UC San Diego
UC San Diego Previously Published Works

Title
Patterns of Prenatal Alcohol Use That Predict Infant Growth and Development

Permalink
https://escholarship.org/uc/item/7707m2xn

Journal
Pediatrics, 143(2)

ISSN
0031-4005

Authors
Bandoli, Gretchen
Coles, Claire D
Kable, Julie A
et al.

Publication Date
2019-02-01

DOI
10.1542/peds.2018-2399

Peer reviewed

Patterns of Prenatal Alcohol Use That Predict Infant Growth and Development

Gretchen Bandoli, PhD,[a,b] Claire D. Coles, PhD,[c] Julie A. Kable, PhD,[c] Wladimir Wertelecki, MD,[a,d,e,f] Lyubov Yevtushok, MD,[d,g] Natalya Zymak-Zakutnya, MD,[d] Alan Wells, MS,[a] Irina V. Granovska,[d] Alla O. Pashtepa,[e] Christina D. Chambers, PhD, MPH,[a,b] the CIFASD

abstract

BACKGROUND: Previous studies have had inconsistent findings regarding the quantity and frequency of prenatal alcohol exposure (PAE) that lead to deficits in growth and neurodevelopment. This may be due to imprecise methods of exposure classification. Our objective in this study was to employ longitudinal trajectory modeling of maternal drinking patterns associated with infant growth or neurodevelopmental deficits to a homogenous sample of mothers and infants.

METHODS: From a sample of 471 pregnant women prospectively enrolled in a longitudinal study in the Ukraine, we performed a longitudinal cluster analysis of drinking patterns across gestation. We employed multivariable regression analyses to determine if each trajectory group was associated with infant weight, length, or head circumference at birth or psychomotor or mental deficits in infancy.

RESULTS: We identified 5 distinct PAE trajectory groups: minimal or no PAE throughout gestation, low-to-moderate PAE with discontinuation early in gestation, low-to-moderate PAE sustained across gestation, moderate-to-high PAE with reduction early in gestation, and high PAE sustained across gestation. The highest-trajectory group was associated with deficits in infant weight and length at birth and deficits in psychomotor and mental performance at 6 to 12 months of age. Although confidence intervals overlapped, low-to-moderate sustained use was more strongly associated with most negative infant outcomes than moderate-to-high PAE with early reduction.

CONCLUSIONS: With these findings, we confirm that high, sustained PAE confers the highest risk for adverse infant outcomes but demonstrate that even low-to-moderate PAE continued across gestation is associated with certain deficits. This approach may be used to help clinicians identify high-risk infants for targeted early intervention.

WHAT'S KNOWN ON THIS SUBJECT: Effect estimates of prenatal alcohol exposure and child growth and development have been inconsistent, particularly regarding low-to-moderate exposure. This may be partially attributable to variability in methods that are used to classify maternal alcohol use, in which complex exposure patterns are often oversimplified.

WHAT THIS STUDY ADDS: In this study, we employ longitudinal cluster analysis to characterize patterns of prenatal alcohol exposure across gestation. This method allows for a more robust estimation of infants at risk for early deficits in growth and neurodevelopment and for earlier and more targeted interventions.

From 2011 to 2013, 10% of pregnant women reported alcohol use in the past 30 days.[1] During this same period, 53.6% of nonpregnant women aged 18 to 44 years reported using alcohol, and 18.2% reported heavy episodic or binge drinking in the previous 30 days.[1] These estimates are alarming because prenatal alcohol exposure (PAE), particularly binge drinking,[2] is the cause of fetal alcohol spectrum disorders (FASDs). FASD is a spectrum of outcomes that can include characteristic facial features and other anomalies, pre- and postnatal growth deficits, and neurodevelopmental impairments.[3] It was recently reported that FASD occurs in 1.1% to 5.0% of first-grade children in 4 regional samples drawn from the US general population, revealing that FASD is a major public health concern.[4]

Across the spectrum of FASD, effects of PAE are the most consistent for neurodevelopmental outcomes, including lower IQ, slower cognitive processing speed, poor attention, and impairments in executive functioning, verbal learning, and memory.[3,5,6] This work has been extended to reveal that alcohol-related neurodevelopmental impairments are of concern even in children who do not meet the threshold for an FASD diagnosis.[7,8] These neurodevelopmental deficits have been consistently associated with prenatal exposure to heavy or binge drinking.[2,9–13] Findings regarding low-to-moderate levels of PAE have been less consistent, with some systematic reviews and meta-analyses revealing no deficits in functional domains at lower levels of exposure.[2,13–15] This heterogeneity in findings contributes to inconsistency in information and advice offered to women regarding alcohol consumption in pregnancy.[16,17]

Some of the discrepancy in previous findings is likely due to methodologic issues arising from exposure classification.[17] Researchers in previous studies have typically classified PAE using categories such as any use in each of the 3 trimesters of pregnancy, any binge-drinking episodes, the average number of alcoholic beverages consumed over the course of a pregnancy or trimester, or the cumulative count of drinking days across gestation.[13–15,18] However, PAE patterns are complex and highly variable within pregnancy and between individuals. Many women who consume alcohol at the time of conception decrease or abstain after pregnancy recognition.[11,19] However, the timing of pregnancy recognition varies markedly, resulting in heterogeneous patterns of exposure even among women who eventually abstain.[19,20] Furthermore, women may continue consumption at low levels when there is a perception of low risk.[14,19,21] Given that dose, frequency, and gestational timing of PAE all contribute to FASD outcomes, failure to incorporate all 3 factors[9,17] will lead to the misclassification and attenuation of risk estimates.

Researchers in recent studies have used longitudinal cluster analysis (LCA) methods to summarize complex individual-level alcohol-exposure trajectories in women,[22] including 2 studies of alcohol use patterns in pregnancy.[20,23] Such methods are used to classify individuals with similar patterns of alcohol dosing and frequency over a specified time period into distinct groups. However, researchers in none of the previously published studies further examined the trajectory groups to predict infant outcomes.[20,23]

Our purpose in this study was to describe trajectories of PAE in a prospective cohort study of pregnant women and determine if those exposure trajectories were associated with adverse infant outcomes.

METHODS

Study Design

Data for this analysis are from a prospective cohort study of pregnant women in western Ukraine conducted as part of the Collaborative Initiative on Fetal Alcohol Spectrum Disorders (CIFASD) (www.cifasd.org), supported by the National Institute on Alcohol Abuse and Alcoholism. This randomized clinical trial of micronutrient supplementation has been described elsewhere in detail.[24,25] Briefly, all pregnant women who presented to 1 of 2 centralized prenatal care facilities in the Ukraine, the Rivne Regional Medical Diagnostic Center and the Khmelnytsky Perinatal Center, between April 2008 and August 2012 were eligible for screening about their alcohol consumption around conception and the most-recent month of pregnancy. Women who reported binge episodes of 4 to 5 alcoholic drinks per occasion at least weekly, at least 5 episodes of 3 to 4 drinks, or at least 10 episodes of 1 to 2 drinks in the month around conception and/or in the most-recent month of pregnancy were recruited. After the identification of a participant who was exposed, the woman who was the next minimally exposed or unexposed (<2 drinks per occasion, ≤2 drinks per week in the month around conception, and no alcohol in the most-recent month of pregnancy) was recruited for participation. Women were interviewed about demographics, behaviors, and pregnancy characteristics by using standard questionnaires on enrollment and again at ~32 weeks' gestation. After birth, information on growth was collected from medical records. Mothers of live-born infants were invited back twice postpartum (~6 and 12 months of age), at which time neurodevelopmental assessments were conducted with the infants.

This analysis was approved by the institutional review board at the University of California, San Diego.

Measures

Alcohol Exposure

After enrollment, women who reported ever being drinkers in their lifetimes completed a timeline follow-back assessment of day-by-day alcohol consumption by type, quantity, and frequency in a typical week around conception and in the most-recent 2 weeks of pregnancy.[26] The quantity and frequency of alcohol consumption in response to these questions were summarized as the average number of drinks per day over the period for which each mother was reporting as a reflection of the overall quantity of alcohol consumed. This information was then converted into absolute ounces of alcohol (ozAA) per day. One standard drink is equivalent to 0.5 ozAA. At a follow-up pregnancy visit at ∼32 weeks' gestation, women were asked if their alcohol consumption had changed since the enrollment visit, and if they answered yes, they were again asked to recall alcohol consumption for the previous 7 days commensurate with the enrollment visit procedures.

Data Preparation for Trajectory Creation

For each participant, a 40-week gestational exposure profile was created from the following information. The average ozAA per day reported at conception was assumed to have continued until the point of self-reported pregnancy recognition (mean: 5.6 weeks' gestation). At the week of pregnancy recognition, exposure was assumed to have changed to the average ozAA per day reported at the enrollment visit. This amount was carried forward until the gestational week of the follow-up pregnancy visit, at which consumption was updated and assumed to have

changed or continued unchanged from enrollment until 40 weeks' gestation. To identify similar clusters of individual PAE trajectories, we employed the R statistical software package "kml."[27,28] Additional information on k-means longitudinal (kml) data is found in the Supplemental Information.

Outcomes and Covariates

Growth and Neurodevelopmental Outcomes

Infant weight, length, and head circumference at birth were abstracted from medical records and converted to sex- and gestational age–specific percentiles based on US Centers for Disease Control and Prevention growth charts.[29] Neurodevelopment was evaluated at 6 and 12 months of age with the Bayley Scales for Infant Development, Second Edition.[30] Testing was administered by 1 of 2 Ukrainian psychologists who were blinded to each mother's alcohol exposure group. Participants who missed the 6-month assessment (*n* = 120) were still eligible to complete the 12-month assessment.

We focused our analyses on the Mental Developmental Index (MDI) and Psychomotor Development Index (PDI), both of which were standardized to a scale with a mean of 100 and an SD of 15. The MDI is used to assess early cognitive and language development through measures of knowledge, problem solving, and memory. The PDI is used to evaluate body control, the manipulation of large muscles, and fine manipulation skills. All scores were age standardized and age corrected for births before 37 weeks' gestation (*n* = 22).

Covariates

Maternal age, gestational age at enrollment, gestational age at pregnancy recognition, cohabitation status (married, single, divorced, or separated), maternal prenatal or

multivitamin use (randomly assigned to a multivitamin supplement for the trial and/or self-report of vitamin use in pregnancy at the time of enrollment), and maternal smoking status (never, quit before pregnancy, quit at recognition of pregnancy, or continued) were captured from the maternal enrollment interview. Socioeconomic status (SES) was calculated by using Hollingshead[31] scores based on maternal report of maternal and paternal occupation and education.

Statistical Analyses

Descriptive characteristics (frequencies and means) were stratified by trajectory groups. To test the association between trajectory group and maternal characteristics, we performed an analysis of variance for continuous variables and χ^2 with Fisher's exact tests (when necessary) for categorical variables.

Generalized linear models were constructed to estimate β coefficients for trajectory group and growth outcomes (weight, length, and head circumference) and neurodevelopment (MDI and PDI) at 6 and 12 months of age. All models were adjusted for vitamin use in pregnancy, Hollingshead SES, maternal age at enrollment, maternal smoking status, and gestational age at enrollment.

To account for 25% to 27% loss to follow-up on the 6- and 12-month neurodevelopmental examinations, respectively, we repeated the neurodevelopment models with the inclusion of stabilized inverse probability of censoring weights (IPCWs).[32] Loss to follow-up at 6 and 12 months of age was associated with lower SES (*P* = .003) and lower educational achievement (*P* = .001) and was marginally associated with younger maternal age (*P* = .16). Also, although alcohol trajectory group was not statistically significant (*P* = .32), 39% of infants born to
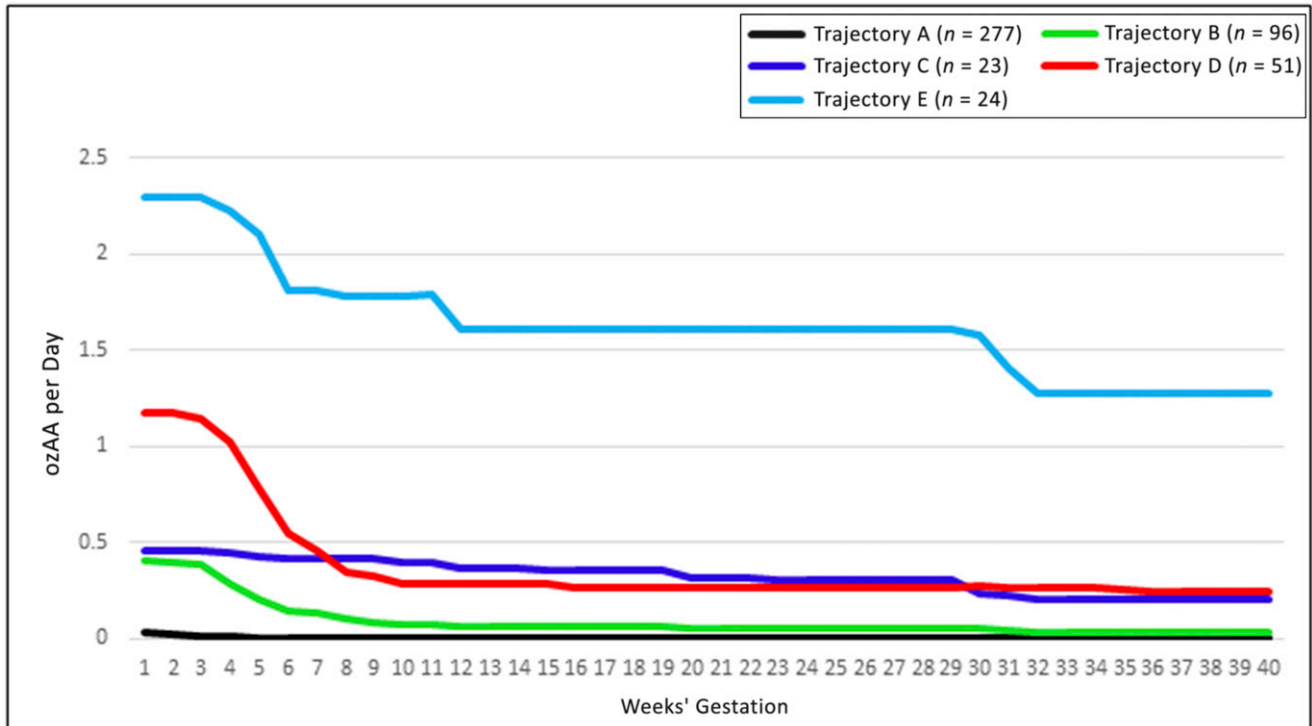
FIGURE 1
Trajectory groups based on ozAA per day across 40 weeks' gestation (*n* = 471).

women in the C trajectory group (low-to-moderate PAE sustained across gestation) and 27% in the D trajectory group (moderate-to-high PAE with reduction early in gestation) did not complete the 6-month neurodevelopmental assessment versus 23% in the A trajectory group (minimal to no PAE throughout gestation). Thus, SES, maternal education, maternal age, and trajectory group were included in the denominator of the stabilized weights.

RESULTS

We enrolled 776 women into the study at a mean gestational age of 18.2 weeks. Of these, 483 (62.2%) completed the second pregnancy interview at a mean gestational age of 31.9 weeks, in which alcohol consumption over the previous 2 weeks was again collected. Eight participants who did not report pregnancy recognition (necessary for trajectory creation) were excluded,

as were 2 twin sets, resulting in 471 women in the final analytic sample. Women who completed both pregnancy visits were more likely to have higher SES, have attended college, and have realized they were pregnant ~1 week earlier in gestation (mean: 5.6 weeks) and were less likely to have had a preterm delivery than women who only completed 1 pregnancy visit. The groups did not differ on smoking behaviors, vitamin use, cohabitation status, age, or amount of alcohol consumption reported at the enrollment visit.

Trajectories

A 5-trajectory solution was selected on the basis of quality criterion and clinical relevance (Fig 1). Trajectories were best described as minimal to no PAE throughout gestation (trajectory A), low-to-moderate PAE with discontinuation early in gestation (trajectory B), low-to-moderate PAE sustained across gestation (trajectory C), moderate-to-high PAE with reduction early in gestation

(trajectory D), and high PAE sustained across gestation (trajectory E). Of note, although trajectory C started at a lower exposure in the first trimester relative to trajectory D (0.42 vs 0.62 ozAA per day), the members in trajectory C maintained a higher dose through the second trimester (0.33 vs 0.27 ozAA per day), resulting in a higher mean consumption over gestation (0.31 vs 0.26 ozAA per day; Table 1).

Descriptive Characteristics

As anticipated on the basis of the study design, 230 women (48.8%) reported no alcohol consumption from the time of conception through the second pregnancy interview. The majority of women in the sample were married or cohabiting with a partner, had medium-to-high SES, used a prenatal or multivitamin in pregnancy, and were an average of 26.0 years of age at enrollment. Overall, the prevalence of preterm birth (<37 weeks' gestation) in the sample was low (4.6%). When these

TABLE 1 Trajectory Characteristics by Group

	Trajectory A (n = 277)	Trajectory B (n = 96)	Trajectory C (n = 23)	Trajectory D (n = 51)	Trajectory E (n = 24)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
ozAA per d across gestation					
Mean	0.00 (0.01)	0.05 (0.06)	0.31 (0.16)	0.26 (0.32)	1.58 (0.65)
Minimum	0.00 (0.00)	0.01 (0.03)	0.19 (0.17)	0.20 (0.31)	1.11 (0.77)
Maximum	0.03 (0.09)	0.41 (0.15)	0.48 (0.13)	1.20 (0.76)	2.67 (1.41)
Mean ozAA per d by trimester					
Trimester 1	0.01 (0.02)	0.18 (0.08)	0.42 (0.12)	0.62 (0.41)	2.14 (1.22)
Trimester 2	0.00 (0.01)	0.06 (0.06)	0.33 (0.14)	0.27 (0.32)	1.61 (0.65)
Trimester 3	0.00 (0.02)	0.04 (0.06)	0.23 (0.16)	0.24 (0.33)	1.36 (0.68)

TABLE 2 Maternal Characteristics and Infant Outcomes by Trajectory Group Assignment

	Trajectory A (n = 277)	Trajectory B (n = 96)	Trajectory C (n = 23)	Trajectory D (n = 51)	Trajectory E (n = 24)	P^a
Gestation wk at enrollment, mean (SD)	17.0 (5.4)	18.5 (5.4)	24.6 (8.6)	20.0 (8.4)	20.6 (7.9)	<.0001
Maternal age, y, mean (SD)	26.1 (4.6)	26.3 (5.8)	25.1 (6.3)	24.4 (4.8)	29.1 (5.7)	.005
Gestational wk at pregnancy recognition, mean (SD)	4.7 (2.3)	5.9 (3.2)	9.1 (6.2)	5.9 (2.2)	9.5 (5.9)	<.0001
Cohabitation status is single, separated, or divorced, n (%)	11 (4.0)	11 (11.5)	6 (26.1)	12 (23.5)	2 (8.3)	<.0001
Maternal education, less than college degree, n (%)	116 (41.9)	61 (63.5)	20 (86.9)	32 (62.8)	19 (79.2)	<.0001
SES, n (%)						
Low (HH <30)	38 (13.7)	29 (30.2)	13 (56.5)	20 (39.2)	11 (45.8)	<.0001
Missing	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	—
Vitamin use in pregnancy, no, n (%)	53 (19.1)	22 (22.9)	10 (43.5)	14 (27.5)	12 (50.0)	.001
Maternal smoking, n (%)						
Active or former pregnancy smoking	37 (13.4)	52 (54.2)	14 (60.9)	29 (56.9)	7 (29.2)	<.0001
Missing	4 (1.4)	0 (0.0)	1 (4.3)	0 (0.0)	1 (4.2)	—
Infant outcomes, mean (SD)						
Birth wt percentile	48.5 (26.3)	41.7 (27.3)	29.7 (27.2)	37.0 (28.2)	27.7 (24.8)	<.001
Length percentile	77.7 (20.1)	70.0 (26.4)	55.0 (31.1)	64.6 (29.3)	59.2 (31.8)	<.001
Head circumference percentile	36.6 (24.9)	35.9 (26.0)	34.7 (28.5)	35.3 (25.2)	28.1 (29.0)	.19
Gestational wk at delivery	39.6 (1.4)	39.5 (1.8)	38.5 (1.8)	38.8 (2.4)	39.0 (1.8)	.0004
6-mo Bayley outcomes, mean (SD)						
MDI	90.9 (7.4)	90.2 (7.9)	85.1 (7.5)	85.4 (11.1)	80.4 (11.7)	<.001
Missing	64 (23.2)	28 (29.2)	9 (39.1)	14 (27.4)	4 (0.20)	—
PDI	89.9 (10.4)	89.6 (11.1)	82.9 (9.9)	86.5 (13.7)	78.6 (12.2)	.0002
Missing	64 (23.2)	28 (29.2)	9 (39.1)	14 (27.4)	4 (0.20)	—
12-mo Bayley outcomes, mean (SD)						
MDI	91.5 (10.4)	89.2 (10.7)	82.0 (7.0)	86.4 (13.2)	76.7 (14.6)	<.001
Missing	67 (24.2)	35 (36.5)	6 (26.1)	14 (27.4)	5 (20.8)	—
PDI	99.6 (11.0)	97.6 (12.6)	90.1 (13.7)	93.6 (14.4)	86.5 (19.6)	<.001
Missing	67 (24.2)	35 (36.5)	6 (26.1)	14 (27.4)	5 (20.8)	—

HH, Hollingshead Four Factor Index of Socioeconomic Status; —, not applicable.

[a] P values were calculated with a χ^2 test or an analysis of variance.

factors were analyzed by trajectory group, women in trajectories C and E (sustained-use trajectories) reported later recognition of pregnancy, were less likely to have a college degree, and were less likely to use prenatal and/or multivitamins than those in the other trajectories (Table 2).
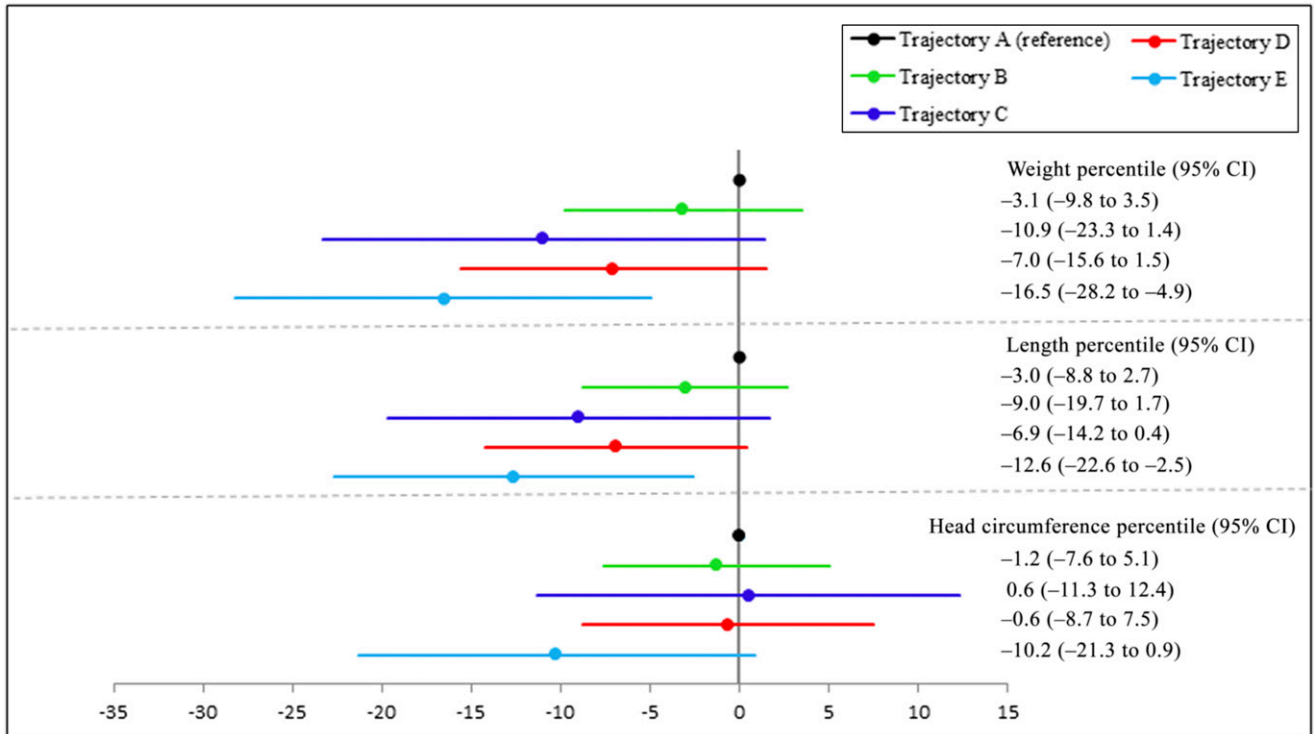
Birth Outcome Models

In multivariable models adjusted for vitamin use in pregnancy, Hollingshead SES, maternal age at enrollment, maternal smoking status, and gestational age at enrollment (Fig 2), only trajectory E (sustained high use) was associated with a reduced birth weight percentile (−16.5; 95% confidence interval [CI] −28.2 to −4.9) and length percentile (−12.6; 95% CI −22.6 to −2.5) compared with trajectory A (minimal or no use). There were no statistically significant effects observed between PAE trajectories and head circumference.

Greater alcohol use in pregnancy was associated with lower neurodevelopmental scores (Fig 3). Trajectory E (highest sustained use) was associated with deficits in MDI and PDI scores at both 6 and 12 months of age relative to trajectory A (minimal or no use). Moderate-to-high use with reduction (trajectory D) was associated with reduced MDI scores at 6 and 12 months of age, and low-to-moderate sustained use (trajectory C) was associated with reduced performance on the PDI at 6 months of age and the MDI at 12 months of age. PAE characterized

FIGURE 2
Multivariable linear regression of prenatal alcohol consumption by trajectory group and infant growth outcomes. Models were adjusted for vitamin use in pregnancy, Hollingshead SES, maternal age at enrollment, maternal smoking status, and gestational age at enrollment.

by trajectory B (low-to-moderate discontinued use) was not associated with any neurodevelopmental deficits. IPCWs did not meaningfully change any estimates or conclusions; thus, results adjusted with IPCWs are presented.

DISCUSSION

Group-based trajectory methods allow for the retention of quantity, frequency, and timing of PAE in the exposure categorization. Using LCA, we identified 5 distinct trajectories of alcohol consumption in pregnancy: a minimal or no use group, 2 groups with low-to-moderate or moderate-to-high consumption with reduction early in pregnancy, and 2 groups with low-to-moderate or high consumption with sustained use. As anticipated, the trajectory with the highest sustained use was associated with reduced weight and length at birth and deficits in neurodevelopmental domains at both

6 and 12 months of age, replicating decades of research.[2,3,13,33]

Interestingly, on most neurodevelopmental outcomes, trajectory C (low-to-moderate sustained use) had larger deficits compared with trajectory D (early moderate-to-high consumption), although CIs overlapped widely, and not all findings were statistically significant. These differences, although modest and not statistically significant, persisted through the 12-month follow-up period. This same pattern was also observed with birth weight and length percentiles, although again with overlapping CIs that crossed the null. These observations reveal that for certain infant adverse outcomes, prolonged exposure to alcohol through gestational weeks 10 to 20, even at modest amounts, may be more detrimental than brief periods of higher consumption limited to earlier in pregnancy. Researchers in previous studies have reported a

dose-response pattern between PAE and neurodevelopmental outcomes, although low-to-moderate levels of consumption tend to have more variation and be more difficult to interpret.[33] Although our findings are generally in concurrence, the nuance between sustained low-to-moderate exposure and discontinued moderate-to-high exposure are intriguing and reinforce the notion that intervention, even after the first trimester, should be strongly encouraged.[9,34,35]

This methodology of exposure assessment is not without precedent. In a recent analysis of 11 692 pregnancies in the Safe Passage Study, Dukes et al[20] performed Proc Traj to describe alcohol (drinks per drinking day) and tobacco exposure measured up to 4 times in pregnancy. Proc Traj is another LCA methodology that is available in SAS (SAS Institute, Inc, Cary, NC)[36]; yet unlike kml, this methodology allows for formal checks of the validity of
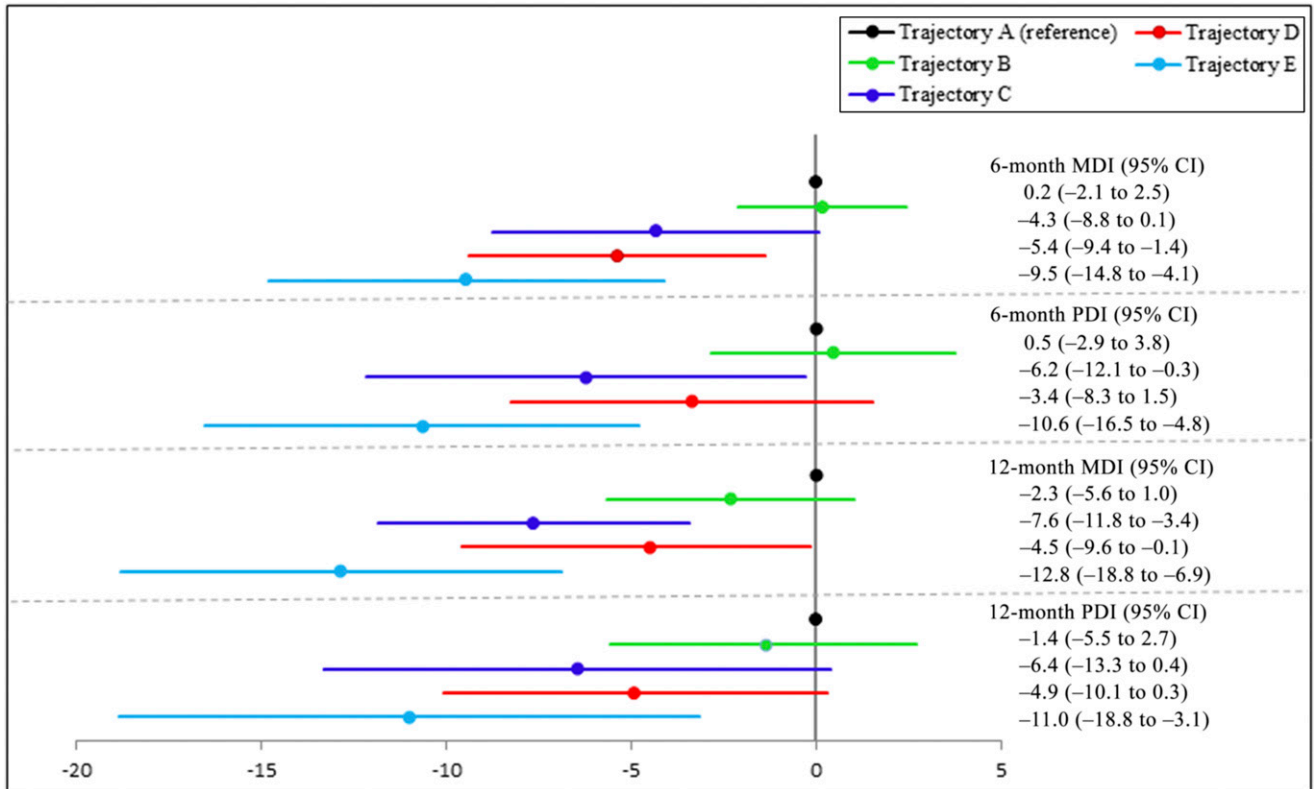
FIGURE 3
Multivariable linear regression of prenatal alcohol consumption by trajectory group and neurodevelopmental outcomes. Models were adjusted for vitamin use in pregnancy, Hollingshead SES, maternal age at enrollment, maternal smoking status, and gestational age at enrollment. Stabilized IPCWs were applied to account for loss to follow-up.

partitioning trajectory groups. Their sample included participants from the Northern Plains of the United States and South Africa. Remarkably, despite the differences in sample characteristics and size, both studies revealed 5 trajectories that were used to best describe PAE with the same general patterns of consumption: 2 with high or low continuous use, 2 with high or moderate use with early pregnancy discontinuation, and a group with no use. Similar to our sample of pregnant women in the Ukraine, participants from the Safe Passage Study who continued drinking were less likely to have completed higher education and were more likely to have enrolled later in pregnancy. In a second study of 6597 women recruited in Australia between 1981 and 1983, the investigators performed LCA on drinking measured at 4 time points: prepregnancy, early pregnancy,

late pregnancy, and 6 months postpartum.[23] Exposure was defined at each time point as the product of the frequency and quantity of alcohol consumption. Three trajectories were identified: high consumption (with reduction in early pregnancy), light consumption (<0.5 glass per day), and abstainers. Mothers who were unmarried and multiparous were more likely to be in the high-use category.[23]

To our knowledge, our study is the first in which researchers report on LCA for PAE and associated growth and neurodevelopmental outcomes in offspring. The relatively homogenous sample of women, recruited 1:1 for alcohol exposure, allowed for a broad and heterogeneous distribution of alcohol consumption in a relatively small sample. The 2 structured interviews on alcohol exposure in pregnancy and the clinician-assessed

growth and neurodevelopmental outcomes are additional strengths of the study. This study has several limitations. PAE is not deterministic; some children who are exposed to low doses of alcohol are affected, whereas others who are exposed to high or sustained doses are not.[9] Physiologic, genetic, and epigenetic factors, such as placental functioning, maternal IQ, illicit and licit substances, and nutritional and sociodemographic factors may all contribute to outcomes. Many of these covariates were not collected or vary over the course of a pregnancy, which could result in residual confounding. Additionally, we relied on maternal recall of alcohol exposure, which if differentially reported by trajectory group could result in biased estimates. Similarly, women with only 1 pregnancy visit were excluded from analysis and differed on select baseline characteristics. This could

limit the generalizability of results in those strata. Also, in LCA, there is subjectivity in the number of trajectories selected. Although we used the quality criterion available in kml, strata size and clinical relevance were also considered. Although we were reassured that the same basic trajectories were found in the Safe Passage Study when using LCA with formal group partitioning criteria, we recognize that both samples consist of high-risk populations, which is likely the reason for the difference in trajectory shapes in the Australian sample. As a result, other samples will probably not have the same patterns of use, and the generalizability of these consumption patterns may be limited. Finally, infant screening measures are relatively insensitive to mild-to-moderate developmental deficits due to the participants' young age; thus, future developmental testing is appropriate.[25] Future work with the methodology will include an exploration of associations between trajectory groups and cardinal and noncardinal physical features as well as the repetition of these analyses with preschool and school-aged growth and neurodevelopmental evaluations to determine if these observations in infancy are enduring.

CONCLUSIONS

Classifying PAE by using group-based trajectory methods allows for a more nuanced approach for describing complex exposure patterns. Using this method, with our findings, we confirmed that high, sustained PAE across gestation confers the highest risk for adverse infant outcomes but demonstrated that even low-to-moderate PAE continued across gestation is associated with certain deficits. This strongly reinforces the important message that no matter the initial amount of consumption, cessation increases the chances for improved offspring outcomes. Trajectory methods of classifying the dose, timing, and duration of PAE may be more informative than other methods when predicting the effects of PAE on infant outcomes. With our findings, we support the continued use of the methodology to further delineate risk by different patterns of consumption. This approach can be used to help clinicians counsel pregnant women on the risk of alcohol use even at moderate-to-low levels. Furthermore, it can be used to help identify high-risk infants for targeted early intervention.

ABBREVIATIONS

CI: confidence interval
CIFASD: Collaborative Initiative on Fetal Alcohol Spectrum Disorders
FASD: fetal alcohol spectrum disorder
IPCW: inverse probability of censoring weight
kml: k-means longitudinal
LCA: longitudinal cluster analysis
MDI: Mental Developmental Index
ozAA: absolute ounces of alcohol
PAE: prenatal alcohol exposure
PDI: Psychomotor Development Index
SES: socioeconomic status

REFERENCES

1. Tan CH, Denny CH, Cheal NE, Sniezek JE, Kanny D. Alcohol use and binge drinking among women of childbearing age - United States, 2011-2013. *MMWR Morb Mortal Wkly Rep*. 2015;64(37):1042–1046

2. Flak AL, Su S, Bertrand J, Denny CH, Kesmodel US, Cogswell ME. The association of mild, moderate, and

binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. *Alcohol Clin Exp Res*. 2014;38(1):214–226

3. Riley EP, Infante MA, Warren KR. Fetal alcohol spectrum disorders: an overview. *Neuropsychol Rev*. 2011;21(2):73–80

4. May PA, Chambers CD, Kalberg WO, et al. Prevalence of fetal alcohol spectrum disorders in 4 US communities. *JAMA*. 2018;319(5):474–482

5. Jacobson SW, Jacobson JL, Stanton ME, Meintjes EM, Molteno CD. Biobehavioral markers of adverse effect in fetal alcohol spectrum disorders. *Neuropsychol Rev*. 2011;21(2):148–166

6. Glass L, Ware AL, Mattson SN. Neurobehavioral, neurologic, and neuroimaging characteristics of fetal alcohol spectrum disorders. *Handb Clin Neurol*. 2014;125:435–462

7. Paolozza A, Rasmussen C, Pei J, et al. Deficits in response inhibition correlate with oculomotor control in children with fetal alcohol spectrum disorder and prenatal alcohol exposure. *Behav Brain Res*. 2014;259:97–105

8. Landgren M, Svensson L, Strömland K, Andersson Grönlund M. Prenatal alcohol exposure and neurodevelopmental disorders in children adopted from eastern Europe. *Pediatrics*. 2010;125(5). Available at: www.pediatrics.org/cgi/content/full/125/5/e1178

9. May PA, Blankenship J, Marais AS, et al. Maternal alcohol consumption producing fetal alcohol spectrum disorders (FASD): quantity, frequency, and timing of drinking. *Drug Alcohol Depend*. 2013;133(2):502–512

10. May PA, Gossage JP. Maternal risk factors for fetal alcohol spectrum disorders: not as simple as it might seem. *Alcohol Res Health*. 2011;34(1):15–26

11. Conover EA, Jones KL. Safety concerns regarding binge drinking in pregnancy: a review. *Birth Defects Res A Clin Mol Teratol*. 2012;94(8):570–575

12. Henderson J, Kesmodel U, Gray R. Systematic review of the fetal effects of prenatal binge-drinking. *J Epidemiol Community Health*. 2007;61(12):1069–1073

13. Bay B, Kesmodel US. Prenatal alcohol exposure - a systematic review of the effects on child motor function. *Acta Obstet Gynecol Scand*. 2011;90(3):210–226

14. Henderson J, Gray R, Brocklehurst P. Systematic review of effects of low-moderate prenatal alcohol exposure on pregnancy outcome [published correction appears in *BJOG*. 2007;114(7):914–915]. *BJOG*. 2007;114(3):243–252

15. Kesmodel US, Bertrand J, Støvring H, Skarpness B, Denny CH, Mortensen EL; Lifestyle During Pregnancy Study Group. The effect of different alcohol drinking patterns in early to mid pregnancy on the child's intelligence, attention, and executive function. *BJOG*. 2012;119(10):1180–1190

16. Anderson AE, Hure AJ, Kay-Lambkin FJ, Loxton DJ. Women's perceptions of information about alcohol use during pregnancy: a qualitative study. *BMC Public Health*. 2014;14:1048

17. Niclasen J. Prenatal exposure to alcohol and the developing fetus: methodological issues. *BJOG*. 2015;122(6):770–772

18. Skogerbø Å, Kesmodel US, Wimberley T, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on executive function in 5-year-old children [published correction appears in *BJOG*. 2012;119(13):1683; *BJOG*. 2013;120(10):1302]. *BJOG*. 2012;119(10):1201–1210

19. Kitsantas P, Gaffney KF, Wu H, Kastello JC. Determinants of alcohol cessation, reduction and no reduction during pregnancy. *Arch Gynecol Obstet*. 2014;289(4):771–779

20. Dukes K, Tripp T, Willinger M, et al; PASS Network. Drinking and smoking patterns during pregnancy: development of group-based trajectories in the Safe Passage Study. *Alcohol*. 2017;62:49–60

21. Toutain S. What women in France say about alcohol abstinence during pregnancy. *Drug Alcohol Rev*. 2010;29(2):184–188

22. Tran NT, Clavarino A, Williams GM, Najman JM. Life course outcomes for women with different alcohol consumption trajectories: a population-based longitudinal study. *Drug Alcohol Rev*. 2016;35(6):763–771

23. Tran NT, Najman JM, Hayatbakhsh R. Predictors of maternal drinking trajectories before and after pregnancy: evidence from a longitudinal study. *Aust N Z J Obstet Gynaecol*. 2015;55(2):123–130

24. Chambers CD, Yevtushok L, Zymak-Zakutnya N, et al. Prevalence and predictors of maternal alcohol consumption in 2 regions of Ukraine. *Alcohol Clin Exp Res*. 2014;38(4):1012–1019

25. Coles CD, Kable JA, Keen CL, et al; CIFASD. Dose and timing of prenatal alcohol exposure and maternal nutritional supplements: developmental effects on 6-month-old infants. *Matern Child Health J*. 2015;19(12):2605–2614

26. Sobell LC, Sobell MB. Alcohol timeline follow-back (TLFB). In: Rush AJ, ed. *Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Association; 2000:477–479

27. Genolini C, Falissard B. KmL: K-means for longitudinal data. *Comput Stat*. 2010;25(2):317–328

28. Genolini C, Falissard B. Package 'kml'. Available at: https://cran.r-project.org/web/packages/kml/kml.pdf. Accessed December 6, 2018

29. Moriarty DG, Zack MM, Holt JB, Chapman DP, Safran MA. Geographic patterns of frequent mental distress: U.S. adults, 1993-2001 and 2003-2006. *Am J Prev Med*. 2009;36(6):497–505

30. Bayley N. *Bayley Scales of Infant Development Manual*, 2nd ed. San Antonio, TX: The Psychological Corporation; 1993

31. Hollingshead A. Four factor index of social status. *J Sociol (Melb)*. 2011;8(23):21–51

32. Mansournia MA, Altman DG. Inverse probability weighting. *BMJ*. 2016;352:i189

33. Day NL, Leech SL, Richardson GA, Cornelius MD, Robles N, Larkby C. Prenatal alcohol exposure predicts

continued deficits in offspring size at 14 years of age. *Alcohol Clin Exp Res*. 2002;26(10):1584–1591

34. Coles CD, Smith I, Fernhoff PM, Falek A. Neonatal neurobehavioral characteristics as correlates of

maternal alcohol use during gestation. *Alcohol Clin Exp Res*. 1985;9(5): 454–460

35. Rosett HL, Weiner L, Lee A, Zuckerman B, Dooling E, Oppenheimer E. Patterns of alcohol consumption and fetal

development. *Obstet Gynecol*. 1983;61(5):539–546

36. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res*. 2018;27(7):2015–2023