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Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14

Nancy L. Day, Lidush Goldschmidt & Carrie A. Thomas

Western Psychiatric Institute and Clinic, Pittsburgh, USA

ABSTRACT

Aim To evaluate the effects of prenatal marijuana exposure (PME) on the age of onset and frequency of marijuana use while controlling for identified confounds of early marijuana use among 14-year-olds. **Design** In this longitudinal cohort study, women were recruited in their fourth prenatal month. Women and children were followed throughout pregnancy and at multiple time-points into adolescence. **Setting and participants** Recruitment was from a hospital-based prenatal clinic. The women ranged in age from 18 to 42, half were African American and half Caucasian, and most were of lower socio-economic status. The women were generally light to moderate substance users during pregnancy and subsequently. At 14 years, 580 of the 763 offspring–mother pairs (76%) were assessed. A total of 563 pairs (74%) was included in this analysis. **Measurements** Socio-demographic, environmental, psychological, behavioral, biological and developmental factors were assessed. Outcomes were age of onset and frequency of marijuana use at age 14. **Findings** PME predicted age of onset and frequency of marijuana use among the 14-year-old offspring. This finding was significant after controlling for other variables including the child's current alcohol and tobacco use, pubertal stage, sexual activity, delinquency, peer drug use, family history of drug abuse and characteristics of the home environment including parental depression, current drug use and strictness/supervision. **Conclusions** Prenatal exposure to marijuana, in addition to other factors, is a significant predictor of marijuana use at age 14.

Keywords Adolescent, marijuana, prenatal marijuana.

Correspondence to: Nancy L. Day, WPIC, 3811 O'Hara Street, Pittsburgh, PA 15213–2593, USA. E-mail: nday@pitt.edu
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INTRODUCTION

Substance use is common in early adolescence. In the Monitoring the Future Study, 16.3% of 8th graders reported using marijuana at least once [1], and 13% of Seattle public school students had tried marijuana by age 13 [2]. Early use predicts higher rates of antisocial behaviors, psychological problems [3], health consequences and adult substance use compared to later initiation or no use [4–9]. Exposure to drugs in adolescence may also affect ongoing brain maturation [10]. Thus, it is important to identify predictors and covariates of early substance use and to define pathways for intervention.

One pathway that is rarely explored is the relation between prenatal exposure to substances and subsequent substance use, although there is accumulating evidence that prenatal exposures predict substance use and abuse. In the Maternal Health Practices and Child Development (MHPCD) study, prenatal tobacco exposure (PTE) predicted tobacco use among the offspring at age 14 [11], controlling for other prenatal exposures and significant covariates. There have been similar reports of this association from Buka and colleagues [12] and Kandel *et al.* [13], although in the latter report the relation was significant only for females. Porath & Fried [14] have recently reported a significant association between prenatal marijuana exposure (PME) and initiation and use of marijuana among 16–21-year-olds, although only in males, after controlling for other prenatal exposures and prenatal demographic factors. Baer and colleagues [15] found an association between prenatal exposure to alcohol and subsequent alcohol use at 14 years and alcohol problems at 21 years [16], controlling for family history of alcohol abuse and PTE.

There is biological evidence that PME directly affects the development of the central nervous system (CNS) in both animals and humans. Cannabinoid receptors are found in the fetal brain around the 14th week of

gestation [17]. These receptors interact with exogenous substances such as delta-9-tetrahydrocannabinol (THC) as well as with the endogenous cannabinoids. Prenatally administered THC in rats causes direct changes in the cannabinoid receptor system [18]. Although the role of these cannabinoid receptors is not well understood, it is clear that they affect brain development and functioning across vital domains including analgesia, cognition, memory, locomotion, appetite and immune control [19].

There is also evidence from studies of birth cohorts that PME affects the development of the CNS. The MHPCD project has demonstrated effects on sleep patterns at birth [20] and 3 years of age [21], and on cognitive development at age 3 [22]. Among preteens and adolescents, PME predicted poorer performance on tests of memory [23], attention and executive functioning [24]. At age 10, exposed offspring had significantly higher rates of depression and anxiety [25,26]. These findings parallel those of the Ottawa Prenatal Prospective Study (OPPS) of deficits in cognitive development [27], attention [28] and executive functioning [29].

In the ecological model [30], environmental context, parental, child and social factors must all be considered to understand patterns of substance use. Dishion, Capaldi & Yoerger [31] used this model and identified family context and child management practices, parental substance use/abuse, child characteristics and the peer environment as significant predictors of substance use. This model was used in the analyses to identify and organize the covariates for inclusion.

Genetic factors [32], demographic characteristics [1,4,33], the family and home environment [31,34–36] and parental substance use and abuse [37–39] are significant predictors or correlates of adolescent substance use. Child factors including age of pubertal onset [40,41], intelligence [42–44], externalizing behavior [45,46], association with substance-using peers [46–48], aggression [43] and neurobehavioral disinhibition [37] are also important factors in understanding substance use.

This investigation had three aims: (1) to determine whether there is a relation between prenatal marijuana exposure and marijuana use at age 14, (2) to identify predictors and correlates of marijuana use at age 14 and (3) to explore whether the association between PME and marijuana use remains significant when other predictors of early onset marijuana use are considered.

METHODS

This study was begun in 1982 when the mothers were in their 4th prenatal month. The protocol was approved by the Human Subjects Review Boards of Magee–Women's Hospital and the University of Pittsburgh.

Study design

The data used in these analyses are from the MHPCD Project. Women who were at least 18 years old and in their 4th prenatal month were recruited from a hospital-based prenatal clinic. There were 1360 completed interviews. The refusal rate at this phase was 15%. After this interview, two study cohorts were selected. Women who used marijuana at least twice per month and the next woman interviewed after that who used less or none were selected to study the effects of PME ($n = 564$). Women who drank three or more drinks per week in the 1st trimester and the next woman interviewed who drank less than that amount, or not at all, were selected for a study of prenatal alcohol exposure (PAE) ($n = 650$). A subject could be in one or both cohorts. The studies ran in parallel and the methods and personnel for both studies were the same. The cohorts were combined for this report ($n = 829$).

Women were interviewed in their 7th prenatal month. At delivery, 8 and 18 months, and 3, 6, 10 and 14 years postpartum, the women and their children were evaluated. At each phase, a standardized protocol assessed maternal psychological, social and environmental factors, demographic status and substance use, and the children's cognitive, behavioral, psychological and physical development.

There were 763 live-born singleton infants. At the 14-year follow-up, 580 subjects were interviewed. Losses between birth and this phase occurred because subjects had moved out of the Pittsburgh area ($n = 49$), refused participation at this phase ($n = 52$) or were lost to follow-up ($n = 69$). An additional six children died and seven were placed for adoption or were in foster care. There were no differences in maternal education, income, marital status, prenatal alcohol or tobacco use between women who participated in the study at 14 years ($n = 580$) and those who did not ($n = 183$). Women interviewed at 14 years were more likely to be African American and to have used marijuana during pregnancy: 55% of the subjects who participated at 14 years were African American compared to 42% among the non-participants, and 20% of those interviewed reported marijuana use during the 3rd trimester of pregnancy compared to 11% among those who were not interviewed.

Adolescents who had medical conditions that interfered with study participation, including cerebral palsy ($n = 2$), fibrous dysplasia ($n = 1$) and mental retardation ($n = 8$), were excluded from these analyses. Three teenagers had missing data on the drug use questions and three reported no marijuana use, but their urine test was positive for THC. These subjects were also excluded, resulting in a sample of 563 mother–child pairs. One adolescent with a positive urinalysis reported use in the past, but not

currently. This case was included in the analyses of age of onset, but was removed from the analyses of current frequency of use. The offspring were aged 14 and 15 years at follow-up; for convenience, we refer to them as 14 years old.

Measures

Questions about the age of onset and the quantity and frequency of marijuana use over the past year were from the Health Behavior Questionnaire [49]. The adolescents were separated from their mothers when they answered the self-report questionnaire. The interviewer remained in the room to answer questions. For children with reading difficulty, the interviewer read the questions aloud and the subject completed the appropriate answers.

Two outcome variables were used for these analyses: age of marijuana onset and current frequency of marijuana use. Age of onset was measured by asking 'How old were you when you first tried marijuana?'. Adolescents were asked how often they used marijuana: (1) every day, (2) almost every day, (3) three to four times a week, (4) one to two times a week, (5) two to three times a month, (6) once a month, (7) six to 11 times a year and (8) one to five times a year. Frequency was collapsed into categories of: (1) no use, (2) less than three to four times/week (non-regular) and (3) three to four times/week or more (regular). These latter categories were chosen to parallel definitions used by Kandel & Chen [50]. It was necessary to reduce the number of categories because the frequency data were asymmetrical. The Health Behavior Questionnaire asks similar questions about alcohol and tobacco use and these data were used to categorize use of these substances. Adolescents were asked about peer substance use on a 4-point scale from none to all and about peer approval of substance use using a dichotomous choice (approve/disapprove).

As a check on the adolescent's self-report, a biological validation of substance use was included. The adolescents were asked to provide a urine sample during their appointment and were informed that the sample would be analyzed for substance use. The time-frame for the detection of THC is 48 hours. Among the adolescents with negative tests, 100 reported using marijuana over the past year. The specificity for marijuana use was 78% when the adolescent's self-report report was compared to his/her urine test.

Cognitive development was measured with the Wechsler Intelligence Scale for Children (WISC-III) [51] at age 14. The reliability of the Full Scale IQ at 14 years is 0.95. Childhood depressive symptoms were self-reported on the Children's Depression Inventory (CDI) [52], a measure that has a test–retest reliability of 0.82 and an internal consistency of 0.86. The Revised Children's Manifest Anxiety Scale (RCMAS) [53] measured self-reports of anxiety. The reliability of this scale is 0.85.

The Child Behavior Checklist (CBCL) [54], which was completed by the mother, was used to assess attention problems and aggression. These measures had test–retest reliabilities of 0.90 and 0.91, respectively. Delinquent acts were assessed using the Self-Report Delinquency Scale (SRD) [55]. The authors of the SRD identified four subscales: damage, theft, violence and status offenses. The reliability coefficients ranged from 0.45 to 0.52 for these subscales. The subscales were combined into a summary score for these analyses.

One item from the Petersen Development Scale [56], 'Do you think your development is any earlier or later than most other boys/girls your age?', was used to measure pubertal status. The question has five categories scored from 1 (much earlier) to 5 (much later). A low score indicates early maturation.

The Home Observation for Measurement of the Environment-Short Form (HOME) [57] was used to evaluate the cognitive stimulation and emotional support provided by the adolescent's family. This instrument was administered to the mothers. The reliability coefficient is 0.92. All items were yes/no choices or 4–5-point scales and included questions such as 'Does your family get a daily newspaper?' and 'About how often does your whole family get together with friends or relatives?'. A variable indicating the presence of an adult male in the household was also included. Parenting practices were assessed with the My Parents instrument [58], which assessed the adolescents' perceptions of their parents' behaviors on three dimensions: acceptance/involvement, strictness/supervision and psychological autonomy. The alphas of these scales were 0.72, 0.76 and 0.82, respectively.

Demographic variables included the mother's education, work status, age and race/ethnicity. Maternal anxiety and anger were measured by the State–Trait Anxiety Inventory (STAI) [59] and depressive symptoms were assessed with the Center for Epidemiological Studies–Depression Scale (CES-D) [60]. Eleven per cent of the adolescents were not with their biological mothers at 14 years: In these cases, the current caregiver was interviewed. For simplicity, we will refer to the caregivers as mothers.

The maternal substance use measures were developed by the MHPCD Project [61]. Marijuana and alcohol use were measured for the year prior to pregnancy, for each month of the 1st trimester, across the 3 months of the 2nd and 3rd trimesters and for the previous year at subsequent phases. The usual, maximum and minimum quantity and frequency were measured for marijuana and five alcoholic beverages (wine, beer, liquor, wine coolers and beer coolers). Women reported on their marijuana and alcohol use across three time-periods of the 1st

trimester, from conception to pregnancy recognition, pregnancy recognition to pregnancy confirmation and from confirmation to the end of the 1st trimester. The measure of 1st-trimester use was weighted by the length of time in each time-period and then summarized across the 1st trimester. Because substance use decreased over the 1st trimester, this method provided a more accurate assessment [62]. Marijuana use was summarized as the average number of joints per day (ADJ, average daily joints) and alcohol use as the average number of drinks per day (ADV, average daily volume). Tobacco use was expressed as the number of cigarettes smoked per day. Because few women continued their marijuana use past the 1st trimester, 1st-trimester marijuana, alcohol and tobacco use were used in the analyses.

Two dichotomous variables described the family history of substance use: (1) whether any relatives from the mother's or father's families had a history of alcohol problems and (2) whether any relative had a history of drug problems.

Statistical analysis

The variables were organized and tested within the following blocks: (1) prenatal substance exposure and family history of drug and alcohol problems; (2) mother's current (14-year) substance use, demographic and psychological status; (3) home environment and parenting practices; (4) adolescent's gender, race, pubertal stage, psychological status, attention problems and executive functioning; and (5) delinquency, aggression, peer use, peer approval of use, child's sexual activity, alcohol and tobacco use at age 14. Initial analyses tested the associations between the outcomes and variables within each block. Then, variables from blocks 1–4 that were significant were entered into the analysis in a stepwise manner. After this analysis, the significant variables from block 5 were added to the model to explore whether the identified risk factors from the previous step remained significant after controlling for current adolescent behaviors.

A Cox proportional hazards regression model was used to identify antecedent and concurrent risk factors associated with age of initiation of marijuana use. In Cox proportional hazards models, age at assessment is integrated within the model as the survival time and so was not considered separately. An ordinal polytomous logistic regression was used to identify factors that predicted the frequency of marijuana use. The ordinal polytomous logistic regression is an extension of logistic regression to ordinal responses. It simultaneously describes the effects of the exploratory variables on the cumulative logits, improving parsimony and power. The coefficients that are generated in polytomous logistic regression are per unit of measurement, the odds ratios represent the probability of being in a higher category of use.

We also tested two interactions that have been suggested in the literature. In the first, we tested whether the influence of peer use on adolescent's marijuana use differed by race. A second interaction evaluated whether there were gender differences in the association between depression and marijuana use. Each interaction was tested separately.

To adjust for sample loss, we repeated the analyses with weights to reflect the differential loss by race and by 3rd-trimester PME. Weights were constructed using the inverse of the probability of response for each racial group and for each exposure group in the 3rd trimester. The results did not differ from the unweighted results and we have presented the unweighted data.

RESULTS

Maternal and adolescent substance use

In the 1st trimester, 41.6% of the women in the cohort used marijuana. This proportion decreased over pregnancy and at postpartum, resulting in a rate of 15.1% use among the mothers at the 14-year assessment (Table 1). Mean marijuana use among users also decreased across time from 1.02 joints/day in the 1st trimester to 0.38 joints/day at 14 years. Alcohol use also decreased across pregnancy, from 64.1% in the 1st trimester to 31.8% in the 3rd, but increased at postpartum to 75%. By contrast, the rates of tobacco use remained at approximately 50% across pregnancy and at 14 years postpartum.

Thirty per cent of the adolescents reported using marijuana in the past year and 7.5% used marijuana regularly (at least three to four times/week). Thirteen additional adolescents had initiated marijuana use but did not report use in the past year. Alcohol use was reported by 37% of the adolescents and tobacco by 21% (Table 1). The earliest onset of marijuana use was 9 years of age and the incidence rate (new initiations/population at risk) at that age was 0.4%. Incidence increased to age 14, when 13% initiated use (Table 2).

Block 1 (Table 3), the prenatal and family history variables, represented potential early determinants of marijuana use. When all the variables in the block were considered, PME was a significant predictor of both age of initiation and the frequency of use among the adolescents. PTE predicted age of onset and frequency of use, while PAE and family history of alcohol problems were not associated with adolescent marijuana use. Family history of drug problems predicted age of onset.

Current maternal tobacco use was significantly associated with the frequency of adolescent marijuana use (Table 3, block 2); current maternal marijuana use was marginally associated with frequency, and current maternal alcohol and cocaine use were not associated

Table 1 Maternal substance use across study phases.

	Mother's use				
Substance	*1st trimester*	*2nd trimester*	*3rd trimester*	*14 years*	*Adolescent's use 14 years*
Marijuana					
% Users	41.6	24.1	20.1	15.1	30%
Mean use (joints/day)[a]	1.02	0.67	0.88	0.38	0.55
Range	0.002–8.8	0.01–6.5	0.01–9.4	0.002–5.0	0.001–8.0
Alcohol					
% Users	64.1	36.5	31.8	75.1	37%
Mean use (drinks/day)[a]	0.89	0.32	0.5	1.1	0.37
Range	0.006–19.6	0.01–6.7	0.02–24.7	0.005–13.7	0.005–7.03
Tobacco					
% Users	53.5	52.8	51.3	53.4	21%
Mean use (cigarettes/day)[a]	14.7	15.7	17.3	14.6	5.5
Range	0.5–50	0.5–70	0.5–70	0.5–60	0.005–45.0

[a]Calculation of mean use included users only.

Table 2 Hazard rates of marijuana use initiation.

Age	*Incidence rate*[a]	*n/N*[b]
9–9.9	0.4	2/563
10–10.9	0.5	3/561
11–11.9	1.6	9/558
12–12.9	5.5	30/549
13–13.9	12.7	66/519
14–14.9	13.0	59/453
15–[c]	3.3	13/394

[a]Calculated as the percentage of adolescents who initiated use during the interval relative to those who had not yet initiated use at the beginning of the interval. [b]Number beginning use (*n*)/number at risk (N). [c]Some subjects were interviewed at age 15.

with either age of onset or current frequency of use. Maternal depression was significantly associated with an earlier age of initiation in the offspring. Other maternal psychological factors, and whether the mother worked or attended school, were not significant. The quality of the home environment was significantly associated with both age of onset and frequency of marijuana use, as was parental strictness/supervision (Table 3, block 3). Other environmental measures were not significant.

Child's gender, race and IQ did not predict age of onset or frequency of marijuana use at age 14 (Table 3, block 4). Age at assessment also did not differ across the frequency groups, the average ages of non-users, non-regular users and regular users at assessment were 14.8, 14.9 and 14.9 years, respectively. Earlier pubertal maturation predicted an earlier age of onset and higher frequency of marijuana use. Attention problems were significantly associated with the frequency of use, but not the age of onset. More symptoms of depression predicted a higher frequency of use and a younger age of onset. The gender × depression interaction was not significant.

We also evaluated the adolescent's behavior at age 14 (Table 3, block 5). Peer use, sexual activity, current alcohol and tobacco use were significantly associated with age of onset of use. These variables and delinquency were also significantly associated with frequency of use. Aggression and peer approval of use were not associated with either outcome after controlling for the other factors in the block, and there was no interaction between peer use and race.

Age of onset of marijuana use, multivariate models

Variables that were significantly associated with age of onset in the first four blocks were entered into a stepwise Cox proportional hazards regression analysis (Table 4a). Table 4 shows the hazard coefficients, hazard rates, and the significance of these variables. Positive coefficients indicate an increased risk of initiation, while negative coefficients indicate an inverse, or negative, association between the variable and the outcome. PME significantly predicted the age of onset of marijuana use. For each daily joint of marijuana exposure in the 1st trimester, the rate of initiating marijuana use among those with PME was increased by 1.14 compared to those with no exposure after controlling for other significant predictors. Other significant factors included family history of drug abuse, quality of the home environment, parental strictness/supervision, child's depressive symptoms and pubertal stage.

When the significant current child behavioral characteristics from block 5 (Table 3) were added, PME was marginally ($P = 0.07$) associated with age of onset (Table 4b). Adolescent tobacco and alcohol use, peer use and whether the adolescent was sexually active, as well as

Table 3 Maternal and adolescent characteristics associated with marijuana use at age 14.

				Significance levels[c]	
	No use $n = 393$	*Non-regular*[a] $n = 127$	*Regular*[b] $n = 42$	*Age of onset*[d]	*Frequency of use*[e]
Block 1. Prenatal and family history					
Prenatal no. joints/day(ADJ)	0.35	0.58	0.69	0.02	0.02
Prenatal no. drinks/day (ADV)	0.51	0.53	1.26	0.11	0.41
Prenatal no. cigarettes/day	6.9	10.3	9.8	0.05	0.006
Family history drug problems (%)	43.8	50.8	50.0	0.02	0.16
Family history alcohol problems (%)	67.9	65.1	71.4	0.26	0.78
Block 2. Current maternal characteristics					
Caregiver's current age	39.1	39.6	39.7	0.45	0.56
Education (years)	12.5	12.3	12.3	0.06	0.20
Working status (% work)	78.1	69.8	69.0	0.10	0.08
Depression	37.5	39.2	39.6	0.02	0.15
Hostility	15.7	16.6	16.5	0.40	0.09
Anxiety	16.2	17.1	16.3	0.77	0.28
Current no. drinks/day	0.79	0.89	0.94	0.60	0.70
Current no. cigarettes/day	7.0	9.7	10.0	0.13	0.005
Current marijuana use (% use)	12.6	23.0	14.6	0.11	0.06
Current cocaine use (% use)	3.4	4.8	2.4	0.94	0.74
Block 3. Home environment					
Home environment (HOME)	11.7	10.5	9.9	0.000	0.000
Male in household (%)	54.2	53.2	35.7	0.65	0.72
Parental autonomy	23.6	22.6	23.2	0.99	0.37
Parental strictness/supervision	20.7	19.2	18.3	0.0001	0.000
Parental involvement	30.3	30.4	28.8	0.85	0.61
Block 4. Child characteristics at age 14					
Gender (%male)	47.6	49.6	47.6	0.21	0.33
Race (% Caucasian)	46.3	49.6	33.3	0.14	0.10
IQ (full-scale WISC)	89.1	89.7	83.6	0.25	0.52
Depression (CDI)	6.7	9.2	13.7	0.000	0.000
Anxiety (RCMAS)	6.7	8.1	10.3	0.09	0.13
Pubertal Status[f]	2.9	2.8	2.6	0.001	0.006
Attention (CBCL)	54.2	55.4	60.8	0.12	0.03
Block 5. Behavior at age 14					
Delinquency (SRD)	4.0	7.4	11.3	0.08	0.007
Aggression (CBCL)	54.5	57.2	61.4	0.84	0.87
Peer use (1 = none; 4 = all)	1.5	2.4	3.1	0.000	0.000
Peer approval (% approve)	8.7	23.6	26.2	0.24	0.22
Sexually active (% active)	13.8	56.0	76.2	0.000	0.000
Adolescent alcohol use (% use)	21.7	60.6	78.6	0.000	0.000
Adolescent tobacco use (% use)	9.7	42.5	61.9	0.000	0.000

[a]Non-regular: less than three times/week. [b]Regular: three or more times/week. [c]Controlling for other variables within the block. [d]Cox proportional hazard regression. [e]Ordinal polytomous logistic regression. [f]Coded on a 5-point scale from developed very early relative to peers (1) to developed much later than peers (5).

measures of the home environment and a family history of drug problems remained in the final model. Parental strictness/supervision was marginally significant ($P = 0.07$).

Frequency of marijuana use, multivariate models

When the significant variables from blocks 1 to 4 were entered into the model, PME significantly predicted frequency of marijuana use. Other significant factors included home environment, parental strictness/supervision, child's depressive symptoms, stage of pubertal development and attention problems (Table 5a).

When the current behavioral characteristics of the adolescents were entered into the analysis, PME remained significantly associated with the frequency of marijuana use. The odds of having a higher frequency were 1.3 times higher among adolescents who were exposed to one joint/day compared to adolescents with

Table 4 Factors associated with age of onset (Cox proportional hazards model).

	Coefficient	*Significance (P)*	*Hazard ratio*
(a) Results with current behavior and peer use excluded			
Depression (CDI)[a]	0.06	0.000	1.06
Home Environment[b]	–0.13	0.000	0.88
Parental strictness/supervision[c]	–0.07	0.001	0.93
Pubertal Development[d]	–0.25	0.003	0.78
Prenatal marijuana exposure[e]	0.13	0.04	1.14
Family history drug problems[f]	0.31	0.04	1.36
(b) Current behavior and peer use included			
Depression[a]	0.01	0.27	1.01
Home environment[b]	–0.07	0.03	0.93
Parental strictness/supervision[c]	–0.05	0.07	0.95
Pubertal development[d]	–0.16	0.054	0.85
Prenatal marijuana use[e]	0.11	0.07	1.12
Family history drug problems[f]	0.34	0.03	1.40
Peer use[g]	0.61	0.000	1.84
Adolescent cigarette use[h]	0.82	0.000	2.27
Adolescent alcohol use[h]	0.71	0.000	2.04
Sexually active[h]	0.51	0.004	1.67

[a]Ranged from 0 to 40. Higher scores indicate more depressive symptoms. [b]Ranged from 2 to 18. Higher score indicates a better home environment. [c]Ranged from 6 to 30. Higher score indicates more supervision/strictness. [d]Coded on a 5-point scale: (1) developed very early relative to peers, to (5) much later than peers. [e]Average daily joints. [f]0 = no history; 1 = history. [g]Ranged 1–4. 0 = none; 4 = all. [h]0 = no; 1 = yes.

Table 5 Factors associated with frequency of use (ordinal polytomous logistic model)

	Coefficient	*Significance (P)*	*Cumulative odds ratio*
(a) Current behavior and peer use excluded			
Depression (CDI)[a]	0.09	0.000	1.1
Home environment[b]	–0.15	0.000	0.86
Parental strictness/supervision[c]	–0.08	0.003	0.92
Pubertal development[d]	–0.30	0.008	0.74
Attention problem[e]	0.03	0.02	1.03
Prenatal marijuana exposure[f]	0.19	0.05	1.2
(b) Current behavior and peer use included			
Depression[a]	0.02	0.36	1.0
Home environment[b]	–0.12	0.02	0.89
Parental strictness/supervision[c]	0.002	0.95	1.0
Pubertal development[d]	–0.15	0.28	0.86
Attention problem[e]	0.005	0.78	1.0
Prenatal marijuana use[f]	0.25	0.02	1.3
Sexually active[g]	1.26	0.000	3.5
Peer use[h]	1.19	0.000	3.3
Adolescent tobacco use[g]	1.1	0.000	3.0
Adolescent alcohol use[g]	1.2	0.000	3.3
Delinquency[h]	0.06	0.04	1.1

[a]Ranged from 0 to 40. Higher scores indicate more depressive symptoms. [b]Ranged from 2 to 18. Higher score indicates a better home environment. [c]Ranged from 6 to 30. Higher score indicates more supervision/strictness. [d]Coded on a 5-point scale: (1) developed very early relative to peers, to (5) much later than peers. [e]Ranged from 50 to 86. Higher score indicates more attention problems. [f]Average daily joints. [g]0 = no; 1 = yes. [h]Ranged 1–4. 0 = none; 4 = all.

no prenatal marijuana exposure after all other factors were taken into consideration. Other significant factors were the quality of the home environment, sexual activity, peer use, adolescent's tobacco and alcohol use and delinquency (Table 5b).

In a final analysis, we evaluated whether the effects of PME were specific. We ran parallel analyses using the final models (Tables 4 and 5) to evaluate whether PME predicted the age of onset or frequency of use for adolescent alcohol or tobacco use. PME did not pre-

dict age of onset or frequency for either alcohol or tobacco.

DISCUSSION

We have found a marginally significant association between PME and age of onset and a significant association between exposure to marijuana during gestation and the frequency of marijuana use of at age 14. Adolescents with PME have an earlier onset of marijuana use and use marijuana more frequently compared to adolescents who were not exposed. One other report documented an association between PME and marijuana use [14], although these authors controlled only for the prenatal environment.

There are three mechanisms by which PME could predict marijuana use at 14 years. This association could result from: (1) genetic or familial factors, (2) characteristics of the current environment and (3) gestational exposures. We controlled for family history of alcohol and drug problems and current maternal substance use. Although family history of drug problems was a significant predictor of onset of marijuana use, it did not explain the effects of PME. Similar results were found by Baer *et al*. [15,16] for prenatal alcohol exposure. Significant environmental factors were identified and controlled for in the model. Therefore, although these results must be replicated, these findings demonstrate that PME predicts subsequent marijuana use, after controlling for familial and environmental factors.

There are two routes by which prenatal effects might occur. First, others and we have demonstrated that PME is a teratogen affecting the CNS and the development of functions such as sleep patterns, memory, attention, executive functioning and mood. These changes in the CNS may result in behaviors such as early onset and increased frequency of marijuana use. An additional possibility is that learning during gestation or in the early perinatal period led to the early and increased use of marijuana. The fetus and newborn are capable of discriminating odors [63], and animal data using alcohol demonstrate that early learning leads to an enhanced response to alcohol at later ages [64]. Learned effects should be specific to the exposure, and we found that the effects of PME were specific to marijuana use in early adolescence. Therefore, it is possible that both mechanisms may be factors in predicting earlier and increased marijuana use.

The results agree with other reports that have found a preponderance of child factors as predictors of early onset substance use [37,65]. We also found significant effects of environmental and parental factors and peer use, which paralleled the results of a number of studies [39,66–69). These findings differ from the results of White *et al*. [69], that social and environmental variables were more important predictors of initiation, while psychological and biogenetic factors were more critical in predicting the change to regular or frequent use. These different associations, however, may result from the young age of our cohort and the fact that few of these offspring have established patterns of use or problem use.

Current maternal psychological status and substance use were not significantly associated with marijuana use in our findings, in contrast to other reports [37,39]. However, the effects of these factors may be mediated by other variables that were in the final model, such as the child's depression and the home environment. In addition, the women in this cohort were generally light to moderate substance users who decreased their marijuana use across time and maintained moderate levels of alcohol and tobacco use, while most of the above associations were for parents who had substance use disorders.

There are limitations to these analyses. The cohort was selected to study maternal substance use during pregnancy, and although most of the women were light to moderate users during pregnancy the cohort was weighted toward substance-using women, making it less generalizable. This also an advantage, however, as we had an adequate number of women who used marijuana prenatally so we could estimate the long-term effects of PME as well as other significant factors in the pre- and postnatal environment. The women in the prenatal clinic had lower incomes and less education than the general population, and while this cohort is generally representative of a lower socio-economic status population, it is not representative of a general population of pregnant women.

Onset and frequency of marijuana use at age 14 were both associated with environmental, family and parenting measures, maternal substance use, and child and peer factors, as has been reported in previous studies. The new finding in these analyses was that prenatal marijuana exposure predicted age of onset of marijuana use and the frequency of use, even after controlling for the other important and influential factors in the model.

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