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# Dietary Intake Among Opioid Dependent and Alcohol Using Pregnant Women

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## Abstract

**Background—**Substance abuse in non-pregnant adults has been associated with increased intake in calories and decreased intake of nutrient-dense foods; however, studies examining dietary intake in opioid-dependent and alcohol-using pregnant women are lacking.

**Objective—**The objective of this study was to evaluate dietary intake in opioid-dependent pregnant women with or without concurrent light-to-moderate alcohol use as compared to abstaining controls.

**Methods—**This prospective birth cohort included 102 pregnant women classified into four study groups: controls (n=27), medication assisted treatment (MAT; n=26), alcohol (ALC; n=22), and concurrent use of both substances (MAT+ALC; n=27). Percentage differences in macro- and micronutrient intake were estimated from the food frequency questionnaire and compared among the study groups. Proportions of participants with intakes below the estimated average requirements (EAR) based on diet and diet with supplements were estimated.

**Results—**Three exposed groups had lower prevalence of multivitamin use in periconceptional period (11.5-31.8%) than controls (44.4%). Unadjusted mean energy intake was significantly

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higher in the MAT+ALC group compared to controls, while micronutrient intake per 1000 kcal was the highest in the control group for almost all of the micronutrients analyzed. After adjustment for energy intake and socio-demographic characteristics, MAT group had lower estimated dietary intake of iron (-15.0%, p=0.04) and folate (-16.8%, p=0.04) compared to controls. A high proportion of participants in all study groups had dietary intake below the EAR for vitamin E, iron and folate.

**Conclusion—**Results highlight the need for targeted dietary interventions for opioid-dependent pregnant women.

### Keywords

Pregnancy; Nutrition; Medication Assisted Treatment; Alcohol

## Introduction

Adequate nutrient intake around conception and throughout pregnancy is essential for maternal health, proper fetal growth and neurodevelopment (Allen, 2005; Procter & Campbell, 2014). Inadequate dietary intake during pregnancy is a risk factor for adverse pregnancy outcomes, such as neural tube defects, intrauterine growth restriction, preterm delivery, and low birth weight (Abu-Saad & Fraser, 2010). Women with substance use disorders may be at a high risk for poor dietary intake during pregnancy due to a number of reasons, including inconsistent eating patterns, unstable housing situations, food insecurity, high rates of co-existing psychiatric disorders and tobacco use, unemployment and consequent poor socioeconomic status, inadequate social support, and a history of sexual or physical abuse and partner violence (Alexander, 2013; Best et al., 1998; Himmelgreen et al., 1998). In addition, substance abuse has been linked to addictive eating patterns and binge eating behaviors associated with excessive consumption of sweets and carbohydrates, and decreased intake of nutrient-dense foods (Grilo, White, & Masheb, 2009; Holderness, Brooks-Gunn, & Warren, 1994; Pelchat, 2002; Saeland et al., 2011; Tomedi, Bogen, Hanusa, Wisner, & Bodnar, 2012; Zador, Wall, & Webster, 1996). Alcohol intake has also been associated with higher energy intake and lower total diet quality among U.S. adults (Breslow, Guenther, Juan, & Graubard, 2010). The association of substance use disorder and poor dietary intake is of significant public health concern because of alarming rates of alcohol and substance abuse during pregnancy in the U.S., with approximately 5.4% of pregnant women reporting current illicit drug use, 10% reporting any alcohol use, and 3.1% reporting a binge drinking pattern of alcohol consumption (Substance Abuse and Mental Health Services Administration, 2014; Tan, Denny, Cheal, Sniezek, & Kanny, 2015).

Mirroring an epidemic of prescription opioid abuse/misuse in the general population, a six-fold increase in opioid use in pregnant women has been observed in the last decade (S. Patrick, Davis, Lehmann, & Cooper, 2015; S. W. Patrick et al., 2012). These numbers could be fairly conservative estimates considering the stigma associated with reporting substance use during pregnancy (Garg et al., 2016). Abrupt discontinuation of opioids in pregnancy is known to increase the risk of serious adverse perinatal outcomes, including fetal distress, fetal demise and preterm delivery, while medication assisted treatment (MAT) with methadone or buprenorphine is a standard of care and is recommended by major

professional organizations, such as American Congress of Obstetricians and Gynecologists and American Academy of Pediatrics (ACOG, 2012; Hudak & Tan, 2012). While neonatal abstinence syndrome is an expected adverse outcome, benefits of MAT outweigh the risks associated with illicit opioids. Specifically, MAT offers social stabilization, increased utilization of prenatal care, minimization of the blood-born pathogen transmission associated with injectable drug use, while preventing cute withdrawal symptoms and minimizing opioid craving (Hudak & Tan, 2012).

Few studies have examined the relationship between substance use and diet quality during pregnancy. A single pilot study found that pregnant women on MAT, specifically methadone, had a significantly lower pre-pregnancy BMI compared to non-drug using pregnant women, and also reported significantly higher intake of energy compared to controls (Tomedi et al., 2012). In addition, women on MAT had significantly lower serum concentrations of carotenoids and elevated homocysteine levels compared to controls, indicating potentially insufficient intake of vitamin $B_6$, vitamin $B_{12}$, and folic acid in their diet (Tomedi et al., 2012). The objective of the current study was to evaluate estimated dietary intake in pregnant women on MAT with or without concurrent alcohol use in pregnancy as compared to abstaining controls. We hypothesized that substance and alcohol using pregnant women would have higher dietary caloric intake but lower intake of micronutrients compared to abstaining controls.

## Methods

### Study design and participants

This report presents a cross-sectional analysis of dietary intake data from pregnant women recruited into the Ethanol, Neurodevelopment, Infant and Child Health (ENRICH) study at the University of New Mexico (UNM). ENRICH is a prospective ongoing birth cohort initiated in 2013, which recruits pregnant women and follows up children born to cohort participants through 20 months of age. Detailed methodology of the birth cohort is described elsewhere (Bakhireva, Lowe, Gutierrez, & Stephen, 2015). The UNM Human Research Review Committee approved the study, and all participants signed an informed consent. In addition to traditional safeguards provided by a standard IRB approval, a National Institutes of Health Certificate of Confidentiality was obtained for this study.

Participants were recruited into the ENRICH study from UNM-affiliated clinics, including general obstetrics and midwifery clinics, as well as a specialized prenatal care clinic, called Milagro, dedicated to women with substance use disorders, during one of their first prenatal care visits. Eligibility criteria for the parent study were: 1) ≥ 18 years old; 2) singleton pregnancy confirmed by ultrasound; 3) intention to stay in the Albuquerque metropolitan area for the next two years; 4) able to consent in English; 5) no more than occasional use (less than monthly or no more than one positive urine drug screen) of cocaine, crack-cocaine or methamphetamine during the periconceptional period or pregnancy; and 6) absence of fetal structural anomalies per prenatal ultrasound. This report includes data collected from participants during study Visit 1 (at enrollment, on average 24.2±7.1 gestational weeks) and Visit 2 (during the hospital stay for labor and delivery).

### Self-report and biomarker assessment for substance use

The study included state-of-the-art measures to ascertain alcohol use among study participants. The Alcohol Use Disorder Identification Test-C (AUDIT-C), a short questionnaire designed to identify patients with alcohol use disorders or hazardous drinking behaviors, was initially used as a screening tool (Bush, Kivlahan, McDonell, Fihn, & Bradley, 1998). After enrollment, repeated, prospective 30-day Timeline Follow-back (TLFB) interviews were administered by a trained researcher at Visits 1 and 2, capturing a total of 3 time periods: a) the periconceptional period (2 weeks prior to and 2 weeks after LMP); b) mid-gestation (30 days prior to enrollment); and c) 30 days before delivery. The prospective TLFB calendar method is considered a 'gold standard' to ascertain alcohol use in pregnancy (Jacobson, Chiodo, Sokol, & Jacobson, 2002; Sobell & Sobell, 1992). Participants were also asked to report drinking on any "special occasions" outside of the three TLFB calendars and their total number of binge drinking episodes (≥4 drinks on one occasion) during pregnancy. Prior studies have shown that questions about pre-pregnancy or periconceptional alcohol use may more accurately reflect alcohol use during pregnancy, especially among heavy drinkers, since self-report is less likely to be influenced by the social desirability biases during those time periods (Jacobson et al., 2002). Participants were asked to report the use of any nicotine or tobacco-based products in the past 3 years and since the LMP at Visit 1, and to report any changes in use of these products since enrollment at Visit 2. Finally, a structured questionnaire based on the survey questions from the 2011 National Survey on Drug Use and Health (United States Department of Health Human Services. Substance Abuse Mental Health Services Administration. Center for Behavioral Health Statistics and Quality, 2011) ascertained the use of the following substances between the LMP and delivery: marijuana, cocaine/crack, heroin, methamphetamines, methadone, buprenorphine, ecstasy, opioid analgesics, benzodiazepines, and barbiturates. To facilitate recall, street names of the substances were provided. Polysubstance use, which was calculated using the above data, was defined as use of any substance in addition to methadone or buprenorphine in any frequency during pregnancy.

Self-reported information on alcohol use was verified by a comprehensive panel of ethanol biomarkers. The following ethanol biomarkers were ascertained in maternal specimens at both study visits: gamma-glutamyl transferase (GGT), carbohydrate deficient transferrin (%dCDT), phosphatidylethanol (PEth), urine ethyl sulphate (uEtS), and urine ethyl glucuronate (uEtG), additionally, PEth was evaluated in newborn dry blood spots as a measure of newborn exposure (Bakhireva & Savage, 2011). GGT, PEth, uEtG, uEtS analyses were conducted at the United States Drug Testing Laboratory (USDTL; Des Plaines, IA), and %dCDT was analyzed at the Medical University of South Carolina (Charleston, SC). The following cut-points were used to identify a 'positive' test: uEtG ≥ 38.7 ng/mL, uEtS ≥7.2 ng/mL, GGT>40 U/L, %dCDT>2.0%, maternal PEth > 8 ng/mL, and PEth dry blood spot > 25 ng/mL, as previously reported (Bakhireva et al., 2014).

Self-reported information on drug use and MAT was verified by a review of electronic medical records, urine drug screens (UDS) conducted at the clinic, and study-specific urine drug tests. We have previously reported substantial-to-perfect agreement between self-reported and urine tests for methadone and buprenorphine use (Garg et al., 2016). During

prenatal care appointments, all patients at the Milagro clinic participated in routine UDS for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, methadone, buprenorphine, and other opioids (heroin and prescription opioids). Urine samples were sent to the Tricore Reference Laboratories (Albuquerque, NM), and analyzed using enzyme multiplied immunoassay technique (EMIT). EMIT is a reliable, highly-sensitive and commonly-used test for drug monitoring in substance use treatment programs, and has an accuracy range of 87-95% (Melanson, 2012; Reisfield, Salazar, & Bertholf, 2007). Finally, a study-specific urine samples were collected at each visit and analyzed for a Urine Drug Panel-7 (amphetamines, barbiturates, benzodiazepines, cocaine, phencyclidine, cannabinoids, and opioids) at the USDTL where all presumptive positive results are verified by LC-MS/MS or GC-MS (USDTL, 2016). It should be noted that New Mexico legislation does not support the use of clinical evidence of prenatal substance use to justify punitive measures taken against this population (Stone-Manista, 2009), and UDS results remain confidential.

## Classification of participants into study groups

Participants met criteria for the *control group* if all of the following conditions were met: 1) AUDIT-C<2; 2) self-report of <2 drinks/week in the periconceptional period and abstinence from any alcohol use throughout pregnancy; 3) negative test results on all ethanol biomarkers and UDS; 4) no use of tobacco or other substances. To be classified in the *MAT group*, participants had to meet criteria 1-3 listed above and be on MAT (either methadone or buprenorphine) with or without concurrent use of other opioids. Participants were assigned to the *ALC group* if they met one or more of the following criteria: 1) AUDIT-C ≥2; 2) self-report of ≥3 drinks per week on average during pregnancy; 3) self-report of ≥1 binge episode during pregnancy; 4) self-report of ≥84 drinks total during pregnancy; 5) positive for any alcohol biomarker. Participants who were on MAT and met the above-mentioned alcohol criteria were assigned to the *ALC+MAT group*. Concurrent nicotine exposure was allowed in all study groups except the control group.

## Socio-demographic characteristics and assessment of dietary intake

A structured maternal interview administered at Visit 1 collected the socio-demographic (e.g., age, ethnicity, race, education attainment, employment status, insurance type) and medical (pregnancy complications, medical conditions, reproductive history, pre-pregnancy weight and height) characteristics of the study participants. Pre-pregnancy body mass index (BMI) was calculated from the weight and height measurements collected at V1. Use of prescription and over-the-counter medications, including use of multivitamins and micronutrient supplements in periconceptional period and during pregnancy, was also queried. The Block Brief 2000 Food Frequency Questionnaire (FFQ) was administered at Visit 2 and analyzed by NutritionQuest (Berkeley, CA). The FFQ was used to estimate the participants' energy and micronutrient intake for the past 12 months, including the duration of pregnancy. The Block Brief 2000 FFQ includes approximately 72 food items and asks about portion size and frequency of consumption for each food.

### Sample size, power, and statistical analyses

As of February 2016, 111 ENRICH patients met the eligibility criteria described above, completed Visit 2, and had FFQ data analyzed. Nine participants were excluded as outliers, based on estimated energy intake <1000 Kcal/day or >6000 Kcal/day. Thus, the final sample size included 102 study participants. Based on the estimates of mean energy intake in the methadone versus control groups reported in the Tomedi's pilot study, the sample size of 26-27 subjects per group available in our sample will result in 92% power to detect differences of a similar magnitude.

Maternal demographic and medical characteristics were compared among the four study groups using Analysis of Variance (ANOVA) for continuous variables and Fisher's exact tests for categorical variables. Means and standard deviations of macro- and micronutrient intake were calculated by study group. Micronutrient intake was adjusted for energy intake using the Willett method (Willett, Howe, & Kushi, 1997). Differences in micronutrient intake between study groups were examined after log-transformation of the energy-adjusted variables. In addition, we assessed differences in energy-adjusted micronutrient intake in multivariable models comprised of maternal BMI, ethnicity, marital status, employment and smoking status along with categorical dummy variable for study group as predictors. Selection of covariates was based on association of potential risk and protective factors with the study group and a multiple analysis of variance (MANOVA) for correlated micro/macronutrient intake. MANOVA allows for comparison of multiple outcomes (micronutrients) with a specific predictor. Covariates were selected initially if they significantly affected the results of a two-way MANOVA where the other predictor was the study group. After selection of initial set of covariates, final model was based on maximizing adjusted r-squared (indicative of model fit) after exclusion of non-significant covariates. Control participants were used as the reference groups for all comparisons. Differences in dietary intake for MAT and/or alcohol groups are presented as percentage difference when compared to controls. The proportion of individuals in each group with micronutrient intake below the Estimated Average Requirement (EAR) was calculated, first considering dietary intake alone and then including supplements (Institute of Medicine, 2000). Adequate intake values were used for choline instead of EAR (National Research Council and National Research Council, 2000). All analyses were conducted in STATA v.12 (StataCorp LP, College Station, TX); p-values <0.05 were considered significant.

## Results

The demographic characteristics of the study participants are presented in Table 1. Overall, the mean (±SD) age of the study participants was 27.3±5.7 years, and the gestational age at enrollment was 24.2±7.3 weeks. A majority of participants characterized themselves as White (89%) and Hispanic/Latina (60.8%). About half of the study participants were single, separated or divorced (51.0%), and had a high school or lower level of education (53.9%). Almost two-thirds had an unplanned pregnancy (61.8%). Maternal age, ethnicity, race, pre-pregnancy BMI category, and multivitamin and iron supplement use did not vary significantly among the study groups. MAT users (with or without alcohol use) were more likely to be single/separated or divorced, to have lower education level, at least one medical

condition, and an unplanned pregnancy compared to controls. There was a high prevalence of polysubstance use in the MAT (65.4%), ALC (40.9%), and MAT+ALC (74.1%) groups, and a high prevalence of tobacco use in the MAT (53.8%) and MAT+ALC (66.7%) groups. Among exposed groups (MAT, ALC and MAT+ALC), most of the polysubstance use (45.1%) was due to concurrent marijuana (21.6 %) and heroin (16.7%) use (data not shown).

The description of the MAT regimen during pregnancy is presented in Table 2. Among patients in the MAT groups (both MAT and MAT+ALC, total n=53), 35 (66%) were on MAT before pregnancy recognition. Among those, 65.7% were on methadone and 34.5% on buprenorphine+naloxone. All patients on buprenorphine+naloxone (Suboxone®) were switched to buprenorphine after their pregnancy was confirmed and they were established with the Milagro program. In this sample, 17 participants were initiated on MAT (16 with buprenorphine and 1 on methadone) during pregnancy. One patient was on Oxycodone® throughout pregnancy for a medical condition and was also included in the MAT group. The mean doses of both buprenorphine and methadone increased as the pregnancy progressed.

Trends in the reported use of multivitamins (>4 times per week) showed that only about 30% of all the study participants used multivitamins during the periconceptional period, with highest use in the control group (44.4%) and lowest use in the MAT group (11.5%). Multivitamin use in periconceptional period was much higher among participants who reported that their pregnancy was planned (44%) compared to those with unplanned pregnancy (21%; p=0.01). Across all study groups, reported use of multivitamins increased to about 80% at the time of enrollment and 87% at the time of delivery. About 17.6% of the participants reported using iron supplements at study enrollment; highest use was observed in the healthy controls (25.9%) and lowest use was observed in the ALC group (9.1%).

Log-transformed, unadjusted mean energy intake was significantly higher in the MAT+ALC group compared to controls, but this difference became non-significant after controlling for BMI, smoking, ethnicity, marital status and employment (Table 3). Similarly, there were no statistically significant differences between the exposed groups and the control group for percentage of energy intake from carbohydrate, protein, or fat. In the ALC and MAT+ALC groups, percent of energy intake from alcohol, as estimated by the FFQ, ranged from 0 to 10.2% and 0 to 4.8%, respectively.

The unadjusted estimated average intake of several micronutrients was slightly higher in the MAT and MAT+ALC groups compared to the control group; however, differences did not reach statistical significance (Table 4). After adjusting for energy intake, micronutrient intake (per 1000 kcal) was the highest in the control group for almost all of the micronutrients analyzed. Statistically significant differences were observed in the daily intake of vitamin A (MAT vs controls -21.6%, p=0.03, MAT+ALC vs controls: -23.1%, p=0.02), vitamin E (MAT vs controls: -16.9%, p=0.003, MAT+ALC vs controls: -14.3%, p=0.01), iron (MAT vs controls: -13.8%, p=0.03), folate (MAT vs controls: -19.6%, p=0.003, MAT+ALC vs controls: -15.8%, p=0.02) and choline (MAT+ALC controls:-13.9%, p=0.02). In the multivariable models only the intakes of energy-adjusted iron (-15.0%, p=0.04) and folate (-16.8%, p=0.04) were found to be significantly lower in the MAT group compared to the control group.

A significant proportion of the participants in all groups did not meet the EAR for vitamin D, vitamin E, iron, and folate based on dietary intake alone (Table 5). After inclusion of supplements in addition to dietary intake, the estimated intake for most participants across all groups exceeded the EAR. In the MAT group, 11.5-15.4% of participants had intake of vitamin D, vitamin E, iron, and folate below EAR in the diet plus supplements analysis. Significant proportions of participants in each study group (controls: 85.2%, MAT: 73.1%, ALC: 68.2%, MAT+ALC: 77.8%) had inadequate choline intake compared against adequate intake values.

## Discussion

Our results indicate that opioid-dependent patients had diets with poorer nutrient density compared to controls, that is, the diet of patients undergoing MAT primarily consisted of food items that were rich in calories but contained lower amounts of essential micronutrients compared to controls. After adjustment for the total amount of calories, the MAT and MAT +ALC groups had lower intake of vitamin A, vitamin $B_6$, vitamin E, iron, folate, and choline. Even after additional adjustments for demographic characteristics and BMI, the MAT group had lower intake of iron and folate compared to controls. These results are consistent with other studies, which also found higher energy intake, derived primarily from refined carbohydrates, in opioid-dependent non-pregnant populations (Himmelgreen et al., 1998; Nolan & Scagnelli, 2007; Saeland et al., 2011). Tomedi et al. also reported higher energy intake among pregnant women on methadone maintenance therapy compared to controls (Tomedi et al., 2012). While results of our study indicate poorer nutrient density in opioid-dependent patients, the effect was significantly reduced after controlling for other covariates. This suggests that most of the observed effect could be mediated through modification of social factors.

Across all study groups, our findings related to dietary adequacy reinforce recommendations from the Academy of Nutrition and Dietetics related to the potential need for vitamin and mineral supplementation during pregnancy for populations with alcohol, tobacco and other substance abuse dependency and socioeconomic risk of food insecurity (Kaiser & Allen, 2008; Procter & Campbell, 2014). Of particular interest are reported disparities in multivitamin use during the periconceptional period, with less than a third of substance-using patients reporting routine multivitamin use during this crucial period of organogenesis (Ramakrishnan, Grant, Goldenberg, Zongrone, & Martorell, 2012).

This study, however, did not observe significant differences in the dietary intake of participants classified in the alcohol only group compared to controls. While there is growing interest in a potential amelioration of the effects of prenatal alcohol exposure on the developing fetus by micronutrient supplementation (Wozniak et al., 2015; Wozniak et al., 2013; Young, Giesbrecht, Eskin, Aliani, & Suh, 2014), we are not aware of any studies that have systematically examined dietary patterns in alcohol-using pregnant women. While alcohol intake has been associated with higher energy intake and lower total diet quality among U.S. adults from the general population (Breslow et al., 2010), our “alcohol only” group reported relatively light drinking (on average, 112 drinks during pregnancy or ~3 drinks per week), which potentially would not strongly influence dietary patterns. The effect

of heavy (≥ 14 drinks/week) or repeated binge (≥4 drinks on occasion) drinking patterns on diet quality in women of child-bearing age, and especially pregnant women, needs to be examined in future studies.

Interestingly, MAT patients who concurrently used alcohol (but not patients who had either MAT or alcohol only exposure) had lower energy-adjusted intake of vitamin B6 and choline – important micronutrients involved in DNA synthesis, cellular growth and homocysteine metabolism, stem cell growth, and cellular differentiation (Furness et al., 2013; Zeisel, 2006, 2013). Given that choline is an established neuro-protector and can potentially mediate the damaging effect of prenatal alcohol exposure on the developing fetus (Wozniak et al., 2013; Zeisel, 2006, 2013), these findings highlight the need for targeted dietary interventions in substance-using populations. The necessity for such interventions is further emphasized by the fact that choline is not routinely included in prenatal multi-vitamins. We also observed that a significant proportion of the participants in all study groups did not meet the requirements for vitamin D intake based on diet alone. This is expected given that the major sources of vitamin D are from exposure of the human skin to ultraviolet rays from sunlight (Holick et al., 1980), fortified foods and dietary supplement (Calvo, Whiting, & Barton, 2005).

Strengths of this study included rigorous assessment of substance use with repeated prospective self-reported measures and a comprehensive battery of biomarkers. Additionally, dietary intake was assessed by a food frequency questionnaire, and thus is expected to reflect usual intake during the pregnancy, as opposed to a 24-hour recall which reflect only recent intake (Barrett-Connor, 1991). However, the results of this study should be considered in light of its limitations. First, the generalizability of the results might be limited due to the unique nature of our study population. New Mexico is a minority-majority state and 60.8% of our study sample self-identified themselves as Hispanic/Latina. Similar to our results, non-pregnant women on MAT in Puerto Rico also reported high consumption of sweets and low consumption of vegetables and fruits (Himmelgreen et al., 1998). However, nutritional deficiencies observed among Hispanic/Latina women cannot be necessarily generalized to other racial/ethnic groups. Nevertheless, it should be noted that there were no significant differences in race/ethnicity among the study groups in our sample. Second, a relatively small sample size per group potentially identified only moderate-to-large differences in dietary intake among the groups. This could be one possible explanation for largely non-significant results observed in the ALC group (another possible explanation is that ALC group included light drinkers, thus was more similar to the controls than to other exposed groups). Additionally, due to a small sample size, results could not be stratified by the type of MAT; however, currently there is no evidence suggesting a difference in dietary intake between methadone and buprenorphine users. Third, a 72-food item Block Brief 2000 FFQ was used to ascertain dietary intake, instead of some of the longer versions of Block FFQs. Although Block Brief 2000 FFQ is an effective tool to estimate distributions of intake in study populations, since it includes a reduced food list compared to the longer Block FFQs, it may underestimate energy and macronutrient intake (Block, Hartman, & Naughton, 1990). Fourth, while the MAT exposure is relatively constant throughout pregnancy, alcohol exposure is not uniform and more challenging to quantify. It should be noted that the study employed a state-of-the-art battery of ethanol biomarkers and repeated prospective TLFB

interviews – a current ‘gold standard’ for assessment of alcohol exposure. Fifth, the focus of the study was on dietary intake and did not include assessment of nutrient biomarkers. Sixth, we recognize that lower proportion of controls had unplanned pregnancy, and that pregnancy planning can potentially affect dietary patterns. However, this is expected to have minimal effect on the observed group differences since dietary patterns obtained from a FFQ are averaged across 12 months. Finally, assessment of inadequate dietary intake on adverse perinatal outcomes was beyond the scope of this study, but will be examined in subsequent analyses.

Future studies should include assessment of dietary intake coupled with biomarker analysis of micronutrients to better understand the impact of multiple negative exposures during pregnancy (substance abuse and potentially inadequate micronutrient status) on maternal and infant health. It is also important, perhaps through qualitative data collection, to gain a better understanding of the interventions and support systems that could best improve diet quality and multivitamin use early in pregnancy for substance using women. In summary, our study demonstrated that pregnant, opioid-dependent women may have inadequate micronutrient intake during pregnancy. MAT programs should consider integrating nutrition assessment, intervention, and family planning services into their model of care to improve diet quality and multivitamin use among opioid-dependent women of childbearing age and pregnant women.

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**Table 1**

**Demographic, Medical Characteristics, and Substance Use among Study Participants**

| | Controls (n=27) | OMT (n=26) | ALC (n=22) | OMT+ALC (n=27) | $p^a$ |
|---|---|---|---|---|---|
| Age (mean years ± SD) | 27.2 ± 6.1 | 28.4 ± 5.4 | 27 ± 5.9 | 26.8 ± 5.5 | 0.11 |
| Gestational age at enrollment (mean years ± SD) | 25.2 ± 7.3 | 21.3 ± 6.0 | 27.6 ± 6.7 | 23.3 ± 7.6 | 0.01 |
| Marital status, n (%) | | | | | 0.01 |
| *single/separated/divorced* | 8 (29.6) | 18 (69.2) | 9 (40.9) | 17 (62.9) | |
| *married/co-habitating* | 19 (70.4) | 8 (30.8) | 13 (59.1) | 10 (37.0) | |
| Race: White, n (%) | 27 (100) | 23 (88.5) | 18 (81.8) | 23 (85.2) | 0.11 |
| Hispanic, n (%) | 16 (59.3) | 17 (65.4) | 10 (45.4) | 19 (70.4) | 0.33 |
| Education, n (%) | | | | | 0.003 |
| *high-school or lower* | 8 (29.6) | 16 (61.5) | 10 (45.4) | 21 (77.8) | |
| *some college or higher* | 19 (70.4) | 10 (38.5) | 12 (54.6) | 6 (22.2) | |
| Employed, n (%) | 12 (44.4) | 7 (26.9) | 13 (59.1) | 5 (18.5) | 0.01 |
| Health insurance, n (%) | | | | | <0.001 |
| *Medicaid* | 16 (57.1) | 24 (100.0) | 9 (60.0) | 11 (78.6) | |
| Pre-pregnancy BMI, n (%) | | | | | 0.38 |
| *<=24.9* | 15 (55.6) | 16 (65.5) | 8 (36.4) | 18 (66.7) | |
| *>=25.0 to 29.9* | 7 (25.9) | 6 (23.1) | 6 (27.3) | 6 (22.2) | |
| *>=30.0* | 5 (18.5) | 4 (15.4) | 8 (36.4) | 3 (11.1) | |
| Any medical condition, n (%) | 6 (22.2) | 18 (69.2) | 8 (36.4) | 22 (81.5) | <0.001 |
| Unplanned pregnancy, n (%) | 9 (33.3) | 19 (73.1) | 12 (54.5) | 23 (85.2) | 0.001 |
| Multivitamin use (>4 times/week), n (%) | | | | | |
| *around LMP* | 12 (44.4) | 3 (11.5) | 7 (31.8) | 8 (29.6) | 0.06 |
| *at enrollment* | 24 (88.9) | 21 (80.8) | 18 (81.8) | 21 (77.8) | 0.76 |
| *at delivery* | 26 (96.3) | 21 (80.8) | 20 (90.9) | 22 (81.5) | 0.24 |
| Iron supplements, n (%) | | | | | |
| *at enrollment* | 7 (25.9) | 5 (19.2) | 2 (9.1) | 4 (14.8) | 0.46 |
| Poly-drug use, n (%) | 0 (0.0) | 17 (65.4) | 9 (40.9) | 20 (74.1) | <0.001 |
| Tobacco use, n (%) | 0 (0.0) | 14 (53.8) | 0 (0.0) | 18 (66.7) | <0.001 |
| Alcohol exposure, mean ± SD) | | | | | |

| | Controls (n=27) | OMT (n=26) | ALC (n=22) | OMT+ALC (n=27) | *p*[a] |
|---|---|---|---|---|---|
| *around LMP (SDU/month)* | 0.1 ± 0.3 | 0 | 61.5 ± 124.6 | 45.1 ± 115.1 | |
| *total during pregnancy* | 0 | 0 | 112.5 ± 289.3 | 64.2 ± 197.7 | |

Abbreviations: OMT: Opioid maintenance therapy; ALC: Alcohol exposed; OMT+ALC: concurrent exposure to OMT and alcohol; SDU: Standard drinking units, a drink that equals 14 gram of alcohol.

[a]Based on ANOVA and Fisher's exact tests for continuous and categorical variables, respectively

## Table 2
## Description of MAT therapy in study participants

| Drug | Frequency (%) | Mean dose ± SD (mg) | Range (mg) |
|---|---|---|---|
| Participants on MAT before they found out that they were pregnant (n=35) | | | |
| Methadone | 23 (65.7) | 102.7±34.2 | 50 - 210 |
| Buprenorphine + Naloxone | 12 ( 34.3) | 16±8.3 | 4 - 32 |
| Participants who began MAT after pregnancy recognition (n=17) | | | |
| Methadone | 1 (5.9) | 75 | |
| Buprenorphine | 16 (94.1) | 17±6.28 | 8 - 32 |
| MAT use at the admission for labor and delivery (n=52 *) | | | |
| Methadone | 24 (46.2) | 125.8±35.6 | 55 - 210 |
| Buprenorphine | 28 (53.8) | 22.8±4.2 | 8 - 32 |

* Overall, 53 patients were classified into the MAT group: 52 were on methadone or buprenorphine and 1 was on Oxycodone® throughout the pregnancy

## Table 3
## Estimated Macronutrient Intake by Study Group

| Macronutrient intake [a] | Controls (n=27) | OMT (n=26) | ALC (n=22) | OMT+ALC (n=27) |
|---|---|---|---|---|
| Total energy intake (Kcal/day) | | | | |
| Unadjusted | 2089.0 ± 912.1 | 2512.7 ± 1259.5 | 2070 ± 783.3 | 2652.6 ± 971.3 |
| Log-transformed | Ref | 15.1% | 0.05% | 28.3% * |
| Adjusted MVR [b] | Ref | -1.3% | -5.6% | 5.5% |
| % energy from carbohydrates | | | | |
| Unadjusted | 47.1 ± 6.1 | 50.3 ± 6.4 | 43.9 ± 8.9 | 49.9 ± 7.3 |
| Adjusted MVR [b] | Ref | 7.6% | -6.9% | 6.2% |
| % energy from protein | | | | |
| Unadjusted | 15.9 ± 3.4 | 14.5 ± 2.4 | 16.5 ± 2.5 | 13.4 ± 2.9 |
| Adjusted MVR [b] | Ref | -4.9% | 3.8% | -11.7% |
| % energy from fat | | | | |
| Unadjusted | 39.5 ± 5.1 | 37.5 ± 5.1 | 40.1 ± 7.7 | 38.3 ± 6.0 |
| Adjusted MVR [b] | Ref | -6.8% | 0.02% | -5.0% |

[a] Unadjusted values expressed as mean±SD. Adjusted values presented are percentage difference compared to intake in controls. Percentage difference = (exp(β)-1)*100%

[b] MVR, multivariable regression adjusted for BMI, ethnicity, marital status, employment status, and tobacco use.

* Statistically significant difference when compared to controls ($p<0.05$)

## Table 4
## Estimated Micronutrient Intake by Study Group

| Micronutrient intake from diet[a] | Controls (n=27) | OMT (n=26) | ALC (n=22) | OMT+ALC (n=27) |
|---|---|---|---|---|
| Vitamin A (mcg-RAE) | | | | |
| Unadjusted | 958.0 ± 406.4 | 917.5 ± 505.3 | 1033.7 ± 552.6 | 946.8 ± 4445.5 |
| Energy-adjusted | Ref | -21.6%* | 2.2% | -23.1%* |
| Energy adjusted + MVR[b] | Ref | -11.6% | 4.6% | -11.5% |
| Vitamin B6 (mg) | | | | |
| Unadjusted | 2.0 ± 0.7 | 2.4 ± 1.2 | 2.1 ± 0.8 | 2.3 ± 0.9 |
| Energy-adjusted | Ref | -6.3% | -1.7% | -13.7%* |
| Energy adjusted + MVR | Ref | 1.7% | 0.7% | -5.5% |
| Vitamin B12 (mcg) | | | | |
| Unadjusted | 4.7 ± 2.3 | 6.1 ± 4.3 | 6.4 ± 6.5 | 6.9 ± 7.9 |
| Energy-adjusted | Ref | 3.6% | 17.2% | -3.9% |
| Energy adjusted + MVR | Ref | 15.8% | 14.2% | 11.2% |
| Vitamin C (mg) | | | | |
| Unadjusted | 152.4 ± 118.7 | 199.7 ± 145.8 | 133.5 ± 83.1 | 179.9 ± 106.1 |
| Energy-adjusted | Ref | 2.9% | -24.6% | -6.6% |
| Energy adjusted + MVR | Ref | 3.1% | -23.7% | -8.8% |
| Vitamin D (mcg) | | | | |
| Unadjusted | 5.3 ± 3.3 | 5.9 ± 4.8 | 5.2 ± 5.4 | 7.1 ± 7.1 |
| Energy-adjusted | Ref | -12.8% | -7.2% | -1.3% |
| Energy adjusted + MVR | Ref | -13.2% | -15.0% | 2.2% |
| Vitamin E (a-TE) | | | | |
| Unadjusted | 11.0 ± 4.7 | 11.0 ± 5.6 | 10.4 ± 4.9 | 12.2 ± 5.3 |
| Energy-adjusted | Ref | -16.9%** | -6.9% | -14.3%* |
| Energy adjusted + MVR | Ref | -12.7% | -5.6% | -10.1% |
| Iron (mg) | | | | |
| Unadjusted | 15.5 ± 6.4 | 16.4 ± 8.6 | 16.1 ± 6.2 | 19.5 ± 9.2 |
| Energy-adjusted | Ref | -13.8%* | 4.3% | -4.3% |
| Energy adjusted + MVR | Ref | -15.0%* | 3.0% | -3.8% |
| Folate (DFE) | | | | |
| Unadjusted | 583.5 ± 218.4 | 587.1 ± 327.7 | 546.4 ± 249.9 | 641.38 ± 277.5 |
| Energy-adjusted | Ref | -19.6%** | -8.6% | -15.8%* |
| Energy adjusted + MVR | Ref | -16.8%* | -8.2% | -12.1% |
| Choline (mg) | | | | |
| Unadjusted | 325.9 ± 110.5 | 382.8 ± 212.2 | 362.6 ± 153.9 | 368.8 ± 159.8 |

| Micronutrient intake from diet[a] | Controls (n=27) | OMT (n=26) | ALC (n=22) | OMT+ALC (n=27) |
|---|---|---|---|---|
| Energy-adjusted | Ref | -5.1% | 7.77% | -13.9% * |
| Energy adjusted + MVR | Ref | -0.5% | 7.7% | -8.6% |

Abbreviations: mcg-RAE: microgram – retinol activity equivalents, a-TE: alpha-tocopherol equivalents, DFE: dietary folate equivalents

[a] Unadjusted values expressed as mean ± standard deviation. Energy adjusted (micronutrient intake per 1000 Kcal per day energy intake) and energy adjusted + MVR values presented are percentage difference compared to intake in controls. Percentage difference = (exp(B)-1)*100%.

[b] MVR: multivariable regression adjusted for BMI (categorical), tobacco use (anytime during pregnancy), ethnicity, marital status, employment status.

* $p<0.05$,

** $p<0.01$

**Table 5**

**Proportion of Participants with Nutrient Intake Below Estimated Average Requirements by Study Group**

| | Controls(n=27) | | OMT (n=26) | | ALC (n=22) | | OMT+ ALC (n=27) | |
|---|---|---|---|---|---|---|---|---|
| | **A** | **B** | **A** | **B** | **A** | **B** | **A** | **B** |
| Vitamin A (mcg-RAE) | 18.5% | 3.7% | 23.1% | 3.8% | 18.2% | 0.0% | 14.8% | 3.7% |
| Vitamin B6 (mg) | 25.9% | 0.0% | 26.9% | 3.8% | 36.4% | 4.6% | 22.2 | 7.4% |
| Vitamin B12 (mcg) | 7.4% | 0.0% | 7.7% | 0.0% | 0.0% | 0.0% | 0.0% | 0.0% |
| Vitamin C (mg) | 11.1% | 0.0% | 23.1% | 7.7% | 31.8% | 4.6% | 11.1% | 3.7% |
| Vitamin D (mcg) | 96.3% | 7.4% | 80.8% | 11.5% | 90.9% | 4.6% | 77.8% | 7.4% |
| Vitamin E (mg a-TE) | 59.3% | 3.7% | 61.5% | 15.4% | 63.6% | 4.6% | 59.3% | 7.4% |
| Iron (mg) | 85.2% | 0.0% | 80.8% | 15.4% | 77.3% | 4.6% | 70.4% | 7.4% |
| Folate (DFE) | 48.2% | 3.7% | 53.9% | 11.5% | 63.6% | 4.6% | 37.0% | 3.7% |

Abbreviations: A: based on dietary intake only, B: based on dietary intake and supplements; mcg-RAE: microgram – retinol activity equivalents, a-TE: alpha-tocopherol equivalents, DFE: dietary folate equivalents