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Title: The relationship between dietary intake and behaviours with oxytocin: a systematic review of studies in adults

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Abstract

Context: Oxytocin plays an important hormonal role in the regulation of feeding and energy intake. *Objectives*: To 1) determine the effects of dietary intake/behaviours on endogenous oxytocin, and 2) examine the effect of exogenous oxytocin on dietary intake/behaviours. Data sources: Published studies up to December 2016 were identified through searches of five electronic databases. *Data extraction*: Eligible studies included those in adults reporting a

measure related to an individuals' diet and a measure of oxytocin, and the relationship between the two outcomes. *Data analysis*: Twenty-six studies (n=912 participants; 77% female) were included. The most common dietary outcomes assessed were alcohol, caffeine, calcium, sodium, fat and calorie intake. It was found endogenous oxytocin (n=13) in non-clinical samples did not change significantly through altered diet or behaviours (neutral effect), in contrast significant differences (increases and decreases) were identified in clinical samples. Exogenous oxytocin studies (n=13) reported reduced indices of food intake (positive effect) in clinical and non-clinical samples. *Conclusion*: Overall, few studies included comprehensive investigation of dietary intakes through the use of validated assessment tools. Dietary intake and behaviours appear to have some influence on oxytocin with more pronounced effects found with exogenously administered oxytocin.

Key words: dietary intake, oxytocin, addiction

Introduction

The dietary intake patterns and behaviour of humans depend on the complex interplay of many neuroendocrine processes within the body.[1] The neurophysiological mechanisms that modulate these processes involve a network of pathways that are regulated by an intricate feedback system.[1-3] These processes are sensitive to emotional and cognitive control, as well as external influences, such as environmental cues and food availability.[3] Research in animal models and pilot studies in humans have indicated that oxytocin can play a significant role in food intake, metabolism and brain reward functions.[2,4]

Oxytocin, a neuropeptide produced primarily in the paraventricular and supraoptic nuclei of the hypothalamus, is secreted by the pituitary gland in response to a variety of interactive

48 behaviours and stimuli involved in food motivation and food intake.[5,6] The role of oxytocin
49 includes the regulation of feeding, energy intake and expenditure, in conjunction with related
50 aspects such as controlling appetite and satiety.[5,7,8]

51 Animal studies support a hypothesis that oxytocin can function as an anorexigenic hormone. For
52 example, centrally (via intracerebroventricular and intraperitoneal application) and peripherally
53 (via subcutaneous and intranasal application) administered oxytocin significantly reduces overall
54 food intake,[9-12] alcohol,[13,14] sucrose[15,16] and saccharin[17] intakes in both obese and lean animals.
55 Additionally, oxytocin has been found to increase the latency to begin feeding and reduce meal
56 durations in both hungry and satiated animals.[10,11,18,19] Furthermore, pre-treatment with
57 oxytocin receptor antagonists blocked these anorexigenic actions.[20-22] Oxytocin knockout mice
58 also display significantly increased preference for sucrose,[23,24] saccharin,[25] and sodium
59 compared to wild-type controls.[26,27]

60 Oxytocin is best known for its hormonal role in reproductive function in women, particularly
61 childbirth and lactation.[28] Oxytocin is also known to fluctuate at various times throughout the
62 menstrual cycle with higher concentrations during the follicular and ovulatory phases.[29,30] Of
63 late, oxytocin has been recognised for its influence in neurophysiological behaviours, such as
64 social recognition, stress, trust and empathy.[31-35] Furthermore, oxytocin has been associated
65 with psychiatric disorders such as autism spectrum disorder,[29] schizophrenia,[36] depression,
66 anxiety[34]; and addictive disorders, such as drug and alcohol abuse.[31] It has been suggested that
67 individuals with psychiatric conditions and those exhibiting addictive behaviours have decreased
68 oxytocin levels.[31,37] Many of the psychosocial characteristics that are common to these disorders
69 are also common to the pathologies of disturbed eating patterns, such as anorexia nervosa,

70 binge eating, and obesity.[38-41] More recently, research has investigated oxytocin in relation to
71 addictive eating behaviours.[42]

72 Traditionally, research has focused on the contribution of endogenous oxytocin (i.e. oxytocin
73 produced and secreted within the body in response to stimuli[5]) in the regulation of food intake
74 and eating behaviours. During the last decade several preclinical studies have reported that
75 administration of exogenous intranasal oxytocin inhibits eating behaviours driven by hunger and
76 extends to limiting the intake of palatable food.[43-45] To date published studies examining the
77 effects of endogenous or exogenous oxytocin in relation to human nutrition have not been
78 systematically reviewed. To promote further understanding, examination of the neuropeptide
79 and its role in dietary intake is warranted. Oxytocin may present as a biomarker of disordered
80 eating patterns, which could have implications for characterising disordered eating patterns and
81 the comorbidities associated with these behaviours. Exogenous oxytocin administration may
82 offer a potential therapeutic approach to moderate dietary intake and behaviours.

83 The aim of this systematic review was to examine published literature to determine the
84 interrelationship between diet and oxytocin in adults. The primary objectives being 1) to
85 examine the effect of dietary intake/behaviours on endogenous oxytocin, and 2) to examine the
86 effect of exogenous oxytocin on dietary intake/behaviours.

87 **Methods**

88 *Study Criteria*

89 To be included in this review, a study had to be conducted in an adult population, or a
90 population sample in which the majority of individuals were over the age of 18 years. The study
91 needed to report 1) an outcome measure related to the individuals' dietary intake (i.e. food or

nutrient) and/or behaviour (e.g. meal consumption patterns) 2) an outcome measure of endogenous oxytocin [e.g. cerebrospinal fluid blood (CSF), plasma, urine or saliva]; or exogenous oxytocin administration, and 3) the relationship between the two measures. For outcomes related to dietary behaviours, measures included behavioural responses associated with eating (e.g. craving, satiety and appetite); behavioural models of eating (e.g. anorexia nervosa, binge eating); patterns or time intervals of eating (e.g. fasting). To maintain homogeneity of the outcomes and clearly define the interrelationship between oxytocin and specific dietary intake patterns or behaviours, studies examining the physiological mechanisms of metabolism and digestive processes (e.g. gastric emptying rates, sodium clearance rates) were not included in the present review.

For the purposes of this paper all study designs were considered, exclusion criteria were narrative reviews, case reports/series, commentaries, editorials, letters to the editor, theses and conference proceedings. Because of the range of experimental approaches used in pre-clinical studies, reports involving animal populations were excluded. Additionally, human studies focusing on pregnant or lactating females in which there is expected biological changes in oxytocin levels, and hormonal-related alterations in food intake and eating behaviours; and populations with health conditions/diseases known to alter oxytocin function (e.g. pituitary gland disorders) were excluded. The review methodology was prospectively registered in PROSPERO (Registration number: CRD42016053015) and follows PRISMA guidelines[46] (Table 1 PICOS criteria).

Search Strategy

A systematic search strategy of electronic databases, Cochrane, CINAHL, MEDLINE, EMBASE and Scopus was performed. Collectively these databases report that they reliably index records, from

115 1970 onwards. Limits were applied to include studies published in English language from 1970
116 to December 2016. The search strategy (available through Supplementary material) was created
117 using key search words and combinations included: [Diet OR diet therapy OR dietary intake OR
118 dietary behaviour OR dietary quality OR dietary habit OR dietary pattern OR dietary records OR
119 food intake OR food habits OR dietary fats OR dietary carbohydrates OR sucrose/sugar
120 consumption OR alcohol OR alcoholic beverages OR alcoholic drinking OR alcohol abstinence OR
121 caffeine] AND [Oxytocin/receptors]. In addition, to ensure no relevant articles were missed a
122 manual search of the reference lists of relevant publications was conducted.

123 Duplicate articles were first removed, and articles were manually coded as human or animal
124 subjects (JS). Articles based on animal research, along with human studies focusing on pregnant
125 or lactating females were excluded. The remaining title and abstracts identified through the
126 search were imported into Covidence[47] (web-based screening tool) and screened by two
127 independent reviewers (JS and TB) using the predetermined inclusion/exclusion criterion. For
128 abstracts that met the inclusion criteria, or where eligibility was unclear, full-text articles
129 including supplementary materials were retrieved for further screening. These were then
130 evaluated for inclusion by two independent reviewers (JS and TB), with discrepancies resolved
131 by discussion with a third reviewer (CD). In this paper consensus was reached for all included
132 articles.

133 *Data Extraction*

134 Data extraction was conducted using a standardised table developed for this review. The tool
135 was pilot tested on six randomly selected included studies and refined to ensure all relevant
136 data was being captured. One review author (JS) extracted the data from included studies and
137 the second author (TB) independently checked the extracted data.

Data Synthesis

Most studies in this systematic review were highly diverse with regard to study design, participants, clinical characteristics, interventions and outcome measures presented. Additionally, endogenous oxytocin measurements were performed using different assay methods, in a range of biological fluids (saliva, CSF, unextracted and extracted serum), which is known to influence findings.[48-50] Therefore, a meaningful meta-analysis was not possible and studies are described in a narrative summary.

Quality of Evidence

The risk of bias and strength of evidence from individual studies was assessed, by two independent reviewers (JS and SF), using a standardised tool from the American Academy of Nutrition and Dietetics.[51] This 10-point checklist; including four validity criteria questions; assesses population bias, study blinding, description of the intervention and assessment tool, statistical methods, and study funding. The quality of evidence for each outcome was rated as being absent, present or unclear in each study. An overall quality rating was assigned, with each study being rated as positive (=4 validity criteria plus ≥1 additional criteria met), neutral or negative (<4 validity criteria met). No studies were excluded based on quality ratings. In cases of uncertainty regarding quality assessment a third independent reviewer (TB) was consulted until consensus was reached.

Results

Description of studies

The search strategy, summarised in Figure 1, identified 1635 potentially eligible articles after exclusion of duplicates. After the removal of animal studies, and human studies focusing on

pregnant or lactating females, the search strategy yielded 412 articles for initial screening. Initial screening of titles and abstracts identified 115 articles that received a detailed assessment of the full text article. Of these 91 were excluded because they did not meet the inclusion criteria. The wrong study design (n=67; e.g. narrative review articles, commentaries and conference abstracts) was the main reason for exclusion. A total of 24 articles (n=26 studies) are presented in the current review.[42-45,52-70]

Quality of included studies

The quality assessment appraisals of included studies deemed 24 studies as having a positive rating and two as having a neutral rating (Supplementary material, Table 1). The studies rated as neutral comprised study groups that were not comparable, in addition study limitations and biases were not described.

Study characteristics

A total of 912 participants (204 males and 708 females) were included across the studies, and study sample sizes ranged from 4 to 162 (median 24). Eleven of the 26 studies included females exlcusively,[56,58,60-64,66,68,70] seven included only males,[43-45,52,55,57,69] and eight included both males and females.[42,53,54,59,65,67] Fourteen of the studies included participants with clinical characteristics: diabetes mellitus [T1DM] (n=2),[53,62] gastroparesis (n=1),[53] functional dyspepsia (n=1),[53] chronic normal-transit constipation (n=1),[68] anorexia nervosa [AN] (n=5),[58,60,61,63,66] bulimia nervosa [BN] (n=3),[58,62,66] binge-eating disorder [BED] (n=1)[71] and food addiction (n=1).[42] Participants were recruited from seven countries: USA (n=7 studies),[44,52,55,58,62-65] Germany (n= 4),[43,45,59,70] Italy (n=3),[56,57,71] Sweden (n = 4),[53,54,67,68] South Korea (n=2)[60,61] and one study each from Denmark,[69] and Canada[42]. Participants ranged in age from 16 to 65 years (mean 31.1 ± 9.0). The average age of participants was under 45 years for all but two studies.[53,71] Across all the

included studies the most common secondary measures examined, in descending order, were appetite hormones and blood parameters (n=8), mood states (n=5), gastric emptying rates (n=3), energy expenditure (n=3), anxiety and depression (n=3), temperament traits (n=2), emotional recognition (n=2), and Autism spectrum traits (n=1).

Endogenous oxytocin studies

Thirteen studies (Table 2[42–45,52–71]) which were published between 1991 and 2016 examined the effects of dietary intake and behaviours on endogenous oxytocin in healthy individuals (n=7)[52,55-57,59,64,69] and individuals with clinical characteristics (n=6; T1DM, chronic normal-transit constipation, AN, BN and food addiction).[42,58,62,63,66,68] Sample sizes ranged from 4 to 162 (median 24). Over half the studies (n=7) included females exclusively,[56,58,62-64,66,68] four included only males[52,55,57,69] and two included both males and females.[42,59] Participants ranged in age from 16 to 43 years (mean 28.9±6.4).

Exogenous oxytocin studies

Thirteen studies (Table 2[42–45,52–71]) which were published between 2006 and 2016, examined the effect of exogenous oxytocin on dietary intake and behaviours in healthy individuals (n=8)[43-45,54,65,67,70] and individuals with clinical characteristics (n=5; functional dyspepsia, gastroparesis, AN, BN and BED).[53,60,61,71] Sample sizes ranged from 10 to 102 (median 20). Four the studies included females exclusively,[60,61,70,71] three included only males[43-45] and five included both males and females.[53,54,65,67] Participants ranged in age from 16 to 62 years (mean 34.1±11.1).

Dietary characteristics and assessment methods

The studies varied in the particular dietary characteristics examined (Table 2). Endogenous oxytocin concentrations were examined in relation to the following dietary exposures, intakes

and behaviours in descending order: alcohol (n=6), eating disorders [AN and BN] (n=3), caffeine (n=1), dietary and supplemental calcium (n=1), fat-rich meal (n=1), low and high sodium diets (n=1), short-term fasting (n=1) and food addiction (n=1). The dietary intake and behaviours examined following exogenous oxytocin administration included: appetite and satiety (n=8), consummatory behaviour [food or volume intake; binge eating] (n=6), craving (n=3) and attentional biases to diet related stimuli (n=2).

Dietary assessment methods were highly varied across the included studies and very few (n=5) reported using a validated measure. Two cross-sectional studies, using a validated food frequency questionnaire, assessed macro- and micronutrient intakes in relation to plasma oxytocin levels.[42,62] Following oxytocin and/or placebo administration, two studies assessed food intake relevant to the eating pathologies of the specific populations being studied, rather than specific nutrient intakes. For instance, in BED individuals, a self-report diary was kept over the 8-week intervention period to monitor binge-eating episodes, including the types of foods consumed.[71] In AN and bulimic individuals a 24 hour food diary was recorded, following oxytocin administration, to quantify calories consumed post-intervention.[60] Lawson (2015) et al.[44] used a 72-hour pre-intervention self-reported food diary to track food intake prior to the first experimental procedure. This allowed participants to replicate a similar food intake pattern prior to their second study visit. Three experimental crossover studies reported participant's usual intakes of alcohol[52,59,64] prior to experimental dietary exposures.[44] However, these studies did not describe the dietary assessment method used and intakes were not directly compared with oxytocin concentrations. Within these studies, usual alcohol intake was used as a priori measure to ensure inclusion criteria was met i.e. abstainers or abusers of alcohol were excluded. Self-report questionnaires and semi-structured interviews were the main assessment methods used to measure eating disorders (AN and BN) and binge eating disorder symptoms and behaviours

(n=6).[58,60,61,63,66,71] Of the 16 studies measuring the effect of a dietary exposure, compliance was measured in 11 studies through biomarkers,[69] blood alcohol concentrations[52,57,59,64] or weighed food designs.[43-45,60,61,63]

The effect of dietary intake and behaviour on endogenous oxytocin

Of the 13 studies examining dietary intake and behaviours on endogenous oxytocin (Table 2) the majority (n=12) assessed oxytocin concentrations in blood plasma via enzyme immunoassay (EIA), radioimmunoassay (RIA) or magnetic bead-based immunoassay; with only one[58] in cerebrospinal fluid (CSF) via radioimmunoassay. Ten studies reported baseline oxytocin levels (pg/mL) measured in extracted or unextracted serum.[42,52,56,57,59,62-64,66,68] There was a wide variation in concentrations of oxytocin, ranging from 1.0 to 120.2 pg/mL. Depending on the study design the number of oxytocin measurements (median 7; range 1 to 186), and the time points taken (range -40min to +31h) differed between studies. Of the nine studies involving eumenorrheic female participants, four studies were conducted during the follicular phase of the menstrual cycle,[58,63,64,66] and two studies during the luteal phase[56,62]; menstrual cycle phase was not reported in the remaining three studies.[42,59,68] Experimental sessions were most often conducted following an overnight fast (n=9 studies).[42,55-58,63,64,66,68] (Table 2)

Alcohol intake

Six studies assessed alcohol intake in relation to endogenous oxytocin.[52,56,57,59,62,64] One cross-sectional study[62] found alcohol intake was associated with decreased plasma oxytocin levels in premenopausal women with T1DM, but not in non-diabetic matched controls. Across the five placebo-controlled crossover trials, [52,56,57,59,64] four studies found alcohol had no significant effect on plasma oxytocin concentrations in either males or females,[52,56,57,59] and a non-significant decrease was found in one study in females.[64] The types of alcoholic beverages

consumed varied between studies and included alcohol mixed with fruit juice (n=2), ethanol mixed with whisky (n=2) and beer (n=1). The dosages also varied and it is estimated that low to high doses ranging between ~10 to ~70 grams of alcohol were consumed. Beverage consumption was monitored over a 15–30 minute period.

Eating Disorders

Of the studies examining eating disorders (n=3), two studies found peripheral and central oxytocin levels to be lower in individuals with AN than those with BN or healthy controls.[58,66] When restrictive and binge-purging AN subtypes were compared, Monteleone et al.[66] found no significant differences in plasma oxytocin levels between the two subtypes, while Demitrack et al.[58] found significantly lower CSF oxytocin concentrations in restrictive AN. During the course of recovery Demitrack et al. observed a significant increase in oxytocin levels in all AN. In contrast, Lawson (2013) et al. found baseline and post-prandial oxytocin levels to be significantly lower in ANWR (weight-recovered anorexia nervosa) individuals compared to AN and controls.

Other dietary measures

Of the studies examining other dietary measures (n=5), one study[62] found caffeine intake and calcium supplement use was associated with increased plasma oxytocin levels in women with T1DM, but not in non-diabetic matched controls. Of the remaining studies a fat-rich meal was found to significantly increase plasma oxytocin levels,[68] while varying levels of sodium intake (30-690mmol NaCl/day) did not alter plasma oxytocin levels.[69] There was no significant difference in plasma oxytocin found in food addicted vs. non-food addicted obese individuals,[42] or in males in short-term fasted (~24 hours) vs. fed state.[55]

The effect of exogenous oxytocin on dietary intake and behaviours

Of the 13 studies examining the effects of exogenous oxytocin on dietary intake and behaviour, the majority of studies (n=8)[43-45,60,61,65,70,71] administered oxytocin intranasally (Table 2[42–45,52–71]). All, but one study,[69] examined oxytocin in relation to a placebo (nasal spray containing same ingredients as the treatment spray except for oxytocin, or a saline infusion). The composition of the placebo nasal spray was not specified in two studies.[43,65] Mid to high range doses of oxytocin[50,72-74] were administered, intranasal dosages ranged from 24 to 40IU,[43-45,60,61,65,70] and oxytocin infusions from 20 to 160mU min^{-1}.[53,54,67] There were no major side-effects reported. This is consistent with prior research in which short-term use of dosage amounts up to 40IU (per dose) have been prescribed.[75] Only three studies[44,54,70] reported the change in oxytocin values from baseline following oxytocin administration. These were not directly comparable due to the differing types of biological samples (i.e. saliva and plasma) and reporting methods used. Two of the nine crossover studies involving eumenorrheic females were conducted during the follicular phase of the menstrual cycle,[60,61] and one study during the follicular or luteal phase.[70] Menstrual cycle phase was not reported in the remaining seven studies.[53,54,65,67,71] In the crossover studies (n=12), experimental sessions were mostly conducted following an overnight fast (n=8).[43-45,53,54,67] Outcomes of included exogenous studies are detailed in Table 4.

Appetite and satiety

Of the studies examining the effects of exogenous oxytocin on subjective appetite and satiety (n=8), seven studies[43-45,53,54,67] found no effect in either healthy participants, diabetics with gastroparesis or those with functional dyspepsia. In contrast, Borg (2011) et al. [54] reported oxytocin (40mU min^{-1}) decreased satiety scores after a liquid meal in healthy males and females.

Consummatory behaviour

Of the studies examining consummatory behaviours (n=6), the administration of intranasal oxytocin had a positive effect on dietary intake in normal-weight[43,44] (n=2 studies) and overweight/obese males (n=3 studies).[43-45] This included a reduction in hunger-driven food consumption (decrease in overall caloric intake); a reduction in postprandial reward-driven snack consumption (decrease in total snack and sweet snack intake); and an increase in perceived palatability of bland snacks (n=2 studies),[43,45] but not sweet or salty snacks. Energy expenditure, assessed in three studies as a secondary measure by indirect calorimetry, was comparable between the placebo and the oxytocin condition during the entire experimental periods.[43-45] A positive effect, in BN individuals, was also observed with a decrease in their 24-hour food intake post-oxytocin administration.[60] Oxytocin had no effect on hunger-driven food intake in two studies in normal-weight men[43,45]; volume of liquid meal intake in individuals with functional dyspepsia[53]; consumption of fruit juice in individuals with AN or BN[60,61]; or binge eating episodes in BED individuals.[71]

Craving and attentional biases

Across the four studies[61,65,70,71] examining craving and attentional biases, oxytocin had no effect on cue-induced alcohol craving, but did have a positive effect on approach bias towards palatable food images in those with alcohol use disorder.[65] A decrease in attentional biases toward eating and negative shape (fat) stimuli was found in AN individuals.[61] A neuroimaging study in healthy females,[70] found oxytocin reduced cravings towards palatable foods when the long-term consequences of eating high calorie foods were thought about. No effect was found when participants thought about the immediate consequences of eating these foods. Oxytocin had no effect on reducing cravings in individuals with binge eating disorder.[71]

Effect sizes

319 Moderate to large effect sizes were found in 2 studies in disordered eating population groups.
320 Specifically, oxytocin had moderate (i.e. ≥0.5 to <0.8) and large (i.e. ≥0.8) effect sizes on
321 reducing attentional biases toward negative shape stimuli (d=0.52) and eating-related stimuli in
322 individuals with AN (d=0.81)[61] and on reducing calorie consumption in individuals with BN
323 (d=0.56).[60] The remaining 2 studies found the administration of oxytocin had a small (i.e. 0.20 to
324 <0.5) effect on improving cognitive control of food craving in females when the long-term
325 consequences of eating high calorie foods where thought of (d=0.15)[70] and a small effect on
326 reducing approach bias to images of palatable food items65 in individuals with alcohol abuse
327 disorder (d=0.21).

328 **Discussion**

329 This review evaluated food intake and eating behaviour characteristics in relation to endogenous
330 and exogenous oxytocin. The number of studies identified in each area was modest. The bulk of
331 previously published literature, regarding oxytocin and nutritional behaviours in humans, have
332 been narrative reviews as opposed to experimental or observational studies.[76] In this review the
333 majority of studies were intervention studies (n=22), with many using an experimental within-
334 subject crossover design (n=19). The remaining studies (n=4) were cross-sectional. Notably, all
335 the exogenous intervention studies were published after 2005. In comparison, six endogenous
336 studies were published before this time. This may be reflective of the gaining interest in oxytocin
337 in general,[29] and also as a possible treatment for nutritional-related behaviours and disorders.
338 This pattern parallels substance addiction research, whereby oxytocin is now being explored as a
339 new treatment for drug and alcohol addiction.[4,77] Overall, the majority of included studies
340 comprised small sample sizes of participants aged 45 years or less, predominantly female, and
341 more than half of the studies were conducted in populations with co-morbidities. This limits the

generalisability of findings to broader populations. With respect to the primary objectives of this review we found that in general endogenous oxytocin levels in non-clinical samples were mostly unaltered by dietary intake patterns or behaviours (neutral effect), while in contrast in clinical samples significant alterations (increases and decreases) were found. Overall, exogenous oxytocin had a positive effect in non-clinical samples by reducing indices of food intake. In clinical samples positive improvements in eating attitudes were found.

Of the dietary intervention studies assessing endogenous oxytocin (n=9), the intake of a fat-rich meal increased plasma oxytocin levels, whereas no changes in oxytocin levels were observed following the intake of alcohol, low and high sodium diets, or short-term fasting. One cross-sectional study found there was no association between the intake of alcohol, caffeine or calcium and endogenous plasma oxytocin levels in healthy individuals. In contrast, in females with T1DM, alcohol use was negatively associated with plasma oxytocin levels, and caffeine intake and calcium supplement use was positively associated. Mean baseline oxytocin levels in females with T1DM were found to be lower when compared to healthy controls. This highlights the complexity of dietary intakes, which comprise multiple nutrients, and possible influences on neuropeptides within the different population groups found in this review.

Several of the included endogenous studies (n=3) suggest that the oxytocin system becomes dysregulated in AN resulting in lower peripheral and CSF levels, and increased post-prandial oxytocin levels. This is consistent with findings from a recent meta-analysis of four studies that reported levels of endogenous oxytocin were significantly lower in AN relative to normal weight controls.[37] There is some evidence to suggest that over the course of recovery from AN the oxytocin system returns to normal levels. However, this remains inconclusive, with one study in this review finding oxytocin levels to be lower in weight recovered AN than active AN. It is not

known whether the changes in oxytocin levels are a consequence of aberrant eating behaviours or malnutrition, or if the existence of premorbid traits increases an individual's vulnerability to developing eating disorders.[66,78] Interestingly, the current review found plasma oxytocin levels in BN were similar to healthy controls. Abstinence from binge eating and purging in this population had no effect on oxytocin levels. In this review obese individuals with and without food addiction displayed similar levels of plasma oxytocin (n=1 study). However, the study sample was predominantly female and it is unknown if blood collections were standardised for menstrual cycle phase. It has previously been reported, obese individuals have significantly lower serum oxytocin concentrations than normal-weight individuals.[79] To further examine the influence of food addiction on oxytocin outcomes future studies would benefit from the inclusion of both healthy weight and overweight/obese groups.

The current review found a single-dose (40IU) of exogenously administered oxytocin exerted a favourable effect on reducing biases to food stimuli (n=2) in individuals with AN, and individuals with alcohol use disorder. However, oxytocin did not have a significant effect on alcohol cravings (n=1). A single-dose (24IU) of oxytocin was also found to improve cognitive control of food cravings in a sample of healthy normal-weight females. In contrast, the chronic administration (24IU 4x/day) of oxytocin in individuals with BED had no effect on cravings or binge-eating episodes. There was little evidence to support the use of exogenous oxytocin in modulating satiety (the sensation of fullness). Four studies reported oxytocin had no effect on satiety outcomes. Unexpectedly, one study found oxytocin (40IU) reduced instead of increased the sensation of satiety. However, it should be noted that some of the dietary assessment measures (e.g. VAS, surveys) used in these studies may be associated with self-reporting bias.

Exogenous oxytocin produced positive changes in food intake behaviour in healthy individuals, and females with BN. A single-dose (24IU) of oxytocin reduced hunger-driven food intake, without affecting subjective appetite, in overweight/obese males. However, of the two studies including normal-weight males, only one found a reduction in hunger-driven food intake. Correspondingly, oxytocin has been found to have a more pronounced anorexigenic effect in diet-induced obese rats compared to control rats.[80] Irrespective of weight status, the current review found oxytocin significantly decreased high-sugar snack consumption in human males. These findings are consistent with animal studies,[81-83] suggesting that the effects of oxytocin to limit consumption of sugar may extend to humans. At this time the exact biological mechanisms of oxytocin remain unknown. However, exogenous oxytocin delivery may act to improve glucose tolerance through actions in the periphery, for example in the pancreas or via fat metabolism. While exogenous oxytocin does have limitations for direct use in humans, such as a short half-life (approximately 1-6 min)[29,48] and possible off-target effects[35] (e.g. anti-social behaviours such as increased aggression,[84] decreased trust and co-operation[85]), overall the studies in this review reported no adverse side effects.

The majority of the included studies (n=17) investigated only 1 aspect of dietary intake (e.g. calorie intake, alcohol intake), and the dietary assessment tools used were not specified for most. The included studies represent a wide variety of study designs, and for this reason a wide variety of dietary assessment tools were used and, subsequently, a range of dietary outcomes reported. It is acknowledged that different dietary assessment tools are appropriate and useful in different research settings (i.e. epidemiological research, clinical settings, and laboratory-based experiments). The choice of dietary assessment tool is dependent on numerous factors, including the outcome of interest (energy intake, food groups, amount of food), population group, budget, time, and both participant and researcher burden. In a number of the dietary

411 intervention studies (n=6), the applied intervention doses exceeded national nutritional
412 recommendations. For instance, 4 studies provided an intervention dose of alcohol exceeding
413 the current recommendation of 2 standard drinks (20 g of alcohol) per day.[87] One study exposed
414 participants to a short-term high sodium diet. The intervention diet containing 5290mg of
415 sodium per day, exceeded the suggested dietary target (1600mg/day) by 230%.[88] Prescribing
416 participants a high level intervention dose limits the generalisability, translation and clinical
417 significance of findings. This does not allow for experimental replication in longer term feeding
418 trials.

419 Plasma oxytocin values varied markedly across studies which is likely due to the various analysis
420 techniques used. Szeto et al.[48] reported that sample extraction is necessary to obtain valid assay
421 results, as without extraction plasma oxytocin levels by enzyme immunoassay can be > 100-fold
422 higher than the same extracted sample, and radioimmunoassay of unextracted plasma can have
423 values that are 10-fold higher than the extracted sample. A gold standard methodology for
424 oxytocin measurement may facilitate further research in this area and may help resolve existing
425 controversies.[48,49]

426 In animal models oxytocin levels can be measured and manipulated through a number of
427 experimental approaches[88] not possible in humans. For example, the effects on eating
428 behaviour after the targeted delivery of synthetic oxytocin, receptor antagonists or in genetic
429 animals involving knockdown or overexpression of oxytocin genes or receptors can be
430 assessed.[37] Because these approaches involve invasive procedures they are generally not
431 feasible in humans and researchers in human studies often rely on peripheral oxytocin
432 measurements, such as plasma or saliva, as proxy measures.[37] Further work is required to
433 determine whether circulating blood levels of oxytocin is an accurate measurement of central

nervous system (CNS) release and activity. Findings from a recent meta-analysis of human and animal studies (n=17) [90] indicate the use of peripheral oxytocin levels to estimate CNS levels under basal conditions must be interpreted with caution. This may be due to variability in the sensitivity of the current immunoassays available. Notably, a positive association between central and peripheral concentrations after the intranasal administration of oxytocin was found ($r=0.66$, $p < 0.0001$).[90] Further, it has been reported that intranasal-delivery of oxytocin has the ability to enter the brain via uptake through the olfactory and/or trigeminal nerves in the nasal epithelium.[65,91,92] Peripheral measurements remain informative as oxytocin released in the circulation from the pituitary gland would have effects on oxytocin receptors in peripheral tissues and potentially produce central effects via the vagus nerve.

A number of recommendations for future research to further understand the complex interrelationship between diet and oxytocin arise from this review. First, given how complex dietary intakes can be and the substantial variation that can occur in day-to-day intake, where possible (dependent on factors such as study design and outcome of interest) population-specific validated tools, such as food frequency questionnaires, or standardized measures, such as multiple-pass 24-hour recall, should be used to comprehensively and accurately capture usual dietary intakes. These tools will be valuable to provide a more holistic approach when evaluating the possible range of effects of exogenous oxytocin on dietary intake and assessing correlations between endogenous oxytocin levels and specific nutrients or aspects of food intake. Importantly, the use of validated dietary assessment tools will allow for reproducibility in subsequent trials and translation. The use of standardized reporting guidelines, such as Strengthening the Reporting of Observational Studies in Nutritional Epidemiology (STROBE-nut),[92] may assist in improving the reporting of methods used for the assessment of dietary

intake. Consideration should also be given to dietary intervention dosages. Applications of dosages comparable with recommended intakes of nutrients or amounts commonly consumed by populations will make results more generalizable. Second, the findings of this review point to the need for longer-term intervention studies in larger sample sizes to evaluate the relationship between nutrients or foods with changes in oxytocin concentrations over time. Studies evaluating the longer-term effects of exogenous oxytocin on dietary intake patterns and consequent alterations in eating behaviours are also needed to extend the current findings. Additionally, clinical studies will benefit from measuring endogenous oxytocin levels in conjunction with oxytocin administration to determine how endogenous oxytocin levels respond. Third, standardising the menstrual cycle phase in which female participants are tested will minimise possible confounding effects due to hormonal variations.

This review was limited to studies published in English, contributions of literature outside of these parameters may have been missed. The limitations of this paper relate primarily to the quality of evidence that is presently available. The sample size of most studies was small, and the majority of studies were performed in younger adult population groups. The majority of participants in the identified studies were female, which makes it unclear whether the relationships observed in the current review will generalise to male participants. Fasting times and menstrual phase were not always reported and accounted for in the study design which may potentially influence the findings. Finally, the pronounced heterogeneity in study designs hinders cross-study comparisons. Given these limitations and the small number of studies currently available for these outcomes, it is important to view these results with caution.

This is the first systematic review to investigate oxytocin in relation to dietary intakes and behaviours. A strength of this paper is its rigorous systematic methodology. The search strategy

480 was developed in consultation with an experienced research librarian, and the screening process
481 included three independent reviewers who came to consensus on all included studies. Quality of
482 the evidence was assessed using a standardised tool. Finally, the paper was prospectively
483 registered with PROSPERO.

484 **Conclusion**

485 Evidence to pursue investigations into the role of oxytocin in dietary behaviours is accumulating.
486 Currently, this analysis supports a role for exogenous oxytocin delivery in the negative regulation
487 of food intake. Although the exact mechanisms are yet to be determined, exogenous oxytocin
488 may have positive effects on dietary behaviours via periphery actions involved in metabolism. It
489 is also possible that oxytocin may feedback to central sites involved with reward and energy
490 expenditure. At this time, it is unclear if lower basal levels of oxytocin observed in individuals
491 with clinical co-morbidities, such as diabetes mellitus or disordered eating (e.g. AN and BN) are
492 caused by dysregulation of oxytocin pathways. To further examine dietary effects on
493 endogenous oxytocin more comprehensive investigations of dietary intakes, using validated
494 assessment tools, in larger sample sizes is required. In addition, longer-term feeding trials with
495 consideration given to intervention dosages of nutrients that are more aligned with population
496 consumption levels will be of importance. Studies seeking to further understand the
497 neurobiological basis for oxytocin induced suppression of food intake would also seem
498 warranted.

499 **Author Contributions**

500 JS and TB developed review premise. JS and TB reviewed all identified abstracts, and JS and TB
501 reviewed all identified articles in consultation with CD. JS extracted data from articles and TB
502 checked data. JS and SF appraised study quality of included articles in consultation with TB. JS

developed initial draft of paper, and TB, MG and CD contributed to and approved the final version of the manuscript.

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760 **Table 1.** PICO criteria for studies assessing the effect of a) dietary intakes/behaviours on
761 endogenous oxytocin, and studies assessing the effect of b) exogenous oxytocin on dietary
762 intakes/behaviours

	a) Endogenous oxytocin	**b) Exogenous oxytocin**
Population	Adults with or without clinical characteristics, or a population sample in which the majority of individuals are over the age of 18	Adults with or without clinical characteristics, or a population sample in which the majority of individuals are over the age of 18
Intervention	Dietary intake (i.e. food or nutrient) and/or behaviour (e.g. disordered models of eating such as anorexia nervosa, binge eating; meal consumption patterns)	Exogenous oxytocin administration
Comparators	No comparator or high vs low dietary intakes or healthy control group	No treatment
Outcomes	Effect on endogenous oxytocin (e.g. cerebrospinal fluid blood, plasma, urine or saliva) concentrations	Effect on dietary intake or behaviours, including behavioural responses associated with eating (e.g. craving, satiety and appetite); behavioural models of eating (e.g. anorexia nervosa, binge eating); patterns or time intervals of eating (e.g. fasting)
Setting	All settings (observational or experimental study designs)	All settings (experimental study designs)

763

Figure 1. Flow diagram of article identification retrieval and inclusion for the systematic review

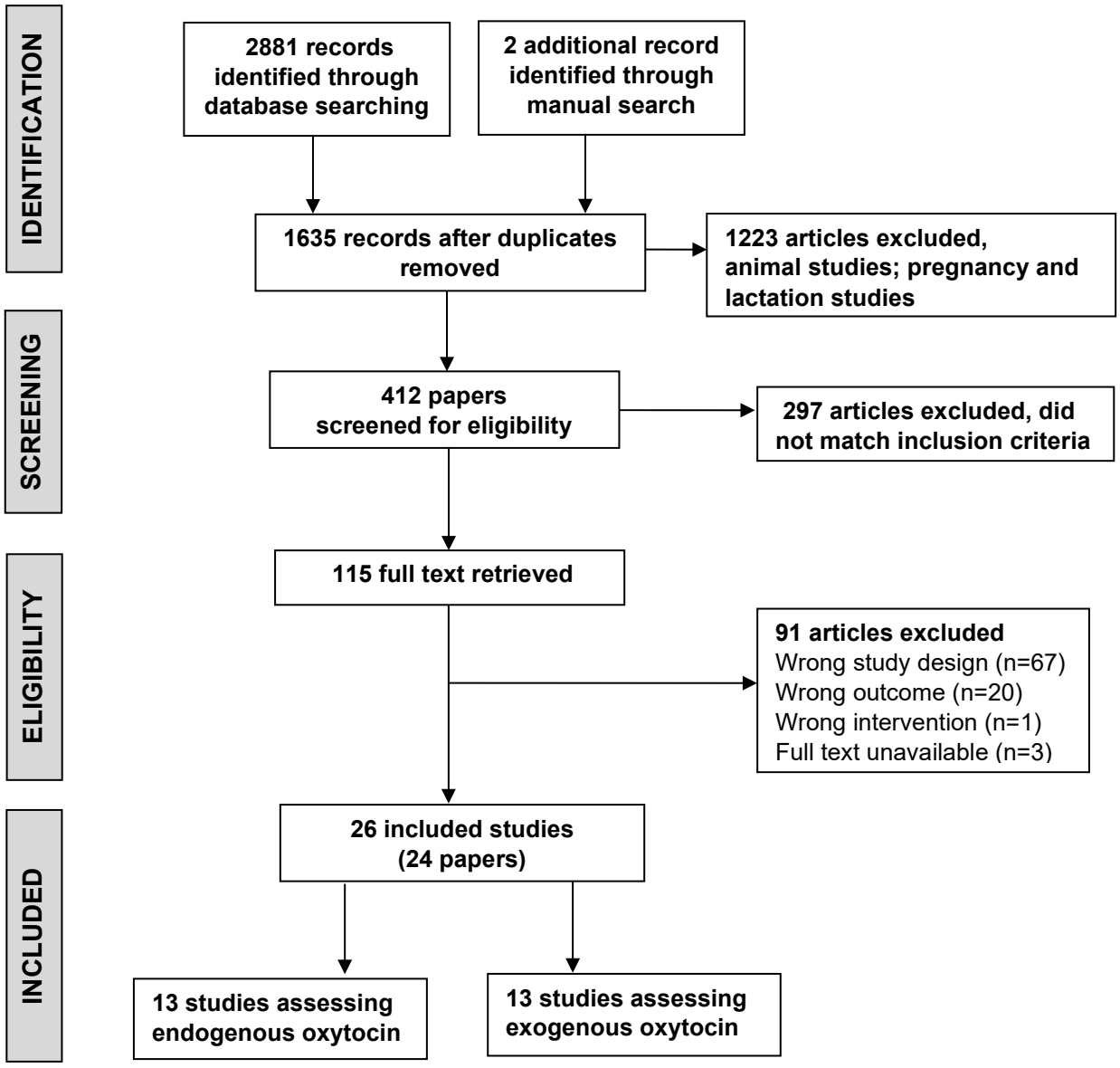

Table 2. Description of included endogenous and exogenous oxytocin studies

Author (year)	Study design	Country	n	Age	Gender	Dietary exposure/intake/behaviour measure	Oxytocin measure
ENDOGENOUS OXYTOCIN							
Bershad et al.[52] (2015)	Experimental crossover study	USA	8 healthy	25.5±3.3 yrs	100% M	Alcoholic (dose=0.8g/kg alcohol in 16% solution with cranberry juice + 1% alcohol) vs placebo (cranberry juice + 1% alcohol) beverage. BAC measured using Alco-sensor III at time points 1-6. Usual intake of alcohol and caffeine measured, method/validation unclear.	Plasma OT measured (enzyme immunoassay) at 6 time points: 1) 15 min prior to placebo, 2) following placebo (i.e. 30 min from baseline), and 3) 60 min from baseline; 4) following alcohol intake (i.e. 1 hour after placebo intake), 5) 30min after alcohol intake, and 6) 60 min after alcohol intake. Fasting not specified.
Coiro et al.[57] (1991)	Experimental crossover study	Italy	24 healthy	23-33 yrs	100% M	50ml ethanol in 110ml of whisky administered 45 min before insulin-induced hypoglycaemic state [i.e. insulin tolerance test (ITT)]. BAC measured after alcohol administration using gas chromatography. Blood glucose measured 15, 30, 45 and 60 post-ITT to determine hypoglycaemic nadir. Usual dietary intake not assessed.	Plasma OT measured (radioimmunoassay of extracted serum) before (-45, -30, -15 and 0 min), and after (15, 30, 45 and 60 min) ITT in 4 treatment conditions (weekly intervals): 1) Control ITT = IV bolus 0.15IU/kg Actrapid insulin), 2) Ethanol + ITT, 3) Naloxone (groups 1, 2 and 3 received different concentrations) + ITT, 4) Ethanol + naloxone + ITT. Additional experiment: Ethanol + naloxone in the absence of insulin. Overnight fasting prior.
Coiro et al.[56] (1992)	Experimental crossover study	Italy	16 healthy	24-32 yrs	100% F	50ml ethanol in 110ml of whisky, administered 45 min before breast stimulation. Compliance not specified. Usual dietary intake not assessed.	Plasma OT measured (radioimmunoassay of extracted serum), before, immediately after, and 15, 30 and 45 min after alcoholic beverage intake. Subjects underwent breast stimulation (for 10 min) 45mins after alcohol administration. OT measured every 2 min for 16 min during breast stimulation. Four treatment conditions assessed (22nd day of consecutive menstrual cycles): 1) Control breast stimulation test (mechanical pump), 2) Ethanol + breast stimulation test, 3) Naloxone (divided into 2 groups of 8, groups 1 and 2 received different OT concentrations) + breast stimulation test, 4) Ethanol + naloxone (groups 1 and 2 received different concentrations) + breast stimulation. Overnight fast prior to study.
Dolder et al. (2016)[59]	Experimental crossover study	Germany	60 healthy	25±4 yrs (range 18-43)	50% F	Alcoholic (dose = low-to-moderate alcoholic beer to achieve BAC of 0.4g/L = ~0.24g/kg women, ~0.29g/kg men) vs non-alcoholic beer (placebo). BAC measured using enzymatic method at baseline and 30, 70 and 95 min after beer administration (alcoholic and non-alcoholic). Intake of alcohol measured; method/validation unclear.	Plasma OT measured (radio immunoassay of extracted serum) in placebo and alcohol condition (≥24 hrs apart) at baseline and 30, 70 and 95 min after non-alcoholic/alcoholic beer administration. Fasting 3h prior. Menstrual cycle phase not specified.

Author (year)	Study design	Country	n	Age	Gender	Dietary exposure/intake/behaviour measure	Oxytocin measure
Mennella et al. (2006)[64]	Experimental crossover study	USA	8 healthy	25.0±1.2 yrs	100% F	Alcoholic [0.4g/kg alcohol dose in orange juice (15%vol/vol)] vs placebo beverage (orange juice + 1% alcohol). BAC estimated using Alco-sensor III following alcohol/placebo administration. Usual intake of alcohol measured; method/validation unclear.	Plasma OT measured (radioimmunoassay of extracted serum) in placebo and alcohol condition [1 week (± 3 days) apart] at -40, -25, and -10 min before, and 35 min after alcohol/ placebo beverage intake, during follicular phase of menstrual cycle. Subjects underwent breast stimulation (for 16 min) 35 min after alcohol administration. OT measured every 2 min during stimulation, and every 15 min for 90 min after stimulation. Overnight fast prior.
Kujath et al. (2015)[62]	Cross-sectional study with non-diabetic matched controls	USA	162 (88 T1DM, 74 controls)	T1DM: 27.9±6.8 yrs; control: 28.4±8.2 yrs	100% F	Caffeine, alcohol and calcium (dietary and supplement) intake measured via semi-quantitative FFQ (Willett 1985), 61-item validated measure.	Plasma OT measured (enzyme immunoassay) during luteal phase of menstrual cycle (days 20–24). Blood drawn without regard to fasting or time of day.
Ohlsson et al. (2002)[68]	Non-randomised intervention study	Sweden	14 (8 healthy, 6 constipated)	Healthy: mean 37 yrs (range 28-40); constipated: mean 42 yrs (range 24-63)	100% F	Fat-rich test meal containing 300mL emulsified corn oil. Macro-nutrient analysis of meal not reported. Compliance not specified. Usual dietary intake not assessed.	Plasma OT levels measured (radioimmunoassay of extracted serum) at -10 min, baseline (pre-meal), and 10, 20, 30, 45 and 60 min (post meal). Overnight fast prior. Menstrual cycle phase not specified.
Rasmussen et al. (2004)[69]	Experimental crossover study	Denmark	8 healthy	21-26 yrs	100% M	Low (30mmol NaCl/day) vs high (230mmol NaCl/day) sodium diet for 4 days. Dietary compliance: sodium turnover verified by measuring 24-h urinary sodium excretion. Usual dietary intake not assessed.	Plasma OT measured (radioimmunoassay of extracted serum) after following 4-day low sodium diet on 2 separate occasions (LS1 and LS2; ≥14 days apart); and after following 4-day high sodium diet on 2 separate occasions (HS1 and HS2; ≥14 days apart). Fasting 3h prior.
Challinor et al. (1994)[55]	Experimental crossover study	USA	4 healthy	18-35 yrs	100% M	Fed vs fasted state. Subjects supplied breakfast (0800-0900 hrs) and lunch (1200-1300 hrs) on day 1. Fed state = Day 1, 900-1600 h; Fasted state = Day 2, 900-1600 h. Dietary intake in fed state not reported.	Plasma OT assessed on 2 consecutive days (radioimmunoassay of extracted serum). Blood drawn every 10 min from 0900 (day 1) -1600 hrs (day 2) = total of 186 blood draws. Fasting occurred from 1300h on day 1, to study completion, 1600h on day 2.
Monteleone et al. (2016)[66]	Cross-sectional study	Italy	69 (23 AN, 27 BN, 9 controls)	AN: 26.9±9.7 yrs; BN: 29.0±11.2 yrs; control: 27.2±5.7 yrs	100% F	Eating disorders measured via SCID-5-RV (patient and non-patient versions) delivered by trained interviewer. Usual dietary intake not assessed.	Plasma OT measured (enzyme immunoassay) after overnight fast. Eumenorrheic subjects tested on day 7 of menstrual cycle.
Demitrack et al. (1990)[58]	Quasi-experimental study (cross-sectional study)	USA	60 (14 AN, 35 BN, 11 controls)	AN: 24.3±5.2 yrs; BN: 24.4±4.4 yrs; control: 25.5±4.3 yrs (range 16-35)	100% F	AN subjects: met DSM-III-R criteria [restrictive AN (no history of binge-eating and vomiting), bulimic AN (binge-eating and vomiting) or chronic vomiting AN (without binge-eating)]; BN subjects: met DSM-III-R criteria; Control group free from medical or psychiatric illness (assessment methods not reported). Usual dietary intake not assessed.	OT levels in CSF measured (radioimmunoassay). AN subjects assessed during underweight, refeeding and short-term recovery (3 weeks of maintaining mean goal weight = 84.7±2.0% of average body weight) phases. BN subjects assessed before and after abstinence from binge-eating and vomiting. Control group assessed

Author (year)	Study design	Country	n	Age	Gender	Dietary exposure/intake/behaviour measure	Oxytocin measure
							during day 1-7 of menstrual cycle (early follicular phase). Overnight fast prior.
Lawson et al. (2013)[63]	Non-randomised intervention study	USA	35 (13 AN, 9 ANWR, 13 controls)	22.2±0.4 yrs	100% F	Eating disorders measured via SCID. Test meal: 400kcal mixed breakfast meal standardised for nutrient content (~20% protein, 20% fat, 60% CHO) provided. Meal weighed on completion to determine caloric intake. Usual dietary intake not assessed.	Plasma OT levels measured (radioimmunoassay of extracted serum) at baseline (pre-meal), and 30, 60, and 120 min post meal. ANWR and control group studied during follicular phase of menstrual cycle. Fasting 12h prior.
Pedram et al. (2015)[42]	Cross-sectional study with non-food addicted matched controls	Canada	58 (29 obese FA, 29 obese controls)*	FA: 42.5±9.4 yrs; control: 42.0±8.9 yrs	83% F	Food addiction measured via YFAS (27-item tool). Macro- and micro-nutrient intake over past 12 mths measured via 61-item semi-quantitative FFQ (Willett 1985).	Plasma OT measured (magnetic bead-based immunoassay). Overnight fast prior. Menstrual cycle phase not specified.
EXOGENOUS OXYTOCIN							
Mitchell et al. (2016)[65]	Experimental crossover study	USA	32 nontreatment-seeking with alcohol abuse	28.9±7.2 yrs (range 22-50)	41% F	Craving assessed using alcohol cue exposure paradigm (3 stimuli: empty glass, glass of water, and alcoholic beverage of choice). Stimulus craving assessed via 8-item AUQ. Approach avoidance task [4 picture categories: alcohol (e.g. bottle of wine), appetitive food images (e.g. canned fruit), general positive and general negative]. Approach bias = reaction times to each image (difference in push/pull of joystick). Usual dietary intake not assessed.	Intranasal 40IU OT vs placebo. Testing 30 min post-administration. Total testing time = 90 min. Fasting not specified. Plasma OT not measured. Menstrual cycle phase not specified.
Striepens et al. (2016)[70]	Experimental crossover study	Germany	31 healthy	25.4±4.4 yrs	100% F	Food craving fMRI task: viewing of candy and dessert images in two trials (30 images per trial): 1) "NOW" trials, subjects instructed to imagine immediate consequence of consuming pictured food, and 2) "LATER" trials, subjects instructed to think about long-term consequences and cognitively control urge to eat the food. After each image craving for displayed food measured via VAS. Usual dietary intake not assessed.	Intranasal 24IU OT vs placebo (≥2 days apart). fMRI task 45 min post-administration. OT in saliva measured before and after experiment (commercial sampling device). Women not using hormonal contraception (n=16) tested during follicular or luteal phase of menstrual cycle (validated by blood assays).Fasting not specified.
Borg et al. (2011)[54]	Study 1: Experimental crossover study	Sweden	10 healthy	42.9±15.8 yrs	60% F	Liquid meal: 13% protein, 48% carbs, 39% fat, 1.5 kcal ml^{-1}. Compliance not specified. Satiety levels measured via VAS before, immediately following, and 30 min after meal intake. Usual dietary intake not assessed.	Infusion of OT (20, 40, and 80mU min^{-1}) vs placebo (saline). Infusions started as meal intake began. Terminated when meal ended. Overnight fast prior. Plasma OT not measured. Menstrual cycle phase not specified.
Borg et al. (2011)[54]	Study 2: Experimental crossover study	Sweden	12 healthy	42.6±14.1 yrs	58% F	Test meal: porridge, glass of oatmeal drink and cheese sandwich (400kcal, 14% protein, 58% carbs, 27% fat) Compliance not specified. Satiety measured following meal via VAS hourly for 8h. Usual dietary intake not assessed.	Infusion of OT (20, 80 and 160mU min^{-1}) vs placebo (saline). Infusions started as meal intake began. Terminated when meal ended. Overnight fast prior. Plasma OT measured (enzyme immunoassay): baseline (before meal and

Author (year)	Study design	Country	n	Age	Gender	Dietary exposure/intake/behaviour measure	Oxytocin measure
							infusions), 30, 60, 120 and min after meal and at 8h. Menstrual cycle phase not specified.
Borg et al. (2012)[53]	Study 1: Experimental crossover study	Sweden	14 functional dyspepsia	Median 37.5 yrs (range 24.0-44.5)	86% F	Test meal: egg on toast and 100mL water. Compliance not specified. Satiety measured via VAS start of meal, and 30 and 70 min after. Usual dietary intake not assessed.	70 min infusion of OT (40, and 80mU min^{-1}) vs placebo (saline) ≥2 days apart. Infusions started as meal intake began. Overnight fast prior. Plasma OT not measured. Menstrual cycle phase not specified.
Borg et al. (2012)[53]	Study 2: Experimental crossover study	Sweden	12 diabetics with gastroparesis	Median 56.5 yrs (range 52.0-64.8)	83% F	Liquid meal: 13% protein, 48% carbs, 39% fat, 1.5 kcal ml^{-1}. Volume intake of meal recorded. Satiety measured via VAS start of meal and at 5-min intervals until maximum volume intake reached; and 30 min after end of meal. Usual dietary intake not assessed.	Infusion of OT (40mU min^{-1}) vs placebo (saline) ≥2 days apart. Infusions started as meal intake began. Terminated when meal ended. Overnight fast prior. Plasma OT not measured. Menstrual cycle phase not specified.
Ohlsson et al. (2006)[67]	Experimental crossover study	Sweden	10 healthy	40 ± 16 yrs (range 25-62)	50% F	Test meal: 300g rice pudding (1386kJ, 10% protein, 58% carbs, 32% fat). Compliance not specified. Satiety measured following meal via VAS 15 and 90 min post-meal. Usual dietary intake not assessed.	90 min infusion of OT (40mU min^{-1}) vs OT receptor antagonist (Atosiban) vs placebo (saline) ≥2 days apart. Fasting 8h prior. Plasma OT not measured. Menstrual cycle phase not specified.
Lawson et al. (2015)[44]	Experimental crossover study	USA	25 (13 normal-weight, 12 overweight/ obese)*	27.1±1.5 yrs	100% M	60min after OT/placebo administration. subjects given double portions of breakfast self-selected from menu, with 30 min to eat. Total calories, fat, CHO and protein consumed measured. Nutrient analysis methods not specified. Appetite measured before and 55min after OT/placebo administration via VAS. 72h food intake prior to test recorded via self-report food diary. Nutrient intake calculated by dietitian.	Intranasal 24IU OT vs placebo (1-8 weeks apart). Fasting 12h prior. Treatment effect of oxytocin on fasting levels of plasma OT measured (enzyme-linked immunosorbent assay of unextracted serum).
Ott et al. (2013)[43]	Experimental crossover study	Germany	20 normal-weight*	26.3±0.9 yrs	100% M	45 min after OT/placebo administration: subjects presented with free-choice ad libitum breakfast buffet, with 30 min to eat. Buffet included: bread and rolls, spreads (e.g. jam, honey), sausages, cheeses, fruits, puddings, milk and juice (total energy = 4562 kcal). Buffet components weighed before and after breakfast. 100 min after buffet: subjects presented with 3 snacks (sweet, bland, and salty; comparable in energy and macronutrient composition). Snack intake measured by weighing snacks before and after test. Snacks rated for taste via VAS (very palatable/sweet/salty). Hunger and thirst measured via VAS ~1h prior and 30 min after OT/placebo administration; 30 min prior to snack test. Usual dietary intake not assessed.	Intranasal 24IU OT vs placebo (≥10 days apart). Fasting 12h prior. Plasma OT not measured.

Author (year)	Study design	Country	n	Age	Gender	Dietary exposure/intake/behaviour measure	Oxytocin measure
Thienel et al. (2016)[45]	Experimental crossover study	Germany	38 (18 obese, and 20 normal-weight)* [normal-weight sample previously described by Ott et al (2013)]	Obese: 27.8±1.2 yrs; normal-weight: 26.3±0.9 yrs	100% M	[Experimental set-up identical to Ott et al (2013)]. Baseline: dietary restraint and tendency toward disinhibition assessed (obese subjects only) via DEBQ-R and TFEQ. Propensity to consume palatable foods measured via PFS in OT/placebo condition (all subjects). Usual dietary intake not assessed.	Intranasal 24IU OT vs placebo (≥10 days apart). Fasting 12h prior. Plasma OT not measured.
Kim et al. (2015)[60]	Experimental crossover study	South Korea	102 (35 AN, 34 BN, 33 controls)	AN: 22.0±8.4 yrs; BN: 23.1±5.2 yrs; control: 22.6±2.3 yrs	100% F	Eating disorders measured via EDE-Q (36-item tool). Quantity of 190ml carton of apple juice consumed, 90 min after OT/placebo administration, recorded. Post 24h energy intake recorded in self-report smartphone food diary (app not specified). AN and BN subjects provided with fixed portion meals plans during experimental period. Post OT/placebo administration: AN subjects received no direct support for eating; BN subjects given meal routine to prevent binge-purging; and controls continued usual eating habits. Usual dietary intake not assessed.	Intranasal 40IU OT vs placebo (4-7 days apart). Fasting 2h prior. Eumenorrheic BN and healthy controls tested during follicular phase of menstrual cycle (days 3-12). Plasma OT not measured.
Kim et al. (2014)[61]	Experimental crossover study	South Korea	64 (31 AN, 33 healthy controls)	16-45 yrs	100% F	Eating disorders measured via EDE-Q (36-item tool). Quantity of 190ml carton of apple juice consumed, following neuropsychological tasks, recorded. Attentional biases for eating, weight and shape stimuli measured via modified dot probe task using targeted (eating/weight/shape stimuli) and non-targeted images (animal). Images classified as positive (e.g. low calorie food), neutral or negative (e.g. high calorie food) stimuli. Usual dietary intake not assessed.	Intranasal 40IU OT vs placebo (4-7 days apart). Controls tested during follicular phase of menstrual cycle (all AN subjects amenorrheic). Fasting 2h prior. Plasma OT not measured.
Agabio et al. (2016)[71]	RCT	Italy	16 obese* with BED	Intervention group: 49.8±10.2; control: 47.5±4.5	100% F	BED: met DSM-V criteria. Subjects received energy restricted (-200 kcal/day of REE; CHO:Fat:Protein = 55:25:20) diet plan. Subjects assessed 1, 4 and 8 weeks. BED severity measured via CGI-S; self-report food diary and binge episodes recorded for duration of 8-week intervention. Food cravings measured via VAS pre- and post- intervention. Dietary intake prior to intervention not assessed.	96IU/day (24IU 4x/day = 20 min before 3 meals, before bed). Plasma OT not measured. Menstrual cycle phase not specified.

* Weight categories [Body Mass Index (BMI)]: normal-weight = 18.50 – 24.99 kg/m^2, overweight = 25.00 – 29.99 kg/m^2, obese = >30 kg/m^2. BAC, Blood Alcohol Concentration; OT, oxytocin; T1DM, Type 1 Diabetes Mellitus; FFQ, Food Frequency Questionnaire; NaCl, Sodium chloride; AN, Anorexia Nervosa; BN, Bulimia Nervosa; SCID-5-RV, Structured Clinical Interview for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) Disorders-Research Version; DSM-III-R, Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised; ANWR, Anorexia Nervosa weight recovered ; SCID, Structured Clinical Interview for DSM (Diagnostic and Statistical Manual of Mental Disorders) Disorders-IV; CHO, carbohydrate; FA, Food addicted; YFAS, Yale Food Addiction Scale; AUQ, Alcohol Urge Questionnaire; fMRI, Functional magnetic resonance

imaging; VAS, Visual Analogue Scale; DEBQ-R, Dutch Eating Behaviour Questionnaire; TFEQ, Three Factor Eating Questionnaire; PFS, Power of Food Scale; EDE-Q, Eating Disorder Examination Questionnaire; BED, Binge Eating Disorder; DSM-V, Diagnostic and Statistical Manual of Mental Disorders , Fifth Edition; CGI-S, Clinical Global Impression Severity scale.

Table 3. Outcomes of included endogenous oxytocin studies

Dietary characteristic	**Author (year)**	**Dietary outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Oxytocin outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Relationship between diet and oxytocin**	**Effect*** [Increased/ Decreased/ Neutral]
Alcohol	Bershad et al. (2015)[52]	AUC change in BAC from baseline: placebo = 0.0 (0.0), alcohol = 0.09 (0.01). Usual intake of alcohol =17.1±8.1 alcoholic drinks/week and 2.1±0.6 servings caffeine/day.	Plasma OT at baseline (as estimated by the graph) = ~21 pg/mL. AUC change in plasma OT from baseline: placebo =0.3 (0.6), alcohol = -1.4 (0.5)	Mean AUC change in BAC alcohol vs placebo: $F_{(1,7)}$=190.44, p<0.001. Mean AUC change in plasma OT alcohol vs placebo: $F_{(1,7)}$=1.581, p=0.255. Alcoholic beverage did not alter plasma OT levels in healthy males (p value not reported; interrupted from graph).	Neutral
Alcohol	Coiro et al. (1991)[57]	BAC (mg/100mL) at time 0 min (i.e. ITT administration) =79.1±4.6; 15 min =73.0±3.6; 30 min =68.2±3.4; 45 min =62.7±3.7; and 60 min =57.0±4.0. Hypoglycaemic nadir reached 30min after insulin injection, similar for all groups.	Plasma OT levels for tests: 1) control insulin tolerance test (ITT), 2) ITT + ethanol, 3) ITT + naloxone, and 4) ITT + ethanol + naloxone, displayed on graph. Mean ± SD plasma OT levels (pg/mL) during ethanol + naloxone test: -45 min =2.3±0.2; -30 min =2.4±0.3; -15min =2.3±0.2; 0 min =2.4±0.3; + 15 min =2.3±0.2; +30 min =2.5±0.2; +45 min =2.4±0.2; and + 60 min =2.3±0.2.	Insulin-induced hypoglycaemia ↑ plasma OT 2.2-fold with maximum peak at 45 min. Administration of ethanol did not modify basal plasma OT before ITT (interpreted from graph). OT response to insulin-induced hypoglycaemia inhibited by alcohol (ethanol + ITT vs control ITT, p<0.001). In ITT + ethanol + naloxone test, ethanol inhibitory effect in response to hypoglycaemia only partial. No significant difference in OT levels during ethanol + naloxone (absence of insulin) test.	Neutral
Alcohol	Coiro et al. (1992)[56]	Dietary compliance not specified.	Plasma OT levels displayed on graph. Breast stimulation significantly ↑ OT (p<0.01). Following stimulation OT levels rapidly decreased to baseline. Alcohol inhibited OT response to breast stimulation (F=27.38, p<0.001). Naloxone did not change OT response to breast stimulation. In ethanol + naloxone + breast stimulation test, ethanol inhibitory effect in response to breast stimulation only partial.	Alcohol did not alter plasma OT levels (prior to breast stimulation) in healthy females (interpreted from graph).	Neutral
Alcohol	Dolder et al. (2016)[59]	Beer intake: 497±133 ml (range 288 - 900ml). Maximal BAC after non-alcoholic beer intake = <0.1 g/L. Maximal BAC after alcoholic beer intake = 0.38±0.1 g/L (range 0.20-0.63 g/L). Maximal BAC: men = 0.41±0.1 g/L, women = 0.35±0.1 g/L ($T_{1,58}$ =2.61, p<0.05). Usual intake of alcohol =4.5±4 (range 0 to 20) drinks/week (males 6.0±3, range 0 to 20; females 3.0±2, range 1 to 8).	Plasma OT levels displayed on graph. Maximal plasma OT: after alcoholic beer = 7.5±3.8 pg/ml, after non-alcoholic beer = 7.7±4.2 pg/ml ($T_{1,58}$=0.37, p=0.7).	Change in plasma OT alcoholic vs non-alcoholic beer ($F_{(3,177)}$=2.07, p=0.11). Alcoholic beer (dose = BAC of ~0.4g/L) did not alter plasma OT in healthy males and females.	Neutral
Alcohol	Mennella et al. (2006)[64]	BAC peaked at ~36.7±5.4 min after alcoholic beverage intake and decreased thereafter. Peak BAC ranged from 0.35 to 0.73 g/l. Usual intake of	Plasma OT at baseline (as estimated by the graph) = ~21 pg/mL. (No significant difference in baseline plasma OT [$F_{(2,14)}$=0.52; p=0.60] b/t groups.	Prior to breast stimulation, alcohol slightly lowered plasma OT levels (interpreted from graph). Significant decrease in OT following alcohol	Decreased

Dietary characteristic	**Author (year)**	**Dietary outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Oxytocin outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Relationship between diet and oxytocin**	**Effect*** [Increased/ Decreased/ Neutral]
		alcohol =5.8±2.0 (range = 0 to 15 drinks) alcoholic beverages and 2.1±0.5 drinks/occasion (range = 0 to 4 drinks) during the preceding 3 weeks.		consumption to end of breast stimulation (AUC 0-51min; $t_{(7)}$=-2.53, p=0.4) compared to placebo. Non-significant decrease in OT from 0-140mins post-alcohol consumption ($t_{(7)}$=-2.15, p=0.07).	
Alcohol	Kujath et al. (2015)[62]	Quartiles of alcohol intake [g/day]: n (%) – 1st [0 to 1.08]: T1DM =31 (35) vs Control =12 (16); 2nd [1.09 to 3.11]: T1DM =20 (23) vs Control =17 (23); 3rd [3.12 to 8.64]: T1DM =21 (24) vs Control =20 (27); 4th [8.65 to 79.18]: T1DM =16 (18) vs Control =25 (34).	Log transformed plasma OT (pg/mL): T1DM =2.3±0.4, Controls =2.4±0.4 (p=0.17). After controlling for confounding by caffeine and alcohol use, log transformed plasma OT levels significantly lower in T1DM than controls (2.2 vs 2.4, p=0.03).	Alcohol intake (quartiles) negatively associated with OT in T1DM (β= -0.08, p=0.03), not associated in controls, and interaction between alcohol intake and presence of T1DM on OT significant (p=0.008). In T1DM regression model - alcohol intake (β= -0.08, p=0.007).	Decreased (in T1DM subjects only)
Caffeine	Kujath et al. (2015)[62]	Quartiles of caffeine intake [mgs/day]: n (%) – 1st [0 to 33.6]: T1DM =17 (19) vs Control =22 (30); 2nd [33.7 to 94.4]: T1DM =18 (20) vs Control =24 (32); 3rd [94.5 to 171.3]: T1DM =27 (31) vs Control =13 (18); 4th [171.4 to 709.1]: T1DM =26 (30) vs Control =15 (20).	Log transformed plasma OT (pg/mL): T1DM = 2.3±0.4, Controls = 2.4±0.4 (p=0.17). After controlling for confounding by caffeine and alcohol use, log transformed plasma OT levels significantly lower in T1DM than controls (2.2 vs 2.4, p=0.03).	Caffeine consumption (quartiles) positively associated with OT in T1DM (β=0.08, p=0.03), not associated in controls. In T2DM regression model - caffeine intake (β=0.09, p=0.005).	Increased (in T1DM subjects only)
Calcium	Kujath et al. (2015)[62]	Calcium intake: dietary calcium consumption not reported; taking calcium supplement - n (%): T1DM = 38 (43%), Control = 36 (49).	Log transformed plasma OT (pg/mL): T1DM =2.3±0.4, Controls =2.4±0.4 (p=0.17). After controlling for confounding by caffeine and alcohol use, log transformed plasma OT levels significantly lower in T1DM than controls (2.2 vs 2.4, p=0.03).	No significant association between OT and dietary calcium consumption or supplement use in either group (all p>0.13). In T1DM regression model - calcium supplement use (β=0.14, p=0.04).	Neutral for dietary calcium; increased for calcium supplement (in T1DM subjects only)
Fat-rich meal intake	Ohlsson et al. (2002)[68]	Dietary compliance not specified.	Baseline plasma OT (pmol/L): Controls =1.0±0.3; Constipated =1.0±0.3. After meal peak OT concentration (pmol/L): Controls =1.3±0.4; Constipated =1.6 ± 0.3. No difference in between groups in plasma values at different time points, or AUC (data not shown).	Plasma OT increased significantly after fat-rich meal in constipated subjects (p=0.03) and controls (p=0.02).	Increase
Low and high sodium diets	Rasmussen et al. (2004)[69]	Adherence to low sodium (LS) and high sodium (HS) diet: 24h urinary sodium excretion (mmol 24 h^{-1}): LS1 =32±7, LS2 =24±5; HS1 =172±30, HS2 =259±26	Plasma OT (pg/mL): LS1 = 2.7±0.3, LS2 = ~2.1 (SD not reported); HS1 = 2.2±0.1, HS2 = ~1.4 (SD not reported).	No significant difference in plasma OT levels between subjects receiving low and high sodium diets.	Neutral
Sort-term fasting	Challinor et al. (1994)[55]	Dietary intake or compliance not reported.	Baseline plasma OT (as estimated by the graph) = ~0.35 µU/ml. Plasma OT concentrations ranges during the 8 hr sampling periods: Fed state =0.3±0.2 to 0.8±0.5µU/ml (p<0.05), Fasted state =0.3±0.2 to 1.9±2.6µU/ml (p<0.05). Fed state peak concentrations 1.3 to 2.3µU/ml, nadir concentrations 0.8 to 3.0µU/ml. Fasted state peak	Comparisons b/t fasted and fed samples not significantly different (p<0.05, paired t test statistic not reported). Plasma OT not affected by short-term fasting.	Neutral

Dietary characteristic	Author (year)	Dietary outcomes [reported as mean ± SD or (SEM) unless specified otherwise]	Oxytocin outcomes [reported as mean ± SD or (SEM) unless specified otherwise]	Relationship between diet and oxytocin	Effect* [Increased/ Decreased/ Neutral]
			concentrations 0.8 to 3.0µU/ml, nadir concentrations 0.2µU/ml.		
Eating disorders	Monteleone et al. (2016)[66]	N/A	Approximate plasma OT levels (as estimated by the graph): AN = ~8pg/mL, BN = ~22pg/mL and control subjects = ~21pg/mL.	Plasma OT levels significantly differed among groups ($F_{(2,66)}$=6.88; p=0.001). AN plasma OT significantly lower than controls ($F_{(1,40)}$=14.15, p=0.0005), BN plasma OT levels not significantly different from controls ($F_{(1,44)}$=0.04, p=0.8). No significant differences in plasma OT b/t binge-purging (6.0±5.5 pg/mL) and restrictive AN (9.1±5.6 pg/mL). Plasma OT of patients with binge eating and purging (regardless of specific eating disorder diagnoses) did not differ significantly from those of controls ($F_{(1,52)}$=0.31, p=0.5).	Decreased (AN subjects)
Eating disorders	Demitrack et al. (1990)[58]	N/A	Overall OT in CSF (pg/ml): restricting AN =4.9±1.2, bulimic AN =6.7±1.7, control =8.0±3.4. OT (pg/mL) in underweight AN subjects according to method of weight loss vs controls: restricting AN = 4.9±1.2; bulimic AN =6.7±1.7 vs controls =8.0±3.4. OT levels (pg/ml) during underweight phase: restrictive AN =4.7±1.4, bulimic AN =6.5±1.7; end of refeeding phase: restrictive AN =5.6±0.7, bulimic AN =7.3±2.2; after short-term recovery phase: restrictive AN =6.4±1.3, bulimic AN =7.0±1.8. OT levels of normal-weight BN at admission (pg/ml) =6.2±1.6, after abstinence of binge-eating and vomiting =6.3±1.7.	No significant difference b/t underweight AN and control groups overall OT levels (z=1.60, p<0.12). Underweight AN divided according to method of weight loss: significantly lower mean OT for underweight restrictive AN vs bulimic AN (z=2.11, p<0.04), and underweight restrictive AN vs controls (z=2.21, p<0.03). OT for bulimic AN vs control group not significantly different. OT levels similar for normal-weight BN and underweight bulimic AN. Significant increase in OT during course of recovery (i.e. refeeding and abstinence from binge-eating and vomiting) for all AN (F=5.67, df=2,26, p<0.01). OT levels not significantly different between restrictive and bulimic AN over course of recovery. No significant difference in OT between controls and normal-weight BN at admission (z=1.64, p=0.10) and after abstinence of binge-eating and vomiting (z=1.59, p=0.11).	Decreased in restrictive AN; increased in AN during course of recovery; neutral in BN during course of recovery
Eating disorders & food intake	Lawson et al. (2013)[63]	Caloric, protein, fat and CHO content consumed at meal did not differ b/t groups (NS). Calories consumed at breakfast: AN =378.5±16.2, ANWR =408.5±6.4, controls =405.8±2.0; Protein (g): AN =18.3±0.7, ANWR =19.4±0.6, controls =19.4±0.2; Fat (g): AN =9.4±0.8, ANWR =10.4±0.6, controls =10.6±0.3; CHO (g): AN =58.2±2.0, ANWR =62.1±1.4, controls =61.5±0.5.	Plasma oxytocin log transformed (pg/mL) – Baseline: AN =15.8±1.1, ANWR =8.1±0.6, controls =16.4±2.3. 30 min after meal: AN =17.6±2.5, ANWR =9.3±1.1, controls =15.4±1.9. 60 min after meal: AN =16.6±2.3, ANWR =9.0±1.0, controls =12.3±1.9. 120 min after meal: AN =19.1±3.7, ANWR =7.7±0.4, controls =12.0±1.2. AUC: AN =2086±195, ANWR =1040±96, controls =1621±125. Post-prandial nadir: AN =13.5±1.1, ANWR =7.7±0.4, controls =9.0±0.7. Post-prandial peak: AN =23.4±4.0, ANWR =9.9±3.2, controls =18.9±1.8.	Baseline OT levels comparable in AN and controls (p>0.05), lower in ANWR (p=0.0005). Groups differed in OT levels at 30 (p=0.012), 60 (p=0.009) and 120 (p<0.0001) min after meal. OT levels higher in AN than controls at 60 (p=0.049) and 120 min (p=0.009), and lower in ANWR than controls at 30 (p=0.024) and 120 min (p=0.018); lower in ANWR than AN all time points [30 min p=0.004), 60 min (p=0.003), 120 min (p<0.0001)]. Postprandial nadir: OT level higher in AN than ANWR (p<0.0001) or controls (p=0.0002). Postprandial peak OT levels differed between groups (p=0.0004); no difference between AN and	Neutral

Dietary characteristic	**Author (year)**	**Dietary outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Oxytocin outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Relationship between diet and oxytocin**	**Effect*** [Increased/ Decreased/ Neutral]
				controls (p>0.05), lower in ANWR than AN (p=0.0001) or controls (p=0.001). [ANOVA: F statistics not reported].	
Food Addiction	Pedram et al. (2015)[42]	Daily nutrient intakes (per kg of body weight) – Calories (kcal/kg): FAO =24.4±10.9, NFO =19.5±6.6, p=0.02; Protein (g/kg): FAO =1.1±0.4, NFO =0.9±0.3, p=0.2; Fat (g/kg): FAO =0.7±0.4, NFO =0.5±0.2, p=0.004; CHO (g/kg): FAO =3.2±1.6, NFO =2.8±1.0, p=0.03; Sugar (g/kg): FAO =1.4±0.8, NFO =0.2±0.5, p=0.03; Saturated fat (g/kg): FAO =0.3±0.1, NFO =0.2±0.1, p=0.01; Trans-fat (g/kg): FAO =1.0±0.0, NFO =0.1±0.0, p=0.01; MUFA (g/kg): FAO =0.3±0.1, NFO =0.2±0.1, p=0.01; PUFA (g/kg): FAO =0.1±0.1, NFO =0.1±0.0, p=0.0; Omega 3 (mg/kg): FAO =7.0±0.0, NFO =5.0±0.0, p=0.01; Omega 6 (g/kg): FAO =0.1±0.0, NFO =0.03±0.0, p=0.0; Vit. B1 (mg/kg): FAO =0.02±0.01, NFO =0.02±0.0, p=0.04; Vit. D (IU/kg): FAO =2.5±2.1, NFO =1.9±1.0, p=0.04; hydrogenated Vit. K (µg/kg): FAO =0.3±0.0, NFO =0.2±0.0, p=0.03; gamma tocopherol (mg/kg): FAO =0.3±0.0, NFO =0.0±0.0, p=0.04; Sodium (mg/kg): FAO =26.1±12.0, NFO =19.4±6.3, p=0.01; Calcium (mg/kg): FAO =13.0±7.1, NFO =10.0±4.0, p=0.02; Potassium (mg/kg): FAO =50.8±21.3, NFO =41.2±16.8, p=0.04; Selenium (mg/kg): FAO =1.4±0.6, NFO =1.1±0.3, p=0.02.	Plasma OT (pg/mL) – FAO =119.5±49.1, NFO =120.2±57.9	No significant difference in OT between FAO and NFO groups (p=0.78, t statistics not reported). FAO consumed significantly higher amounts of calories, fat and CHO per kg of bodyweight. Significant difference in all micronutrient intakes between FAO and NFO (p<0.05).	Neutral

*Effect of dietary exposure/intake/behaviours (reported as increased, decreased or neutral) determined by alteration in endogenous oxytocin concentration. SEM, standard error of the mean; AUC, Area Under the Curve; BAC, Blood Alcohol Concentration; OT, oxytocin; T1DM, Type 1 Diabetes Mellitus; AN, Anorexia Nervosa; BN, Bulimia Nervosa; ANWR, Anorexia Nervosa weight recovered; FAO, Food addicted obese; NFO, Non-food addicted obese; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

Table 4. Outcomes of included exogenous oxytocin studies

Dietary characteristic	**Author (year)**	**Dietary outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Oxytocin outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Relationship between diet and oxytocin**	**Effect*** [Positive/ Negative/ Neutral]
Alcohol craving & approach bias	Mitchell et al. (2016)[65]	Cue-induced craving task scores - Placebo vs OT: AUQ empty glass cue = 2.4 (0.2) vs 2.7 (0.2), p=0.99; AUQ water cue = 2.4 (0.2) vs 2.6 (0.2), p=0.94; AUQ alcohol cue = 3.1 (0.3) vs 3.7 (0.3), p=0.15; AUQ alcohol-water (cue-induced craving) = 0.7 (0.2) vs 1.1 (0.2), p=0.054. AAT approach bias scores - Placebo vs OT: Alcohol images = 20.7 (39.2) vs 29.4 (19.8), (p=0.92); Appetitive images = 62.8 (25.8) vs -31.2 (23.3), (p=0.022); General positive images 43.6 (30.0) vs -14.7 (20.2), p=0.35; General negative images 11.7 (21.9) vs 22.4 (20.7), p=0.82.	Endogenous OT not measured	Non-significant trend for OT to increase cue-induced craving (b=0.578, $t_{(31)}$=2.02, p=0.054). No approach bias toward alcohol images in placebo ($t_{(31)}$=0.529, p=0.60, d = 0.19) or OT conditions (b = -5.06, t(31) = -0.096, p=0.92). Approach bias toward appetitive food images in placebo condition ($t_{(31)}$ = 2.44, p=0.021, d = 0.88). Approach bias toward appetitive food images significantly reduced by OT administration (b = -105.4, $t_{(31)}$= -2.34, p=0.022).	Neutral for alcohol craving; positive for approach bias
Food craving	Striepens et al. (2016)[70]	Food craving significantly lower during LATER compared to NOW trials: Placebo = ↓ 22.8%, OT = ↓ 25.8% [Food craving ratings data not reported]. Neural responses to palatable food stimuli: OT enhanced neural activations in middle and superior frontal gyrus, precuneus and cingulate cortex in LATER trials (p<0.005).	Salivary OT before vs after intranasal OT administration (pg/ml) =2.1±2.7 vs 12.7±6.8 [$t_{(25)}$=8.12, p< 0.01]. Salivary OT in placebo condition before vs after presentation of food stimuli (pg/ml) =1.9±1.8 vs 3.4±4.9. [Supplemental data]	OT reduced craving ratings in LATER trials i.e. when participants thought about the long-term consequences of eating high calorie food ($t_{(30)}$ =521.71, p=0.098, d = -0.21), but not in NOW trials ($t_{(30)}$=21.15, p=0.26, d = -0.15). Findings supported by fMRI. No significant correlations between baseline OT concentrations and neural responses to food stimuli (LATER and NOW) or the cognitive down-regulation of craving (LATER > NOW) in placebo condition. Baseline OT concentrations nor the difference between OT concentrations (i.e. before and after the paradigm) correlated with food craving ratings (p>0.10).	Positive for LATER trials; neutral for NOW trials
Satiety (Study 1)	Borg et al. (2011)[54]	Pre-meal intake most subjects scored 2-3 (= very hungry), end of meal most subjects scored 17-18 (= unpleasant satiety). Significant difference between groups in maximum satiety scores when finishing meal intake, relative to baseline (p=0.031). No difference between groups in AUC for VAS scores (p=0.266).	Endogenous OT not measured	No differences in volume of nutrient intake at maximum satiety between groups (p=0.782). Overall, OT infusions resulted in lower satiety scores at maximum satiety i.e. on meal termination. Only significant difference between placebo and 40mU OT min^{-1} dosage on meal termination (p=0.013), and 30 min after meal (p=0.032). [Results displayed graphically, test statistics not reported]	Neutral for volume of intake; negative for satiety
Satiety (Study 2)	Borg et al. (2011)[54]	VAS score data not shown	No difference in plasma OT concentrations at baseline between groups (ranging between 140.0-180.0pmol L^{-1} as estimated by the graph; p<0.204). Statistically significant differences between saline and OT infusions at 30, 60 and 120 min, and at end of experiment (p<0.0001); increasing plasma concentrations proportional to OT concentrations	Satiety scores did not differ between placebo and OT (p>0.05). [Results displayed graphically, test statistics not reported].	Neutral

Dietary characteristic	Author (year)	Dietary outcomes [reported as mean ± SD or (SEM) unless specified otherwise]	Oxytocin outcomes [reported as mean ± SD or (SEM) unless specified otherwise]	Relationship between diet and oxytocin	Effect* [Positive/ Negative/ Neutral]
			in infusions. [OT concentrations (pmol L^{-1}) represented graphically].		
Satiety (Study 1)	Borg et al. (2012)[53]	VAS score data not shown	Endogenous OT not measured	Satiety scores did not differ between placebo and OT at 30 min (p=0.594) and 70 min (p=0.799) after food intake. [Results displayed graphically, test statistics not reported].	Neutral
Satiety & volume intake (Study 2)	Borg et al. (2012)[53]	Volume intake and VAS score data not shown	Endogenous OT not measured	No difference in total volume of intake between placebo and OT (p=0.149). Satiety scores before (p=0.483), at maximal satiety (p=0.449) and 30 min after end of meal (p=0.450) did not differ between groups. OT did not affect volume of nutrient intake or result in lower satiety in patients with functional dyspepsia. [Results displayed graphically, test statistics not reported]	Neutral
Satiety	Ohlsson et al. (2006)[67]	Median (quartile 1 to quartile 3) satiety scores – AUC 0-15 min (cm x min): Placebo = 934 (736-1077); OT =924 (665-1022); Atosiban = 1025 (707-1189). AUC 0-90 min: Placebo =118 (90-152); OT =132 (76-152); Atosiban =114 (84 -152).	Endogenous OT not measured	No significant difference in relative satiety scores between OT and Atosiban compared to placebo [p values and Wilcoxon test statistics not reported].	Neutral
Food intake & appetite	Lawson et al. (2015)[44]	OT vs placebo conditions: Total calories ordered (kcal) =853±27 vs 878±27. Total calories consumed (kcal) = 1153±636 vs 1275±36. Protein ordered (g) =24.5±1.3 vs 25.7±1.3. Protein consumed (g) =34.9±1.5 vs 38.8±1.5. CHO ordered (g) =119.0±5.3 vs 115.7±5.3. CHO consumed (g) =148.4±6.6 vs 155.6±6.6. Fat ordered (g) =31.7±1.7 vs 35.5±1.7. Fat consumed (g) =47.3±2.7 vs 56.0±2.7. VAS scores not shown. [Recorded 72h food intake prior to OT/placebo experiments did not differ between groups (p>0.05)].	Treatment effect of oxytocin on fasting levels of plasma OT (pg/mL) =965.0±53.7 and treatment effect estimate (pg/mL) = -32.5±20.7 (p=0.1)	OT reduced caloric intake. Effect of OT on dietary intake: Total calories ordered (kcal) = -25.1±37.6, p=0.5. Total calories consumed (kcal) = -122±51, p=0.03. Protein ordered (g) = -1.2±1.8, p=0.5. Protein consumed (g) = -3.9±2.2, p=0.08. CHO ordered (g) =3.3±7.5, p=0.7. CHO consumed (g) = -7.2±9.4, p=0.4. Fat ordered (g) = -3.8 ± 2.4, p=0.1. Fat consumed (g) = -8.7±3.8, p=0.03 (NS after controlling for multiple comparisons). OT had no effect on appetite scores.	Positive for food intake; neutral for appetite
Food intake, hunger & thirst	Ott et al. (2013)[43]	Calorie intake during buffet in placebo vs OT conditions (kcal): Total =1180±103 vs 1190±105 (p=0.84); CHO =517±41 vs 540±41 (p=0.43); Fat =517±54 vs 509±57 (p=0.84); Protein =145±16 vs 142±14 (p=0.82); Savoury foods =314±38 vs 309±29 (p=0.91); Sweet foods = 233±44 vs 206±40 (p=0.22). Hunger and thirst scores not shown. Snack intake during snack test in placebo vs OT conditions (kcal): Sweet snack =185±41 vs 138±38 (p=0.007); Bland snack =18±3 vs 13±2 (p=0.15); Salty snack: 81±19 vs 75±16 (p=0.75); Total snake intake =283±44 vs 227±44 (p=0.03).	Endogenous OT not measured	OT did not affect hunger-driven food intake in fasted state [Breakfast (kcal): Total p=0.84, CHO p=0.43, Fat p=0.84, Protein p=0.82, Savoury foods p=0.91, Sweet foods p=0.22 (t statistics not reported)]. OT had no effect on hunger (p>0.9) or thirst ratings (p>0.12). OT reduced reward-driven total food intake ($F_{(1,19)}$=5.5, p<0.03), 25 % ↓ in sweet snack consumption (p<0.01).	Neutral for hunger-driven food intake, hunger and thirst ratings; positive for reward-driven food intake

Dietary characteristic	**Author (year)**	**Dietary outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Oxytocin outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Relationship between diet and oxytocin**	**Effect*** [Positive/ Negative/ Neutral]
Food intake, hunger & thirst	Thienel et al. (2016)[45]	Calorie intake during buffet in placebo vs OT conditions (kcal) - Obese men: Total =1421±99 vs 1274±92 (p=0.035); CHO =736±51 vs 659±57 (p=0.07); Fat =478±54 vs 430±44 (p=0.15); Protein =207±15 vs 187±13 (p=0.08). Normal-weight men: outcome as described above by Ott et al (2013). Authors note hunger and thirst ratings (data not shown) in both groups comparable at baseline (p>0.2). Snack intake during snack test in placebo vs OT conditions (kcal) - Obese group: Total snake intake =216±24 vs 162±27 (p=0.006); Sweet snack =144±25 vs 116±24 (p=0.030); Bland snack =22±5 vs 16±2 (p=0.26); Salty snack =51±11 vs 30±6 (p=0.07). Normal-weight group: outcome as described above by Ott et al (2013). [Snack ratings not shown]. PFS: Obese subjects = 2.71 (0.13), Normal-weight subjects = 2.42 (0.14) (p=0.13). DEBQ-R: Obese subjects = 2.55 (0.13); TFEQ: Obese subjects = 6.53 (0.80).	Endogenous OT not measured	OT did not affect hunger-driven food intake in normal-weight subjects ($F_{(1,36)}$=3.48, p=0.07), in obese subject's total food consumption ↓10% ($F_{(1,17)}$=5.26, p<0.04). Significant difference in CHO intake between obese and normal-weight subjects in OT condition ($F_{(1,36)}$=4.44, p=0.042). Obese subjects ate more than normal-weight subjects in placebo conditions ($F_{(1,36)}$=4.27, p<0.05). OT had no effect on appetite scores. OT reduced reward-driven total food intake for all subjects, 22% ↓ in total snack consumption ($F_{(1,36)}$=13.37, p<0.001). No difference in effect between obese and normal-weight groups ($F_{(1,36)}$=0.01, p>0.9). In both groups, effect size largest for sweet snack consumption ($F_{(2,56)}$=3.88, p<0.04). OT induced reduction in breakfast intake inversely related to snack intake (r = − 0.48, p<0.05).	Positive for hunger-driven food intake (obese subjects only); neutral for hunger and thirst ratings; positive for reward-driven food intake
Eating disorders & food intake	Kim et al. (2015)[60]	Eating disorder subscales - Restraint: AN =2.2±1.8, BN = 2.3±1.8, controls = 0.8±0.8 (p<0.001); Eating concern: AN =1.88±1.69, BN = 2.8±1.8, controls = 0.6±0.8 (p<0.001); Shape concern: AN =2.4±1.5, BN =3.6±1.8, controls =1.5±1.2 (p<0.001); Weight concern: AN =2.7±1.5, BN =3.9±1.6, controls =2.2±1.3 (p<0.001); Global: AN =2.3±1.5, BN =3.1±1.5, controls =1.3±0.9 (p<0.001). Groups significantly different in all subscales of EDE-Q. Juice consumption in placebo vs OT condition (mL): AN =92.0±83.8 vs 97.5±82.0 (↑5.6%); BN =118.4±64.0 vs 131.5±61.2 (↑10.0%); control =160.2±53.0 vs 172.8±43.3 (↑6.9%). 24h calorie intake in placebo vs OT condition (kcal/day): AN =1988.6±730.0 vs 2151.5±873.3 (↑); BN =2757.8±1047.7 vs 2277.6±942.7 (↓); control = 2295.8±808.2 vs 2179.5±692.6 (↓).	Endogenous OT not measured	Amount of juice consumed in placebo vs OT condition - AN: t= -0.537, p=0.595, d=-0.082; BN: t= -1.662, p=0.106, d=-0.197; control: t= -1.924, p=0.063, d= -0.179. Comparison of groups in placebo condition for amount of juice consumed showed significant difference with large effect size ($F_{(2,99)}$=8.738, p<0.01; Δη2=0.150). AN (p<0.001) and BN (p = 0.030) groups consumed a lower amount of juice than control group. Small effect of OT ($F_{(1,99)}$=4.469, p=0.037, Δη2 = 0.043), and large effect of diagnosis ($F_{(2,99)}$=11.600, p<0.001, Δη2 = 0.190). Amount of kcal/day consumed in placebo vs OT condition - AN: t= -1.492, p=0.145, d= -0.190; BN: t=2.528, p=0.016, d=0.560; control: t=0.882, p=0.384, d=0.136. Comparison of groups in placebo condition for amount of calorie intake during 24h showed significant difference with large effect size [$F_{(2,99)}$=6.581, p=0.002, Δη2=0.120]. BN group reported eating more calories than AN group during the 24h period (p=0.001 for AN vs BN; p=0.372 for AN vs control; p=0.082 for BN vs control). Significant effect of OT in BN group ($F_{(1,33)}$=6.389, p=0.016, Δη2=0.162). BN group consumed fewer calories after receiving OT (p=0.016, d=0.560). No significant effect of OT on	Neutral for juice consumption; positive (BN subjects)

Dietary characteristic	**Author (year)**	**Dietary outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Oxytocin outcomes** [reported as mean ± SD or (SEM) unless specified otherwise]	**Relationship between diet and oxytocin**	**Effect*** [Positive/ Negative/ Neutral]
				AN (p=0.145) or controls (p=0.384) for calories consumed.	
Eating disorders & attentional bias	Kim et al. (2014)[61]	Response to eating stimuli in placebo vs OT condition: AN =19.0± 72.3 vs -14.6±57.5; controls =7.3±49.4 vs -12.9±59.4. Baseline differences between groups insignificant in placebo condition (t(62)= -0.765, p=0.062, d=0.192). Response to weight stimuli in placebo vs OT condition: AN = -0.3±92.1 vs 1.7±75.7; controls =1.5± 96.4 vs -8.0±65.5. Baseline differences between groups insignificant in placebo condition (t(62)=0.075, p=0.707, d=0.190). Response to positive (thin) shape stimuli in placebo vs OT condition: AN =1.6±126.3 vs -18.8±104.9; controls =6.9±94.9 vs 19.7±92.6. Response to neutral (normal) shape stimuli in placebo vs OT condition: AN =21.5±105.8 vs 10.8±106.5; controls =43.9±122.4 vs 14.8±87.8. Response to negative (fat) shape stimuli in placebo vs OT condition: AN =42.0±104.7 vs -7.5±93.8; controls = -1.2± 81.1 vs 12.2±96.1. No differences between AN and controls at baseline in placebo condition for positive shape stimuli (t(62)=0.192, p=0.849, d= -0.048) or for neutral shape stimuli (t(62)=0.764, p=0.448, d= -0.195). Small vigilance bias to negative shape in AN group compared to controls (t(62)= -1.507, p=0.137, d=0.380). Juice consumption in placebo vs OT condition (mL): AN = 89.2±84.8 vs 97.8±84.6 (↑ 8.9%); control =162.9±50.2 vs 173.4±43.4 (↑6.8%).	Endogenous OT not measured	AN subjects: OT ↓ attentional bias to eating stimuli ($t_{(30)}$=2.281, p=0.030, d=0.808; ES=0.192) and toward negative (fat) shape stimuli ($t_{(30)}$=2.592, p=0.015, d=0.498; ES=0.380). OT had no effect on weight stimuli (t (30)=-0.101, p=0.920, d= -0.024), positive shape stimuli ($t_{(30)}$=0.612, p=0.545, d=0.175), or neutral shape stimuli ($t_{(30)}$=0.478, p=0.636, d=0.101). ↑ juice consumption induced by oxytocin not statistically significant in AN (z=0.213, p=0.831, ES=0.038) or controls (z=1.244, p=0.214, ES=0.223).	Positive for eating and negative shape stimuli; neutral for juice consumption
Binge eating disorder	Agabio et al. (2016)[71]	BED severity in placebo vs OT: baseline =4.9 vs 4.0, p=0.086; post-intervention = -2.4 vs -0.5; difference in variation p=0.088. Binge episodes per week in placebo vs OT: baseline =0.7 vs 0.6, p = 0.454; post-intervention = -0.3 vs -0.2; difference in variation p=0.633. Craving for food in placebo vs OT: baseline =81.1 vs 80.3, p=0.919; post-intervention = -46.7 vs -42.5; difference in variation p= 0.758.	Endogenous OT not measured	OT had no significant effect on BED severity, binge episodes or cravings (p<0.05).	Neutral

*Effect of exogenous oxytocin administration (reported as positive, negative or neutral) determined by alteration in dietary intake/behaviours. SEM, standard error of the mean; OT, oxytocin; AUQ, Alcohol Urge Questionnaire; LATER, participants directed to think about the long-term consequences; NOW, participants directed to think about the immediate consequences; fMRI, functional magnetic resonance imaging; AUC, Area Under the Curve; ATT, approach avoidance task; VAS, Visual Analogue Scale; CHO, carbohydrate; PFS, Power of Food Scale; DEBQ-R, Dutch Eating Behaviour Questionnaire; TFEQ, Three Factor Eating Questionnaire; AN, Anorexia Nervosa; BN, Bulimia Nervosa.