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Examining sucrose subjective response among individuals with opioid use disorder

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EXAMINING SUCROSE SUBJECTIVE RESPONSE AMONG INDIVIDUALS WITH OPIOID USE DISORDER

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Abstract

Aims: Opioid use disorder (OUD) is associated with significant morbidity and mortality, and opioid agonist treatment (OAT) with methadone or buprenorphine represents the most efficacious treatment. However, data suggest that chronic administration of opioids may be associated with significant weight gain, possibly by altering an organism's perception of and preference for sweet foods. The primary aim of this laboratory study was to rigorously examine sucrose subjective response among adults receiving OAT and a comparison sample without OUD. As secondary outcomes, we also sought to compare the groups on additional baseline characteristics that may influence subjective sucrose response and weight gain during treatment.

Methods: Participants were 40 adults receiving treatment for OUD (OUD+) and a comparison sample of 40 adults without OUD (OUD-). All participants completed an initial screening visit that included questionnaires on eating behaviors, diet and nutrition, recent substance use, and measurement of body mass index. Eligible participants completed two, same-day outpatient laboratory sessions during which they sampled six experimenter-administered concentrations of sucrose solution (0, 0.1, 0.25, 0.5, 0.75, and 1.0M in distilled water) each three times under double-blind counterbalanced conditions. Following each exposure, participants rated the pleasantness and intensity of each sample using 100-point visual analog scales.

Results: OUD+ participants rated sucrose solutions as less pleasant than OUD- participants ($p<0.001$). However, this effect was limited to the three lowest sucrose concentrations (0, 0.1, 0.25M), and at higher concentrations there were no group differences. There were no between-group differences on ratings of intensity ($p=0.35$). Given these baseline group differences in placebo (0M) responding, sucrose response was also examined in terms of change from baseline. In this analysis, there was a significant group effect, with a higher magnitude of change in pleasantness ratings and a lower magnitude of change in intensity ratings from 0M in OUD+ vs. OUD- participants ($p's<0.05$). With regard to baseline characteristics that may influence sucrose response and eating behavior more generally, the OUD+ group had a higher prevalence of obesity, food insecurity, unhealthy eating behaviors, high sugar consumption, and nutrition knowledge deficits compared to the OUD- group ($p's<0.05$).

Conclusion: Data from preclinical and clinical research have suggested that opioid agonist medications may enhance subjective response to sweet flavors. In the present study, OUD+ participants exhibited a higher magnitude of change in pleasantness ratings from placebo compared to OUD- participants. However, this effect was largely driven by pronounced group differences in perceived pleasantness of essentially unsweet solutions. On the outcome of sucrose intensity, findings were more mixed with no consistent differences between OUD+ and OUD- participants. In contrast, group differences were far more pronounced in participants' daily eating behaviors and nutrition knowledge, with OUD+ participants presenting with a consistently more severe profile. These data highlight the significant risk factors experienced by OUD+ individuals that extend beyond drug-related risks and may inform future scientific and clinical efforts to improve health outcomes in this vulnerable population.

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1. Introduction

The current United States opioid epidemic represents the most devastating public health crisis of our time, with nearly 12 million Americans reporting opioid misuse in 2016 (SAMHSA, 2017). Opioid use disorder (OUD) is associated with a multitude of consequences including infectious disease, overdose and premature death, as well as significant economic costs estimated at over $78 billion annually (Birnbaum et al., 2011; Clausen, Waal, Thoresen, & Gossop, 2009; Gomes, Tadrous, Mamdani, Paterson, & Juurlink, 2018; Hser, Hoffman, Grella, & Anglin, 2001; Scholl, Seth, Kariisa, Wilson, & Baldwin, 2019).

Opioid agonist treatment (OAT) with methadone or buprenorphine is the most efficacious treatment for OUD (Mattick, Breen, Kimber, & Davoli, 2014). Methadone is a μ-opioid full agonist; whereas buprenorphine is a μ-opioid partial agonist that has a distinct pharmacological profile characterized by a ceiling effect on its agonist activity, a long plasma half-life, and slow dissociation from the μ-opioid receptor (Johnson, 2003; Sigmon, Wong, Chausmer, Liebson, & Bigelow, 2004; Walsh, 2003). Maintenance treatment with methadone or buprenorphine has been consistently shown to reduce illicit opioid use, withdrawal symptoms, risky drug use behaviors, contraction of infectious disease, overdoses, criminal activity and premature death (Mattick, Breen, Kimber, & Davoli, 2009; Mattick et al., 2014; National Academies of Sciences, Engineering, and Medicine, 2019; Volkow, Jones, Einstein, & Wargo, 2019).

Despite its undisputed efficacy for reducing morbidity and mortality associated with OUD, OAT may also be associated with several adverse health effects. One that we have become especially interested in is the possibility that chronic administration of

opioids may be associated with significant weight gain. In a recent retrospective chart review we examined body mass index (BMI) and weight changes among 96 patients receiving methadone maintenance treatment at two timepoints: at treatment intake and again approximately two years later (Fenn, Laurent, & Sigmon, 2015). We observed a significant increase in BMI following entry into methadone treatment ($p<0.001$), with mean BMIs increasing from 27.2±6.8 to 30.1±7.7 kg/m^2 at Times 1 and 2, respectively. This translated to an increase from 177.6 to 195.4 pounds, representing a 10% (17.8-pound) increase in body weight. These data are consistent with several prior studies that have found significant weight gains during OAT, particularly during treatment with methadone. A recent study of 114 methadone-maintained patients in Israel, for example, found significant weight gain early in treatment, with mean BMIs increasing 8% within the first year of treatment (Peles, Schreiber, Sason, & Adelson, 2016). Among 55 methadone patients in Iran, a similar increase in BMI was detected within only the first two months of treatment, with mean BMIs increasing by 7% and the percentage of patients meeting criteria for obesity increasing from 3.6% to 7.2% during the eight weeks following treatment entry (Montazerifar, Karajibani, & Lashkaripour, 2012). In a recent study of 74 methadone patients in the U.S., 42% of patients met criteria for overweight, obese, or morbidly obese at treatment entry; this increased to 76%, 82%, and 88% at one, two, and three years post-intake, respectively (Sweeney et al., 2018). A single recent study found similar weight gains during buprenorphine treatment, with 107 adult inpatients in Turkey experiencing a mean body weight increase of 8% by the fourth month of buprenorphine maintenance ($p<0.001$; Baykara & Alban, 2019). Overall, of the 13 published studies that have evaluated changes in weight during OAT, 92% have

reported statistically significant increases following OAT entry (Table 1). These potential shifts of patients into overweight or obese categories may place patients at heightened risk of developing cardiovascular disease, stroke, diabetes, cancer, and premature death (Fenn et al., 2015; Mysels & Sullivan, 2010; Schlienz, Huhn, Speed, Sweeney, & Antoine, 2018).

One possible explanation for these weight gains during treatment is that they may simply be a function of undernourished illicit drug abusers moving toward a healthier weight as they become stabilized in opioid treatment (Gronbladh & Ohlund, 2011; Okruhlica & Slezakova, 2008). However, the data thus far do not strongly support this explanation. Across the studies that have reported BMI changes during treatment, patients generally moved from the normal (rather than underweight) category at intake to an overweight or obese BMI following enrollment into OAT. In our recent investigation in the methadone clinic, for example, patients were generally already in the overweight category at treatment intake (BMIs 25.0-29.9 kg/m^2) and transitioned into the obese category (BMI $\geq$30.0 kg/m^2) by the second assessment timepoint.

1.1 Potential opioid effects on sweet subjective response

Preclinical studies

Another possibility is that administration of opioid agonists may alter, and in particular enhance, an organism's perception of and preference for sweet foods (Mysels & Sullivan, 2010). The most experimentally rigorous studies on this have been conducted in non-human animals and have generally shown that experimenter-administered opioid agonists are associated with increased ingestion of sweetened solutions or food (Castro & Berridge, 2017; Comer, Evans, Pudiak, & Foltin, 2002;

Daniels, Pratt, Zhou, & Leri, 2018; Gagin, Cohen, & Shavit, 1996; Pecina & Berridge, 2005; Zhang & Kelley, 2002). In a recent study examining the effect of methadone administration on consumption of rat chow and a liquid high fructose corn syrup solution, for example, methadone concurrently decreased intake from chow and increased intake of the sweetened solution (Daniels et al., 2018). In another, microinjection of a μ-opioid agonist in rats potentiated measures of liking of a sucrose solution by 200-300% and increased sweet food consumption (Castro & Berridge, 2017).

Providing further evidence of a potential pharmacological effect of opioid agonists on individuals' subjective response to sweet taste, administration of opioid antagonists (e.g., naltrexone, naloxone) has been shown to reduce preference for and intake of sweetened solutions and foods (Kirkham, 1990; Levine, Weldon, Grace, Cleary, & Billington, 1995; Rockwood & Reid, 1982; Yirmiya, Lieblich, & Liebeskind, 1988). For example, naltrexone administration has been associated with reduced preference for and intake of saccharin solution in mice (Yirmiya et al., 1988). In a later study, naloxone reduced intake of sweetened vs. normal chow in both food-deprived and 50% satiated rats (Levine et al., 1995).

Clinical studies

While the pre-clinical evidence with opioid agonists and antagonists has generally supported a potential pharmacological mechanism underlying the influence of opioids on sweet subjective response, the clinical data on this topic have been more mixed. Those studies have generally utilized an experimental procedure called a sweet taste test, wherein individuals sample a variety of sucrose solutions under double-blind conditions and then rate the pleasantness (i.e., self-reported liking) and intensity (i.e., self-reported

sweetness) of each concentration. Two such studies have been conducted evaluating sweet taste response among individuals maintained on methadone or buprenorphine for treatment of OUD (Bogucka-Bonikowska et al., 2002; Green et al., 2013). In the first, 28 male methadone-maintained patients and a comparison sample of 32 male adults without a history of OUD sampled three solutions that varied in sucrose concentration (ranging from 0M to 0.88M) as well as a negative control solution (i.e., 0M sucrose) (Bogucka-Bonikowska et al., 2002). A small amount (10mL) of each solution was administered once on the tongue via a syringe in counterbalanced order across subjects. Following each exposure, participants rated the solution's pleasantness (-50 to +50) and intensity (0 to 100) on a 100mm visual analog scale (VAS). There were no significant between-group differences in ratings of sweet pleasantness or intensity for any sucrose solution. However, in the dietary information collected from both groups at study screening, the methadone-maintained group did report adding significantly more sugar to beverages than controls (2.3 vs. 1.3 spoonfuls per cup, respectively).

In the second study, 14 patients receiving OAT (7 methadone, 7 buprenorphine) and a comparison sample of 65 adults without a history of illicit drug use sampled each of 10 sucrose concentrations ranging from 1.0 millimolar (mM) to 1.0 molar (M) sucrose per liter (L) of distilled water (Green et al., 2013). Each solution was administered five times on the tip of the tongue via cotton swab under double-blind counterbalanced conditions to determine sweet taste threshold, which was operationalized as the concentration at which the participant could detect the solution in 2.5 of 5 (50%) presentations. For the measures of sweet pleasantness and intensity, participants swished 5mL of the highest sucrose solution (1.0M) in their mouth. They then rated the solution's

taste pleasantness (-50 to +50) and intensity (0 to 100). Sucrose threshold recognition ratings were significantly greater in the OMT vs. comparison participants. That is, larger concentrations of sucrose (equal to about 3-4 teaspoons of sugar per mug) were needed for the OMT group to detect sweet taste. Among OMT participants, methadone dose was significantly and positively correlated with sucrose threshold recognition. Ratings of sweet pleasantness and intensity for the largest sucrose concentration (1.0M) were significantly (approximately three- and two-fold, respectively) greater in the opioid-maintained vs. comparison group.

Two additional clinical studies examined the effects of both opioid agonists and antagonists on sweet subjective response (Eikemo et al., 2016; Langleben, Busch, O'Brien, & Elman, 2012). In the first, 15 recently-detoxified heroin users sampled 5 sucrose concentrations (ranging from 0.05 to 0.83M) three times each and provided ratings of sweet taste pleasantness, intensity, and wanting (i.e., extent that they want to have more of the sample) before and after an injection of extended-release naltrexone (Langleben et al., 2012). Compared to the pre-naltrexone baseline, ratings for sweet taste pleasantness were significantly reduced one week after the naltrexone injection. The second study was a randomized, double-blind, placebo-controlled study comparing acute morphine vs. naltrexone administration on sweet taste ratings and intensity in 49 male adults without a history of OUD (Eikemo et al., 2016). Participants sampled five sucrose concentrations (ranging 0.05 to 0.65M) three times each and rated sweet pleasantness and intensity. These sucrose exposures occurred following acute administration of morphine (10 mg), naltrexone (50 mg), or placebo. Participants' ratings of sweet pleasantness in response to the highest sucrose concentration (0.65M) were significantly greater

following morphine administration vs. naltrexone and placebo. In contrast, there were no effects of drug administration on participant ratings of sweet intensity. Contrary to hypotheses, however, ratings of sweet pleasantness following the two lowest sucrose concentrations (0.05 and 0.10M) were actually higher during the naltrexone vs. morphine and placebo conditions, suggesting the association between opioids and sweet subjective response may vary as a function of sucrose concentration and highlighting the importance of evaluating multiple concentrations.

1.2 Nutrition and eating behavior

These data suggesting that administration of opioid agonist medications may increase individuals' liking of and preference for sweetened foods is generally consistent with the larger nutrition literature reporting that opioid-maintained individuals often report elevated craving for and consumption of refined carbohydrates, particularly in the form of the added sugars in desserts and other sweetened foods and beverages (Alves et al., 2011; Gambera & Clarke, 1976; Li., Ryan, & Neale, 2016; Nolan & Scagnelli, 2007; Peles et al., 2016; Szpanowka-Wohn, Dłuzniewska, Groszek, & LangMłynarska, 2000; Tomedi, Bogen, Hanusa, Wisner, & Bodnar, 2012; Zador, Wall, & Webster, 1996). In one study of methadone-maintained females in Australia, for example, patients consumed significantly more sugar per day compared to a nationally representative sample of women (122g vs. 101g, respectively) (Zador et al., 1996). The contribution of sugar to daily total energy intake was higher in the methadone-maintained vs. comparison group (31% vs. 20%, respectively). Additional studies have found higher levels of sugar consumption and craving among individuals with vs. without OUD (Morabia et al., 1989; Nolan & Scagnelli, 2007; Tomedi et al., 2012).

1.3 Summary

Taken together, data suggest that opioid agonists may increase the liking and consumption of sweetened foods, which may play a role in the significant weight gain and place patients at risk for overweight, obesity and their related adverse health consequences. This potential interaction is also important and timely given the increasing numbers of individuals developing OUD and entering methadone or buprenorphine maintenance treatment (Alderks, 2017; Wen, Hockenberry, & Pollack, 2018).

1.4 Current study

The prior studies evaluating the effects of opioids on sweet subjective response in individuals with OUD have had several limitations. Nearly all focused on methadone, rather than the partial agonist buprenorphine which is being increasingly used for treatment of OUD (Volkow et al., 2019; Wen et al., 2018). Most of the study samples were also exclusively (Bogucka-Bonikowska et al., 2002; Eikemo et al., 2016) or predominantly (Langleben et al., 2012) male, limiting the generality of their findings to females with OUD. This may be important as gender was the strongest predictor of BMI changes in our prior study with methadone-maintained patients (Fenn et al., 2015), with significantly greater BMI increases in females than males that translated to a 28-pound (17.5%) increase in females vs. a 12-pound (6.4%) increase in males. Finally, the two prior studies that have examined sweet intensity and pleasantness in opioid-maintained patients did so using a limited number of sucrose concentrations (4 and 1, respectively; Bogucka-Bonikowska et al., 2002; Green et al., 2013).

In the present laboratory study, we sought to improve upon these prior limitations by evaluating sucrose subjective response among adults receiving OAT and a comparison sample of adults without OUD using a larger sample than was used in previous studies. We aimed to enroll generally comparable proportions of individuals receiving methadone or buprenorphine treatment for OUD, as well as comparable numbers of males and females. Additionally, we examined a wider range of sucrose concentrations than in prior studies and also took care to control for timing of the sweet test procedure administration in relation to OAT participants' opioid dose timing (described more below).

Primary aim

Our primary aim in this study was to compare sucrose subjective response among adults receiving OAT for OUD (OUD+) and a comparison sample of adults without opioid or other drug use disorders (OUD-). Under double-blind, counterbalanced conditions, participants sampled six concentrations of sucrose (0, 0.1, 0.25, 0.5, 0.75, and 1.0M in distilled water) each three times and rated the pleasantness and intensity of each sample. We hypothesized that, relative to the OUD- group, OUD+ participants would have a steeper dose effect curve associated with pleasantness and intensity ratings across the six sucrose concentrations, resulting in higher ratings at the highest concentration and greater total area under the sucrose dose curve (AUC). To permit a rigorous evaluation of subjective sucrose response at less risk of confounding by opioid dose timing, participants in both groups completed the sweet taste test sessions twice. Specifically, participants sampled and rated the six sucrose concentrations described above during two same-day experimental sessions, scheduled three hours apart (corresponding to

approximate trough/peak medication levels for the OUD+ group).

Secondary aims

We also sought to examine additional baseline characteristics which may influence eating behavior and weight gain among patients with OUD (Gambera & Clarke, 1976; Nabipour, Said, & Habil, 2014; Neale, Nettleton, Pickering, & Fischer, 2012; Nolan & Scagnelli, 2007). As individuals with OUD and other substance use disorders (SUDs) are particularly vulnerable to food insecurity and food insufficiency (Himmelgreen et al., 1998; McLinden et al., 2018; Sigmon, 2016) and food insecurity is associated with overeating, weight gain and obesity in the general population (Dhurandhar, 2016; Kaiser, Dionne, & Carr, 2019; Rasmusson, Lydecker, Coffino, White, & Grilo, 2019), we examined past-year food security. We also evaluated measures related to eating behaviors, dietary intake and nutrition knowledge, as research has suggested that these may be strongly associated with obesity and may also influence development of SUD and treatment outcomes (Jeynes & Gibson, 2017; Richardson & Wiest, 2015; Schroeder & Higgins, 2017). Overall, as these secondary outcomes were more exploratory in nature, we did not propose directional hypotheses; however, they did provide a unique opportunity to better understand how eating and nutrition related behaviors and knowledge that are important in the general population may differ among individuals with OUD.

2. Methods

2.1 Participants

Participants were 80 adults with (OUD+, n=40) and without (OUD-, n=40) OUD. The primary referral source was IRB-approved flyers posted in the community as well as

local opioid treatment programs. Additional recruitment and referral sources included referrals from community providers, public service announcements, and Facebook advertisements. To be eligible, OUD+ participants had to be ≥18 years old, currently receiving methadone or buprenorphine treatment for OUD and on a stable dose for ≥3 months. OUD- participants had to be ≥18 years old, generally healthy and without current use of opioids or other illicit drugs. For both groups, individuals with a significant psychiatric or medical illness that may interfere with consent or participation were excluded, as were those who were pregnant or nursing. Individuals currently using psychoactive medications including antidepressants in the monoamine oxidase inhibitor and tricyclic classes, antipsychotics (e.g., haloperidol, pimozide, zotepine), mood stabilizers (e.g., valproate or lithium), *d*-amphetamine and other stimulant medications, and benzodiazepines were excluded, as these medications may impact taste function and weight (Schlienz et al., 2018; Weafer, Lyon, Hedeker, & de Wit, 2017). Urine specimens were collected at the intake screening visit (described below) and participants testing positive for any drug other than prescribed allowable medication, cannabis, or cotinine were also excluded. Consistent with prior studies on this topic (Eikemo et al., 2016; Green et al., 2013), we also excluded individuals with high levels of caffeine, alcohol and cigarette use as high doses of those drugs may modulate taste perception and sensitivity to the reinforcing effects of sucrose (Choo, Picket, & Dando, 2017; Kampov-Polevoy, Garbutt, & Janowsky, 1997; Pomerleau, Garcia, Drewnowski, & Pomerleau, 1991). More specifically, those who reported caffeine intake exceeding 6 cups of coffee or 600mg caffeine per day, were physically dependent on alcohol, or smoked >20 cigarettes per day were ineligible for the study. Individuals meeting the above criteria and

interested in the study were eligible to participate. Participants provided written informed consent prior to participating.

2.2 Screening Session

Participants completed an initial eligibility screening assessment that consisted of a Timeline Followback of past-month caffeine intake, opioid use, tobacco use, alcohol use, and prescription and over-the-counter medication use (Sobell & Sobell, 1992), a brief medical history and measurement of height, weight and BMI. Participants also completed the Eating Behavior Questionnaire (Nolan & Scagnelli, 2007), the US Adult Food Security Survey (Economic Research Service, USDA, 2012), NHANES Food Frequency Questionnaire (CDC, 2017), Power of Food Scales (Lowe et al., 2009), and the Nutrition Knowledge Questionnaire (Moynihan et al., 2007; Peles et al., 2016). These instruments were administered either in pencil-and-paper format or via a secure, IRB-approved online platform (Qualtrics, Provo, UT). Participants provided a urine specimen analyzed on-site for opioids (i.e., methadone, buprenorphine, oxycodone, hydrocodone, hydromorphone, heroin, fentanyl, morphine) and other drugs (i.e., cocaine, amphetamines, benzodiazepines, marijuana, cotinine) via enzyme multiplied immunoassay (EMIT; Microgenics, Fremont, CA). Finally, participants provided a breath sample to assess for recent alcohol use (ALCO-SENSOR III, Intoximeters, Inc., St. Louis, MO). Participants received $30 for completing this initial screening session.

2.3 Measures

Screening Session Measures

Body Mass Index. Participants' weight and height were measured at baseline to calculate BMI. BMI is a widely-utilized measurement of the proportion of adiposity to

muscle mass in the body, which is calculated by dividing the mass in kilograms by height in meters squared (kg/m^2) (Fenn et al., 2015). Each participant's BMI value was categorized according to CDC criteria as underweight (BMI <18.5), normal weight (BMI 18.5 to <25), overweight (BMI 25.0 to <30) or obese (BMI ≥30.0) (CDC, 2017).

Food Security Survey. The US Adult Food Security Survey (FSS) is a 10-item measure of past-year food security, which is defined as the availability and accessibility to nutritionally adequate foods and food insecurity is a socioeconomic condition resulting in uncertainty and lack of availability of nutritionally adequate food (Economic Research Service, USDA, 2012). Response options are generally based on the self-reported endorsement of a variety of experiences and behaviors related to low food availability for a possible score range of 0-10. Individuals' food security categories are determined from this score and consist of high (score: 0), marginal (score: 1-2), low (score: 3-5) and very low (score: 6-10) food security. Participants in the first two categories are considered to be relatively food secure and those in the two latter categories as food insecure.

Eating Behavior Rating Questionnaire. The Eating Behavior Rating Questionnaire (EBRQ) measures individuals' self-reported frequency of healthy and unhealthy eating habits (e.g., eating regular meals, maintaining a healthy diet and weight) and preferences for consuming healthy (e.g., salad, meat) and unhealthy (e.g., candy, pizza) food options. The EBRQ consists of 12 items and has been validated in samples with OUD (Nolan & Scagnelli, 2007; Peles et al., 2016). Responses are indicated on a 5-point Likert scale and total eating habit scores are calculated by summing ratings for the 12 items, for a possible range in scores from 12 (not healthy habits) to 60 (very healthy habits). In addition, the EBRQ includes a final item, "do you feel like eating now?"

Participants endorsing this item then complete nine additional ratings measuring their desire (0 (not at all) to 5 (extremely)) to eat a variety of specific foods and the amount (0 (none at all) to 5 (as much as I can hold)) that they would eat of that food item.

Food Frequency Questionnaire. The National Health and Nutrition Examination Survey Food Frequency Questionnaire (CDC, 2017) examines individuals' consumption of a comprehensive list of foods and beverages and has been widely used in population-level research to estimate nutrient intake. Response options for its 139 items focus on the frequency with which the participant consumes each food item in the past year, ranging from never to daily. As the primary focus of this project was on associations between opioids and sucrose response, we focused our analyses on the 24 items of the FFQ assessing frequency of sweet foods and beverages.

Nutrition Knowledge Questionnaire. The Nutrition Knowledge Questionnaire (NKQ) has been used to characterize awareness of dietary standards and nutrient sources in individuals with OUD and is of particular interest because it has been shown to be associated with BMI in individuals receiving OAT (Moynihan et al., 2007; Peles et al., 2016). The NKQ includes 15 items with a total score range from 0 to 47 (Moynihan et al., 2007; Peles et al., 2016). This measure consists of 4 subscales, including: dietary recommendations (score range: 0-17); nutrient sources (score range: 0-16); healthiest meal option (score range: 0-4); and association between diet and disease (score range: 0-10).

Power of Food Scales. The Power of Food Scales (PFS) is a widely-established measure that examines the thoughts, motivations, and perceptions related to appetite in an environment in which palatable foods are readily available and has utility for predicting

individuals who experience elevated craving and overconsumption of palatable foods (Lowe et al., 2009). Across 21 items, participants are asked to select how much they agree that the items describe them on a scale of 1 (don't agree at all) to 5 (strongly agree). A total score is calculated by summing ratings across the items, with scores ranging from 21 to 105.

Yale Food Addiction Scale. The Yale Food Addiction Scale (YFAS) is a widely-used measure in both clinical and non-clinical samples to identify individuals that show markers of substance dependence with the consumption of foods high in fat and/or sugar and thus risk for overweight and obesity (Gearhardt, Corbin, & Brownell, 2009; Pursey, Stanwell, Gearhardt, Collins, & Burrows, 2014) including among those receiving OAT for OUD (Sason, Adelson, Herzman-Harari, & Peles, 2018). The YFAS consists of 26 items assessing eating habits in the past year, with response options and resulting 8 criteria generally resembling DSM-IV symptoms for substance dependence (Gearhardt et al., 2009). It been widely used with adults but was of interest to us given the recently-published study demonstrating an association between food addiction and overweight/obesity among patients receiving methadone for OUD treatment (Sason et al., 2018).

Pre-Session Measures

Upon arrival to each experimental session, participants completed a brief questionnaire assessing the number of hours they slept the previous night and the duration of time since their last food, caffeine, beverage, tobacco, and marijuana intake. For the OUD+ group, research staff also recorded the exact time when they last took their methadone or buprenorphine dose. Finally, participants completed the six subjective

state VAS items described previously evaluating current levels of happiness, sadness, anxiety, sickness, nausea, and hunger.

2.4 Experimental Sessions

The study consisted of two outpatient laboratory sessions, both taking place on the same day and approximately three hours apart. Participants were instructed to refrain from consuming any alcohol 12 hours prior to Session 1 and to refrain from all food, caffeine, tobacco, marijuana or beverages (except water) at least one hour prior to each experimental session. They provided a urine specimen upon arrival to Session 1 and a breath sample prior to each session, with any instances of recent alcohol use prompting a rescheduling of that session. At the beginning of Session 1, participants also completed a Timeline Followback of past day consumption of food and beverages, tobacco, caffeine, marijuana, and prescribed and over-the counter drugs, and this was updated at Session 2 to reflect anything consumed between experimental sessions. Finally, at the beginning of each session participants completed six visual analog scales (VAS) assessing baseline mood and subjective states (i.e., happiness, sadness, anxiety, sickness, nausea, hunger).

Sucrose Taste Test

All sucrose solutions were prepared by the University of Vermont Medical Center's General Clinical Research Center from 50g medical grade sucrose powder (QuinTron, Milwaukee, WI) in distilled water at room temperature. Prepared solutions were then transferred to 2-ounce amber glass bottles and stored in a refrigerator at 37-40 degrees Fahrenheit, with the internal and external refrigerator temperatures monitored via a digital monitor. Prepared solutions were stable for 60 days in refrigerated storage, after which, they were discarded. The solutions were labeled with letters (A-F), with each

letter corresponding to a single sucrose concentration. The solutions were administered at room temperature during the experimental sessions.

Session 1. During the first experimental session, participants completed the pre-session activities described above and a research staff member oriented them to the experimental procedures while supplies (e.g., pipette, cotton swabs, solutions) were laid out next to them. Participants rinsed their mouth out with water and then sampled six sucrose solutions (0, 0.1, 0.25, 0.5, 0.75, and 1.0M) three times each under double-blind conditions and in counterbalanced order (Figure 1). Each solution was applied to the tip of the tongue by research staff using a cotton bud, consistent with procedures used in prior studies (e.g., Green et al., 2013). Participants then rated the solution's pleasantness and intensity using a 100mm VAS. The solution pleasantness scale ("How much do you like this sample?") ranged from 0 (dislike strongly) to 100 (like very much), with an anchor at 50 (neutral: neither like nor dislike) and four additional anchors placed at different segments on the scale (dislike moderately, dislike slightly and like slightly, like moderately). The solution intensity scale ("How sweet is this sample?") ranged from 0 (not at all) to 100 (extremely). Following completion of the VAS items, participants rinsed their mouth with spring water before continuing onto the next solution. The inter-trial interval between each sample was approximately 30 seconds in duration and the overall session duration was approximately 30 minutes. For participants in the OUD+ group, this initial session took place immediately prior to ingestion of their daily methadone or buprenorphine dose; for the OUD- group, this session took place in the morning or early afternoon. At the end of Session 1, the time of Session 2 was confirmed and participants were reminded not to consume any cannabis, tobacco, food or beverages

(except water) at least one hour prior to the next session. OUD+ participants were asked to take their usual methadone or buprenorphine dose as prescribed immediately following the session and to record the time that they took their dose. Participants received $50 for completing Session 1.

Session 2. The second experimental session took place approximately three hours following completion of Session 1. Before completing the sucrose taste test, participants completed the pre-session measures described above, and the TLFB was updated to reflect any foods, beverages, cannabis, tobacco, and prescribed and over-the-counter medications consumed between the experimental sessions. During Session 2, participants again sampled the six sucrose solutions three times each under double-blind counterbalanced conditions and rate each solution's pleasantness and intensity following sampling, as described above for Session 1. Participants were compensated $50 for completing this second session.

2.5 Data analyses

The primary aim in this study was to compare sucrose subjective response (pleasantness and intensity) across the 6 sucrose concentrations (0, 0.1, 0.25, 0.5, 0.75, and 1.0M) among adults receiving OAT for OUD (OUD+) and a comparison sample of adults without opioid or other drug use disorders (OUD-). Mixed model repeated measures analyses (SAS, PROC MIXED) were used to compare groups and sessions (Pre-Post dosing) on the primary outcome measure defined as area under the sucrose dose curve (AUC) for subjective ratings of pleasantness and intensity. We also used mixed model repeated measures analyses to compare groups and sessions on delta area under the sucrose dose curve (ΔAUC), defined as the change in ratings of pleasantness and

intensity at each sucrose dose from placebo. The model included one within-subject fixed factor, session and two across-subject fixed factors, group (OUD+ vs. OUD-) and order of solution presentation. Subject, nested within group and order, was a random factor in the model. Additional mixed model analyses of variance were used to compare OUD+ vs. OUD- groups on mean pleasantness and intensity ratings at each concentration. Fisher's LSD was used to perform pairwise comparisons both between and within groups.

Additionally, multivariate analyses were conducted to examine predictors of sucrose subjective response using stepwise linear regression. Entry criteria for inclusion in the model was set at α=.05. The dependent variables for these analyses were AUC for ratings of sucrose pleasantness and intensity. Candidate predictor variables were selected based on the empirical literature. Age, gender, alcohol use, cigarette smoking, cannabis use, pre-session mood ratings use, BMI, food insecurity, and OAT medication type were considered as potential predictors as there was evidence from the literature that these may be associated with sucrose subjective response and eating behaviors (Cornier et al., 2015; Darmon & Drewnowski, 2008; Ettinger, Duizer, & Caldwell, 2012; Hardikar, Höchenberger, Villringer, & Ohla, 2017; Krahn et al., 2006; Pomerleau, Garcia, Drewnowski, & Pomerleau, 1991).

Finally, to examine several additional baseline characteristics which may influence eating behavior and weight gain among patients receiving OAT, our secondary outcome measures included: BMI, food security, eating behaviors, diet, and nutrition knowledge. T-tests were used to compare groups on measures of body composition and eating measures (BMI) and continuous demographic variables. T-tests were also used to

compare nutrition knowledge scores between groups and to compare groups on other continuous secondary outcome measures (total scores and subscores on FSS, EBR, PFS, etc.). Chi square tests were used for group comparisons on categorical outcome measures (% meeting criterion on FSS and YFAS prevalence and FSS subcategories). All analyses were performed using SAS statistical software Version 9.4 (SAS Institute, Cary, NC).

2.6 Sample size justification

Sample size estimates were based on detecting differences between OUD+ and OUD- participants on our primary outcome measure, which corresponds to a difference in the dose effect curve for ratings of pleasantness and intensity across sucrose concentrations. The sample size of 40 participants/group was estimated to provide sufficient power (80%) using α=.05 to detect an ES=0.65 (Cohen's d) between the two groups on ratings of pleasantness and intensity. This magnitude of difference is similar to that observed by Green and colleagues (Green et al., 2013; d=0.72 for pleasantness and smaller than that observed for intensity, ES=1.40). For secondary outcome measures, this effect size of d=0.65 corresponds to a 4.3-unit (10%) decrease in EBR score, a 1.74 increase in FFS sum, and a 4.5-unit difference in BMI. For dichotomous outcomes such as prevalence on the FSS or meeting criteria on YFAS or FSS subcategories, power was estimated to be greater than 80% to detect an approximate 30% difference.

3. Results

3.1 Participant characteristics

Participant characteristics are presented in Table 2. OUD+ participants were significantly older and had completed fewer years of education than OUD- participants (p's<0.01). Fewer OUD+ participants reported being employed full-time, and the OUD+

group reported lower household income than the OUD- group (p's<0.001). With regard to baseline drug use, a greater percentage of OUD+ participants reported past-month tobacco and cannabis use relative to the OUD- group, while fewer OUD+ participants reported past-month alcohol use (p's<0.001).

3.2 Session characteristics

As there were no significant differences between Sessions 1 and 2 for either group, data have been collapsed across the two sessions. With regard to the ratings collected at the beginning of each visit, with OUD+ participants reporting higher ratings of Anxious, Sad and Nauseous and lower ratings of Happy relative to OUD- participants (p's<0.01; Table 3). The duration of time since last eating was greater for OUD+ than OUD- and, of those who smoked, OUD+ participants reported a shorter interval since last cigarette than OUD- participants (p's<0.01). Sessions averaged 9 minutes in duration and were longer for the OUD+ than OUD- group (9.5 ± 3.0 vs. 8.5 ± 1.4, respectively; p<0.01). Finally, OUD+ participants completed Session 1 approximately 24 hours after taking their prior day's opioid medication dose and completed Session 2 approximately 3 hours after that day's dose (not shown).

3.3 Subjective sucrose response

On the primary outcome of subjective sucrose response, there was a significant group effect in ratings of pleasantness ("How much do you like this sample?"), with the OUD+ group reporting less overall sucrose liking than the OUD- group (AUC: 49.6 ± 1.3 vs. 57.5 ± 1.3, p<0.001) (Figure 2, upper panel). When pleasantness ratings were compared between groups at each sucrose concentration, OUD+ participants' ratings of liking were significantly lower than OUD- participants at the placebo (0M) dose and

lowest sucrose concentrations (0.10M, and 0.25M, *p's*<0.001) (Table 4). In contrast, there was no difference between OUD+ and OUD- groups on ratings of intensity ("How sweet is this sample?") (AUC: 36.4 ± 2.0 vs. 39.1 ± 2.0, respectively, *p*=0.35) (Figure 2, lower panel). Ratings of sucrose intensity for both groups increased in a dose-dependent manner across sucrose concentrations (Table 4).

Considering the pronounced differences between groups in subjective pleasantness response to placebo as noted above, we also examined participants' sucrose response as change from their placebo rating (i.e., subjective response to the 0M solution). Using this approach, there was a significant group effect, with a higher magnitude of change in pleasantness ratings from 0M in OUD+ vs. OUD- participants (AUCΔ: 20.7 ± 1.9 vs. 12.6 ± 1.9, *p*<0.01) (Figure 3, upper panel) and a lower magnitude of change in intensity ratings in OUD+ vs. OUD- (AUCΔ: 29.1 ± 1.9 vs. 35.6 ± 1.9, *p*=0.02) (Figure 3, lower panel).

In multivariate analyses, group (OUD+, OUD-) was the only significant predictor of subjective ratings of sucrose pleasantness (*p*=0.002), but did not predict sucrose intensity (*p*=0.95); age, gender, alcohol use, cigarette smoking, cannabis use, and pre-session mood ratings were not associated with either subjective sucrose response (*p's*>0.05). Within the OUD+ group, there were no significant group differences between those receiving methadone vs. buprenorphine in sucrose pleasantness (AUC: 36.4 ± 2.0 vs. 39.1 ± 2.0, *p*=0.35, not shown) or intensity (AUC: 36.4 ± 2.0 vs. 39.1 ± 2.0, *p*=0.35, not shown). Finally, sucrose response did not vary as a function of food insecurity status or BMI (*p's*>0.05).

3.4 Baseline nutrition and eating behavior

As noted previously, we sought to examine additional baseline characteristics associated with eating behaviors that may differ among patients with and without OUD. With regard to BMI, there was a significant group effect on percentage of participants in normal, overweight, and obese BMI categories (p=0.04) (Figure 4). A smaller percentage of OUD+ participants had a BMI in the normal weight category relative to OUD- participants (23% vs. 43%, respectively; p=0.06), while a greater percentage presented with a BMI value in the obese range (45% vs. 20%, p=0.02). With respect to food availability, prevalence of past-year food insecurity was significantly greater among OUD+ vs. OUD- participants (50%. vs. 10%, p<0.001) (Figure 5). Group differences were also seen in the distribution of participants across the four food security categories (p<0.001), with fewer OUD+ participants reporting high food security relative to OUD- participants (p<0.001) and significantly more reporting very low security (p<0.001).

In terms of eating behaviors, OUD+ participants presented with lower total scores on the Eating Behavior Rating Questionnaire relative to OUD- participants (35.2 ± 6.1 vs. 43.4 ± 4.8, respectively; p<0.001). The OUD+ group consistently reported a lower frequency of healthy individual habits (p's<0.01) (Figure 6, top panel, left side) and a higher frequency of unhealthy habits (p's<0.01) (top panel, right side). Among the subsets of participants that reported feeling like eating during the screening session (38% and 50% in the OUD+ and OUD- groups, respectively), OUD+ participants generally reported a significantly greater eagerness to consume unhealthy foods relative to OUD- participants (p's<0.05) (middle panel). They also reported a desire to consume larger

amounts of unhealthy foods and smaller amounts of healthy foods (*p's*<0.05) (lower panel).

Similar outcomes were seen on the Food Frequency Questionnaire. Of the 23 sweet foods and beverages examined, the OUD+ group reported greater frequency of consumption than OUD- participants on 17 items, including greater daily consumption of 6 sweetened food and beverages. (*p's*<0.05) (Table 5). The Timeline Followback also indicated that OUD+ participants consumed significantly greater amounts of sweetened caffeinated beverages relative to OUD- (*p's*<0.01), translating to 89g vs. 4g of sugar from this source per day for OUD+ vs. OUD- participants, respectively (*p*<0.001) (Figure 7, upper panel). In the OUD+ group, the largest source of added sugar was soda, accounting for 64% of the total average added sugar from caffeinated beverages (lower panel).

Regarding participants' knowledge and awareness of nutritional information, total scores on the Nutrition Knowledge Questionnaire were significantly lower in the OUD+ group, with OUD+ vs. OUD- participants answering 46% vs. 65% of items correctly (*p*<0.001) (Table 6). The OUD+ group had significantly lower scores across all four subscales (*p's*<0.001), with particular knowledge deficits related to associations between diet and disease.

Finally, with respect to food-related reinforcement, there were no significant differences between OUD+ and OUD- participants' scores on the Power of Food Scale (46.1$\pm$20.3 and 46.8$\pm$15.6, respectively (*p*=0.86, not shown), which seeks to measure thoughts and perceptions related to appetite for palatable foods. However, the percentage of participants endorsing Yale Food Addiction Scale criteria was numerically higher

among OUD+ participants for all eight criteria and significantly greater on two criteria (Table 7). A similar pattern was seen on the portion of the Yale Food Addiction questionnaire assessing problems with overconsuming and/or craving palatable foods high in sugar and/or fat (Figure 8), wherein the percentages of OUD+ participants endorsing problems with individual foods were numerically greater on almost all items and significantly greater on two foods: soda (35% vs. 8%, $p<0.01$) and cheeseburgers (25% vs. 8%, $p=0.03$).

4. Discussion

Data from preclinical and clinical research have suggested that opioid agonist medications may enhance subjective response to sweet flavors, and this may place opioid-dependent patients at risk for increased sugar consumption and subsequent weight gain and related problems. In the present study, OUD+ participants exhibited a higher magnitude of change in pleasantness ratings from placebo compared to OUD- participants. However, this effect was largely driven by pronounced group differences in participants' perceived pleasantness of essentially unsweet solutions, with OUD+ participants rating the lowest concentration sucrose solutions as less pleasant than OUD- participants. The only other study to evaluate a 0M sucrose concentration found no significant differences in pleasantness ratings between males receiving methadone maintenance treatment and a comparison sample without OUD (Bogucka-Bonikowska et al., 2002). Our findings of no group differences at the higher sucrose concentrations are generally consistent with a prior study in which there were no differences in perceived sucrose pleasantness between males with and without OUD, including the highest

concentration examined (0.88M) (Bogucka-Bonikowska et al., 2002; but see Green et al., 2013).

On the measure of sucrose intensity, the findings were less clear. On the overall AUC outcome measure, participants' intensity ratings did not vary as a function of opioid status, with both groups showing similar dose-dependent increases. However, OUD+ participants did exhibit a significantly lower magnitude of change in intensity ratings from placebo compared to OUD- participants. Important to note, however, is that the magnitude of group differences in change from placebo was less robust for sucrose intensity than pleasantness. These results are generally consistent with a prior study examining effects of methadone on subjective sucrose intensity, with no between-group differences observed on ratings of intensity at the highest sucrose concentration (Bogucka-Bonikowska et al., 2002). However, the opioid-maintained participants in the prior study by Green and colleagues (2013) rated a 1.0M sucrose dose two-fold higher in sweet intensity compared to adults without OUD. Methodological differences between studies in how sucrose pleasantness and intensity were measured may contribute to these differences. For example, the present study and the prior report by Bogucka-Bonikowska and colleagues (2002) used an 100mm linear VAS for assessing sucrose subjective ratings, while Green and colleagues (2013) used a Generalized Labeled Magnitude Scale (170mm for pleasantness, 150mm for intensity) which uses a quasilogarithmic positive/negative scale and may be more sensitive to between-group differences (Bartoshuk et al., 2004).

Taken together, the data from this and several prior studies suggest that the association between opioids and subjective sucrose response in humans may be less

robust than has been seen in the pre-clinical literature, which has consistently shown a large magnitude of effects of opioids on sweet preference of sweetened solutions and foods (e.g., Berridge, 1996; Castro & Berridge, 2017; Zhang & Kelley, 2002). However, also important to note is that pre-clinical experiments have often utilized choice paradigms to evaluate sweet preference, which involve actual consumption of sweetened solutions or foods vs. water or normal chow. Choice paradigms may assess more of the "wanting" process of reinforcement (i.e., approach toward a food reward or motivation to consume) rather than "liking" (i.e., palatability or pleasantness associated with a food), two possibly independent though not mutually exclusive constructs (Berridge, 1996). This may highlight the potentially complex mechanisms underlying our findings in this study in which opioid-dependent individuals look remarkably similar to comparison participants in terms of subjective ratings of sucrose pleasantness and intensity and yet consistently choose sugar and sweetened foods and beverages over healthier alternatives in their everyday lives (Alves et al., 2011; Gambera & Clarke, 1976; Nolan & Scagnelli, 2007; Tomedi et al., 2012; Zador et al., 1996). However, also critical to remember are the many other complex factors influencing eating and so many other health behaviors among opioid-dependent individuals (e.g., socioeconomic status, educational attainment, co-occurring conditions).

We also sought to examine numerous additional baseline characteristics that may influence sucrose response and eating behavior more generally among patients receiving OAT, including BMI, food security, eating behaviors, diet, and nutrition knowledge. OUD+ participants presented with a higher mean BMI relative to comparison participants and nearly half were in the obese BMI category, which is consistent with prior studies on

this topic by our group and others (Baykara & Alban, 2019; Fenn et al., 2015; Nolan & Scagnelli, 2007; Sweeney et al., 2018). Despite a high prevalence of obesity in the OUD+ group, half of the sample also experienced past-year food insecurity, with over a third endorsing the most severe level. This is consistent with other studies in the general population demonstrating that lower food security is paradoxically associated with overeating and obesity (Dhurandhar, 2016; Kaiser et al., 2019; Rasmusson et al., 2019). It is also consistent with previous studies reporting severe food insecurity among individuals with OUD (Himmelgreen et al., 1998; McLinden et al., 2018; Strike, Rudzinski, Patterson, & Millson, 2012).

OUD+ participants also presented with a markedly different profile of eating behaviors compared to those without OUD, including greater consumption of unhealthy foods as well as increased sugar craving and consumption (i.e., 89g sugar/day). This is consistent with prior studies examining eating behaviors among individuals with OUD (Alves et al., 2011; Gambera & Clarke, 1976; Nolan & Scagnelli, 2007; Peles et al., 2016; Tomedi et al., 2012; Zador et al., 1996). This finding also generally aligns with the earlier observations of enhanced sensitivity to sucrose pleasantness among our OUD+ participants. Peles and colleagues (2016) also reported that regular sweet food and beverage consumption was associated with a higher BMI in MMT patients. OUD+ participants also had significantly lower nutrition knowledge relative to our comparison group as well as previously published knowledge scores among MMT patients in Israel (Peles et al., 2016; Sason et al., 2018). Knowledge deficits in the areas of healthy eating may contribute to participants' unhealthy eating behaviors and excessive sugar consumption, as gaps in nutrition knowledge have been associated with a higher BMI and

obesity in the general population (Moynihan et al., 2007; Valmórbida, Goulart, Busnello, & Pellanda, 2017) as well as among adults with OUD more specifically (Peles et al., 2016).

Finally, the OUD+ group reported having more problems with palatable foods high in sugar (i.e., overeating, craving, trouble controlling consumption, tolerance, interference of problem foods with psychosocial functioning). These data are consistent with a recent study which examined loss-of-control (LOC) eating (i.e., perception that one cannot control what or amount that one is eating) among 447 methadone-maintained patients in the U.S. and found that a third endorsed LOC eating within the past 2 weeks (Goldschmidt et al., 2018). Prevalence of recent LOC in that study was 3-fold higher than in previous studies among community samples of adults (Goldschmidt et al., 2018; Solmi, Hatch, Hotopf, Treasure, & Micali, 2014), and it was associated with greater depressive symptoms, past-month illicit drug use, pain severity, and self-perception of being overweight/obese. Similarly, in another recent study of patients receiving MMT, 10% met Yale criteria for food addiction and this was significantly associated with weight gain during treatment (Sason et al., 2018).

Several methodological strengths of the present study are worth noting. First, our sample of opioid-dependent participants was larger than those used in prior studies (e.g., N=14, Green et al., 2013; N=28, Bogucka-Bonikowska et al., 2002) and included similar numbers of methadone- and buprenorphine-maintained individuals. Second, in an effort to evaluate subjective sucrose response with less confounding by opioid dose timing, participants in both groups completed the sweet taste test sessions twice, scheduled three hours apart (corresponding to approximate trough/peak medication levels for the OUD+

group). Third, we examined a larger range of sucrose concentrations than were evaluated in prior studies (e.g., 1 concentration, Green et al., 2013; 4 concentrations, Bogucka-Bonikowska et al., 2002) and, unlike the study by Green and colleagues (2013), included a 0M sucrose dose to permit an evaluation of baseline placebo responding.

Several limitations also merit mention. First, the two groups differed on a range of baseline demographic and SES characteristics, including age, education, income, and employment status, all of which may be associated with prevalence of food insecurity, eating behaviors, diet, and BMI (Appelhans et al., 2012; Darmon & Drewnowski, 2008; de Mestral, Chatelan, Marques-Vidal, Stringhini, & Bochud, 2019; Kaiser et al., 2019). Thus, while these were not significant predictors of sucrose subjective response in our study sample, they may contribute to the large between-group differences we observed in prevalence of food insecurity and obesity as well as eating behaviors. Second, the study was not sufficiently powered to detect differences in sucrose subjective response as a function of OAT medication type (i.e., methadone vs. buprenorphine). While we were able to conduct a preliminary evaluation of this important question, future studies should more thoroughly investigate whether sucrose subjective response may vary as a function of OAT medication. Finally, while we sought to examine as secondary outcomes the associations between sucrose subjective response and other participant characteristics, such as gender, BMI and food insecurity, our sample size for doing so was limited.

Overall, these differences in eating behaviors and knowledge may place opioid-dependent individuals at elevated risk for a host of serious health consequences. There is a significant association between sugar-sweetened beverage consumption and increased incidence of mortality in the U.S. adults, with an 11% increase in all-cause mortality for

each additional 12 oz. serving/day of a sugar-sweetened beverage (Collin, Judd, Safford, Vaccarino, & Welsh, 2019). Through this lens, the mean amounts of sugar consumed by our study sample in sugar-sweetened, caffeinated beverages alone translates to an approximate 30% increase in all-cause mortality. Several studies have also found elevated blood glucose levels and increased incidence of diabetes mellitus among patients receiving methadone maintenance (Fareed, Byrd-Sellers, Vayalapalli, Drexler, & Phillips, 2013; Reece, 2013; Vallecillo et al., 2018). Poor nutrition and unhealthy eating behaviors can also adversely impact OUD treatment outcomes such as treatment retention, illicit drug use and psychiatric symptoms (Goldschmidt et al., 2018; Richardson & Wiest, 2015).

In summary, despite the well-established efficacy of OAT in reducing the significant health and societal consequences associated with OUD, patients receiving methadone or buprenorphine treatment may be at significant risk for obesity, diabetes, cardiovascular disease, stroke, and premature death (Fenn et al., 2015; Mysels & Sullivan, 2010; Schlienz et al., 2018). While OUD+ participants in this study demonstrated generally similar subjective sucrose response, they presented with a markedly different profile of everyday eating behaviors and knowledge than individuals without SUDs. Efforts to understand and improve nutritional knowledge and eating behaviors may improve health and opioid treatment outcomes in this vulnerable population (Jeynes & Gibson, 2017; Nabipour et al., 2014).

Table 1.
Published studies examining weight changes during opioid agonist treatment

Reference	Location	N	OAT Type	Outcomes
Baykara & Alban (2019)	Turkey	107	buprenorphine	Significant increase in weight (**8%**) from T_0 to T_{4mos}
Fenn et al. (2015)	US	96	methadone	Significant increases in weight (**10%**) and BMI (**11%**) from T_0 to T_{2yrs}
Housova et al. (2005)	Czech Republic	12	methadone	Significant increase in BMI (**1%**) from T_0 to T_{1yr}
Kabrt et al. (1999)	Czech Republic	14	methadone	Significant increases in weight (**13%**) and BMI (**12%**) from T_0 to $T_{1.5yrs}$
Li et al. (2016)	United Kingdom	20	methadone, buprenorphine	Significant increase in BMI (**1%**) from T_0 to T_{1yr}
Montazerifar et al. (2012)	Iran	55	methadone	Significant increase in weight (**6%**) and BMI (**7%**) from T_0 to T_{2mos}
Mysels et al. (2011)	US	16	methadone	**2%** and **4%** increases in weight from T_0 to T_{2mos} and T_{6mos}, respectively
Okruhlica & Slezakova (2008)	Slovakia	274	methadone	Increase in % of participants in BMI categories from T_0 to T_{1yr}: overweight (**15% to 29%**) and obese categories (**3% to 8%**)
Okruhlica & Slezakova (2012)	Slovakia	42	methadone	Significant increases in weight (**12% & 15%**) and BMI (**11% & 14%**) from T_0 to T_{1yr} and to T_{4yrs}, respectively
Parvaresh et al. (2015)	Iran	200	methadone	Significant increase in weight (**3%**) from T_0 to T_{6mos}
Peles et al. (2016)	Israel	114	methadone	Significant increase in BMI (**8%**) from T_0 to T_{1yr}
Reimer et al. (2011)	Germany	1015	methadone	Significant increase in BMI (**5%**) from T_0 to T_{1yr}
Sweeney et al. (2019)	US	74	methadone	Significant increase in % of participants in overweight, obese, or morbidly obese BMI categories from T_0 (**42%**) to T_{1yr} (**76%**), T_{2yrs} (**82%**), and T_{3yrs} (**88%**)

Subscripts below timepoint (T) represent the duration of the interval reflected in the % of weight and/or BMI change, with T_0 representing the baseline timepoint.

Table 2.
Participant characteristics

	OUD+ (n=40)	**OUD- (n=40)**	***p*-value**
Age, yrs	36.8 ± 10.0	30.6 ± 8.7	**0.004**
Male, %	53	50	0.823
Race, Caucasian Non-Hispanic, %	93	88	0.456
Education, yrs	12.7 ± 1.5	14.9 ± 1.7	**<0.001**
Employed full-time, %	23	75	**<0.001**
Annual median household income [IQR]	15000 [5000,25000]	35000 [35000,75000]	**<0.001**
Alcohol consumption, % (N)	28 (11)	65 (26)	**<0.001**
# of days/past 30	11.3 ± 12.9	7.1 ± 7.7	0.23
# drinks per day	1.1 ± 1.4	0.54 ± 0.68	0.12
Tobacco use, % (N)	83 (33)	13 (5)	**<0.001**
# of days/past 30	28.8 ± 5.0	20.4 ± 13.1	**0.01**
# CPD	11.3 ± 6.3	4.1 ± 4.1	**0.02**
Caffeine use, % (N)	98 (39)	98 (39)	1.00
# of days/past 30	26.8 ± 8.2	23.4 ± 9.7	0.09
Amount (mg)	315.1 ± 194.7	201.8 ± 169.7	**0.01**
Cannabis use, % (N)	58 (23)	13 (5)	**<0.001**
OAT type			
Methadone, %	53		
Methadone dose (mg)	97.4 ± 33.6		
Buprenorphine, %	47		
Buprenorphine dose (mg)	12.8 ± 6.0		

Table 3.
Experimental session characteristics

	OUD+ (n=40)	**OUD- (n=40)**	***p-value***
Pre-session ratings (0-100)			
Happy	69.7 ± 22.6	78.9 ± 12.0	**<0.01**
Anxious	26.5 ± 25.0	13.4 ± 16.8	**<0.001**
Sad	11.7 ± 18.6	5.0 ± 10.2	**<0.01**
Sick	5.9 ± 13.2	3.6 ± 6.9	0.17
Nauseous	6.7 ± 13.3	1.6 ± 4.1	**<0.001**
Hungry	35.5 ± 28.8	33.2 ± 27.9	0.60
Session characteristics			
Mean session duration (min)	9.5 ± 3.0	8.5 ± 1.4	**<0.01**
Duration between Sessions 1 and 2 (min)	200.5 ± 22.4	191.1 ± 10.4	**0.02**
Time since last ate (min)	622.0 ± 361.1 (n=33)	368.2 ± 321.1 (n=5)	**<0.001**
Time since last cigarette (min)	393.0 ± 642.4 (n=27)	1439.6 ± 1980.4 (n=9)	**<0.01**
Time since last cannabis use (min)	4086.3 ± 7412.0	4431.9 ± 7567.5	0.87

Mean and standard deviation

Table 4.
Sucrose subjective response ratings

	OUD+ (N=40)	OUD- (N=40)
AUC		
Pleasantness	49.6 ± 1.3	57.5 ± 1.3
Intensity	36.4 ± 2.0	39.1 ± 2.0
Concentration dose (0M)		
Pleasantness	28.9 ± 19.4	45.0 ± 12.4
Intensity	7.4 ± 8.0	3.5 ± 5.1
Concentration dose (.10M)		
Pleasantness	31.9 ± 17.3	46.6 ± 11.5
Intensity	11.1 ± 8.8	9.5 ± 11.5
Concentration dose (.25M)		
Pleasantness	41.4 ± 14.4	53.7 ± 9.7
Intensity	22.7 ± 14.2	25.5 ± 16.8
Concentration dose (.50M)		
Pleasantness	53.7 ± 14.9	58.9 ± 10.1
Intensity	41.2 ± 21.2	45.8 ± 21.8
Concentration dose (.75M)		
Pleasantness	59.5 ± 18.2	64.3 ± 12.1
Intensity	52.2 ± 22.6	55.5 ± 22.5
Concentration dose (1.0M)		
Pleasantness	61.1 ± 17.2	63.4 ± 13.5
Intensity	54.2 ± 23.6	58.2 ± 22.7

Mean and standard deviation

Table 5.
Food Frequency Questionnaire: Sweet food and beverage items

Food items	**OUD+ (n=40)**	**OUD- (n=40)**	***p-value***
Beverages			
Tomato or vegetable juice			
≥1 in past year	30	33	0.81
≥1 weekly	10	8	0.69
≥1 daily	0	3	0.31
Orange juice and grapefruit juice			
≥1 in past year	75	85	0.26
≥1 weekly	35	18	0.08
≥1 daily	5	0	0.15
Apple juice			
≥1 in past year	70	63	0.48
≥1 weekly	45	8	**<0.001**
≥1 daily	0	0	1.0
Grape juice			
≥1 in past year	60	28	**<0.01**
≥1 weekly	18	0	**<0.01**
≥1 daily	0	0	1.0
Other 100% fruit juice or 100% fruit juice mixtures (e.g., pineapple, prune)			
≥1 in past year	73	78	0.61
≥1 weekly	38	5	**<0.001**
≥1 daily	5	0	0.15
Other fruit drinks (e.g., cranberry cocktail, HI-C, lemonade, Kool-Aid)			
≥1 in past year	75	48	**0.01**
≥1 weekly	48	8	**<0.001**
≥1 daily	13	0	**0.02**
Meal replacement, energy, or high-protein beverages			
≥1 in past year	33	30	0.81
≥1 weekly	18	15	0.76
≥1 daily	3	10	0.17
Soft drinks, soda, or pop			
≥1 in past year	85	68	0.07
≥1 weekly	55	20	**<0.01**
≥1 daily	38	0	**<0.001**

Desserts

Frozen yogurt, sorbet, or ices			
≥1 in past year	40	70	**<0.01**
≥1 weekly	5	5	1.0
≥1 daily	0	0	1.0
Ice cream, ice cream bars, or sherbet			
≥1 in past year	88	98	0.09
≥1 weekly	43	25	0.10
≥1 daily	10	0	**0.04**
Pudding or custard			
≥1 in past year	68	35	**<0.01**
≥1 weekly	48	18	**<0.01**
≥1 daily	3	0	0.31
Cake			
≥1 in past year	73	95	**<0.01**
≥1 weekly	20	0	**<0.01**
≥1 daily	3	0	0.31
Cookies or brownies			
≥1 in past year	88	100	**0.02**
≥1 weekly	10	0	**0.04**
≥1 daily	3	0	0.31
Doughnuts, sweet rolls, Danish, or pop-tarts			
≥1 in past year	80	88	0.36
≥1 weekly	48	18	**<0.01**
≥1 daily	5	0	0.15
Sweet muffins or dessert breads			
≥1 in past year	63	85	**0.02**
≥1 weekly	23	13	0.24
≥1 daily	0	0	1.0
Fruit crisp, cobbler, or strudel			
≥1 in past year	50	63	0.26
≥1 weekly	15	0	**0.01**
≥1 daily	0	0	1.0
Pie			
≥1 in past year	70	93	**<0.01**
≥1 weekly	10	0	**<0.05**
≥1 daily	0	0	1.0
Chocolate candy			
≥1 in past year	85	98	**<0.05**
≥1 weekly	55	48	0.50
≥1 daily	13	8	0.46

Other candy			
≥1 in past year	93	88	0.46
≥1 weekly	65	25	**<0.001**
≥1 daily	18	0	**<0.01**
Sugar/sweeteners added to foods and beverages			
Sugar or honey added to coffee or tea			
≥1 in past year	63	63	1.0
≥1 weekly	60	33	**0.01**
≥1 daily	48	10	**<0.001**
Artificial sweetener added to coffee or tea			
≥1 in past year	35	8	**<0.01**
≥1 weekly	25	5	**0.01**
≥1 daily	18	5	0.08
Sugar or honey added to foods			
≥1 in past year	68	60	0.49
≥1 weekly	55	30	**0.02**
≥1 daily	33	10	**0.01**
Jam, jelly, or honey on breads or rolls			
≥1 in past year	75	75	1.0
≥1 weekly	35	15	**0.04**
≥1 daily	8	3	0.30

% of participants endorsing consumption of items at frequency of at least once annually, weekly, and daily

Table 6.
Nutrition Knowledge Questionnaire

Knowledge areas assessed	**OUD+ (n=40)**	**OUD- (n=40)**	***p-value***
Total items correct, %	45 ± 19	64 ± 12	**<0.001**
Dietary recommendations	52 ± 19	65 ± 12	**<0.001**
Awareness of balance of good health food group proportions	42 ± 27	59 ± 21	**<0.01**
Awareness of recommendations for consumption of fruit and vegetables	8 ± 27	23 ± 42	0.06
Awareness to reduce saturated fat	53 ± 51	73 ± 45	0.07
Awareness of which foods experts recommend eating less or more	61 ± 22	71 ± 12	**0.01**
Nutrient sources	47 ± 27	67 ± 16	**<0.001**
Knowledge of sources of oily fish	31 ± 35	38 ± 33	0.32
Knowledge of sources of dietary fiber	51 ± 28	74 ± 17	**<0.001**
Healthiest meal option	43 ± 31	64 ± 20	**<0.001**
Sandwich	25 ± 44	25 ± 44	1.00
High-fiber, low-fat meal	35 ± 48	50 ± 51	0.18
Baked potato	60 ± 50	90 ± 30	**<0.01**
Grilled meat	50 ± 51	93 ± 27	**<0.001**
Association between diet and disease	29 ± 25	57 ± 23	**<0.001**
Fiber	13 ± 33	65 ± 48	**<0.001**
Fruits and vegetables	12 ± 28	30 ± 35	**0.01**
Fat	44 ± 46	79 ± 34	**<0.001**
Sugar	37 ± 26	58 ± 27	**<0.001**
Salt	45 ± 50	85 ± 36	**<0.001**

Mean and SD percent of total items correct

Table 7.
Yale Food Addiction Scale criteria

Criteria	OUD+ (n=40)	OUD- (n=40)	*p*-value
1. Substance taken in larger amount and for longer period than intended	8%	0%	0.24
2. Persistent desire or repeated unsuccessful attempts to quit	93%	83%	0.18
3. Much time/activity to obtain, use, recover	23%	13%	0.24
4. Important social, occupational, or recreational activities given up or reduced	25%	0%	**<0.01**
5. Use continues despite knowledge of adverse consequences	20%	13%	0.36
6. Tolerance	38%	10%	**<0.01**
7. Characteristic withdrawal symptoms	15%	3%	0.12
8. Use causes clinically significant impairment or distress	10%	3%	0.62

% of participants meeting each Yale Food Addiction Scale criterion

Figure Legends

Figure 1. Schematic illustrating experimental session procedures

Figure 2. Sucrose pleasantness (upper panel) and intensity (bottom panel) ratings between OUD+ (circles) and OUD- (squares) participants. Error bars represent SEM and asterisks indicate significant between-group differences in ratings at each sucrose concentration. Filled symbols indicate significant within-group differences in ratings at each concentration from placebo (0M), while unfilled indicates that ratings are not significantly different from placebo.

Figure 3. Change from placebo (0M sucrose concentration) in sucrose pleasantness (upper panel) and intensity (lower panel) ratings between OUD+ (circles) and OUD- (squares) participants. Error bars represent SEM and asterisks indicate significant between-group differences in change in ratings from placebo at each sucrose concentration. Filled symbols indicate significant within-group differences in change in ratings at each concentration from placebo (0M), while unfilled indicates that the change in ratings are not significant from placebo. Y-axes are represented on a smaller scale to permit a more detailed inspection of data.

Figure 4. Percent of OUD+ vs. OUD- participants in normal, overweight, and obese BMI categories. Asterisks indicate significant between-group differences.

Figure 5. Prevalence of past-year food insecurity between OUD+ vs. OUD- participants and percent of OUD+ and OUD- participants across the 4 USDA food security categories (high, marginal, low, and very low). Asterisks indicate significant between-group differences.

Figure 6. Mean frequency ratings on the 12 items of the Eating Behavior Ratings Questionnaire between OUD+ vs. OUD- participants (top panel) and mean ratings on the 9 food items among OUD+ vs. OUD- participants that endorsed that they felt like consuming (middle and bottom panel). The middle panel displays mean eagerness ratings and the bottom panel displays mean amount of consuming the food items. Error bars represent SEM and asterisks indicate significant between-group differences.

Figure 7. Mean amount of added sugar from caffeinated beverages consumed per day (g/day) among OUD+ vs. OUD- participants. An asterisk indicates significant between-group differences.

Figure 8. Comparison in the percent of OUD+ vs. OUD- participants endorsing problems with foods on the Yale Food Addiction Scale. The upper panel represents the percent of participants endorsing problems with the 7 high-sugar items and the bottom panel presents the percent of participants endorsing problems with the 7 high-fat items. Asterisks indicate significant between-group differences.

Figure 1.

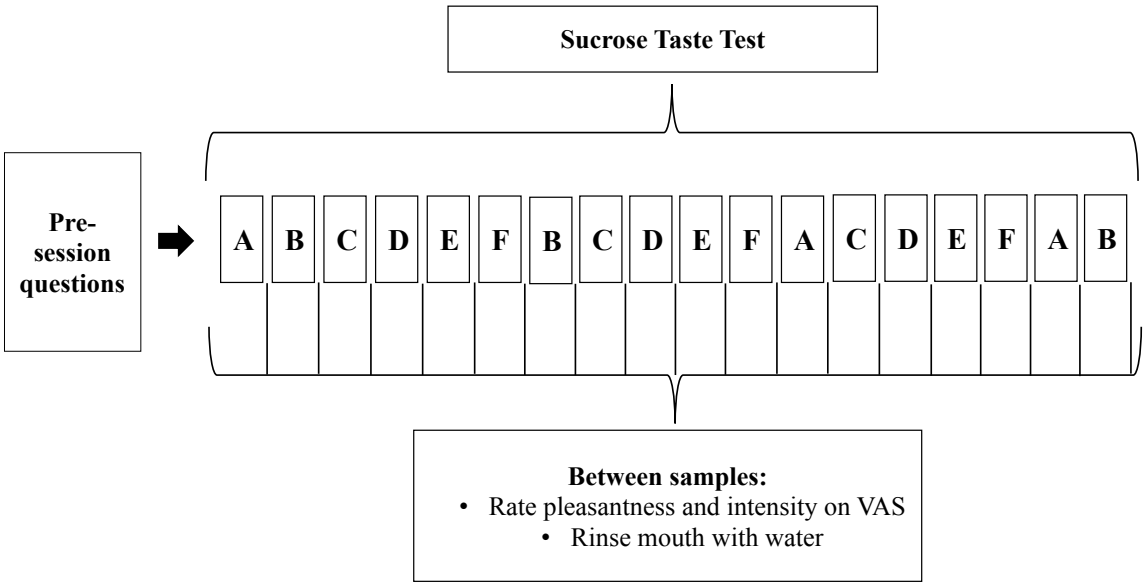

Sucrose Taste Test
Pre-session questions
A B C D E F B C D E F A C D E F A B
Between samples:
• Rate pleasantness and intensity on VAS
• Rinse mouth with water

Figure 2.

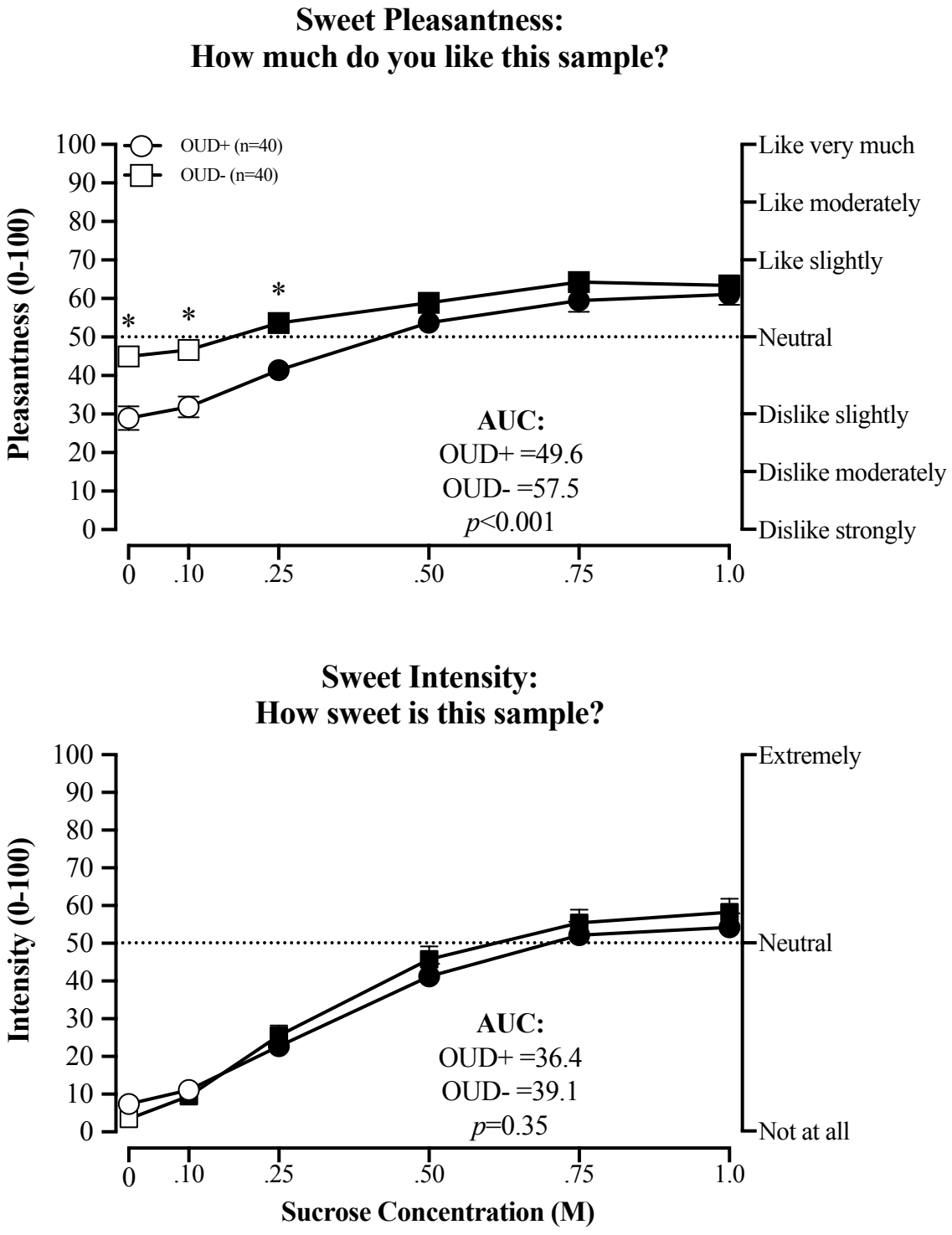

Sweet Pleasantness:
How much do you like this sample?
Pleasantness (0-100)
OUD+ (n=40)
OUD- (n=40)
Like very much
Like moderately
Like slightly
Neutral
Dislike slightly
Dislike moderately
Dislike strongly
AUC:
OUD+ =49.6
OUD- =57.5
p<0.001
Sweet Intensity:
How sweet is this sample?
Intensity (0-100)
Extremely
Neutral
Not at all
AUC:
OUD+ =36.4
OUD- =39.1
p=0.35
Sucrose Concentration (M)

Figure 3.

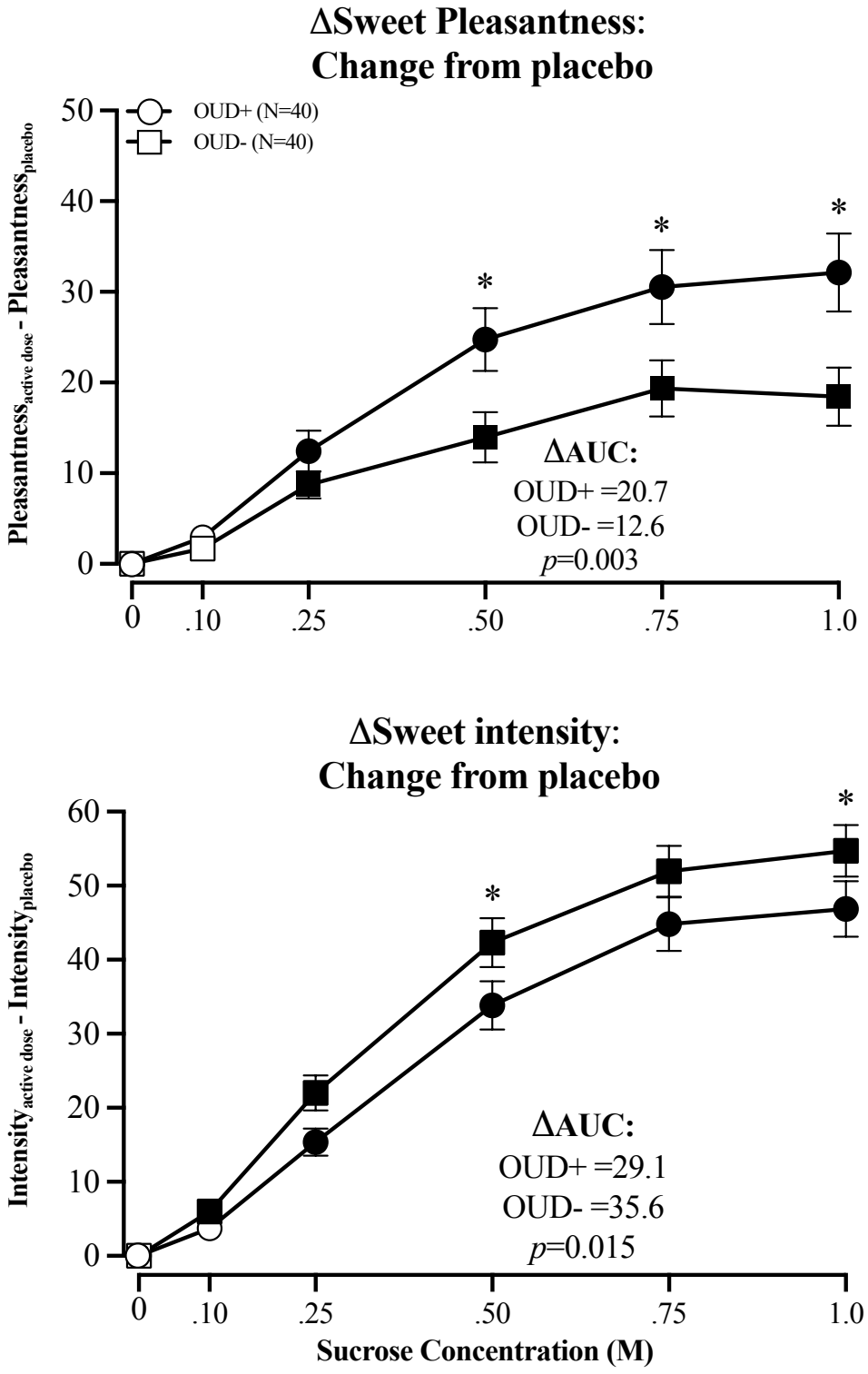

ΔSweet Pleasantness:
Change from placebo
OUD+ (N=40)
OUD- (N=40)
Pleasantness active dose - Pleasantness placebo
50
40
30
20
10
0
*
*
*
ΔAUC:
OUD+ =20.7
OUD- =12.6
p=0.003
0
.10
.25
.50
.75
1.0
ΔSweet intensity:
Change from placebo
Intensity active dose - Intensity placebo
60
50
40
30
20
10
0
*
*
ΔAUC:
OUD+ =29.1
OUD- =35.6
p=0.015
0
.10
.25
.50
.75
1.0
Sucrose Concentration (M)

Figure 4.

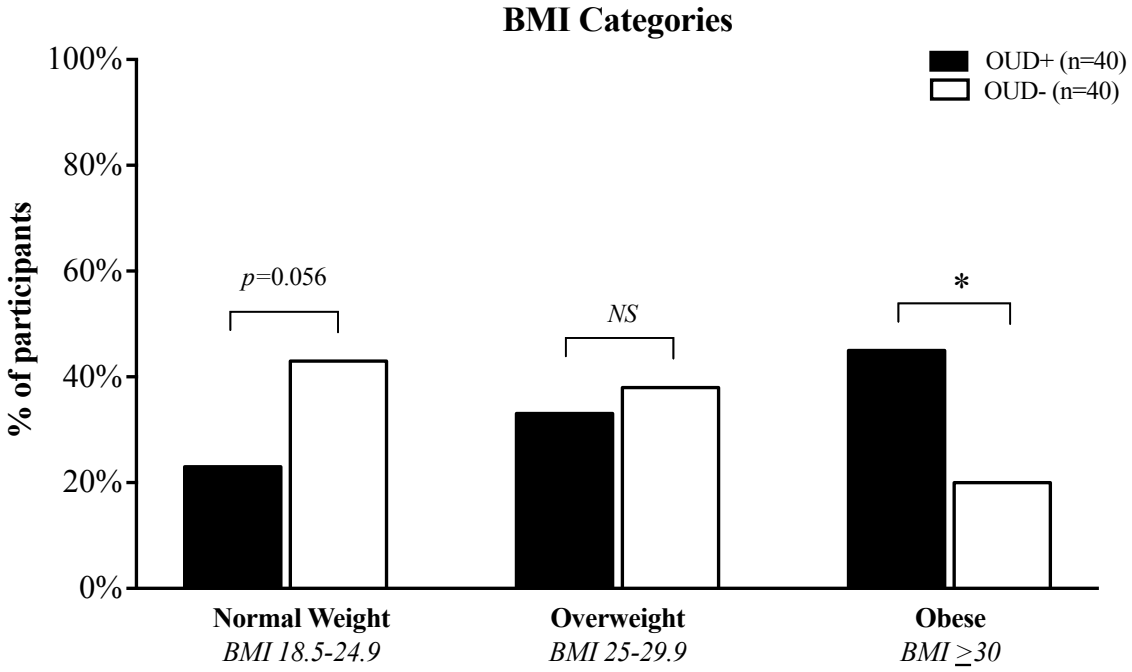

BMI Categories
OUD+ (n=40)
OUD- (n=40)
100%
80%
60%
40%
20%
0%
% of participants
p=0.056
NS
*
Normal Weight
BMI 18.5-24.9
Overweight
BMI 25-29.9
Obese
BMI ≥30

Figure 5.

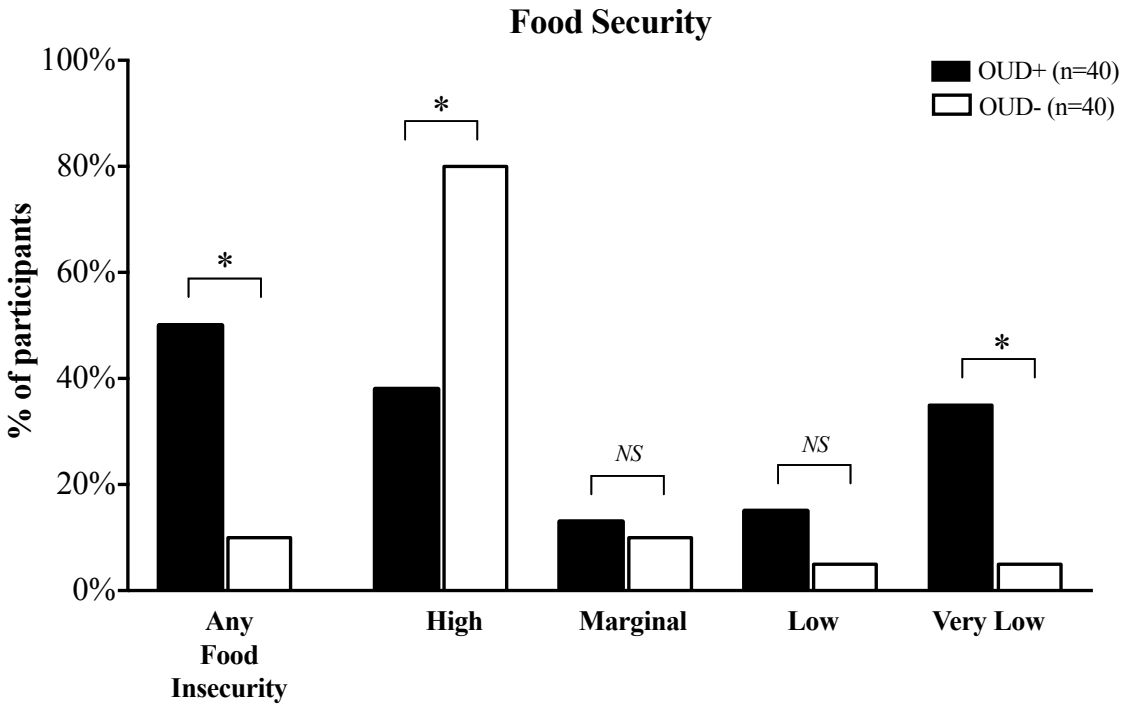

Food Security
OUD+ (n=40)
OUD- (n=40)
% of participants
100%
80%
60%
40%
20%
0%
*
*
NS
NS
*
Any Food Insecurity
High
Marginal
Low
Very Low

Figure 6.

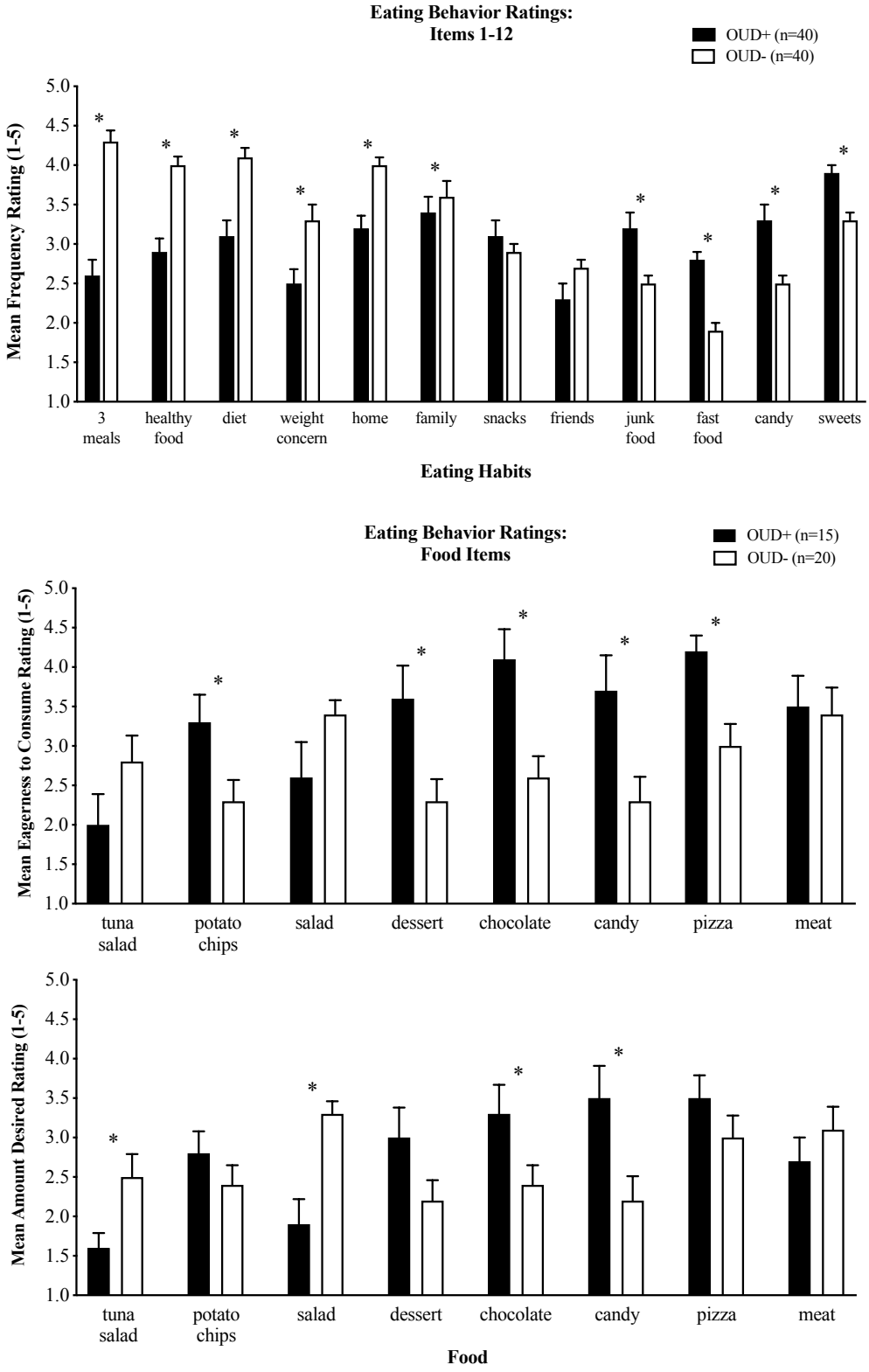

Eating Behavior Ratings:
Items 1-12
OUD+ (n=40)
OUD- (n=40)
Mean Frequency Rating (1-5)
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
3 meals
healthy food
diet
weight concern
home
family
snacks
friends
junk food
fast food
candy
sweets
Eating Habits
Eating Behavior Ratings:
Food Items
OUD+ (n=15)
OUD- (n=20)
Mean Eagerness to Consume Rating (1-5)
Mean Amount Desired Rating (1-5)
tuna salad
potato chips
salad
dessert
chocolate
candy
pizza
meat
Food

Figure 7.

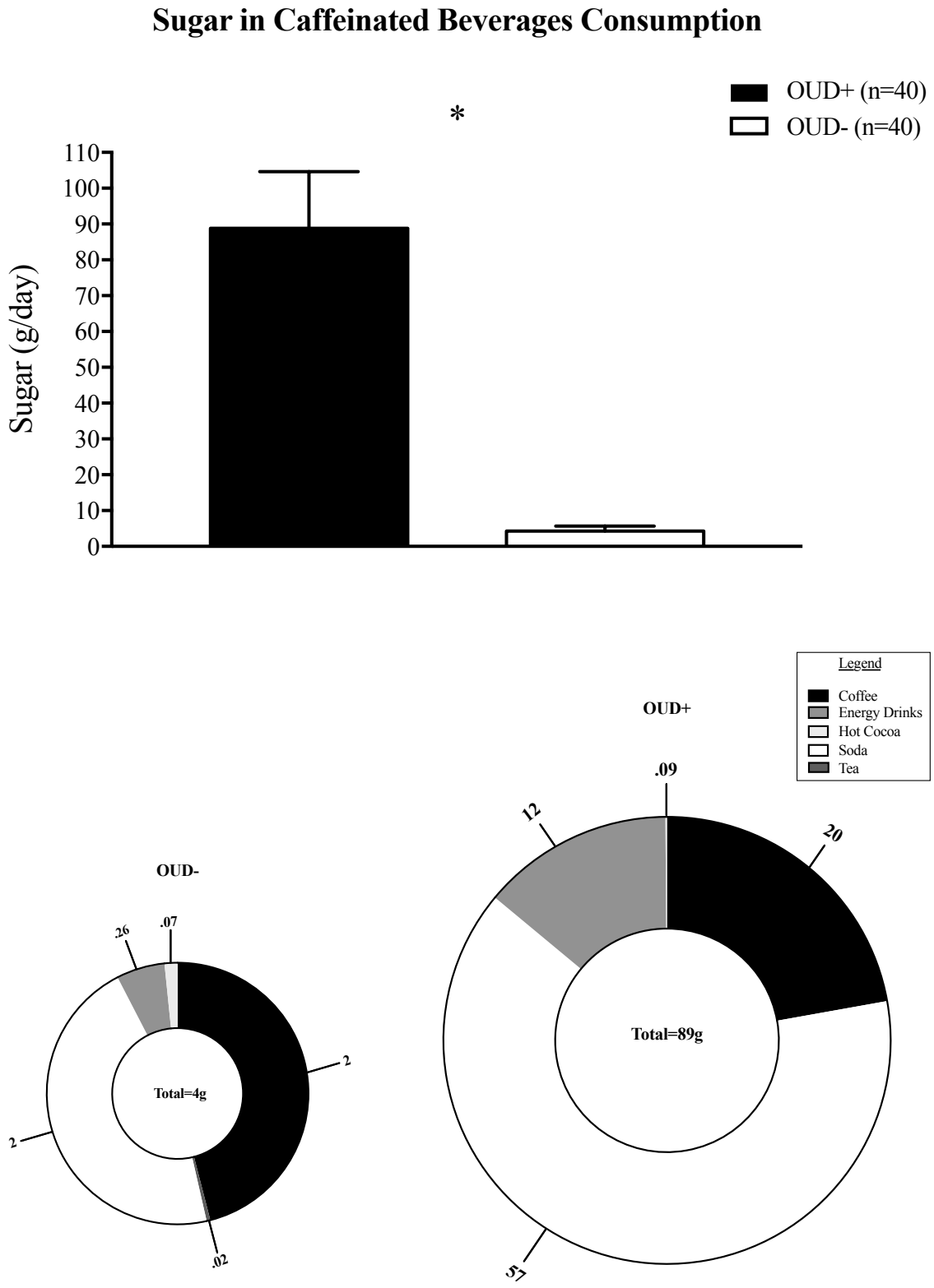
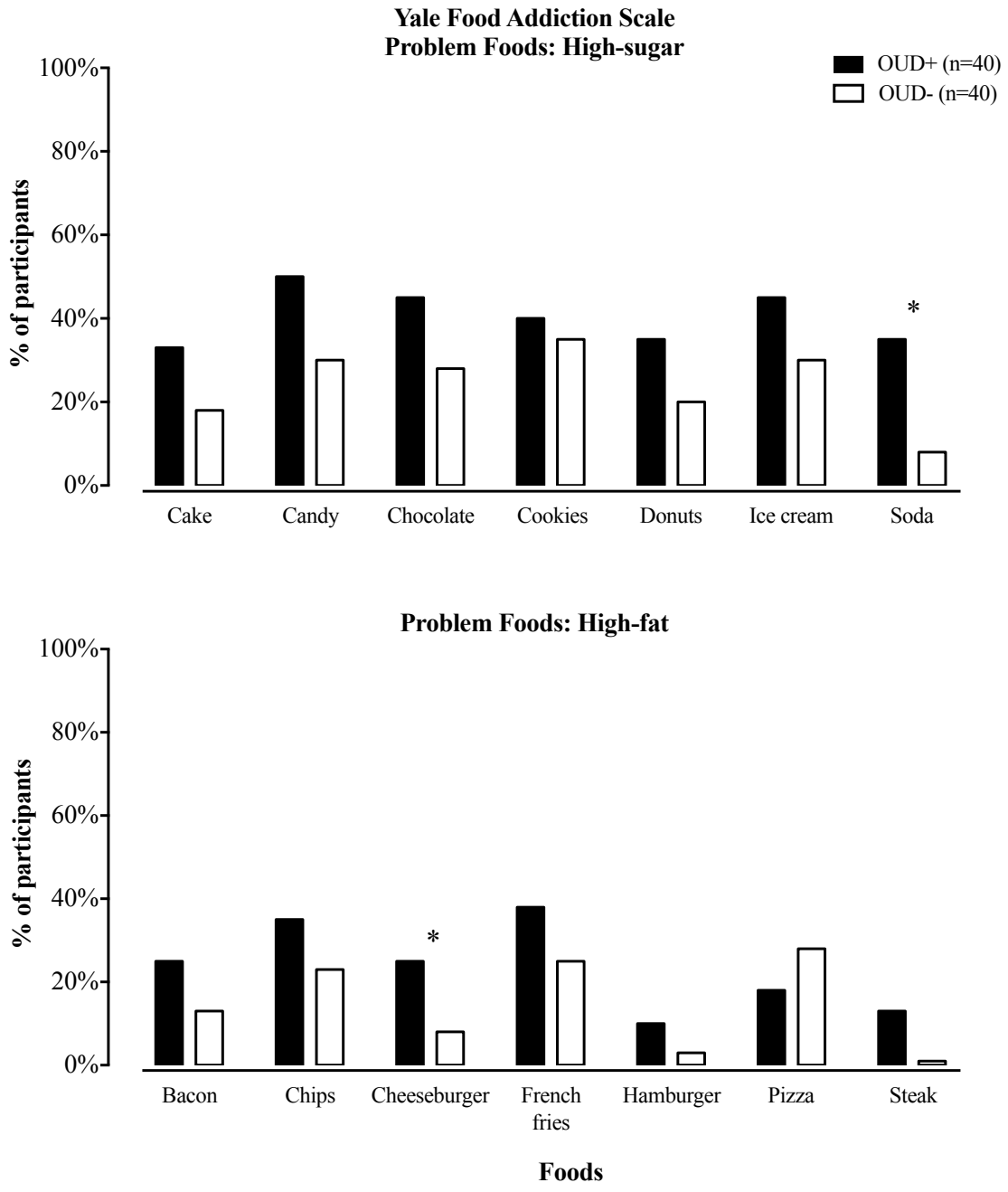

Sugar in Caffeinated Beverages Consumption
OUD+ (n=40)
OUD- (n=40)
*
Sugar (g/day)
110
100
90
80
70
60
50
40
30
20
10
0
Legend
Coffee
Energy Drinks
Hot Cocoa
Soda
Tea
OUD+
.09
12
20
Total=89g
.57
OUD-
.26
.07
2
2
.02
Total=4g

Figure 8.


Yale Food Addiction Scale
Problem Foods: High-sugar
OUD+ (n=40)
OUD- (n=40)
% of participants
100%
80%
60%
40%
20%
0%
*
Cake
Candy
Chocolate
Cookies
Donuts
Ice cream
Soda
Problem Foods: High-fat
% of participants
100%
80%
60%
40%
20%
0%
*
Bacon
Chips
Cheeseburger
French fries
Hamburger
Pizza
Steak
Foods

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