 3 Cognitive scores—Atlanta cohort.

Mean (SD) or %	Mean	Control ($n = 41$)	PAE ($n = 56$)	% missing
Fluid cognition	81.60 (17.27)	85.44 (18.33)	78.79 (16.04)	3.1
Dimensional change (cognitive flexibility)	91.59 (18.74)	97.68 (17.47)	87.13 (18.52)	1
Flanker (inhibition and attention)	78.39 (13.61)	81.41 (14.04)	76.18 (12.96)	1
List sorting (working memory)	85.94 (15.57)	89.83 (14.29)	83.09 (15.97)	2.1
Pattern comparison (processing speed)	86.18 (21.24)	86.63 (23.62)	85.84 (19.53)	2.1
Picture sequence memory (episodic memory)	94.99 (15.58)	98.05 (17.39)	92.75 (13.85)	2.1

Note: Cross-group statistical comparisons can be found in in Tables 6 and 7.

TABLE 4 Cognitive scores—Seattle cohort.

Mean (SD) or %	Mean	Control ($n = 31$)	PAE ($n = 72$)	% missing
Fluid cognition	93.49 (22.94)	115.87 (15.72)	83.85 (18.40)	1
Dimensional change (cognitive flexibility)	97.94 (20.17)	113.71 (18.25)	91.15 (16.99)	0
Flanker (inhibition and attention)	85.10 (17.33)	99.9 (16.37)	78.72 (13.47)	0
List sorting (working memory)	95.76 (18.75)	109.68 (13.11)	89.76 (17.64)	0
Pattern comparison (processing speed)	95.87 (23.22)	113.35 (20.83)	88.35 (20.01)	0
Picture sequence memory (episodic memory)	104.53 (18.06)	118.29 (15.56)	98.61 (15.75)	1

Note: Cross-group statistical comparisons can be found in in Tables 6 and 7.

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performance. There were no additional differences between adults with and without PAE.

DISCUSSION

This is the first study to evaluate the cognitive abilities of middle-aged adults with PAE. The long-term effects of PAE on fluid cognition in middle adulthood were evaluated using the NIH Toolbox. PAE groups had lower mean scores on overall fluid cognitive ability than controls, suggesting these individuals are more likely to exhibit ongoing problems in abilities such as problem solving, adaptively adjusting to environmental changes, impulsivity, and attention. Statistically significant performance deficits associated with PAE were also found on individual measures of inhibition, attention, and cognitive flexibility but not on measures of working memory (List Sorting), episodic memory (Picture Sequence Memory Test) or processing speed (Pattern Comparison). These results suggest there is evidence that deficits previously observed in younger individuals are also evident (and may have persisted) into midlife. Some of our results are consistent with a "deficit" model of development, which is also evident in other neurodevelopmental disorders. Specifically, individuals with PAE were impaired with regard to broad fluid cognition and measures of cognitive flexibility, inhibition, and attention, with performance in the latter subdomains being particularly affected in participants with dysmorphic features. Conversely, however, there is also evidence for a "delay" model, as the performance of individuals with PAE did not differ on measures of working memory, processing speed, or episodic memory. Nonetheless, this study was restricted to a cross-sectional estimate of cognitive functioning in the two samples and evaluated only a limited set of abilities. Understanding the trajectory of cognitive ability among people with PAE will require additional longitudinal studies evaluating the cognitive skills of this population across many domains, sampled using a metric that can be evaluated over time.

In most studies, dysmorphic features are associated with more impaired cognitive outcomes (Bandoli et al., 2022; Ervalahti et al., 2007; Roussotte et al., 2012), presumably because they are associated with higher and more consistent levels of alcohol exposure during pregnancy or because the individual was more vulnerable to alcohol's effects. In this study, we also found that having PAE with dysmorphic features predicted lower scores on specific subtests as well as the overall composite score. However, it was observed that the alcohol-exposed group without dysmorphic features was also

TABLE 5 Intraclass Correlation Coefficients (ICC) values associated with the NIH Toolbox scores.

Measure (domain)	ICC
Fluid cognition	0.15
Dimensional change (cognitive flexibility)	0.04
Flanker (inhibition and attention)	0.08
List sorting (working memory)	0.14
Pattern comparison (processing speed)	0.08
Picture sequence memory (episodic memory)	0.13

TABLE 6 Association of PAE with cognitive outcomes.

Outcome (Measure/Domain)	Predictor	Estimate	SE	df	*t*	*p*
Fluid cognition	Intercept	**117.37**	**9.14**	**1.26**	**12.84**	**<0.05**
	PAE	**−8.80**	**2.89**	**196.00**	**−3.04**	**<0.01**
	PAE propensity	**−37.93**	**5.54**	**196.21**	**−6.85**	**<0.001**
Dimensional change/Cognitive flexibility	Intercept	**118.52**	**6.04**	**1.83**	**19.61**	**<0.01**
	PAE	**−7.44**	**2.97**	**196.00**	**−2.51**	**<0.05**
	PAE propensity	**−29.54**	**5.68**	**196.53**	**−5.20**	**<0.001**
Flanker/Inhibition and attention	Intercept	**98.54**	**5.51**	**1.60**	**17.87**	**<0.01**
	PAE	**−7.10**	**2.42**	**196.00**	**−2.93**	**<0.01**
	PAE propensity	**−19.21**	**4.63**	**196.42**	**−4.15**	**<0.001**
List sorting/Working memory	Intercept	**113.63**	**7.37**	**1.34**	**15.43**	**<0.05**
	PAE	−3.92	2.59	196.00	−1.51	*.ns*
	PAE propensity	**−31.59**	**4.97**	**196.26**	**−6.36**	**<0.001**
Pattern comparison/Processing speed	Intercept	**111.60**	**7.68**	**1.75**	**14.53**	**<0.0.01**
	PAE	−4.70	3.65	196.00	−1.29	*ns*
	PAE propensity	**−27.45**	**6.98**	**196.50**	**−3.93**	**<0.001**
Picture sequence memory/ Episodic memory	Intercept	**120.01**	**6.95**	**1.40**	**17.28**	**<0.01**
	PAE	−4.20	2.62	196.00	−1.60	*ns*
	PAE propensity	**−27.36**	**5.02**	**196.30**	**−5.45**	**<0.001**

Note: Bold values indicate significant values.

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ALCOHOL CLINICAL & EXPERIMENTAL RESEARCH

TABLE 7 Association of PAE with and without dysmorphic features with cognitive outcomes.

Outcome (Measure/Domain)	Predictor	Estimate	SE	df	*t*	*p*
Fluid cognition	Intercept	**113.87**	**9.08**	**1.51**	**12.55**	**<0.05**
	PAE+	**−10.35**	**3.46**	**194.01**	**−2.99**	**<0.01**
	PAE−	**−6.70**	**3.04**	**194.01**	**−2.21**	**<0.05**
	PAE+ propensity	**−53.61**	**10.17**	**194.00**	**−5.27**	**<0.001**
	PAE− propensity	−19.09	13.57	194.20	−1.41	ns
Dimensional change/Cognitive flexibility	Intercept	**117.74**	**6.38**	**2.72**	**18.46**	**<0.001**
	PAE+	**−11.01**	**3.54**	**194.03**	**−3.11**	**<0.01**
	PAE−	−4.00	3.11	194.03	−1.29	ns
	PAE+ propensity	**−33.77**	**10.40**	**194.01**	**−3.25**	**<0.001**
	PAE− propensity	−25.86	13.88	194.50	−1.86	ns
Flanker/Inhibition and attention	Intercept	**96.76**	**5.73**	**2.21**	**16.90**	**<0.01**
	PAE+	**−9.39**	**2.89**	**194.02**	**−3.25**	**<0.001**
	PAE−	−4.82	2.54	194.02	−1.90	ns
	PAE+ propensity	**−26.74**	**8.51**	**194.01**	**−3.14**	**<0.01**
	PAE− propensity	−10.17	11.35	194.39	−0.90	ns
List sorting/Working memory	Intercept	**107.57**	**7.19**	**1.71**	**14.96**	**<0.01**
	PAE+	−5.26	3.07	194.01	−1.71	ns
	PAE−	−3.28	2.70	194.01	−1.22	ns
	PAE+ propensity	**−53.18**	**9.04**	**194.00**	**−5.88**	**<0.001**
	PAE− propensity	−0.30	12.06	194.26	−0.03	ns
Pattern comparison/Processing speed	Intercept	**112.18**	**8.22**	**2.53**	**13.66**	**<0.01**
	PAE+	−6.89	4.42	194.02	−1.56	ns
	PAE−	−2.72	3.88	194.02	−0.70	ns
	PAE+ propensity	−24.48	12.99	194.01	−1.88	ns
	PAE− propensity	−31.95	17.33	194.46	−1.84	ns
Picture sequence memory/ Episodic memory	Intercept	**117.58**	**7.02**	**1.81**	**16.74**	**<0.01**
	PAE+	−4.22	3.14	194.01	−1.34	ns
	PAE−	−2.88	2.75	194.01	−1.05	ns
	PAE+ propensity	**−41.22**	**9.23**	**194.00**	**−4.47**	**<0.001**
	PAE− propensity	−12.78	12.32	194.28	−1.04	ns

Note: Bold values indicate significant values.

significantly different from unexposed controls on the Fluid Cognition Composite Score, but not on any one particular test from which the summary score was derived. Individuals without dysmorphic features may have a global deficit in fluid cognition, which subtly affected their performance across all subtests covered by this construct but only reached significance when scores were aggregated in the form of a summary score. According to this view, those with PAE and dysmorphic features share this global deficit but also suffer from specific impairments in attention, inhibitory control, and cognitive control. Similar patterns of results have been observed in other studies, including members of the Atlanta cohort (Coles et al., 2010), which found that while all individuals with PAE tend to exhibit some degree of cognitive impairment, the cognitive abilities of individuals with dysmorphology were more compromised than those without dysmorphology. An alternative explanation is that the individual subtests of the NIH Toolbox were not sufficiently sensitive to capture subtle alcohol-related deficits, while these were detected by the Fluid Cognition Composite Score because, as a summary score, it is more psychometrically robust (Heaton et al., 2014; Weintraub et al., 2014).

We found substantial variation in performance was attributed to the site location and demographic characteristics (summarized as propensity scores). These observed effects point to the necessity of controlling these and other potentially extraneous factors in analyses aimed at understanding the impact of PAE on developmental outcomes. Using a multilevel modeling approach and propensity scores, we were able to control for many of the environmental and social factors that can obscure the impact of alcohol exposure and gain greater confidence that our findings truly reflect the specific effect of PAE. However, we were limited by the small number of sites from which participants were recruited and the focus on samples in large urban areas. Likewise, there are also differences due to study

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design and recruitment across sites, which may limit the interpretation of our results. We would also be more confident in the generalizability of our results (e.g., to individuals in rural communities) and have greater precision in distinguishing between environmental and PAE effects on cognition if we were able to include additional samples from a variety of locations. Nonetheless, it is evident that environmental and demographic factors significantly impact cognitive function, and the inclusion of participants from two geographically and demographically distinct sites allowed us to distinguish between the effects of PAE and the environment.

There are additional limitations to our study. While we demonstrated that fluid intelligence in those with PAE remains relatively lower than that in matched peers, we did not determine whether this reflected further decline. That is, it is not evident whether these differences are consistent with deficits that might have been observed earlier in life or are exacerbated by early cognitive decline. Variations in historical assessments of cognitive functioning between these two cohorts make such a comparison impossible. We also could not determine whether there may be global reductions in cognitive ability (i.e., in both fluid and crystallized intelligence). Better understanding the long-term trajectory of cognitive functioning in PAE is a worthy goal of future work.

An additional limitation of this study is that only a subset of participants (approximately 25%) of the cohort at each site completed the current study. This partially reflects an a priori intention to recruit a smaller subsample of each cohort but is also the result of constraints imposed by the COVID-19 pandemic and the difficulty inherent in recruiting and retaining individuals with cognitive impairment, lower SES, and family histories of heavy alcohol use. The low participation rate raises the possibility that participant self-selection may have occurred and skewed the results. At both sites a greater number of individuals with PAE completed this visit than did the same-age controls, suggesting recruitment did not favor unimpaired individuals with fewer barriers to participation. However, it is still possible that among the PAE group, individuals with greater impairment were more likely to participate in this study (e.g., perhaps because less-impacted individuals were busier and declined to participate, or perhaps because more impaired individuals had more caregiver support that facilitated their participation).

This study extends recent work to show that PAE is associated with ongoing neurocognitive impairment in addition to physical (Kable et al., 2023) and mental health (Coles et al., 2022) problems in middle age. The impairments reported here appear to have persisted into middle age, and while the presence of dysmorphic features was associated with greater cognitive vulnerability, the *developmental deficit* model was supported regardless of the presence of physical features. The study also found that the relationship between PAE and cognitive ability was not impacted by location, though the environment showed strong, independent effects on cognitive ability. The implications of these findings are both that individuals with PAE are likely to require continued support to reduce the negative impact of cognitive impairment and that environmental factors may provide other means of supporting cognitive function for individuals with and without PAE.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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