One-Year Outcomes of Infants Exposed to MDMA (Ecstasy) and Other Recreational Drugs During Pregnancy

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KEY WORDS

3,4-methylenedioxymethamphetamine, MDMA, ecstasy, infant development, drugs, serotonin, motor skills

ABBREVIATIONS

BSI—Brief Symptom Inventory
MDI—Mental Development Index
MDMA—3,4-methylenedioxymethamphetamine
PDI—Psychomotor Development Index
UEL—University of East London

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WHAT'S KNOWN ON THIS SUBJECT: 3,4-Methylenedioxymethamphetamine (MDMA, ectasy) is a widely used recreational drug affecting the serotonergic system. Preclinical studies indicate learning/memory problems with fetal exposure. Human infant prenatal exposure was related to alterations in gender ratio and poorer motor development at 4 months.

WHAT THIS STUDY ADDS: This is the first study documenting that heavier prenatal 3,4-methylenedioxymethamphetamine exposure predicts poorer infant mental and motor development at 12 months with significant, persistent neurotoxic effects. Language and emotional regulation were unaffected.

abstract

OBJECTIVE: A widely used illicit recreational drug among young adults, 3,4-methylenedioxymethamphetamine (MDMA) or ecstasy, is an indirect monoaminergic agonist/reuptake inhibitor affecting the serotonin system. Preclinical studies found prenatal exposure related to long-term learning and memory impairments. There are no studies of sequelae of prenatal MDMA exposure in humans, despite potential harmful effects to the fetus.

METHODS: A total of 96 women in the United Kingdom (28 MDMA users; 68 non-MDMA) were interviewed about recreational drug use during pregnancy. Their infants were seen at 12 months using standardized assessments of cognitive, language, and motor development (Preschool Language Scale, Bayley Mental and Motor Development and Behavior Rating Scales [Mental Development Index, Psychomotor Development Index, Behavioral Rating Scale]). Mothers completed the Child Domain Scale of the Parenting Stress Index, The Home Observation of the Environment Scale (in interview), the Brief Symptom Inventory, and the Drug Abuse Screening Test. Women were primarily middle class with some university education, in stable partner relationships, and polydrug users. MDMA and other drug effects were assessed through multiple regression analyses controlling for confounding variables, and analysis of covariance comparing heavier versus lighter and nonexposed groups.

RESULTS: Amount of prenatal MDMA exposure predicted poorer infant mental and motor development at 12 months in a dose-dependent manner. Heavily exposed infants were delayed in motor development. Lighter-exposed infants were comparable to nonexposed infants. There were no effects on language, emotional regulation, or parenting stress.

CONCLUSIONS: Findings document persistent neurotoxic effects of heavier prenatal MDMA exposure on motor development through the first year of life. *Pediatrics* 2012;130:1–7

A popular, illicit drug used recreationally worldwide, particularly among young adults in Europe, Australia, and the United States as part of the dance club culture, is 3,4-methylenedioxymethamphetamine (MDMA) or ecstasy.[1,2] A derivative of amphetamine, MDMA has both stimulant and hallucinogenic effects in adults[3] and primarily affects serotonergic (5-HT) neurons, but also activates noradrenergic and dopaminergic sites.[3] Adults experience a range of acute and long-term effects, including immediate feelings of euphoria, openness, and energy, although chronic use is associated with depression and possible cognitive impairments in memory and executive function.[4] Serotonergic neurotoxicity has been confirmed in a number of human neuroimaging studies.[5] Because of maternal physiologic effects of hyperthermia and appetite suppression and direct effects on the fetal serotonin system, MDMA exposure may be harmful to the developing fetus.[6]

Preclinical studies indicate that prenatal MDMA exposure may induce behavioral alterations of long-term memory and learning impairments and increased locomotor activity.[7–9] First-trimester exposure has been related to reduced birth weight, increased locomotor activity, and learning deficits,[9] as well as long-term behavioral alternations of reduced anxiety, heightened response to novelty, and hyperattentiveness during spatial learning.[10] Recent studies indicate structural and functional changes in the noradrenergic system related to attention.[11] Small case series studies of human pregnancy outcomes in the United Kingdom and the Netherlands found a higher incidence of congenital malformations in MDMA-exposed pregnancies.[12,13]

In the first, to our knowledge, human study of MDMA-exposed infants, we found prenatal exposure associated with alterations in gender ratio at birth and poorer motor quality and milestone delays neonatally and at 4 months of age in a middle-class, UK sample of recreational drug users.[14] The current article presents the results of follow-up of that cohort at 12 months of age.

METHODS

All mothers and infants were prospectively recruited through the Case Western Reserve University and University of East London (UEL) Drugs and Infancy Study of recreational drug use in pregnant women.[15,16] Participants were recruited through midwives, response to leaflets distributed at prenatal clinics, or advertisements in pregnancy magazines. Study description requested participation of pregnant women who had used recreational drugs during pregnancy, listing ecstasy, tobacco, cannabis, alcohol, and cocaine as examples. Exclusionary factors included maternal/child HIV-positive status, maternal moderate/severe mental retardation or severe psychiatric or medical illness; or, for the child, other major medical illnesses. All participants were ensured of confidentiality and gave informed written consent approved by university (Case Western Reserve University and UEL) and National Health Service (UK) ethics committees.

Of 126 respondents, 5 did not meet study criteria and 25 did not come to the first visit (4 had miscarriages; 1 withdrew because of depression, 2 to partner's objection, 3 with no reason; 1 moved out of range, and 14 could not be contacted). Of 96 subjects enrolled and seen for infant testing during the course of the study, 79 infants (82%) were seen at 12 months.

Measures of MDMA Exposure and Covariates

Women were interviewed about their substance use by trained research assistants in their homes or at the UEL laboratory, or, for a small number, by telephone. Women were interviewed over the course of pregnancy on 3 separate occasions, but if necessary, a combined set of interviews was given on 1 occasion for enrollment late in pregnancy.[15] Sixty-two women completed the interview during pregnancy, and 24 postnatally.

The interview was an adaptation of the Maternal Post-Partum Interview used in previous studies of substance exposure[17] and asked women to describe their intake of those commonly used in UK cohorts.[18] Information taken included total lifetime drug use, use during the year before conception, and use in the month before and over the trimesters of pregnancy for each drug. Values were computed for tobacco/cigarettes (number), alcohol (number of units), marijuana joints/cigarettes (number), MDMA tablets (number), heroin cigarettes or injections (number), ketamine (grams), crack (number of rocks) or cocaine (number of lines), benzodiazepine and LSD tablets (number), and hallucinogenic mushrooms (number). Frequency of use for each drug was recorded on a scale ranging from 0 (none) to 7 (daily use). An average dose per week for each drug was calculated by multiplying the frequency by the amount taken per occasion. Information was also obtained for typical and highest consumption. Women were considered users if they admitted to MDMA use during pregnancy or in the month before pregnancy.

Women were administered the Drug Abuse Screening Test,[19] a 20-item self-report scale validated against the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition,* that yields a quantitative index of life problems related to drug use. A score of 16 (of 20) indicates a severe level of problems.

The Brief Symptom Inventory (BSI),[20] a widely used reliable, 53-item self-report questionnaire was given to describe experience of a range of psychiatric symptoms at each visit. The BSI yields 9 subscales and a summary

score, the General Severity Index, that measures overall psychological distress. BSI data from the 1-month and 12-month visits were used.

Maternal age, marital status, ethnicity, educational level, and household income were obtained. Two subtests of the Wechsler Abbreviated Scale of Intelligence,[21] a standardized IQ test (Block Design and Similarities), were administered. Each subtest yields a *t* score with mean of 50 and SD of 8.

At the 12-month visit, mothers were administered the Child Domain Scale of the Parenting Stress Index[22] to assess parental stress about child characteristics. The Child Domain has 6 characteristics (adaptability, acceptability, distractibility-hyperactivity, mood, demandingness, and reinforces parent). Normative data were derived from 534 families with children from 1 month to 19 years.

The Home Observation of the Environment[23] was also administered in interview format to measure quality of the caregiving environment.

Infants were given the Bayley Scales of Infant Development,[24] widely used standardized, valid, reliable assessments of development. The Mental Scale yields a Mental Development Index (MDI) reflecting memory, language, and problem-solving abilities. The Psychomotor Index (PDI) measures gross and fine motor control and coordination. Normative data yield a mean of 100 and SD of 15. The Behavioral Rating Scale assesses quality of infant performance across several domains based on assessor observations, including orientation, motor quality, and emotional regulation.

Infants were also given the Preschool Language Scale,[25] a standardized, normative language assessment composed of Auditory Comprehension and Expressive Communication subscales with receptive and expressive language tasks for ages birth to 4 years 11 months.

Assessors were master's level psychology assistants or the equivalent masked to infant drug exposure.

Statistical Analyses

The effects of MDMA were assessed through a series of linear regression analyses using the average dose of MDMA per week consumed during pregnancy and the month previous averaged over the time period as the independent variable. Interaction effects of gender, demographic, and other drug exposures were also tested if significant main effects were found.

To determine covariates, group comparisons were conducted between mothers who used MDMA during pregnancy (n = 28) and those who had not (n = 68) with exposure defined dichotomously (coded as 1 for exposed), and, based on our 4-month findings and because drugs may have effects only at certain thresholds, as heavier, lighter, or nonexposed (2, 1, 0) based on a median split of the exposed group. Differences between exposed and nonexposed groups were examined for maternal use of other drugs and psychological distress using χ^2 or Fisher's exact test for dichotomous variables and *t*-test or Wilcoxon–Mann-Whitney test. Log transformations were used to correct skewness. Univariate analyses were conducted on maternal factors and prenatal drug exposures. Spearman correlation analyses were used to assess the relationships of amount and frequency of drug exposure and other covariates to infant outcomes. Variables included infant age at testing and all maternal demographic and infant birth variables.

Covariates different by group and related to the outcome at $P < .2$ were evaluated in regression models stepwise and retained if, on entry, they were significant at $P < .10$ or caused substantial change ($> 10\%$) in the MDMA coefficient.

Planned analyses of covariance were conducted to illustrate the functioning of the drug-exposed groups, and to compare heavier to lighter and nonexposed infants, based on previous 4-month outcomes. With $\alpha = 0.05$ and power of 0.80, the sample size could detect moderate effect sizes with up to 4 predictors in regression models.

RESULTS

Table 1 reports characteristics of women who used MDMA versus women who did not use MDMA while pregnant. The maternal sample at enrollment was primarily white, married or with a partner, with some university education, middle socioeconomic status, and in the average range of intellectual ability. MDMA-using women differed from nonusing women only in having fewer children. Overall prenatal drug use and the negative sequelae of drug use differed between groups (Tables 1 and 2). Women who used MDMA during pregnancy had higher Drug Abuse Screening Test scores, indicating greater severity of sequelae from drug use, although both groups scored very low.

All births were singleton and birth parameter outcomes did not differ by group except that MDMA-exposed infants were more likely to be male. One child in the MDMA group was diagnosed with Townes-Brocks Syndrome, a rare genetic autosomal dominant multiple malformation of the gene SALL1.[26] All outcomes with significant findings were rerun excluding this child and results did not differ. Thus, the presented findings include all in the MDMA-exposed group.

Compared with mothers who came to the 12-month assessment, mothers who did not come were younger, less educated, had a lower score on the Wechsler Abbreviated Scale of Intelligence Similarities subtest, and used more cigarettes during pregnancy. No other difference was found. Table 2 describes the characteristics of mothers and infants seen at 12 months compared by heavier,

TABLE 1 Maternal and Child Characteristics

	MDMA (n = 28)	Non-MDMA (n = 68)	χ^2/t	P
Maternal characteristics				
White, n (%)	23 (85)	57 (84)	0.3	.87
Registered disabled, n (%)	0 (0)	5 (8)	0.19	.32
Married/with partner, n (%)	22 (79)	57 (84)	0.38	.54
Family income, n (%)			1.59	.81
<10K British Pounds	4 (14)	13 (19)		
10–40K British Pounds	17 (61)	40 (59)		
>40K British Pounds	7 (25)	15 (22)		
Maternal age at birth, mean (SD)	28.4 (6.2)	30.3 (6.4)	1.33	.19
Maternal education, mean (SD)	15.3 (2.7)	14.9 (2.9)	−0.57	.57
WASI Block Design, mean (SD)	57.0 (8.1)	56.0 (9.5)	−0.43	.67
WASI Similarities, mean (SD)	51.4 (8.5)	49.4 (8.9)	−0.88	.38
Parity, mean (SD)	1.21 (0.42)	1.88 (1.11)	4.27	.0001
General Severity Index, mean (SD)	0.71 (0.81)	0.51 (0.47)	−0.61	.54
DAST score, mean (SD)	7.7 (4.1)	4.6 (4.4)	−3.09	.03
Home Observation of the Environment score, mean (SD)	40.2 (3.3)	39.6 (3.53)	−0.69	.49
Child characteristics				
White, n (%)	20 (71)	51 (75)	0.13	.72
Male, n (%)	20 (71)	31 (46)	5.32	.02
Special Baby Care Unit, n (%)	3 (11)	8 (12)	0.27	1.00
Gestation, wk, mean (SD)	40.0 (1.6)	39.5 (1.5)	−1.41	.16
Preterm (<37 wk), n (%)	1 (3.6)	1 (1.5)	0.43	.50
Birth weight, g,[a] mean (SD)	3537 (500)	3344 (511)	2.10	.15
Birth length, cm,[b] mean (SD)	52.0 (2.6)	51.4 (2.7)	−0.56	.58
Head circumference, cm,[c] mean (SD)	34.8 (1.8)	34.3 (1.9)	−0.97	.34

DAST, Drug Abuse Screening Test; WASI, Wechsler Abbreviated Scale of Intelligence.

[a] Adjusted for infant gender.

[b] Based on reduced sample of 31 and 10.

[c] Based on reduced sample of 39 and 16.

lighter, and nonexposed status, indicating similar differences as seen in the dichotomous comparisons.

Table 3 describes the average and median drug use for heavier, lighter, and no-use groups across all substances reported. MDMA users used more tobacco, marijuana, cocaine, amphetamines, LSD, and mushrooms than nonusers. Non-MDMA users were more likely to decrease their use of other drugs during pregnancy than MDMA users (see Moore et al[15] and Singer et al[14] for details). Over the pregnancy, most MDMA users discontinued use, with only 1 woman reporting use in the third trimester.

Before pregnancy, the mean number of tablets ingested per week was 3.2 (SD = 5.2, Range = 0.1–26.3) for those who used MDMA during pregnancy. The mean total amount of MDMA used during pregnancy and the month previous was 25 tablets (SD = 43.7, Range = 0.45–180). Heavier users averaged 3.3 (±4) tablets in the month before pregnancy compared with 0.12 ± 0.2 tablets for lighter users (Wilcoxon test $P < .007$); 1.6 ± 2 vs 0.12 ± 1 tablets in the first trimester ($P < .12$), and 0.15 ± 0.6 vs 0.02 ± 0.1 in the second trimester ($P > .20$).

Child Outcomes at 12 Months

Higher amounts of MDMA exposure predicted poorer mental and motor outcomes and assessor ratings of poorer motor quality at 12 months, controlling for covariates (see Tables 4, 5, 6, and 7). Group outcomes based on heavier, lighter, and no exposure indicated that infants with heavier exposure had a 5-point deficit in MDI, compared with lighter and nonexposed MDI children. Two children in the more heavily exposed group were in the at-risk range (<85), compared with no children in the other groups. Greater deficits related to heavier MDMA exposure were found in motor outcomes, with most of the more heavily exposed children classified as at-risk (PDI < 85), and one-third demonstrating significant developmental delay (PDI < 70), compared with less than a third at-risk and <10% in the delayed range in the lighter and nonexposed groups. There was also a nonsignificant trend for MDMA exposure to predict less orientation and engagement ($\beta = -1.9$, $t = -1.7$, $P < .09$).

MDMA exposure was unrelated to language or emotional regulation outcomes. Lighter MDMA-exposed infants were equivalent to nonexposed infants on all outcomes. There were no differences in maternal report of parenting stress related to child characteristics.

Several family characteristics and drug exposures had effects on outcomes in addition to MDMA. The Home Observation of the Environment was related to higher MDI ($\beta = 0.65$, $t = 2.4$, $P < .02$), and better emotional regulation ($\beta = 3.01$, $t = 3.01$, $P < .004$), orientation ($\beta = 0.24$, t = 2.2, $P < .03$), and language scores (all with $P < .05$). Higher maternal General Severity Index predicted greater child domain stress ($\beta = 0.60$, $t = 1.9$, $P < .057$). Boys had lower MDI ($\beta = -4.0$, $t = 2.0$, $P < .05$), and lower emotional regulation scores ($\beta = -15.3$, $t = -2.1$, $P < .036$). Higher alcohol exposure predicted better orientation ($\beta = 6.8 \pm 3.0$, $t = 2.5$, $P < .02$) and expressive language ($\beta = 2.9 \pm 1.0$, $t = 3.1$, $P < .003$), Q:6 whereas higher crack-cocaine exposure predicted lower expressive language scores ($\beta = -5.3 \pm -2.5$, $t = -2.1$, $P < .04$).

DISCUSSION

At 12 months of age, amount of MDMA exposure had negative effects on infant cognitive and motor outcomes and examiners' ratings of motor quality, suggesting significant developmental

TABLE 2 Sample Characteristics at 1-Year Follow-up by Heavier, Lighter, and Non-MDMA Exposure (n = 79)

	MDMA Status			χ^2/F	P
	Heavier (n = 10)	Lighter (n = 12)	None (n = 57)		
Maternal characteristics					
White, n (%)	9 (90)	10 (83)	40 (70)	2.33	.42
Registered disabled, n (%)	0	0	4 (7)	1.61	.99
Married/with partner, n (%)	9 (90)	9 (75)	48 (84)	0.96	.62
Family income, n (%)				9.88	.32
<10K British Pounds	0	4 (33)	9 (16)		
10–40K British Pounds	6 (60)	6 (50)	34 (60)		
>40K British Pounds	4 (40)	2 (17)	14 (25)		
Maternal age at birth, mean (SD)	28.5 (6.9)	29.5 (5.3)	31.0 (6.4)	0.83	.44
Maternal education, mean (SD)	15.4 (2.7)	15.5 (3.2)	15.3 (2.8)	0.03	.97
WASI Block Design, mean (SD)	55.0 (9.34)	60.0 (5.32)	57.0 (8.94)	0.72	.49
WASI Similarities, mean (SD)	48.2 (6.8)	56.3 (7.8)	50.4 (8.1)	2.43	.10
Parity, mean (SD)	1.10 (0.32)	1.25 (0.45)	1.86 (1.19)	3.44	.04
General Severity Index (at 12 mo), mean (SD)	0.50 (0.43)	0.61 (0.71)	0.50 (0.41)	0.10	.91
General Severity Index (birth), mean (SD)	0.63 (0.78)	0.78 (0.87)	0.51 (0.47)	0.54	.58
DAST score, mean (SD)	6.9 (4.3)	7.8 (3.5)	4.7 (4.6)	3.03	.054
Home Observation of the Environment score, mean (SD)	40.5 (3.66)	39.9 (3.09)	39.6 (3.53)	0.31	.73
Child characteristics					
White, n (%)	8 (80)	9 (75)	42 (74)	0.18	.99
Male, n (%)	6 (60)	10 (83)	26 (46)	5.88	.051
Special Baby Care Unit, n (%)	1 (10)	1 (8.3)	8 (14.3)	0.39	.99
Gestation, wk, mean (SD)	40.0 (1.33)	40.1 (2.11)	39.3 (1.5)	1.72	.19
Preterm (<37 wk), n (%)	0	1 (8.3)	1 (1.8)	2.04	.48
Birth weight, g, mean (SD)	3392 (506)	3513 (553)	3267 (502)	1.25	.29
Birth length, cm, mean (SD)	54.0 (1.41)	50.6 (2.88)	51.1 (2.680)	1.23	.31
Head circumference, cm, mean (SD)	35.3 (1.23)	35.7 (1.83)	34.2 (2.01)	2.04	.14

DAST, Drug Abuse Screening Test; WASI, Wechsler Abbreviated Scale of Intelligence.

risk for the more heavily MDMA-exposed infant. The most pronounced effects were on motor outcomes. Motor delays were consistent with previous findings at 4 months in the same cohort of slower and more delayed movements and 1-month trends of more lethargic behaviors in the MDMA group. At 12 months, delays were noted in standing and walking progressions.

MDMA primarily affects the serotonin (5-HT) neurotransmitter that plays a key role in brain morphogenesis and is one of the first neurotransmitters to appear in the central nervous system.[27] MDMA treatment in animals correspondent to human prenatal exposure has been shown to disrupt the serotonergic system and induces the release of the stress hormone cortisol.[7] Many aspects of motor control have a serotonergic input, and serotonin may be more implicated in gross skeletal rather than fine or discrete muscle movements.[28] At 12 months, the Bayley Mental Scale items also have a strong motor component, as language is not yet well developed, and tasks at 12 months require fine motor skills, such as placement of pegs in a pegboard. Thus, subtle MDI deficits seen may be attributable to fine motor impairments.

Preclinical studies of animals exposed neonatally to MDMA resulted in alterations in dose-dependent learning that persisted to adulthood,[29] as well as spatial and working memory deficits,[30] reduced interest in novelty,[28] and hypoactivity.[28] There are no other comparative human studies of MDMA

TABLE 3 Average Maternal Drug Use During Pregnancy by Heavier, Lighter, and Non-MDMA Exposure

Drug, per wk	MDMA Status						χ^{2a}	P
	Heavier (n = 13)		Lighter (n = 15)		None (n = 68)			
	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)	Mean (SD)	Median (Range)		
Cigarettes	50.2 (39.9)	45.0 (0–118)	23.8 (36.8)	9.6 (0–123)	32.5 (49.1)	13.19 (0–280)	4.63	.10
Alcohol, units	12.5 (16.0)	4.9 (0.06–51)	6.06 (4.52)	5.25 (0–14.7)	6.6 (12.9)	2.3 (0–84)	4.25	.12
Marijuana, joints	9.9 (24.2)	0.25 (0–87.5)	9.51 (14.79)	3.40 (0.01–3.4)	6.3 (15.0)	0.06 (0–88)	6.48	.04
MDMA, tablets	1.3 (1.4)	0.75 (0.17–4.5)	0.07 (0.04)	0.06 (0.01–0.14)	—	—	—	—
Cocaine, doses	0.15 (0.28)	0.05 (0–1.0)	0.24 (0.64)	0.005 (0–2.4)	0.02 (0.1)	0 (0–0.8)	28.6	.0001[b]
Crack, rocks	0.04 (0.11)	0 (0–0.37)	0.01 (0.04)	0 (0–0.17)	1.0 (5.0)	0 (0–38)	0.43	.81
Amphetamine, doses	0.03 (0.10)	0 (0–0.33)	0.05 (0.14)	0 (0–0.52)	0.0003 (0.001)	0 (0–0.01)	4.8	.09
Mushrooms, doses	0.02 (0.07)	0 (0–0.25)	0.003 (0.007)	0 (0–0.02)	0 (0)	0 (0–0)	8.2	.02
Tranquilizers, doses	0.23 (0.83)	0 (0–3)	0.003 (0.01)	0 (0–0.04	0.4 (1.9)	0 (0–11)	0.27	.87
Opiates, doses	0.25 (0.86)	0 (0–3.13)	0.02 (0.08)	0 (0–0.31)	0.2 (1.2)	0 (0–8)	0.70	.71
LSD, doses	0	0	0.03 (0.07)	0 (0–0.25)	0 (0)	0 (0–0)	16.5	.0003
Ketamine	0.13 (0.49)	0 (0–1.75)	0.001 (0.005)	0 (0–0.02)	0	0	5.0	.08

[a] Kruskal-Wallis test.

[b] Post hoc test Lighter group differ from None (P < .02).

TABLE 4 Effects of Amount of MDMA Exposure Over Pregnancy and Month Previous on Bayley Mental Development Index at 12 Months

Predictor	Parameter Estimate (b)	SE	*t*	*P*	β
MDMA	−8.19	3.17	−2.58	<.012	−0.28
Gender	−4.32	1.84	−2.35	<.021	−0.25
Home Observation of the Environment	0.59	0.27	2.23	<.029	0.24

$F(3, 76) = 5.28$, $P < .002$, $R^2 = 0.18$.

TABLE 5 Effects of Amount of MDMA Exposure Over Pregnancy and Month Previous on Bayley Psychomotor Development Index at 12 Months

Predictor	Parameter Estimate (b)	SE	*t*	*P*	β
MDMA	−15.75 (6.2)	6.19	−2.54	<.013	−0.28
Marijuana	2.55 (1.3)	1.33	1.92	<.058	0.21

$F(2, 77) = 5.67$, $P < .005$, $R^2 = 0.13$.

TABLE 6 Effects of MDMA Exposure Over Pregnancy and Month Previous on Bayley Behavioral Rating Scale Motor Quality at 12 Months

Predictor	Parameter Estimate (b)	SE	*t*	*P*	β
MDMA	−17.40	7.45	−2.33	<.022	−0.26
Home Observation of the Environment	0.91	0.63	1.45	.15	0.16

$F(2, 76) = 3.89$, $P < .025$, $R^2 = 0.10$.

TABLE 7 Twelve-Month (Adjusted) Outcomes by Heavier Versus Lighter and Nonexposed MDMA Status, Mean (SD)

	MDMA Status				
	Heavier (*n* = 10)	Lighter (*n* = 12)	None (*n* = 57)	F/ χ^2	*P*
Age, mo	12.6 (0.65)	13.2 (2.1)	12.8 (0.56)	0.60	.44
MDI[a]	98.5 (11.4)	103.4 (6.3)	103.4 (8.5)	3.50	<.07
% < 85, *n* (%)	2 (20)	0	0	—	—
% < 70, *n* (%)	0	0	0	—	—
PDI[b]	76.0 (11.8)	99.8 (12.3)	92.0 (16.4)	10.65	<.002
% < 85, *n* (%)	8 (80%)	2 (17%)	17 (30%)	10.69	<.002
% < 70, *n* (%)	3 (30%)	0	4 (7%)	6.34	<.04
Behavioral Rating Percentile					
Emotional Regulation[a]	66.4 (32)	57.8 (34)	61.8 (32)	0.15	<.71
Orientation[c]	54.9 (33)	70.6 (26)	65.5 (25)	2.7	<.11
Motor Quality[d]	71.3 (32)	88.8 (15)	87.6 (17)	12.4	<.001
Preschool Language Scale					
Auditory Comprehension[d]	93.1 (6.9)	87.5 (5.1)	92.7 (8.9)	0.16	<.69
Expressive Communication[e]	97.2 (10.4)	99.5 (7.8)	95.8 (9.9)	0.10	<.75
Total Language[e]	94.9 (8.5)	93.0 (5.9)	94.4 (8.4)	0.00	<.98
Parenting Stress Child Domain[f]	92.2 (29)	89.6 (11)	90.9 (18)	0.07	<.79

[a] Adjusted for gender, Home Observation of the Environment.
[b] Adjusted for marijuana.
[c] Adjusted for alcohol, marijuana, Home Observation of the Environment, gender.
[d] Adjusted for Home Observation of the Environment.
[e] Adjusted for alcohol, crack-cocaine, Home Observation of the Environment.
[f] Adjusted for General Severity Index.

exposure on infant mental or motor development.

Strengths of this study include the measurement of potential confounders of maternal education, quality of the caregiving environment, and other drug exposures. Women were recruited voluntarily during pregnancy without threat of legal action, enhancing reliability of drug information obtained through self-report. Although self-report of drug use may be unreliable, particularly when women may have concerns about fetal health and social stigma, minimization of drug use would serve to mask differences between groups; however, functional outcomes in this study differed by amount of MDMA exposure, suggesting validity to maternal self-report.

Selection bias may be a concern if participants had concerns for risk that precipitated their study involvement, although both MDMA and non-MDMA users could be presumed to have been similar in that regard. Because fetal exposure was almost entirely restricted to the first and second trimesters, results are not generalizable to longer-term exposure. Women with greater concern for pregnancy and fetal health may have been more likely to enroll and discontinue or decrease drug use than those who chose not to enroll, and may not be representative of all users. The present findings suggest that even the offspring of women who discontinue use are at increased risk for developmental delays at higher exposure levels. Although there were no effects at lighter exposures, sample size may have been too small to detect subtle effects at lower exposure levels.

The sample size for MDMA users was small but did not contain confounding factors seen in most drug-exposure studies, allowing greater statistical power. Participants were largely of middle socioeconomic status, had average intelligence and education, were employed, and most were married or in stable partnered relationships.

Despite some limitations, the current study provides the first prospective developmental follow-up of MDMA-exposed infants. Findings of poorer cognitive and motor development at 1 year of age with heavier exposure to MDMA in the first 2 trimesters suggest significant risk for later learning problems. Because infant outcomes in

the range found in this cohort are not necessarily predictive of long-term outcomes, follow-up to older ages is important to determine whether these early cognitive and motor differences persist or resolve.

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