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Prenatal exposure to methadone or buprenorphine: Early childhood developmental outcomes

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ABSTRACT

Background: Methadone and buprenorphine are recommended to treat opioid use disorders during pregnancy. However, the literature on the relationship between longer-term effects of prenatal exposure to these medications and childhood development is both spare and inconsistent.
Methods: Participants were 96 children and their mothers who participated in MOTHER, a randomized controlled trial of opioid-agonist pharmacotherapy during pregnancy. The present study examined child growth parameters, cognition, language abilities, sensory processing, and temperament from 0 to 36 months of the child's life. Maternal perceptions of parenting stress, home environment, and addiction severity were also examined.
Results: Tests of mean differences between children prenatally exposed to methadone vs. buprenorphine over the three-year period yielded 2/37 significant findings for children. Similarly, tests of mean differences between children treated for NAS relative to those not treated for NAS yielded 1/37 significant finding. Changes over time occurred for 27/37 child outcomes including expected child increases in weight, head and height, and overall gains in cognitive development, language abilities, sensory processing, and temperament. For mothers, significant changes over time in parenting stress (9/17 scales) suggested increasing difficulties with their children, notably seen in increasing parenting stress, but also an increasingly enriched home environment (4/7 scales)
Conclusions: Findings strongly suggest no deleterious effects of buprenorphine relative to methadone or of treatment for NAS severity relative to not-treated for NAS on growth, cognitive development, language abilities, sensory processing, and temperament. Moreover, findings suggest that prenatal opioid agonist exposure is not deleterious to normal physical and mental development.

1. Introduction

Methadone and buprenorphine, if taken in adequate doses, can stabilize pregnant women with opioid use disorder and prevent relapse (Hulse and O'Neil, 2002; Jones et al., 2010; Jones et al., 2006; Kaltenbach et al., 1998). However, concern is often raised regarding effects of such prenatal exposure to these medications on the developmental outcome of the children. Studies to date have produced inconsistent findings. A review by Maguire and colleagues (Maguire et al., 2016) suggests that prenatal exposure to opioids may be associated

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with deficits in cognition, psychomotor, and behavioral processes in infants and young children. However, a review by Behnke and Smith (2013) found long-term effects on behavior but no consensus on cognition and suggest studies with positive findings were usually confounded by environmental factors. Most publications included in the reviews have concerning methodological limitations (e.g., conflating different opioid exposures, not controlling for tobacco and alcohol exposure) (Jones et al., 2015) and reported on cross-sectional case-control studies in small, heterogeneous samples, with few prospective longitudinal studies (Konijnenberg and Melinder, 2011).

Systematic reviews and meta-analyses (Brogly et al., 2014; Zedler et al., 2016) have generally supported the contention that buprenorphine is superior to methadone in terms of neonatal outcomes. Zedler and colleagues (Zedler et al., 2016) concluded that prenatal exposure to buprenorphine relative to methadone has a lower risk of preterm birth, greater birth weight, and larger head circumference. Brogly and colleagues (Brogly et al., 2014) also report greater birth weight and larger head circumference as well as a higher mean gestational age and a lower risk for treatment for neonatal abstinence syndrome (NAS) and shorter length of hospital stay for buprenorphine than methadone-exposed neonates. Neonates treated for NAS had a shorter duration of NAS treatment and a lower total dosage of morphine dose in buprenorphine- than methadone-exposed neonates. Yet there are only two studies to date that compare the outcome of children prenatally exposed to buprenorphine to children prenatally exposed to methadone, both of which were retrospective pediatric clinical chart reviews at birth and 4 months of age (Bier et al., 2015) and through 2 years of age (Humbarger et al., 2016). To date, there are no studies that prospectively examine developmental outcomes of children prenatally exposed to buprenorphine compared to children prenatally exposed to methadone, although a longitudinal study assessed visual evoked potential scores at 4 months of age (Whitham et al., 2010) and at 3 years of age (Whitham et al., 2015) and found little difference between buprenorphine and methadone exposure.

The question of the long-term effect of NAS has recently received new emphasis given the rising opioid epidemic and the significant increase in prenatal opioid exposure (Patrick et al., 2015). NAS has been used as an index of risk in recent legislation (Child Abuse Prevention Act (CAPTA) of 2010; the Comprehensive Addiction and Recovery Act (CARA) of 2016) resulting in potential consequences for mothers receiving opioid medication for treatment of OUD while pregnant. However, the only study that has examined if developmental outcome differs for infants who required treatment for NAS compared to infants who exhibited mid NAS and required no treatment found no difference in development at 6 months of age (Kaltenbach and Fnnegan, 1986). There are no data regarding the effect of severity of NAS on development during late infancy and early childhood.

The primary interest of the present study was threefold. First, to determine whether changes in child growth parameters, cognition, language abilities, sensory processing, and temperament over the 36-month period were differentially related to prenatal buprenorphine versus methadone exposure. Significant results would indicate that the children develop differently over the first three years of life as a result of exposure to one of the two opioid agonists. Second, to determine whether changes in child developmental outcomes over this 36-month period were differentially related to treatment for NAS. Significant results would suggest that children who were treated for NAS as neonates develop differently over the first three years of life as a result of NAS severity and/or exposure to morphine treatment. Third, to determine the extent to which young children prenatally exposed to opioid agonist medication follow a normal course of development and the extent to which maternal perceptions of parenting stress, home environment, and addiction severity might have changed over the three-year period.

This study examined secondary outcomes of child growth parameters, cognitive development, language abilities, sensory processing, and temperament, and maternal perceptions of parenting stress, home environment, and addiction severity during the child's first 36 months of life in a sample of 96 children and their mothers who participated in a randomized controlled trial of opioid-agonist pharmacotherapy during pregnancy. This study has multiple strengths relative to previous research: (1) the maternal sample is clearly defined by study eligibility criteria; (2) use of substances other than either methadone or buprenorphine during pregnancy was minimal; (3) both child and maternal functioning are examined; (4) the potentially adverse impact on development of neonatal abstinence syndrome (NAS) that requires treatment following prenatal exposure to either methadone and buprenorphine is examined; and (5) it is longitudinal and prospective.

2. Methods

2.1. Maternal opioid treatment: human experimental research (MOTHER) study

Methodological aspects of the MOTHER trial relevant to this article, including the inclusion/exclusion criteria and the CONSORT diagram, as well as maternal baseline characteristics and secondary neonatal and maternal outcomes (i.e., amount of prenatal care, positive drug screen at delivery, etc.) have already been published (Jones et al., 2012; Jones et al., 2010). MOTHER (Jones et al., 2010) was a double-blind, double-dummy, flexible-dosing, two-group randomized controlled trial. Either methadone or buprenorphine was provided to 175 opioid-dependent pregnant women with a singleton fetus (6–30 weeks), of whom 58 women in the buprenorphine and 73 in the methadone condition delivered an infant while enrolled in the study. Buprenorphine (2–32 mg) and methadone (20–140 mg) dosing followed a flexible dose protocol (Jones et al., 2010).

NAS assessment was performed for all infants for a minimum period of 10 days post-delivery. The MOTHER NAS Scale (MNS) (Jones et al., 2010) measured NAS. Supplementary Material (Jones et al., 2010) and Table 2 in Weaver et al. (Weaver et al., 2014) provide MNS development and scoring principles. Jones et al. (Jones et al., 2010) provide rater training and inter-rater agreement information. The NAS treatment protocol was based on MNS scores. Neonates requiring pharmacotherapy were treated with oral morphine sulfate.

2.2. Procedures

The present study was approved by the Institutional Review Boards of the participating sites: Brown University, Johns Hopkins University, The Medical University of Vienna, the University of Vermont, Thomas Jefferson University and the City of Philadelphia, Vanderbilt University, and Wayne State University. Study participants were recruited at study sites following completion of MOTHER participation. Examiners trained in developmental evaluations assessed infants and research staff assessed mothers. All assessments were conducted at the hospital sites and all examiners were blind to the maternal-infant Medication Condition.

2.3. Measures and assessment schedule

Measures were a multidimensional set of well-validated instruments that are widely used both for clinical diagnoses and research assessment, with child measures of developmental outcomes focusing on growth parameters, cognitive development, sensory processing, temperament, and language abilities. Maternal measures focused on perceptions of parenting stress, home environment, and addiction severity. Assessments were conducted when infants were 3, 6, 12, 24, and 36 months of age. Table 1 includes descriptions of measures and their assessment schedule. Because first enrollment in MOTHER occurred in May 2005 and the follow-up National Institute on Drug Abuse supplement award for this study was not received until Spring 2008, some infants were too old to be administered the assessment battery at the

Table 1
Assessment Instruments and Assessment Schedule

	Assessment Time Point (month)
Child Measures	
Growth Measurements: Weight (gm), Height (in), Head Circumference (cm) (See Table 2 for an explanation of the transformation of these outcomes for purposes of analysis.)	3, 6, 12, 24, 36
Bayley Scale of Infant Toddler Development III (BSI-III):[25] The BSI-III provides an extremely thorough, standardized assessment of infant development. In the present paper we report Cognitive, Language, Motor, Social-Emotional, and Adaptive Behavior scores. The composite scores are norm-referenced and standardized with a mean of 100 and a standard deviation of 15.	6, 12, 24, 36
Receptive-Expressive Emergent Language (REEL)-3:[26] The REEL-3 is a 66-item, norm-referenced test administered to caregivers, developed to identify young children who have developmental problems in use or understanding of language. It is composed of two subtests, for emerging receptive and expressive language skills. The present paper reports on the Receptive and Expressive Ability scores and percentile ranks, and the Language Ability scores. The three Ability scores are scored according to population norms, in a manner similar to intelligence tests, with means of 100 and standard deviations of 15.	12, 24, 36
Infant Toddler Sensory Profile (ITSP):[27] A standardized instrument for assessing a child's sensory processing abilities and to profile the effect of sensory processing on functional performance in daily life. There are 36 items for children 0–6 months, and 48 items for children 7–36 months. There are four quadrants: Low Registration (13 items for 0–6 month form; 11 items for 7–36 month form), Sensation Seeking (6; 14), Sensory Sensitivity (12; 11), and Sensation Avoiding (5; 12), and a Low Threshold score representing a sum of the Sensory Sensitivity and Sensation Avoiding quadrant scores. Quadrant scores are computed by summing the responses to each item on a 5-point scale, ranging from 1 ("Almost always") to 5 ("Almost never"), so that lower scores indicate relatively more functional problems in a given area of sensory processing.	3, 6, 12, 24, 36
Infant Behavior Questionnaire Revised (IBQ-R):[28,29] A 91-item inventory of infant behavior in 14 domains: Activity Level; Distress to Limitations; Fear; Duration of Orienting; Smiling and Laughter; High Intensity Pleasure; Low Intensity Pleasure; Soothability; Falling Reactivity/Rate of Recovery from Distress; Cuddliness; Perceptual Sensitivity; Sadness; Approach; and Vocal Reactivity. Respondents score the frequency of infant behavior on a scale of 1 ("Never") – 7 ("Always"). Scores on each domain are the mean of the item ratings in that domain, so in some cases, higher scores indicate more of a negative behavior (eg, Fear) while in other cases, higher scores indicate more of a positive behavior (eg, Cuddliness).	3, 6, 12
Maternal Measures	
Parenting Stress Index (PSI):[30] A 120-item inventory of parental stress in three domains: Child, with 6 subscales (Distractibility/Hyperactivity, Adaptability, Reinforces Parent, Demandingness, Mood, and Acceptability) that measures sources of stress from child behavior, as reported by the parent; Parent, with 7 subscales (Competence, Isolation, Attachment, Health, Role Restriction, Depression, and Spouse/Parenting Partner Relationship) that measure sources of stress related to parent functioning; and a Life Stress scale that measures the amount of parent stress caused by situational factors other than from the child or parent. The Child and Parent domains combine to yield the Total Stress scale. The 101 Child and Parent items are each scored on a 5-point scale (1 "Strongly Agree" – 5 "Strongly Disagree"), with the 19 Life Stress item responses indicating whether the events have occurred (0 "No" 1 "Yes:) in the past 12 months. Higher scores for each subscale and the two domain scores and the total score reflect more stress in that area.	3, 6, 12, 24, 36
Infant Toddler Home Observation for Measurement of the Environment (IT-HOME):[31] A 45-item inventory measuring 6 domains of the home environment important to child development: Responsivity (11 items) Acceptance (8), Organization (6), Learning Materials (9), Involvement (6), and Variety (5). Each domain has a separate score ranging from 0 to the number of items in the respective scale; the domain scores are then added to yield a Total Score (range: 0–45), with higher scores indicating a relatively more enriched home environment.	6, 24, 36
Addiction Severity Index (ASI):[32] A clinical assessment of addiction severity that measures functioning in 7 areas of the respondent's life: Medical, Employment, Drug, Alcohol, Legal, Family/Social, and Psychiatric. Items from each section are weighted and contribute to a composite score for each area, with scores ranging from 0 to 1, with higher scores indicating greater problem severity.	3, 6, 12, 24, 36

early ages, and the assessment battery was not administered to some infants at the later ages due to study close-out before they reached three years of age.

2.4. Statistical analyses

For all outcomes except child growth parameters, the statistical model had two fixed between-subject factors, Treatment (Buprenorphine *v*. Methadone), NAS Treatment (Treated *v*. not-Treated), and one fixed within-group factor for assessment Time point. [The Time effect could involve up to 5 levels (3 months *v*. 6 months *v*. 12 months *v*. 24 months *v*. 36 months). Not all outcomes were measured on all occasions; for these latter outcomes, Time included only a subset of these 5 levels, as appropriate to the assessment schedule for that outcome (see Table 1)] The statistical model for the three growth parameters also includes a fixed effect for child Sex. A linear mixed model (Littell et al., 2006; Verbeke and Molenberghs, 2000) examined the main effects and their respective interactions, assuming the outcome measures were normally distributed. To maximize detection of differences associated with each test of significance, the Type I error rate was set to 0.05 for all main and interaction tests of significance. Post hoc testing for interaction effects involved testing simple interaction or simple main effects, followed by testing pairwise mean differences, as appropriate to the outcome (Kirk, 2013). Post hoc testing for the Time main effect involved testing for linear trend and deviations from linearity to determine if change over time followed a systematic linear or non-linear progression or retrogression, with the spacing for the polynomial determined by the month of assessment, given the assessments were not conducted with equal intervening lengths of time. Sidak's adjustment (Kirk, 2013; Šidák, 1967) was applied to all post hoc tests. All analyses were performed with SAS version 9.3.

There were three effects of interest for all outcomes: Medication Condition X Time interaction, NAS Treatment X Time interaction, and the Time main effect. The Medication Condition X Time interaction tested whether the change over the three-year period differed between the Buprenorphine and Methadone conditions. The NAS Treatment X Time interaction tested whether the change over the three-year period differed between the Treated- and not-Treated-for-NAS groups (for the child in the case of child outcomes and for the mothers in the case of maternal outcomes, respectively). The Time main effect tested for change over the three-year period, and assessed the general growth and development of the children. The associated tests for linearity assessed whether change in the outcome measure over time was uniform (e.g., followed a uniform or straight-line pattern).

Therefore, Other Effects, discussed in the Results, refer to those effects other than the Medication Condition X Time interaction effect, the NAS Treatment Group X Time interaction effect, and the Time main effect.

The principal focus in this study was on the child measures, as there was no research basis to expect maternal effects. Maternal effects were examined to help contextualize child differences, particularly to the extent the latter changed over time.

Table 2
Estimates of Effect Size f^2 for Effects in the Inferential Statistical Model for 3, 4, and 5 Occasions of Measurement for $N = 96$ observations, $\alpha = 0.05$, and power (1-β) = 0.80.

	Number of Measurement Occasions		
	3	4	5
Effect			
Medication Condition (M)	0.104	0.119	0.131
Treated-for-NAS Group (N)	0.104	0.119	0.131
Time (T)	0.065	0.071	0.070
M x N	0.104	0.119	0.131
M x T	0.065	0.071	0.070
N x T	0.065	0.071	0.070
M x N x T	0.065	0.071	0.070

Note. Effect Size f^2 was estimated using the set correlation method. See text for details.

2.5. Minimum detectable effect size

To provide some context for examining results in addition to *P* values, we calculated the minimum detectable effect size, f^2 (Cohen, 1988), for each effect in the statistical model. Table 2 displays the resulting effect size estimates f^2.

3. Results

3.1. Participants

This subsample largely reflects the MOTHER sample as a whole. The maternal participants were relatively young [$M = 26.1$ ($SD = 5.4$)], with 75/96 (78%) less than 30 years of age], majority White [90/96 (94%)], with 39/96 (41%) having less than a high school education [years of education $M = 11.5$ ($SD = 2.1$)], largely unemployed [76/96 (79%)] and never married [71.96 (74%)]. They were maintained on their agonist medication as part of study participation for almost 20 weeks [$M = 143.7$ ($SD = 41.4$) days in the buprenorphine condition, $M = 136.0$ ($SD = 57.7$) days in the methadone condition, $p > .4$]. Overall, neonates were healthy [5-minute Apgar $M = 9.1$ ($SD = .9$), with 3/96 (3%) having a 5-minute Apgar ≤7], only 8/96 (8%) born prior to early term [estimated gestational age at delivery $M = 38.8$ ($SD = 2.0$)]. In addition, 54/96 (56%) neonates were treated for NAS; for these 54 neonates, NAS treatment lasted for an average of almost two weeks [$M = 16.9$ ($SD = 15.4$)]. Of the original 131 MOTHER participants, 52/73 methadone and 44/58 buprenorphine condition participants provided longer-term follow-up data, $p > .5$. Relative to present study non-participants, study participants were more likely to be White (94% v. 71%, $p < .001$), less likely to be unemployed (79% v. 99%, $p = .013$), with neonates with a higher mean 5-minute Apgar [$M = 9.1$ ($SD = .9$) v. $M = 8.5$ ($SD = 1.3$), $p < .002$], later mean gestational age at delivery [$M = 38.8$ ($SD = 2.0$) v. $M = 37.4$ ($SD = 2.9$), $p < .002$], and a shorter mean duration of NAS treatment [$M = 13.2$ ($SD = 10.9$) v. $M = 31.4$ ($SD = 21.3$), P < .001].

3.2. Outcomes

The data reported in this paper are unique because they present findings on the largest and most comprehensive assessment of neonates prenatally exposed to agonist medications, with minimal to no additional drug exposure. Thus, a set of Supplementary Tables for child and maternal outcomes are included. These tables contain the test statistics and *P* values and the associated estimated marginal means and 95% confidence intervals for all effects except the Medication Condition X NAS Treatment and Medication Condition X NAS Treatment Group X Time interactions.

3.2.1. Child results

3.2.1.1. Medication condition x time effects. There were two significant Medication Condition X Time interaction effects

3.2.1.2. Receptive-Expressive emergent language test – third edition. The Medication Condition X Time interaction effect was significant for the REEL-3 Receptive Percentile Rank. Means showed a distinct pattern in which the percentile rank mean for the Buprenorphine Condition was significantly lower than the percentile rank mean for the Methadone Condition at 12 months [$M = 28.8$ ($SE = 5.9$) v. $M = 45.9$ ($SE = 5.0$), respectively, $p < .03$], with percentile rank means of the two conditions rising and closing with each other at 24 [$M = 70.9$ ($SE = 4.4$) v. $M = 60.2$ ($SE = 4.5$), respectively, $p.66$] (see Supplement > .09] and 36 months [$M = 67.2$ ($SE = 4.9$) v. $M = 64.5$ ($SE = 4.1$), respectively, $p > .66$] (see Supplementary Table S3).

3.2.1.3. Infant behavior questionnaire revised. The Medication Condition X Time interaction effect was significant for the IBQ-R Approach scale, largely due to the fact that the Buprenorphine Condition mean was significantly lower than the Methadone Condition mean at 3 months [$M = 4.1$ ($SE = 0.2$) v. $M = 5.0$ ($SE = 0.3$), respectively, $p = < .66$] (see Supplement.66] (see Supplement.03, while the means of the two conditions at 6 [$M = 5.5$ ($SE = 0.2$) v. $M = 5.3$ ($SE = 0.2$, respectively, $p > .5$] and 12 months [$M = 6.0$ ($SE = 0.2$ v. $M = 6.1$ ($SE = 0.2$), respectively, $p = > .8$] were not significantly different from one another (see Supplementary Table S3[3]).

3.2.2. NAS treatment group x time effects

There was one significant NAS Treatment Group X Time interaction effect

3.2.2.1. Infant behavior questionnaire revised. The NAS Treatment Group X Time interaction effect was significant for the IBQ-R Distress to Limitations scale. Examination of the means showed that the Treated-for-NAS group means were higher than the not-Treated-for-NAS group at 6 months [$M = 3.9$ ($SE = 0.2$) v. $M = 3.3$ ($SE = 0.3$), respectively, $p < .05$] but not at 3 [$M = 3.7$ ($SE = 0.2$) v. $M = 3.3$ ($SE = 0.3$), respectively, $p = > .2$] and 12 months [$M = 4.1$ ($SE = 0.2$) v. $M = 4.4$ ($SE = 0.2$), respectively, $p > .2$] (see Supplementary Table S3).

3.2.3. Time main effects

Test statistics, P values, and the estimated marginal means and their 95% confidence intervals for the Time main effect for growth parameters are given in Table 3 for growth parameters and in Table 4 for developmental outcomes.

3.2.3.1. Growth parameters. Mean z-scores for weight, height, and head circumference increased from 3 to 36 months (see Table 3). Beginning below the 50th percentile at 3 months and ending exceeding the 50th percentile at 36 months – and, in the case of weight and head circumference, significantly higher than the 50th percentile.

3.2.3.2. BSID-III. The Time effect was significant for nine of 10 BSID-III scales, the exception being the General Adaptive Percentile Rank Score (see Table 4). Changes over the period from 6 to 36 months for these nine scales could not be considered consistent (see Supplementary Table S6 for tests of linearity) – the only exception being the Cognitive Percentile Rank Score, which showed a general decline over the time period. However, six of the nine significant scales – excepting Motor Composite and General Adaptive Composite Scores and Social-Emotional Percentile Ranks – showed non-uniform change (see Supplementary Table S6 for tests of deviations from linearity), with means reflecting a weak decline and then a general upturn in scores at 36 months.

3.2.3.3. REEL-3. Three of the five REEL-3 measures showed significant changes over Time- the two Receptive Scores and the combined Language Ability Score (see Table 4). All three measures showed non-

Table 3
Growth Parameters: Wald χ^2 Tests of Significance, *P* Values, and Estimated Marginal Means (95% Confidence Intervals) and Mean Percentile for the Time Main Effect ($N = 96$).

Time																	
				3 months			6 months			12 months			24 months			36 months	
	χ^2	*P*	*M*	*95% CI*	*Percentile*	*M*	*95% CI*	*Percentile*	*M*	*95% CI*	*Percentile*	*M*	*95% CI*	*Percentile*	*M*	*95% CI*	*Percentile*
Weight	32.1	< .001	−0.41	(−0.92, 0.10)	0.39	−0.33	(−0.67, 0.01)	0.43	−0.33	(−0.70, 0.03)	0.43	0.23	(−0.04, 0.51)	0.55	**0.64**	(0.29, 0.98)	0.68
Height	20.3	< .001	**−1.09**	(−1.85, −0.33)	0.25	−0.40	(−0.77, −0.01)	0.40	−0.37	(−0.89, 0.16)	0.42	−0.19	(−0.59, 0.20)	42.00	0.43	(0.04, 0.80)	0.60
Head Circumference	48.0	< .001	**−0.89**	(−1.43, −0.35)	0.26	−0.30	(−0.66, 0.58)	0.42	0.31	(−0.04, 0.65)	0.59	**0.58**	(0.29, 0.86)	0.64	**0.74**	(0.44, 1.04)	0.70

Notes. Raw data for each of the three growth parameters were transformed to *z*-scores and percentiles for the purposes of analysis (see http://www.cdc.gov/growthcharts/percentile_data_files.htm for more information and the formula needed for the transformations). All measures were assumed to be normally distributed in the population, so normal-theory-based estimation and tests of significance were utilized. Test statistics are Wald χ^2 tests of significance for the test of the Time main effect for the respective growth parameter. Summary data presented in this table are the mean *z*-scores (*M*) and their 95% confidence intervals (*95% CI*), together with their corresponding mean percentiles (Percentile). The mean *z* scores indicates the distance in standard deviation units the sample means were at the given time point from the normative sample means found in the CDC growth charts. Thus, for example, the mean *z*-score weight for the sample at 3 months was −0.41, indicating that the sample was 0.41 standard deviations below the normative sample mean. The Percentile score indicates the percentage of the normative sample estimated to be at or below that *z*-score. Thus, a percentile of 0.39 at 3 months for weight indicates that 39% of the normative sample fall at or below the *z*-score of −0.41. *z*-scores were used in all inferential analyses. Analysis of *z*-scores allowed for the inclusion of data from both girls and boys in the same analysis, and allowed for testing whether the *z*-score at each time period was 0, that is, whether the deviation from the 50th percentile at each time period was significant. (All such tests were conducted using the standard error for the respective mean *z*-score, with Sidak's post hoc adjustment). Mean *z*-scores in bold indicate that the mean for the highlighted cell was significantly lower (in the case of height and head circumference at 3 months) or significantly higher (for weight at 36 months and head circumference at 24 and 36 months) than the 50th percentile reported for the normative date by the CDC (see http://www.cdc.gov/growth charts/percentile_data_files.htm for US growth charts).

uniform changes over the period from 12 to 36 months (see Supplementary Table S6). Examination of the means suggested an increase in mean scores for the three significant measures from 12 to 24 months, leveling off from 24 to 36 months.

3.2.3.4. ITSP. Only two of four significant ITSP scales – Sensation Avoiding and Low Threshold − showed significant change over Time (see Table 4) that could be seen as showing a consistent pattern or as deviations from a consistent pattern of change (see Supplementary Table S6). For both scales, change was non-uniform. Examination of the means indicated that for both scales, there was a pronounced change from 6 to 12 months, flattening out at 24 months, and then an increase at 36 months.

3.2.3.5. IBQ-R. Of the 14 IBQ-R scores, eight tests of Time were significant (see Table 4). Seven of these eight scales showed consistent increases from 3 to 12 months (see Supplementary Table S6). In contrast, Cuddliness showed a consistent decline over this period. The rate of change for Activity Level rose from 3 to 6 months, and remained unchanged from 6 to 12 months.

3.2.4. Other effects

There were three significant Other Effects: One Sex X NAS Treatment Group interaction effect, one NAS Treatment Group main effect, and two significant Medication Condition X NAS Treatment effects.

3.2.4.1. Growth parameters. There was a significant Sex X NAS Treatment Group interaction effect for head circumference, although the means were found not to significantly differ from each other, with all *ps* > 0.05 The pattern of means would suggest that the interaction arose due to the fact that girls had a slightly larger head circumference in the not-Treated-for-NAS group [$M = 0.47$ (95% CI: −0.08, 1.03), Percentile = 0.61] than in the Treated-for-NAS group [$M = -0.17$ (95% CI: −0.54, 0.20), Percentile = 0.45], while boys had slightly larger head circumference in the Treated-for-NAS group [$M = 0.24$ (95% CI: −0.18, 0.65), Percentile = 0.56] than in the not-Treated-for-NAS group [$M = -0.20$ (95% CI: −0.62, 0.23), Percentile = .47].

3.2.4.2. Infant toddler sensory profile. The NAS Treatment Group main effect was significant for the ITSP Sensation Seeking scale, with the not-Treated-for-NAS group mean significantly higher than the mean for the Treated-for-NAS group.

3.2.4.3. Infant behavior questionnaire revised. The Medication Condition X NAS Treatment interaction effect was significant for IBQ-R Distress to Limitations and Sadness scales. Examination of the means for the IBR-Q Distress to Limitations scale indicated that the only significant mean difference was that the mean for the Treated-for-NAS group was larger than the mean of the not-Treated-for-NAS group. For the Sadness scale, the four means were not found to be significantly different from one another. The pattern of means would suggest that the interaction arose due to the fact that the not-Treated-for-NAS group had a smaller mean than did the Treated-for-NAS group in the Methadone condition, while the not-Treated-for-NAS group had a larger mean than did the Treated-for-NAS group in the Buprenorphine condition.

3.2.5. Supplementary results

Supplementary Table S1 contains the test statistics and *P* values for the child growth parameters while Supplementary Table S2 contains the test statistics and *P* values for the cognition, language abilities, sensory processing, and temperament. Supplementary Table S3 contains the associated estimated marginal means and 95% confidence intervals for these latter outcomes for all effects except the Medication Condition X NAS Treatment and Medication Condition X NAS Treatment Group X Time interactions.

Table 4
Child Mental Development, Language Abilities, Sensory Processing, and Temperament Measures: Wald χ^2 Tests of Significance, *P* Values, and Estimated Marginal Means (95% Confidence Intervals) for the Time Main Effect ($N = 96$).

Time:			3 months		6 months		12 months		24 months		36 months	
	χ^2	*P*	*M*	*95% CI*	*M*	*95% CI*	*M*	*95% CI*	*M*	*95% CI*	*M*	*95% CI*
Bayley Scale of Infant Development (BSID-III):												
Cognitive Subtest Composite Score	**12.7**	**.01**			103.1	(99.58, 106.58)	98.6	(95.21, 102.02)	96.3	(93.30, 99.33)	98.5	(95.41, 101.57)
Cognitive Subtest Percentile Rank	**19.2**	**< .001**			57.9	(51.02, 64.80)	47.6	(40.83, 54.29)	40.7	(34.86, 46.57)	44.4	(38.45, 50.45)
Language Composite Score	**20.6**	**< .001**			102.4	(98.72, 106.01)	96.5	(92.83, 100.19)	92.7	(89.62, 95.73)	98.4	(95.25, 101.47)
Language Percentile Rank	**18.6**	**< .001**			54.8	(47.16, 62.45)	41.8	(34.08, 49.53)	35.3	(28.87, 41.70)	46.1	(39.57, 52.61)
Motor Test Composite Score	**10.8**	**.01**			99.3	(95.55, 103.10)	94.3	(90.63, 98.05)	99.8	(96.61, 102.95)	101.6	(98.29, 104.85)
Motor Test Percentile Rank	**13.4**	**.004**			50.6	(43.02, 58.11)	37.3	(29.93, 44.76)	48.5	(42.18, 54.84)	52.8	(46.25, 59.34)
Social-Emotional Scale Composite Score	**12.0**	**.01**			114.2	(108.13, 120.24)	102.0	(96.06, 107.92)	107.1	(102.23, 111.92)	102.4	(97.38, 107.41)
Social-Emotional Scale Percentile Rank	**9.8**	**.02**			70.2	(60.40, 80.00)	53.6	(44.00, 63.14)	61.5	(53.62, 69.40)	53.5	(45.36, 61.68)
General Adaptive Composite Score	**8.4**	**.04**			104.6	(99.75, 109.37)	100.8	(96.20, 105.31)	97.1	(93.08, 101.10)	100.6	(96.46, 104.74)
General Adaptive Percentile Rank	7.6	0.06			58.3	(49.18, 67.38)	51.2	(42.59, 59.81)	44.8	(37.20, 52.34)	51.2	(43.40, 59.02)
Receptive-Expressive Emergent Language Test-Third Edition (REEL-3):												
Receptive Ability Score	**29.6**	**< .001**					94.1	(89.53, 98.70)	108.8	(105.14, 112.56)	105.2	(101.47, 109.02)
Receptive Percentile Rank	**46.8**	**< .001**					37.4	(29.71, 45.06)	65.5	(59.27, 71.76)	65.9	(59.52, 72.21)
Expressive Ability Score	1.7	.44					99.2	(94.54, 103.87)	101.8	(97.98, 105.56)	102.6	(98.85, 106.35)
Expressive Percentile Rank	5.1	.08					47.5	(37.83, 57.21)	53.2	(45.48, 60.87)	60.4	(52.77, 67.95)
Language Ability Score	**12.3**	**.002**					96.6	(91.56, 101.70)	106.3	(102.24, 110.44)	104.8	(100.77, 108.88)
Infant Toddler Sensory Profile (ITSP):												
Low Registration	**25.4**	**< .001**	49.5	(46.17, 52.74)	49.6	(47.87, 51.42)	46.6	(44.10, 49.16)	45.7	(43.72, 47.72)	47.4	(45.38, 49.34)
Sensation Seeking	**142.9**	**< .001**	9.2	(6.54, 11.92)	7.8	(6.73, 8.95)	23.6	(20.98, 26.16)	29.6	(27.33, 31.82)	35.3	(32.88, 37.71)
Sensory Sensitivity	8.9	.06	49.7	(46.93, 52.56)	49.7	(47.78, 51.66)	41.6	(39.13, 44.00)	41.7	(39.72, 43.74)	43.3	(41.33, 45.21)
Sensation Avoiding	**19.1**	**< .001**	22.1	(20.26, 23.94)	21.3	(19.76, 22.89)	47.1	(44.48, 49.80)	47.6	(45.50, 49.65)	49.8	(47.57, 52.04)
Low Threshold	**17.8**	**< .001**	72.3	(68.97, 75.73)	69.7	(65.66, 73.74)	88.2	(83.37, 93.01)	89.1	(85.31, 92.99)	92.8	(88.83, 96.72)

Tests of significant and *P* values that are significant are listed in bold.

3.2.6. Maternal results

3.2.6.1. Medication condition x time effects. There was one significant Medication Condition X Time interaction effect

3.2.6.2. Addiction severity index. Examination of the means for the ASI Legal composite score indicated a general pattern in which the means for both conditions fell off over the period from 3 to 36 months (*M*s = 0.03, 0.08, 0.01, 0.00, and 0.01 for the Buprenorphine condition respectively and *M*s = 0.10, 0.13, 0.10, 0.12, and 0.05 respectively for Methadone condition), but the Buprenorphine condition had significantly lower mean scores at 12 and 24 months than did the Methadone condition [$M = 0.01$ ($SE = 0.03$) v. $M = 0.10$ ($SE = 0.03$) at 12 months respectively, $p < .03$; $M = 0.00$ (SE.03) v. $M = 0.12$ ($SE = 0.03$) at 24 months respectively, $p < .002$] (see Supplementary Table S5).

3.2.6.3. NAS treatment group x time effects. There was one significant NAS Treatment Group X Time interaction effect.

3.2.6.4. Addiction severity index. The ASI Legal composite score showed significant differences between the means of Time within the not-Treated-for-NAS group [*M*s = 0.08, 0.15, 0.07, 0.05, and 0.01, respectively; $F(4.69) = 4.2$, $p < .005$}, but not for the means of Time within the Treated-for-NAS group [*M*s = 0.05, 0.05, 0.05, 0.06, and 0.05, respectively; $F(4.69) = 0.2$, $p > .9$] (see Supplementary Table S5).

3.2.7. Time main effects

Table 5 presents the test statistics, *P* values, and the estimated marginal means and their 95% confidence intervals for the Time main effect for all maternal outcomes

3.2.7.1. PSI. PSI scores showed significant changes for nine of seventeen scales over Time, largely indicative of increased stress from child behaviors as the child enters the toddler stage and corresponding stress associated with parenting competence (see Table 5).

3.2.7.2. HOME. HOME scores showed significant changes for four of seven scales over Time (see Table 5), with scores rising from 6 to 24 to 36 months for those variables that were significant, as seen in the HOME total score (see Table 5).

3.2.7.3. ASI. There was no significant change over Time for the ASI composite scores (see Table 5)

3.2.8. Other effects

There were 14 significant Other Effects

3.2.8.1. Parenting stress index. There was a significant main effect for NAS Treatment Group for the PSI Reinforces Parent scale, with the mean for the Treated-for-NAS group significantly higher than the mean for the not-Treated-for-NAS group. There were significant Medication Condition X NAS Treatment Group interaction effects for the PSI Adaptability and Health scales. The PSI Adaptability mean was significantly higher for mothers in the Methadone condition whose neonates were Treated-for-NAS than the mean for the mothers in the Methadone condition whose neonates were not-treated-for-NAS, while the remaining three tests of the mean differences were nonsignificant. Regarding the PSI Health scale, post hoc testing indicated all simple mean differences were nonsignificant. There was a significant Medication Condition X NAS Treatment Group X Time interaction effect for the PSI Health scale. The simple interaction of Medication Condition X NAS Treatment at each level of Time was only significant at 6 months; however, none of the mean differences at 6 months were

Table 5
Maternal Parenting Stress, Home Environment, and Addiction Severity Measures: Wald χ^2 Tests of Significance, *P* Values, Estimated Marginal Means (95% Confidence Intervals) for the Time Main Effect ($N = 96$).

Time:			3 months		6 months		12 months		24 months		36 months	
	χ^2	*P*	*M*	*95% CI*	*M*	*95% CI*	*M*	*95% CI*	*M*	*95% CI*	*M*	*95% CI*
Parenting Stress Index (PSI):												
Distractibility/Hyperactivity	8.3	.08	24.8	(22.77, 26.77)	23.9	(22.58, 25.13)	24.9	(23.29, 26.42)	26.0	(24.76, 27.31)	25.1	(23.68, 26.43)
Adaptability	8.3	.08	22.5	(19.86, 25.24)	22.7	(21.01, 24.39)	24.4	(22.27, 26.55)	25.3	(23.71, 26.84)	25.1	(23.42, 26.78)
Reinforces Parent	**11.5**	**.02**	9.1	(7.95, 10.25)	7.9	(7.14, 8.62)	8.8	(7.97, 9.69)	8.8	(8.16, 9.43)	9.3	(8.55, 10.07)
Demandingness	**5.0**	**< .001**	16.0	(13.58, 18.34)	15.3	(13.91, 16.71)	17.4	(15.84, 18.98)	19.0	(17.58, 20.40)	18.8	(17.22, 20.37)
Mood	**38.2**	**< .001**	7.7	(6.57, 8.93)	7.9	(7.07, 8.67)	8.5	(7.73, 9.31)	10.2	(9.35, 10.98)	10.1	(9.44, 10.83)
Acceptability	**11.3**	**0.02**	10.0	(8.38, 11.69)	9.7	(8.61, 10.70)	11.1	(10.04, 12.22)	11.4	(10.51, 12.28)	11.8	(10.70, 12.83)
Competence	**14.1**	**.01**	27.0	(24.49, 29.41)	26.6	(24.79, 28.41)	28.3	(26.19, 30.42)	28.3	(26.61, 30.01)	30.1	(28.53, 31.65)
Isolation	**12.9**	**.01**	11.4	(9.71, 13.15)	13.3	(12.08, 14.61)	14.3	(13.05, 15.54)	13.4	(12.23, 14.61)	14.0	(12.88, 15.05)
Attachment	8.9	.06	11.8	(10.30, 13.20)	10.4	(9.51, 11.24)	11.8	(10.67, 12.84)	11.5	(10.67, 12.37)	11.7	(10.84, 12.58)
Health	5.7	.22	12.9	(11.45, 14.26)	12.0	(11.22, 12.73)	12.8	(11.66, 13.86)	11.6	(10.52, 12.68)	12.0	(10.92, 13.06)
Role Restriction	3.0	.56	18.6	(16.14, 20.97)	16.9	(15.16, 18.72)	18.0	(16.42, 19.65)	17.9	(16.56, 19.20)	18.3	(16.91, 19.74)
Depression	5.2	.27	18.7	(16.41, 21.01)	17.5	(15.77, 19.21)	19.3	(17.38, 21.20)	17.9	(16.56, 19.31)	18.0	(16.48, 19.42)
Spouse/Parenting Partner Relationship	2.3	.68	16.4	(13.90, 18.80)	17.3	(15.08, 19.56)	18.0	(16.12, 19.80)	17.5	(15.91, 19.12)	17.1	(15.80, 18.38)
Child Domain	**24.6**	**< .001**	90.0	(81.66, 98.37)	86.9	(82.04, 91.70)	95.5	(89.00, 101.93)	100.6	(95.49, 105.65)	100.2	(94.60, 105.84)
Parent Domain	5.1	.27	117.0	(107.13, 126.85)	115.0	(107.86, 122.19)	122.5	(114.51, 130.47)	118.1	(111.39, 124.76)	120.7	(114.30, 127.19)
Total Score	**13.5**	**.01**	210.0	(194.25, 225.75)	202.5	(191.92, 213.18)	220.4	(208.82, 232.06)	220.1	(209.65, 230.53)	222.2	(211.74, 232.65)
Life Stress	**10.0**	**.04**	17.0	(12.64, 21.45)	15.0	(11.40, 18.52)	12.1	(8.66, 15.47)	11.4	(8.59, 14.15)	10.5	(7.99, 12.96)
Medical Composite Score	6.5	.16	0.08	(−0.03, 0.20)	0.24	(0.13, 0.35)	0.12	(0.05, 0.19)	0.19	(0.12, 0.27)	0.22	(0.12, 0.31)
Employment Composite Score	4.2	.38	0.76	(0.65, 0.87)	0.76	(0.68, 0.84)	0.75	(0.67, 0.82)	0.75	(0.68, 0.82)	0.70	(0.62, 0.77)
Drug Composite Score	6.5	.17	0.14	(0.10, 0.19)	0.16	(0.13, 0.19)	0.17	(0.14, 0.20)	0.14	(0.11, 0.17)	0.12	(0.08, 0.15)
Alcohol Composite Score	5.3	.26	0.01	(−0.00, 0.02)	0.00	(−0.00, 0.01)	0.01	(0.00, 0.02)	0.01	(0.00, 0.01)	0.01	(0.01, 0.02)
Legal Composite Score	7.8	.10	0.06	(0.02, 0.11)	0.10	(0.05, 0.15)	0.06	(0.02, 0.10)	0.06	(0.02, 0.10)	0.03	(−0.01, 0.07)
Family/Social Composite Score	2.3	.68	0.10	(0.02, 0.18)	0.12	(0.07, 0.17)	0.14	(0.08, 0.20)	0.13	(0.07, 0.18)	0.09	(0.03, 0.15)
Psychiatric Composite Score	1.6	.80	0.20	(0.10, 0.30)	0.18	(0.11, 0.26)	0.17	(0.10, 0.24)	0.14	(0.08, 0.21)	0.16	(0.10, 0.22)

Tests of significant and *P* values that are significant are listed in bold.

significant.

3.2.8.2. Home observation for measurement of the environment. There was a significant Medication Condition main effect for HOME Organization, with the mean of the Buprenorphine condition significantly higher than mean for the Methadone condition.

3.2.8.3. Addiction severity index. There were significant Medication Condition main effects for the ASI Alcohol and Legal composite scores. For Alcohol, the Buprenorphine condition mean was significantly larger than the Methadone condition mean, while for Legal, the Buprenorphine condition mean was significantly smaller than the Methadone condition mean. There were significant NAS Treatment group main effects for the ASI Employment and Family/Social composite scores. For both ASI composite scores, the Treated-for-NAS group means were significantly larger than the not-Treated-for-NAS group means. The Medication Condition X NAS Treatment group interaction effect was significant for the ASI Medical composite score. The mean for the mothers whose neonates were Treated-for-NAS was significantly higher than the mean for the mothers whose neonates were not-treated-for-NAS, while the remaining tests of differences between the means were non-significant. The Medication Condition X NAS Treatment X Time interaction effect was significant for both the ASI Medical and Alcohol composite scores. For the Medical composite, the interaction was due to the fact that the means for both the Treated-for-NAS and not-Treated-for-NAS groups in the Buprenorphine condition rose over the three-year period, while this was not the case in the Methadone condition. In contrast, the interaction for the Alcohol composite was due to the fact that the means at 6 months was substantially lower in both the Treated-for-NAS and not-Treated-for-NAS groups in the Buprenorphine condition than the corresponding means in the Methadone condition

3.2.9. Supplementary results

Supplementary Table S4 contains the test statistics and *P* values for maternal parenting stress, home environment, and addiction severity measures. The estimated marginal means and 95% confidence intervals for all effects except the Medication Condition X NAS Treatment and Medication Condition X NAS Treatment Group X Time interactions are reported in Supplementary Table S5.

4. Discussion

Overall, this study found that from 3 months through 36 months of age, children prenatally exposed to buprenorphine or methadone were well within the range of normal development in physical growth measures, cognitive development and language development. Also, mothers maintained on buprenorphine or methadone did not differ on any of the measures, other than the ASI legal section.

4.1. Child findings

In this study, up to 36 months, children follow a path of normal development. Thus, findings for growth parameters suggest that prenatal opioid agonist exposure does not affect normal physical development. Conclusions are similar in terms of cognitive development, language abilities, sensory processing, and temperament. Changes over time in some, though not all Bayley mean composite scale and percentile rank scores as well as the ITSP scale scores, with a general upturn in scores at 36 months, argue against any conclusion of some overall pattern of loss of abilities in these areas.

Moreover, significant changes over time in the mean scores did not indicate any substantive developmental decline. Mean scores continued to be within the average range. The changes in language ability found in the Bayley language composite scale indicate that language development was within normal limits.

There are two significant Medication Condition X Time and one significant NAS Treatment Group X Time interaction, out of 37 such tests conducted for each effect. These results offer strong support for two conclusions. First, there is no apparent pattern of results that would argue for differential impact of prenatal exposure to methadone or buprenorphine on early childhood growth and development. Second, NAS severity does not have an adverse impact on early childhood growth and development. This finding is consistent with a previous study in neonates prenatally exposed to methadone (Kaltenbach and Finnegan, 1987) and provides important contemporary information for clinicians and policymakers.

4.2. Maternal findings

Maternal findings strongly indicated that, on average, neither methadone and buprenorphine mothers nor the mothers whose neonate was or was not treated for NAS differed from each other in terms of any characteristic over the three-year period, with the possible exception of ASI-defined legal problems. Scores on the PSI would suggest that the mothers, as a group, reported increasing difficulties with their children over the three-year period, notably seen in increasing Child Domain mean scores and increases in the parental competence mean score. It is unclear whether the children actually exhibit more challenging behaviors; whether mothers who experience high levels of parenting stress rate typical child behaviors as more severe; or whether the relationship is bi-directional. In contrast to the PSI findings, HOME scores show a consistently more enriched home environment over the period from 6 to 36 months. Taken together, these results counteract the assumption that mothers with a history of opioid use disorder are unable to create a positive home environment (Kaltenbach, 2013) and suggest that developmental risk for their children may be related more to problems in the parent-child relationship.

4.3. Limitations

The study has several limitations. First, only 96 of the 131 women who participated in the MOTHER trial were recruited. While the subsample appears to be largely representative of the MOTHER sample, it is possible that unknown factor(s) may have operated to impact subsampling that may have biased the findings. Second, constraints placed on sampling due to cost and time limitations led to not all of the 96 mothers and their children being measured at each time point. Further, this sample size limited the statistical model complexity (e.g., no control for recruitment site, for child variables, or maternal covariates). Third, the MOTHER study emphasized internal, not external, validity, so the ability to generalize the current findings may be limited. However, the MOTHER sample was unique in that, with the exception of tobacco, there was minimal to no concomitant prenatal substance exposure, including alcohol. Fourth, the subsample of MOTHER mothers and infants examined in this paper may differ in important ways from the MOTHER women and infants who were non-participants. Inclusion of non-participants could have impacted findings in unknown ways. Fifth, there was no comparison group of mother and children whose mothers were of similar socioeconomic status who did not use psychoactive substances. Lastly, the per-comparison α was set at 0.05, and as a result, the cumulative error rate in the study may be sizeable, with some unknown number of findings Type I errors. However, α was set at 0.05 in order to maintain our ability to detect relatively weaker medication and NAS treatment effect differences- effect sizes determined to be in the small-to-medium range (see Table 2). Setting α to some value lower than 0.05 would have prevented detection of weaker relationships that might prove important to examine in future research.

5. Conclusions

The present study is the first longitudinal study to examine early

childhood developmental outcomes of infants born to pregnant women who were enrolled in a randomized, controlled trial examining maternal treatment with methadone or buprenorphine with rigorous assessment and treatment protocols for NAS. Findings suggest that children prenatally exposed to opioid agonist medications follow a pattern of normal development during the first three years of life. These results are consistent with studies that find no differences in development between infants prenatally exposed to opioids and non-exposed infants. They also provide important comparison data to studies that have reported differences as such studies have all been confounded by multiple illicit and licit drugs.

Findings strongly suggest no deleterious effects for buprenorphine relative to methadone. Findings also strongly indicate no deleterious effects for NAS requiring treatment relative to not-treated-for-NAS in children 0–3 years old prenatally exposed to opioid agonist medication as part of a randomized controlled trial. Over the first three years, mothers in general struggled with parenting skills at the same time they reported they were able to provide an increasingly enriched home environment to address child needs. Findings suggest future research could profitably focus on intervention trials that examine the impact of parenting practices and parent training on the development of children who are prenatally exposed to opioid agonist medications.

Conflict of interest

None.

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Contributors

Karol Kaltenbach: Dr. Kaltenbach conceptualized and designed the study, oversaw the completion of the draft of the initial manuscript, and critically reviewed and revised the manuscript.

Kevin E. O'Grady: Dr. O'Grady conducted the analyses, collaborated with Drs. Kaltenbach and Jones in drafting the results section of the initial draft, and critically reviewed and revised the manuscript.

Sarah H. Heil: Dr. Heil participated with Drs. Kaltenbach and Jones in the conceptualization and design of the study, oversaw the implementation of the study protocol at the University of Vermont site, and critically reviewed and revised the manuscript.

Amy L. Salisbury: Dr. Salisbury assisted with implementation of the study protocol at the Brown University Site, and critically reviewed and revised the manuscript.

Mara G. Coyle: Dr. Coyle participated with Drs. Kaltenbach and Jones in the conceptualization and design of the study, oversaw the implementation of the study protocol at the Brown University site, and critically reviewed and revised the manuscript.

Gabriele Fischer: Dr. Fischer participated with Drs. Kaltenbach and Jones in the conceptualization and design of the study, oversaw the implementation of the study protocol at the Medical University Vienna site, and critically reviewed and revised the manuscript.

Peter R. Martin: Dr. Martin participated with Drs. Kaltenbach and Jones in the conceptualization and design of the study, oversaw the implementation of the study protocol at the Vanderbilt University site, and critically reviewed and revised the manuscript.

Susan M. Stine: Dr. Stine participated with Drs. Kaltenbach and Jones in the conceptualization and design of the study, oversaw the implementation of the study protocol at the Wayne State University site, and critically reviewed and revised the manuscript.

Hendrée E. Jones: Dr. Jones collaborated with Dr. Kaltenbach in the conceptualization and design of the study and selection of the data collection instruments, assisted in the initial draft of the manuscript, critically reviewed and revised the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2017.11.030.

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