Review

Semaglutide and craving

Effects on the experience of craving in treatment with semaglutide for weight loss

Translation of thesis written in Swedish 2024 for the three year programme BSc Health & Biomedical Science att Linné University in Sweden

Abstract

Review of semaglutide's effects on craving in weight loss treatment without diabetes

Overweight and obesity present significant global health challenges today, with serious consequences such as type 2 diabetes, cardiovascular diseases, and certain cancers. This literature review examines semaglutide and its impact on craving as a crucial factor in weight loss among individuals with obesity. The aim is to evaluate whether semaglutide affects individuals' ability to manage craving and if there is a correlation between the ability to manage craving and weight loss.

By reviewing three randomized, controlled trials, the effects of semaglutide on craving over periods of up to two years are analyzed. The results show that semaglutide initially reduces craving, but its effect on craving diminishes over time. At twelve weeks, 64% of the questions in the quantitative evaluation of perceived craving showed significant improvements, while this proportion decreased to 58% at 20 weeks and to 32% at 104 weeks. The results from the analyzed studies further indicate that the effects of semaglutide on sweet cravings and positive mood did not exhibit statistical significance over the measured two-year period. In contrast, cravings for savoury foods and control over eating demonstrated consistent statistical significance, showing a positive effect from semaglutide treatment throughout the entire study duration. Consequently, the studies suggested that semaglutide may be an effective tool for reducing cravings for palatable foods and improving control over eating in individuals with obesity or overweight. However, there is no clear evidence that semaglutide reduces sweet cravings or positively affects mood.

The study highlights the need for a holistic treatment strategy that combines pharmacological intervention with psychological support to address emotional eating and addictive behaviors. In summary, further research is required to understand the complex mechanisms behind semaglutide's effects on appetite regulation and to develop sustainable solutions for the pharmacological treatment of obesity.

Keywords
Semaglutide, Obesity, Craving, Weightmanagement, GLP-1-analogs.

Wordlist

BDNF	Brain Derived Neurothrophic Factor
BOLD-signal	Blood Oxygen Level Dependent signal
CoEQ	Control of Eating Questionnaire
Craving	Intensely specific craving for something, In this context, specifically food-related
EMA	European Medicines Agency
FDA	Food and Drug Administration
fMRI	funktional Magnetic Resonance Imaging
GLP-1	Glucagon Like Peptide 1
MRI	Magnetic resonance Imaging
RCT	Randomized Controlled Trial
YFAS2.0	Yale Food Addiction Scale version 2.0

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1 Introduction

Overweight and obesity are among the most prominent global health challenges today. The World Health Organization (WHO) reports that one in eight people currently live with obesity, and this number has nearly doubled since 1990. This increase has led to heightened health risks, including type 2 diabetes, cardiovascular diseases, certain cancers, and musculoskeletal conditions such as osteoarthritis. This epidemiological trend underscores the urgent need for effective intervention strategies (1).

A central but often overlooked element in the treatment and understanding of obesity is the phenomenon of "craving." When it comes to food cravings, this involves an intense, specific desire for food, often of a high-calorie and palatable nature (2). This definition is particularly relevant in the context of obesity and weight loss treatment, as it directly impacts an individual's ability to adhere to dietary restrictions and can lead to relapses into unhealthy eating behaviors after periods of dieting (3,4). The experience of "craving" is individual and can manifest with varying intensity, expressed as a strong emotional desire in response to factors such as stress, emotions, environmental triggers, social triggers, hunger, fatigue, or thoughts. In this work, the term "craving" is used as defined above.

Appetite regulation involves the interaction of both homeostatic and hedonic systems (5), making it a complex target for treatments. Craving is linked to the brain's reward centers, which respond to neurotransmitters such as dopamine and endogenous opioids, produced when consuming substances like sugar and fat (6). Psychological aspects include emotional eating, often triggered by stress and negative emotions (4,7). Craving is also clearly associated with addiction (8). Thus, a holistic understanding of both the biological and behavioral drivers behind craving is crucial for designing effective obesity treatments.

Semaglutide is a substance that mimics the satiety hormone GLP-1 (Glucagon-Like Peptide 1). It affects not only blood sugar control and weight loss but also craving (9) through receptors in the brain that reduce what is otherwise described as "food noise" (10), a preoccupation with food that affects eating behavior and consumes mental energy and focus. However, semaglutide treatments show varying long-term results, with some individuals achieving substantial weight loss of up to 20% over two years, while others see little effect, and some even gain weight (11).

Given the growing prevalence of obesity, which, according to a Lancet report from February 29, 2024 (12), continues to increase globally, the need for effective treatments is more urgent than ever. The global prevalence of obesity contributes not only to individual suffering but also to significant socioeconomic costs, making it imperative to explore and understand the mechanisms through which treatments like semaglutide can modulate not only the physiological aspects of homeostatic appetite regulation but also the hedonic/behavioral aspects expressed through craving.

2 Background

2.1 Appetite regulation, hunger, and satiety

Humans, like all living organisms, consume food to obtain the nutrients necessary to ensure the survival of the organism. Fundamentally, this nutrient intake occurs to

maintain cellular homeostasis – a balance between molecules that are oxidized and broken down through catabolic processes and those that ensure function, repair, and cell division at the cellular level through anabolic processes (13,14).

To ensure homeostasis, food intake is regulated through a complex interaction of various physiological regulatory systems. Digestion, gastric motor function, and hormonal signals from energy stores and the digestive system all work together to regulate intake by increasing or decreasing appetite through feelings of hunger and satiety (15,16).

In addition to this homeostatic appetite regulation, there is another regulation driven by the desire for pleasure and reward. Humans eat to obtain nutrients but are also driven by the expectation of positive responses such as feelings of pleasure and reward (hedonic) (5) to ensure the repetition of beneficial behaviors. Homeostatic/hedonic appetite has traditionally been studied as two separate regulatory systems, but a review article by Campos et al. from 2022 (17) points out that these two are clearly interconnected and that both are involved in regulating appetite, hunger, and satiety.

Figure 1 shows how hedonic and homeostatic signals are integrated to regulate food intake (17). Food stimuli create reward feedback via the senses, which is processed by both conscious cortical areas (such as the insula, cortical limbic system, and cingulate cortex) and unconscious subcortical areas (such as the striatum, midbrain, and subcortical limbic system). These process information and communicate with the hypothalamus in the deeper parts of the brain, responsible for, among other things, hunger and satiety, and the brainstem, which controls basic bodily functions.
The hypothalamus and brainstem also receive metabolic feedback signals from the body's hormones and visceral feedback signals (such as feelings of satiety or nausea) via the vagus nerve. These various signaling pathways (understood as pre-ingestive/cephalic (18) and post-ingestive stimuli) work together to regulate hunger, the motivation to eat, and satiety. This complex integration of signals helps guide food intake both to maintain energy balance and for enjoyment (17).

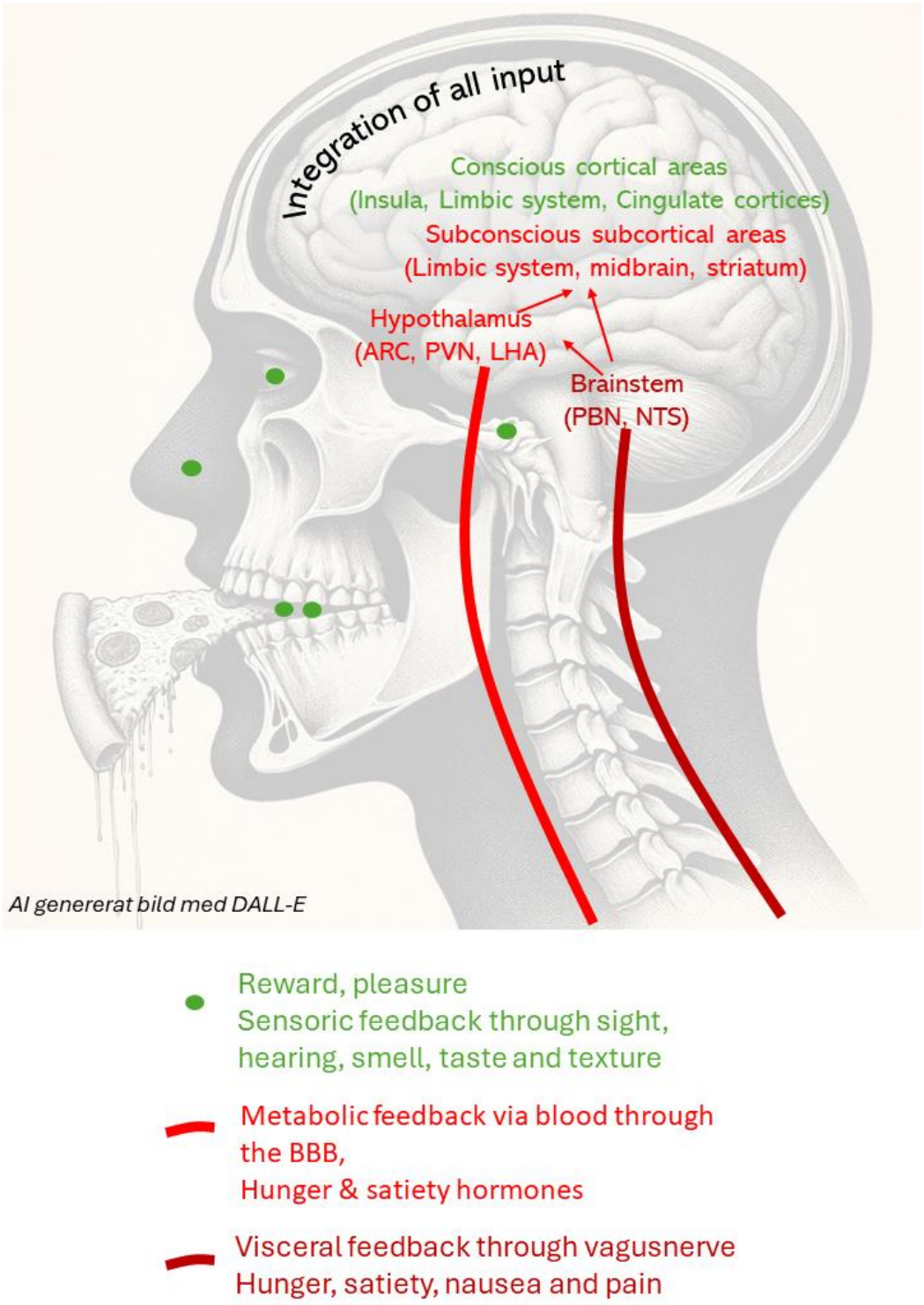

Figure 1 Hedonic and homeostatic pathways for appetiteregulation. Illustration created based upon information in

Campos et al (17) ARC=Arcuate nucleus , PVN=Paraventricular nucleus, LHA=Lateral hypothalamic area, PBN=Parabrachial nucleus, NTS=Nucleus tractus solitarius, BBB=Blood brain barrier

Regulation of eating:
To date, 29 different hormones, neurotransmitters, and peptides have been identified as central to the regulation of human eating behavior (18–24). These are described in Appendix A.

Below is a schematic summary from these sources of the substances secreted from adipose tissue, the digestive system, and the pancreas that are transported to the hypothalamus and brainstem to regulate appetite, hunger, and satiety. Furthermore, the diagram illustrates how POMC (ProOpioMelanoCortin), CART (Cocaine- and Amphetamine-Regulated Transcript), Alpha MSH (alpha-melanocyte-stimulating hormone), CRH (Corticotropin-Releasing Hormone), SST (Somatostatin), and ORX (Orexin) in the hypothalamus modulate this along with several other peptides and neurotransmitters in the brain. See Figur**e 2.**

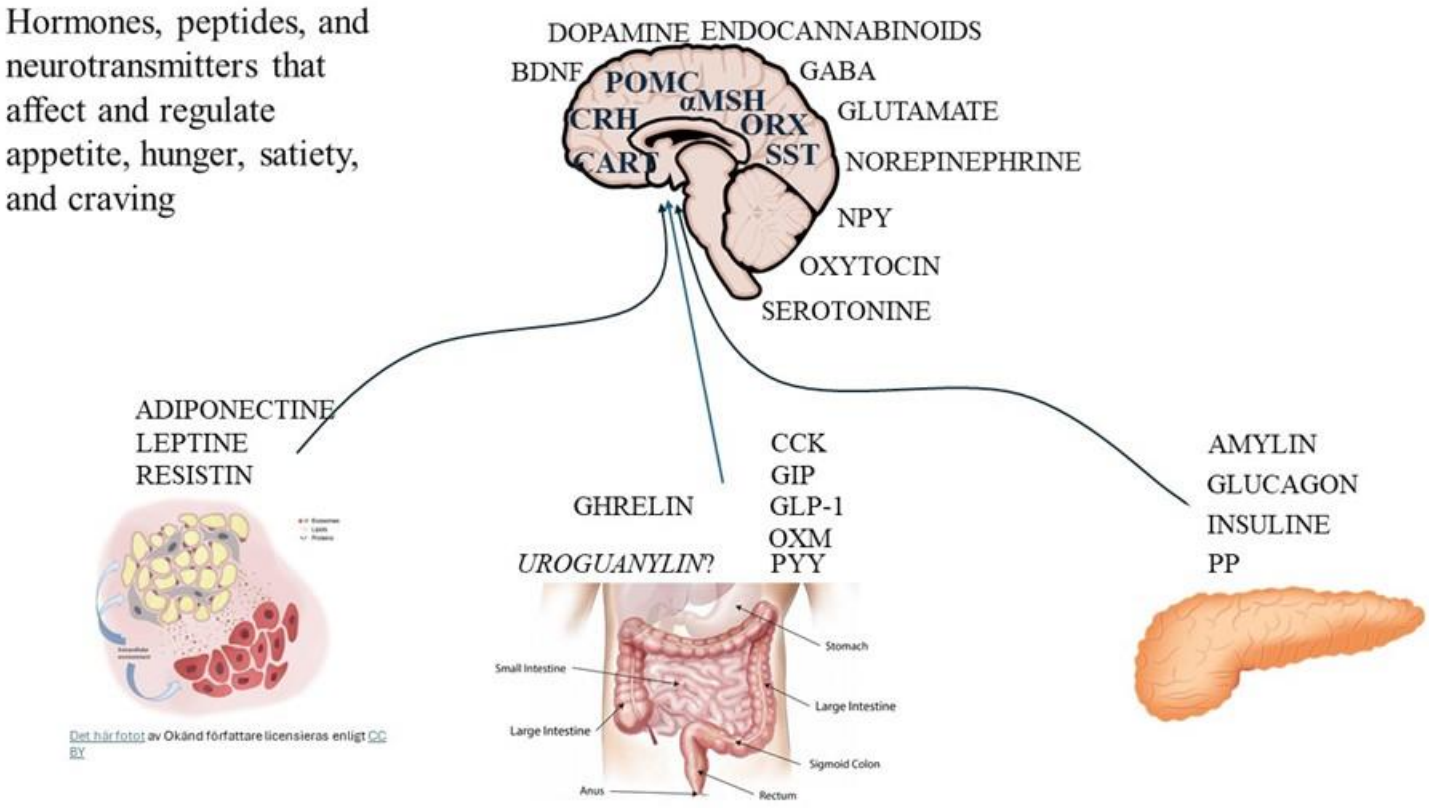

Figure 2:Illustration of peripheral hormones, peptides, and neurotransmitters influencing homeostatic and hedonic hunger and satiety. Each peripheral agent is graphically linked to its origin organ—adipose tissue, the digestive system, and the pancreas—and is listed in alphabetical order. POMC, CART, CRH, MSH, somatostatin, and orexin are shown modulating incoming signals within the hypothalamus. Additionally, peptides and hormones encircling the brain, also arranged alphabetically, regulate hunger and satiety through neuroadaptive mechanisms. This figure is compiled based on the referenced sources(18–24) and each agent is described in higher detail in appendix A

Visceral feedback via the vagus nerve:
Figure 1 illustrates how visceral signals reach the brain via the brainstem. Loewenstein's theory (25) highlights how signals from the gastrointestinal tract via the vagus nerve can influence our cognitive functions and behavior, focusing on hedonic drive and decision-making. The theory identifies two main influences: glucose regulation and signaling from the digestive system about hunger, satiety, nausea, and pain. Blood glucose levels (plasma glucose) affect cognition and behavior, where low levels lead to impaired

decision-making, impulsivity, and increased craving for sweet food to quickly return to blood glucose homeostasis. Signals about hunger, satiety, nausea, and pain can also affect cognition and behavior. Loewenstein connects these visceral influences to hedonic eating behavior. According to Loewenstein, hedonic eating can be driven by a combination of physiological needs and expected pleasure. He theorizes that low blood sugar can cause cravings for sweet food, partly due to the body's energy needs but also because sweetness is associated with pleasure and reward. This theory highlights how visceral signals can influence our ability to make rational decisions and resist temptations. Loewenstein concludes that when blood sugar is low or when we feel intense hunger, we may be more likely to succumb to our cravings, despite cognitively understanding that it may not be the best choice for our long-term health.

Weygandt et al. confirm in their study "Interactions between neural decision-making circuits predict long-term dietary treatment success in obesity" (26) how the ability to adhere to weight loss regimens can be linked to how well decision-making functions cognitively, and that cravings have a significant negative effect on this.

In summary, human appetite regulation is an intricate interplay between numerous bodily and neurological signals that affect our ability to maintain nutritional balance and manage our behavior regarding food intake and food choices. This interplay is influenced by thoughts of food, the sensory experience of food, and both hormonal and neurological responses to food intake.

2.2 What is semaglutide?

Semaglutide mimics GLP-1, one of the many hormones secreted in the digestive system. GLP-1 is a natural hormone secreted in large amounts from L-cells in the epithelial layer of the small intestine (27) and through the activation of GLP-1 receptors, both peripherally and in the brain, mediates several effects including stimulation of insulin secretion in a glucose-dependent manner, reduction of glucagon levels, delay of gastric emptying, stimulation of insulin biosynthesis, and reduction of food intake. See Figure 2.

There are significant challenges associated with the natural biological form of GLP-1 that affect its availability in the body. GLP-1 is rapidly broken down into an inactive or even antagonistic form (GLP-1 [9–36 amide]), making its natural peptide form ineffective for therapeutic use. Due to its short half-life after secretion, it is difficult to maintain therapeutic plasma levels of GLP-1 with subcutaneous injections of the natural peptide hormone.

To address its short plasma half-life, research in recent years has focused on developing GLP-1 analogs with better pharmacokinetic properties than the original peptide. Semaglutide is a representative of these analogs and is designed to be more stable in the body and require less frequent dosing (27).

Semaglutide is described as a polypeptide consisting of a linear sequence of 31 amino acids linked by peptide bonds (28). It is an agonist for glucagon-like peptide-1 (GLP-1 RA) receptors and is prescribed in Sweden for the treatment of type 2 diabetes.

Over the past five years, several GLP-1 RA substances have been developed, and Handelsman's review (29) lists semaglutide as a current GLP1-RA in the same group as exenatide, liraglutide, lixisenatide, and dulaglutide. Semaglutide was developed by

Novo Nordisk and has been approved by the FDA since 2017 as a drug for subcutaneous injection (trade names Wegovy® and Ozempic®). In September 2019 (FDA) and March 2021 (Sweden, Medical Products Agency (30)), semaglutide was approved for oral administration in tablet form (Rybelsus®) (29). Subcutaneous injection is administered once a week, and oral treatment once a day. Semaglutide offers advantages over other diabetes medications that may require multiple daily doses (29).

The EMA indicates the safety profile for semaglutide (Wegovy®) when administered as a weight loss drug (31), and describes several very common side effects. These include nausea, vomiting, abdominal pain, diarrhea, and constipation, which occur in at least one in ten users (≥1/10).

2.3 Why is semaglutide used for weight loss?

Several clinical studies have played a crucial role in establishing semaglutide's effectiveness in weight loss, and here are some of the most significant:

One of the first studies linking semaglutide to weight loss was published as early as 2013, associated with the treatment of type 2 diabetes (32). The later SUSTAIN and STEP studies showed the relationship between semaglutide treatment and weight loss in patients without diabetes.

SUSTAIN Studies (33):

- SUSTAIN 1 and 2: These studies showed that semaglutide was effective in causing weight loss in people with type 2 diabetes.
- SUSTAIN 3 and 4: These studies showed that semaglutide was effective in causing weight loss in people with overweight or obesity without diabetes.

STEP Studies (34):

- STEP 1, 2: These studies showed that semaglutide was effective in causing weight loss in people with type 2 diabetes, and the effect was comparable to liraglutide (Victoza®).
- STEP 5: This study showed that semaglutide was effective in causing weight loss in people with overweight and obesity without diabetes.

These studies are funded by Novo Nordisk. Researchers have concluded from these studies that semaglutide is an effective and safe drug for weight loss in people with type 2 diabetes and those with overweight or obesity without diabetes.

Semaglutide (Wegovy®) is currently approved by the FDA (35,36) and EMA (31) for weight loss in children from twelve years of age with obesity and adults with a BMI ≥ 30 kg/m² or ≥ 27 kg/m² with weight-related complications.

2.4 Current hypotheses on mechanisms of action for weight loss

It is well documented that semaglutide works for weight loss for many individuals over a time perspective of up to two years (33,34).

There are also several hypotheses today that explain the mechanisms of action for this weight loss effect, where slow gastric emptying, suppression of appetite signaling, and improved homeostatic satiety signaling are among the effects described in published studies. An article in Svenska Farmaci describes the effect, "How Semaglutide Works

as a Weight Reducer" (37), as well as in Medscape's infographic from March 12, 2024, "Where GLP-1s Work Now and What's Coming" (38).

According to Hayashi et al. (10), GLP-1 receptor agonists such as semaglutide also affect cravings and food desires. It reduces the obsession with food, known as "food noise," and this suggests that it is an active mechanism for weight loss. There are GLP-1 receptors in the brain's parietal cortex as part of sensory feedback. There are receptors in the hypothalamus for metabolic feedback and in the medulla for visceral feedback (17,39). In summary, current hypotheses suggest that semaglutide can affect both homeostatic and hedonic appetite regulation and is beneficial as an active mechanism for weight loss.

2.5 The effect of food on the regulation of appetite, hunger, and satiety

Both homeostatic and hedonic regulation of food intake ensures homeostasis and the organism's survival. The food consumed has its own direct effect on this signaling, where insulin, for example, is secreted in response to increased glucose in the blood, and CCK (cholecystokinin) and PYY (Peptide YY) are secreted during fat intake (19).

2.5.1 Homeostatic effect of food intake

Food intake is traditionally measured in calories (Kcal) and is often described as energy intake. When food is broken down in the digestive system, it is not separated into energy but into nutrients such as amino acids, peptides, fatty acids, and simple and complex carbohydrates (40). Not only specific nutrients but also the quantity affects homeostasis, and for example, satiety is signaled via mechanoreceptors in the intestinal wall, through the vagus nerve to the brainstem, in response to volume (41). Nausea is signaled via the vagus nerve during overeating (25).

2.5.2 Hedonic effect of food

Taste, smell, appearance, and texture are significant for the hedonic enjoyment of food (6). The intense anticipation of a hedonic response from food intake can be a significant driving force to eat, as defined in "Hedonic Eating and the Delicious Circle of Craving" (42).

Ultra-processed foods are designed to maximize pleasure and reward, achieved through a well-balanced combination of sweetness, fat, salt, color, shape, smell, and texture (43). This type of food can trigger intense cravings, as Teicholz discusses in her review article "Are Ultra-Processed Foods Uniquely Addictive?" (6). Craving for food is equated here with craving for other addictive substances as the core of addictive behaviors.

Ultra-processed foods can be used to enhance positive feelings and suppress negative emotions (7,43), and the volume of food can also be used for emotional regulation, such as in the eating disorder "binge eating disorder" (44).

Craving is not only triggered by sensory input from food or the thought of food. For some, the craving for the hedonic effect of food also arises in response to the need for emotional regulation (7).

On an individual level, craving is caused and experienced differently. In a previous study on craving, brain activity was compared between different groups with and without addictive behaviors around food. It showed that craving is expressed differently in the brain between these groups (45). Participants were either overweight or obese, and brain activity was measured using fMRI. Before the study, participants were separated into different groups through screening with YFAS2.0 (Yale Food Addiction Scale version 2.0) (46).

2.5.3 Craving and the Combined Hedonic/Homeostatic Effect of Food as a Substance

In summary, based on this section and its sources, the combined hedonic and homeostatic effect of food can be expressed as follows:

- The direct impact of food on the body's regulation of appetite, hunger, and satiety involves a complex interaction between homeostatic and hedonic mechanisms, which is crucial for our survival.
- Both the nutritional value and quantity of food affect satiety and hunger through hormonal and neural signals from the digestive tract.
- Hedonic aspects such as taste, smell, and texture play a significant role in food enjoyment, and anticipation of this can lead to cravings.
- Cravings can be triggered by the expectation of the food's directly rewarding nature, but also by the expectation of emotional suppression or enhancement (emotional eating).
- Ultra-processed food (47) is often designed to maximize palatability and enjoyment, thus becoming an effective component that reinforces addictive behaviors and emotional eating.
- The hedonic factor is expressed differently in different individuals, as clear differences in craving expression are seen in the brain through fMRI in people with and without food addiction. This contributes to the understanding that appetite regulation is an extremely complex behavior.

In summary, emotional eating, eating disorders, and addiction are visible expressions of a changed balance in the complex signaling that regulates homeostatic and hedonic appetite through satiety, hunger, and cravings (3,7,26,43–45).

2.6 Qualitative measurement instruments for assessing experienced craving

As summarized earlier, craving is an extremely complex emotion that can be triggered by the sensory perception of food, the thought of food, or the thought of the effect that food can provide. Since this response is emotional, it is often measured subjectively through quantitative questionnaires. There are many such instruments designed, and below is one of them described in more detail, which has been used in studies in the present literature review.

2.6.1 CoEQ

The Control of Eating Questionnaire (CoEQ) is designed to assess various dimensions of eating behavior, particularly those related to control over food intake and experiences of cravings (2,48). The questionnaire contains 21 questions or statements that respondents rate based on a VAS scale from 1-100, usually based on their experiences

over a specific period. The questions cover four different domains to capture different degrees of craving experience such as:

Craving for wweet: This domain relates to the intensity and frequency of cravings specifically for sweet foods, such as candy, chocolate, and other sugary products.

Craving for savory: This domain relates to the intensity and frequency of cravings specifically for savory foods, such as high-fat, salty, or umami-flavored foods. This includes chips, cheese, and other non-sweet products.

Mood: This domain examines how eating affects an individual's mood and general sense of well-being, such as happiness, anxiety, alertness, and satisfaction.

Control of eating: This domain relates to the individual's ability to control their eating behavior, such as resisting impulses/cravings, the frequency and strength of cravings, and how difficult it has been to control their eating.

Furthermore, questions directly related to feelings of hunger and satiety are also included (2).

An evaluation of the validity and reliability of this measurement tool concludes, based on a review of 4 studies and 225 study participants, that:

"CoEQ subscales were associated with eating behavior traits that predict overeating, measures of adiposity, and selection and intake of snack foods. This preliminary examination suggests that the CoEQ is a reliable and valid measure of the experience of food cravings." (48)

2.7 fMRI (Functional Magnetic Resonance Imaging)

Functional magnetic resonance imaging (fMRI) is described in an article in the journal Nature by Finn, Poldrack, and Shine (49) as a non-invasive measurement of activity in the awake, behaviorally active human brain. By tracking brain signals across a broad spectrum of cognitive and behavioral states or mapping differences associated with specific traits or clinical conditions, fMRI has, according to Finn, enhanced our understanding of brain function and its connections to both normal and atypical behavior.

fMRI uses BOLD (Blood Oxygen Level Dependent) to detect brain activity, an indirect measure of neural activity based on changes in blood flow and oxygen levels (50). High oxygenation of blood flow results in low magnetism in hemoglobin, which translates to a high BOLD signal in areas of the brain with high neural activity. However, the BOLD signal has some latency, meaning it is slower than the actual neural activity. This limits fMRI's ability to capture rapid changes in brain activity.

Finn describes in Nature (49) that functional magnetic resonance imaging (fMRI) has several strengths that make it a valuable tool in neuroscience research and clinical diagnostics, such as:

- Non-invasive: fMRI does not require surgical interventions, allowing the exploration of brain functions in both healthy individuals and patients without the risk of physical harm.

- High spatial resolution: fMRI offers detailed imaging of blood flow and oxygen levels in the brain, enabling the identification of activity down to the millimeter level in various brain regions.
- Whole-brain coverage: The technique allows researchers to study activity across the entire brain simultaneously, providing a comprehensive view of brain functions during different tasks or states.
- Measurement of brain activity during activity: fMRI enables the examination of the brain while individuals perform specific cognitive or motor tasks, contributing to the understanding of the brain's dynamic functions regarding oxygenation and blood flow.
- Temporal and spatial patterns of brain activity: Despite the latency in the BOLD signal, fMRI can show both where and when activity occurs in the brain, which can be crucial for understanding complex neural networks and their function.

According to Finn, these properties make fMRI and the mapping of blood flow and oxygenation a powerful tool for studying brain structure and function in both fundamental research and clinical contexts.

2.8 Craving measured as neural activity in the brain with fMRI

A review article published in 2022 (51) summarizes how research with the older technique of Magnetic Resonance Imaging (MRI) has primarily focused on effects in the cortex and basal ganglia due to technical limitations in standard MRI scanners and suggests that research with newer techniques should consider subcortical networks, such as those involving the hypothalamus, brainstem, and thalamus, to better understand more interacting parts of the brain. The review emphasizes the role of subcortical brain regions in reward processing, habit formation, cognitive control, and emotional regulation, all of which are relevant for understanding hunger, satiety, and eating behavior, and stresses the importance of understanding how neural signals in these areas can converge to drive eating behaviors.

fMRI is thus a good way to attempt to form an objective understanding of craving and its neural expression in the human brain.

2.8.1 Recent findings on craving in response to visual food-related stimuli

To understand the latest research findings related to mechanisms associated with craving, a search was conducted on PUBMED focusing on the most recent studies performed with fMRI technology related to the activation of brain areas during craving based on visual food-related stimuli.

The fMRI studies presented in this section are experimental original articles conducted on small populations totaling 89 individuals.

The majority of the population has a BMI indicating overweight and obesity. One of the studies includes a control group of normal-weight individuals with a BMI between 18 and 25. All participants are selected based on the absence of endocrine diseases, including type 2 diabetes.

All three studies conducted a food cue reactivity protocol (response to food-related stimuli) on the individuals simultaneously with fMRI of the brain. The studies examined how individuals reacted to visual stimuli of food images compared to neutral images

and how different types of images were reported to affect cravings or the desire to eat by the participants.

The BDNF (Brain Derived Neurotrophic Factor) study investigates whether BDNF levels can be associated with neural reactivity to visual food stimuli and linked to craving (52). The BDNF study compares data between populations of overweight/obese and normal-weight individuals.

Two of the studies (the task-dependent study and the habituation study) are based on the same population and intervention but with different focuses in their data analysis (53)(54).

The brain's neural activation areas were identified by an increase in the fMRI-generated BOLD signal and differ in the three studies, but all draw similar conclusions where visual food images in the interventions lead to increased neural activity through increased oxygenation and blood flow in specific regions of the brain. This measured neural activity is linked through subjective responses about craving to the participants' experienced craving.

All three studies seek to identify which regions and areas of the brain are neurally activated during experienced craving, with the habituation study also relating to changes over time.

No consistent results are shown regarding specific activation areas during craving. In the BDNF study, craving is linked to high neural activity in the insula (55), the task-dependent study shows high neural activation in the amygdala (56), VTA (57), and orbitofrontal cortex (58), and the habituation study's neural activation areas related to craving were the amygdala (56), striatum (59), and frontal gyrus (60). This confirms the complexity of experienced craving through many parts of the brain being implicated. GLP-1 receptors are represented in many areas of the brain such as the amygdala, hypothalamus, insula, medulla, orbitofrontal cortex, and nucleus accumbens (10,17,19,39), which also supports that semaglutide administered for weight loss can affect craving.

The BDNF study concludes that increased BDNF levels in the brain lead to reduced craving, i.e., the amount of BDNF as a neurotransmitter affects the experience of craving. The task-dependent study concludes that neural activity during visual stimulation with food images can be linked to reported craving. The habituation study concludes that participants report habituation to the images with repeated visual stimulation with food images, i.e., reduced feelings of craving with repeated stimulation.

Huang et al. confirm the complexity of the neural expression of craving in their review article from 2023, "Neuroimaging and neuroendocrine insights into food cravings and appetite interventions in obesity" (61), by summarizing that food cravings are complex and multifaceted phenomena that require a holistic and multidisciplinary approach for effective management. Distinguishing cravings from appetite and understanding their neuroendocrine foundations is crucial for developing better treatment strategies for obesity and related metabolic diseases.

3 Purpose and Hypothesis

Previous studies indicate that the effect of semaglutide on weight loss varies. Weight loss can be up to 20% of body weight over time in some patients (12 weeks to 2 years), while semaglutide in the same period leads to weight gain in others.

The purpose of this literature review is to investigate whether semaglutide as an active substance can affect the ability of individuals to manage cravings. Furthermore, it examines whether there is a correlation between the ability to manage cravings and weight loss.

Based on this purpose, two hypotheses were proposed:

- **H0:** Treatment with semaglutide for weight loss does not lead to any statistically significant change in the long-term effects on the experience of craving.
- **H1:** Treatment with semaglutide for weight loss leads to a statistically significant change in the long-term effects on the experience of craving.

To measure participants' experience of cravings among patients treated with semaglutide, data collected via the CoEQ questionnaire used in selected studies was utilized.

4 Method

This work is conducted as a literature review where studies were searched on PUBMED based on specific search criteria and then summarized and analyzed.

4.1 Keywords

To find a basis for analyzing semaglutide's impact on cravings for individuals using semaglutide for weight loss, the focus was directed at literature searches regarding current research investigating the GLP1 agonist semaglutide in combination with craving.

The keywords used were obesity, semaglutide, craving, and clinical trials, and inclusion criteria were applied.

Studies involving participants with diabetes mellitus were excluded.

Searches were conducted from January 15 to 25, 2024. Any later publications are not reflected in this work.

Four published scientific studies were the result, of which three focused on obesity and one directed towards diabetes mellitus. Since the focus is specifically on weight loss, the study directed towards diabetes mellitus was excluded. According to the standardized protocol CoEQ (Control of Eating Questionnaire) (2,48), all included studies recorded participants' experience of cravings over different periods while taking semaglutide or placebo.

- **"Effects of once-weekly semaglutide on appetite, energy intake, control of eating, food preference, and body weight in subjects with obesity"** (62). This collected data to compare effects after twelve weeks from the initial measurement at study start. The treatment was solely through the use of

semaglutide or placebo with titration up to a maximum dose of 1 mg after 12 weeks.

- **"The effect of semaglutide 2.4 mg once weekly on energy intake, appetite, control of eating, and gastric emptying in adults with obesity"** (63) collected data to compare effects after 20 weeks from measurement at study start. The treatment was solely through the use of semaglutide or placebo with titration up to a maximum dose of 2.4 mg over 20 weeks.

- **"Two-year effect of semaglutide 2.4 mg on control of eating in adults with overweight/obesity: STEP 5"** (11) collected data on cravings at the start of the study and after 20, 52, and 104 weeks of medication with semaglutide or placebo with titration up to a maximum dose of 2.4 mg over 20 weeks, or the highest tolerated dose. The same weekly dose was then given to participants for the remainder of the study. In addition to treatment with semaglutide or placebo, the treatment also included a dietary restriction with a 500 Kcal deficit and participants were also required to engage in 150 minutes of pulse-raising activity each week.

5 Results

5.1 Demographics

The three studies had a total of 274 adult participants with varying genders, a homogeneously ethnically white grouping with a BMI over 30 indicating obesity, and with HbA1c < 48 mmol/mol indicating the absence of type 2 diabetes.
A demographic summary can be seen in Table 1.

Table 1: Demografic distribution of participants in the three studies as base for this litterature review

	Blundell et al (2016)	Friedrichsen et al (2021)		Wharton et al (2023)	
	12 weeks RCT	20 weeks RCT		104 weeks RCT	
	Crossover	Semaglutide	Placebo	Semaglutide	Placebo
No# completing participants	28	36	36	88	86
Age (average)	42	40,7(12,2)	45,0(9,5)	47,3 (12,3)	47,3(10,7)
Women (%)	33,3	33,30%	44,40%	80,70%	74,40%
Ethnic white (%)	90%	97,20%	100%	87,50%	89,50%
Weight (Kg) (average)	101,3	106,2 (16,2)	104,9(14,0)	107 (20,8)	105,9(26,2)
BMI (average)	33,8	34,2 (3,0)	34,6 (3,1)	39,3 (6,9)	38,1 (7,9)
Waist (cm) (average)	not published	not published	not published	116,3 (13,9)	114,7 (16,2)
Initial Craving control	not published	not published	not published	4,6 (2,4)	5,0 (2,4)
Initial mood	not published	not published	not published	7,4 (1,4)	7,5 (1,3)
Initial Craving savory	not published	not published	not published	4,9 (2,1)	5.0(2,2)
Initial Craving sweet	not published	not published	not published	4,5 (2,1)	4,3 (2,3)
Initial Hunger	not published	not published	not published	5,5 (2,0)	5,8 (1,9)
Initial satiety	not published	not published	not published	6,3 (2,0)	5,9 (1,9)
Diabetes	No	No	No	No	No
HbA1c	< 48 mmol*	< 48 mmol*		< 48 mmol*	

* 42 - 48 mmol/mol indicates prediabetic with risk of insulin resistance

5.2 Safety profile of the RCT studies

The safety profile of the three RCT studies (11,62,63) is summarized here based on the available reporting of common gastrointestinal side effects [n >10%]. Blundell (2016) did not report details regarding side effects. In the publications by Frierichsen et al. (2021) and Wharton et al. (2023), detailed reporting included gastrointestinal events and side effects, which are summarized in Table 2.

Table 2: Safety profile on commonly reported GI events with prevalence >10%

	Blundell et al (2016)		Friedrichsen et al (2021)		Wharton et al (2023)	
	Semaglutide	Placebo	Semaglutide	Placebo	Semaglutide	Placebo
Decreased appetite	N.A	N.A	55,6%	27,8%	11,2%	3,9%
Nausea	N.A	N.A	47,2%	16,7%	53,3%	21,7%
Diarrhea	N.A	N.A	44,4%	11,1%	34,9%	23,7%
Constipation	N.A	N.A	N.A	N.A	30,9%	11,2%
Vomiting	N.A	N.A	22,2%	2,8%	30,3%	4,6%
Dyspepsi	N.A	N.A	13,9%	0,0%	13,2%	4,6%

Based on Table 2 above, significant differences between semaglutide and placebo can be observed. Nausea was experienced by 47.2% and 53.3% of participants on active semaglutide treatment, compared to 16.7% and 21.7% on placebo.

Decreased appetite was reported as a side effect, with 55.6% of participants in the 20-week study experiencing decreased appetite on semaglutide, compared to only 11.2% of participants in the long-term study.

5.3 Semaglutide and craving

The three double-blind, randomized, placebo-controlled studies were conducted over different durations (12, 20, and 104 weeks). The interventions consisted of weekly injections of semaglutide, with the 12-week study titrating up to a maximum dose of 1 mg per week and the 20-week and 104-week studies titrating up to a maximum dose of 2.4 mg. The length of the study was the determining factor for the maximum titration, with escalation occurring in blocks of four weeks between 0.25, 0.5, 1, 1.7, and finally 2.4 mg.

The placebo treatment was volume-matched, meaning that participants in the placebo group received injections with an inactive solution corresponding to the amount of semaglutide.

All participants in the selected studies were obese at enrollment, without indications of type 2 diabetes (HbA1c < 48 mmol/mol), and had not attempted weight loss in the three months prior to the study.

The standardized CoEQ (Control of Eating Questionnaire) was used for qualitative data collection regarding cravings and control of eating in all three studies.

According to Table 1, 274 individuals were included in the data collection with CoEQ for cravings in the three studies. Of these, 28 individuals were part of a crossover study and thus served as their own controls.

The setup for quantitative data collection in the three studies is described in Table 3.

Table 3: Design of the three RCT studies used to evaluate the effect that semaglutide interventions has on craving

	Blundell et al (2016) Study 1	Friedrichsen et al (2021) Study 2	Wharton et al (2023) Study 3
Published	2016	2020	2022
Duration	12 weeks	20 weeks	104 weeks
Type of study	RCT, single center, two period crossover, washout 5-7 weeks in-between	RCT, Single center, parallell groups	RCT, multi center, parallell groups
Intervention	Semaglutide subcutaneous or placebo once a week 4 w, 0,25mg 4 w, 0,5 mg 4 w, 1,0 mg	Semaglutide subcutaneous or placebo once a week, Dosescalation 16 w from 0,25 > 0,5 > 1,0 > 1,7 mg>2,4 mg 5 weeks with 2,4 mg	Semaglutide subcutaneous or placebo once a week, 16 weeks dose escalation from 0,25 to 2,4 mg maintenance dose W16 - 104 : 2,4 mg (less if object could not manage 2,4) + 150 min exercise weekly and 500 kcal energy deficit in diet Contact with dietician/healthcoach every 4th week
No# of participants	28	36+36	86+88 (subset av total på 304, selektion USA&Canada
Primary endpoint	ad-libitum energy consumption during lunch after 12 weeks of treatment	Gastric emptying	Weightloss
Craving	sekondary endpoint, 14 questions from CoEQ	Exploratory, 19 questions from CoEQ	Exploratory, 19 questions from CoEQ
CoEQ datacollection	baseline, 12 weeks	baseline, 20 weeks	baseline, 20, 52 och 104 weeks

As illustrated in Table 3, the interventions differed among the three studies, with a maximum dose of 1 mg semaglutide in the 12-week study and a maximum dose of 2.4 mg in the 20- and 104-week studies. The 104-week study included altered dietary and exercise patterns as part of the intervention, while the 12- and 20-week studies involved only semaglutide/placebo intervention.

All studies had primary outcome variables other than craving. Craving was a secondary endpoint in the 12-week study and was examined exploratorily without a predefined endpoint in the 20- and 104-week studies. Given that the requirements for analysis and interpretation of secondary and exploratory outcome variables according to the FDA's guidance on multiple endpoints (64) are not as strict and clearly regulated as for primary endpoints, it is particularly important to carefully review these results.

The use of CoEQ was homogeneous in 14 of the questionnaire's 19 questions across all three studies, as illustrated in Table 4. This homogeneity makes the results of the CoEQ questionnaires comparable across the three studies from this perspective.

Table 4: Comparison of the CoEQ data collection in the three selected studies evalutating the effect of semaglutide on craving

	Blundell et al (2016) 12 weeks	Friedrichsen et al (2021) 20 weeks	Wharton et al (2023) 104 weeks
No# of questions from CoEQ	15 (14*)	19** (14*)	19** (14*)
Domains	3 (craving domain mood missing)	4	4
Reference data collection	Day 1	Day 1	Day 1
Sampling time	2 days after last dose	day 141, 2 days after last dose	week 20, 52 and 104
Evaluation criteria	experience in the last 7 days	experience in the last 7 days	experience in the last 7 days
Scale	100 mm VAS	100 mm VAS	100 mm VAS

* comparable over all three studies ** Comparable over Friedrichsen- and Whaton et al

5.3.1 Summary of craving results after 12, 20, and 104 weeks of semaglutide use

The three studies examined craving either as a secondary or exploratory endpoint, and the conclusions from these studies suggest that semaglutide has a clear and positive effect in reducing cravings.

This literature review chooses to disregard these conclusions of a positive effect and instead focuses on comparing the actual data on cravings presented in the studies. Since all three studies used the same quantitative protocol defined as CoEQ (Control of Eating Questionnaire) for recording cravings, it is possible to compile a comparative table.

Table 5 presents the 19 questions from the CoEQ questionnaire in their original English format, divided into six defined craving domains. The table focuses on the statistical significance (p-value) of the results rather than the actual effect (increase for satiety, happiness, alertness, and satisfaction, and decrease for all others). This is shown with different color codes (pink and green) indicating the statistical significance of the results for each question within the various craving domains, compared to placebo. Green indicates statistical significance ($p<0.05$) and pink indicates not statistically significant ($p\geq0.05$), suggesting that a positive effect in the question is caused by treatment with semaglutide. The change in results is valued differently in different questions – for example, for the question about hunger, a decrease is the desired outcome that is valued, and for the question about satiety, an increase is desirable and what the p-value is based on. Upward and downward arrows to the right in the table show the valued direction of the effect.

Table 5: Results from the Control of Eating Questionnaire (CoEQ) are segmented by study. The outcomes are summarized according to craving domain and study, with light green indicating a statistically significant positive effect with semaglutide, and pink denoting p>0.05 with no statistically significant difference between semaglutide and placebo

Statistical significance
No statistical significance

		Blundell et al (2016)	Friedrichsen et al (2021)	Wharton et al (2023)	
	COEQ	12 weeks	20 weeks	104 weeks	
	1				↓ How hungry have your felt
	2				↑ How full have you felt
	3				↓ How strong was your desire to eat sweet foods
Group Craving sweet	13				↓ How often have you had cravings for chocolate or chocolate-flavoured food?
	14				↓ How often have you had cravings for other sweet food?
	15				↓ How often have you had cravings for fruit or fruitjuice?
	4	Not answered			↓ How strong was your desire to eat salty and spicy foods
Group Craving savory	16				↓ How often have you had cravings for dairy food?
	17				↓ How often have you had cravings for starchy food?
	18				↓ How often have you had cravings for salty and spicy food?
	5	Not answered			↑ How happy have your felt
Group Mood	6	Not answered			↓ How anxious have you felt
	7	Not answered			↑ How alert have you felt
	8	Not answered			↑ How contented have you felt
	9				↓ During the past 7 days, how often have you had food cravings
	10				↓ How strong have any food cravings been
Group Craving control	11				↓ How difficult has itt been to resist any food cravings been
	12				↓ How often have you eaten in response to cravings
	19				↓ How difficult has it been to control your eating
The proportion of statistically significant responses to questions		64%	58%	32%	

Table 5 shows that the craving domains "craving for savory food" and "managing cravings" had a high degree of statistical significance ($p<0.05$) for a positive effect of semaglutide from start to finish in all three studies, whereas the domains "mood" and "craving for sweets" had a low degree of statistical significance ($p\geq0.05$) for the effect caused by semaglutide treatment.

Reduction in hunger was significant after the 12- and 20-week studies but not after the 104-week study. An increase in satiety was significant after the 20-week study, but the 12- and 104-week studies showed no clear positive change between start and finish compared to placebo.

The percentage of questions with a confirmed effect on the improvement of craving-related parameters caused by semaglutide ($p<0.05$) is indicated by the percentage under each study column. The statistical significance of the results decreased over time. Table 5 shows that the 12-week study had 64% of the answered questions (9 out of 15) leading to improvements in craving-related parameters that were statistically significant. The 20-week study reduced its share of statistically significant results to 58% (11 out of 19), and the 104-week study's results showed only 32% with statistically significant relevance (6 out of 19). This means that the effect on craving-related parameters treated with CoEQ gradually equalized between semaglutide and placebo treatment over time.

5.3.2 Wanting specifically registered in the 12-week study

In the 12-week study, changes in food preferences over the 12-week period were also examined, and a significant change was found, with a greater "wanting" ("wanting" in the study defined as a lower degree of craving) for foods that were both sweet and low-fat ($P=0.0401$) after the use of semaglutide over the 12-week period. This means that the craving for sweets statistically significantly increased with the use of semaglutide in this 12-week cohort.

5.3.3 Change between 20, 52, and 104 weeks in the 104-week study

In the long-term study, which lasted 104 weeks, CoEQ was also used for quantitative data collection after week 20 and week 52, providing 3 datasamples for comparing the effectiveness of semaglutide on craving. This, combined with the altered exercise and dietary patterns that were part of the intervention for the long-term study, offers comprehensive insight into the longitudinal effectiveness of semaglutide on cravings.

Table 6: Results from the long-term study with semaglutide (Study 3 in Table 1) on craving domains over time (20 weeks, 52 weeks, and 104 weeks). The results are marked in light green for statistical significance and positive effect of semaglutide as a function of craving domain and time throughout the long-term study. Pink marking indicates p>0.05 and no statistically significant difference between semaglutide and placebo. The text across each row with result indicates the positive effect of semaglutide over time in the long-term study, as interpreted from the curves and tables in the study.

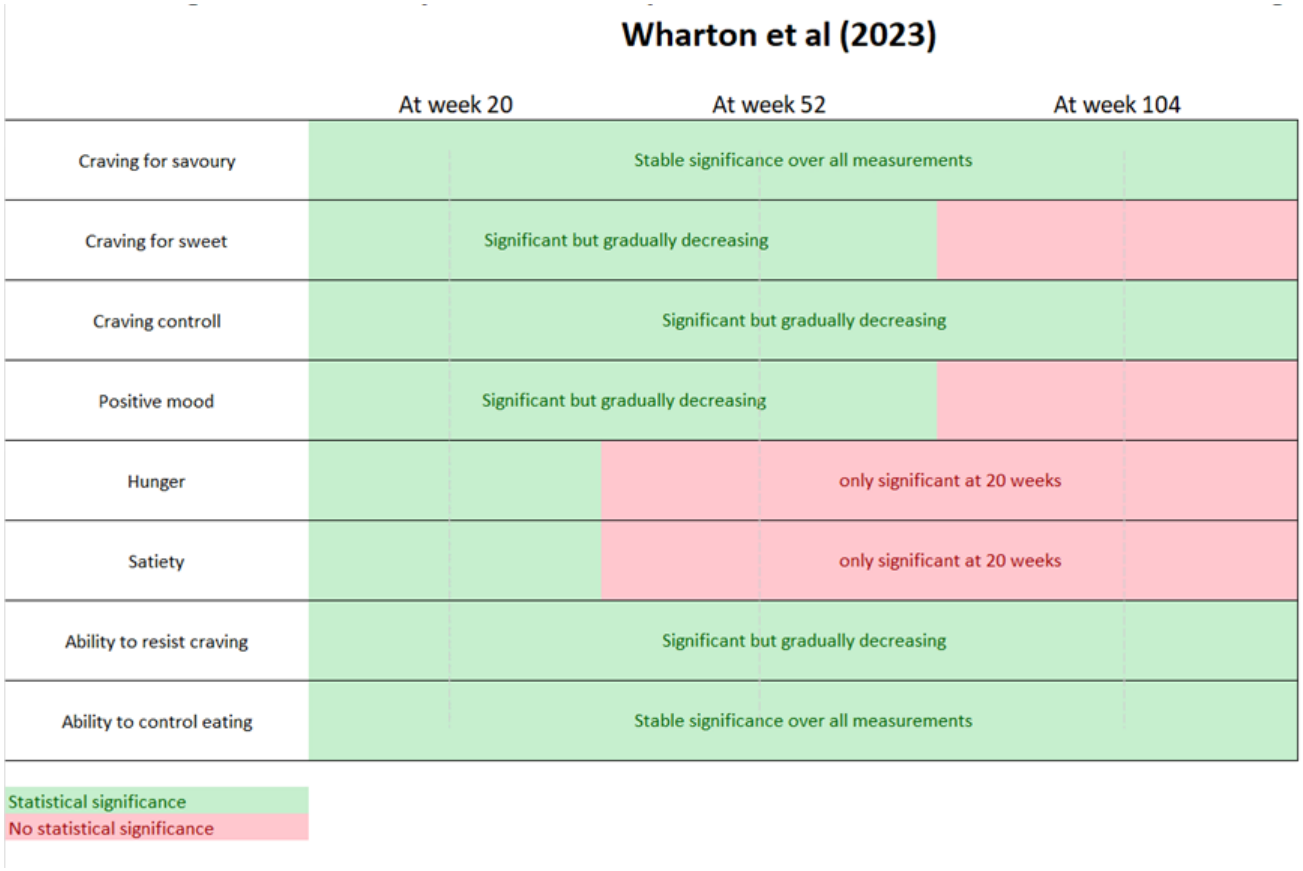

Table 6 shows red markings which indicate that the effect of the intervention at 104 weeks did not have statistical significance with $p \geq 0.05$ in the reduction of craving for sweets, positive effect on mood, reduction of hunger, and increase in satiety.

Decreased craving for savory food, increased craving control, increased ability to resist cravings, and increased ability to control eating showed statistical significance throughout the study period, but craving for savory food and the ability to control eating are the only two measurements that showed a stable positive result over all 104 weeks. This occurred after 16 weeks of titration to the tolerated dose, which was then maintained for the remainder of the time as described in Table 3.

For all other quantitative measures—feelings of hunger, satiety, positive mood, craving control, and craving for sweets—the positive effect of semaglutide intervention on cravings clearly decreased over time.

5.3.3.1 Craving Related to Weight Loss in the 104-Week Study

In the 104-week study, the five domains—craving control, craving for savory food, craving for sweets, hunger, and satiety—were divided into specific subgroups for exploratory purposes based on high and low experiences of cravings at the start of the study.

The results showed a significant connection between higher levels of craving for sweets before semaglutide treatment and greater relative weight loss after 104 weeks. No significant associations were observed between the level of initial cravings and the weight loss effect in the other four domains.

6 Discussion

In the ongoing effort to find effective treatments for overweight and obesity, semaglutide has positioned itself as a promising pharmacological option with high efficacy in weight loss and many metabolic benefits. It has been enthusiastically received by both physicians and consumers for its marketed ability to reduce hunger and improve satiety, thereby leading to substantial weight loss for many with overweight or obesity. As of now (May 2024), semaglutide is not prescribed in Sweden with subsidies for the indication of weight loss, and diabetes patients who lack a good effect from previously tried diabetes treatments are prioritized for treatment. However, many private companies offer non-subsidized prescriptions of semaglutide for weight loss, which complicates matters for those who truly need the medication. In Norway, rationing for patients with the greatest need is being discussed (65).

Media coverage of semaglutide as a miracle drug should be nuanced as this literature review highlights the drug's limitations and the lack of sufficient knowledge regarding its long-term effects. This is particularly true for its effectiveness in managing fundamental aspects of eating behavior characterized by cravings as defined in this work.

The results of this review show that weight loss achieved through weekly injections of semaglutide for up to two years is not caused by a reduced effect on cravings, i.e., the hedonic regulation of seeking pleasure and reward. Thus, treatment with semaglutide for weight loss does not lead to a statistically significant change in the long-term effects on the experience of cravings as confirmed by these studies.

The results mean that the thesis that there is a statistically significant reduction in cravings with semaglutide treatment for weight loss is rejected.

As part of the analysis of the 104-week study (11), the authors of the long-term study explored the data based on high or low scores in different craving domains before the start of treatment and concluded that the baseline levels of hunger, satiety, craving control, and craving for savory food, according to their analysis, had no differential impact on the resulting weight loss. In the same exploratory analysis, it was concluded that the greater the craving for sweets before medication began, the greater the relative weight loss semaglutide could cause, leading the authors of the long-term study to

conclude that semaglutide might be most effective for individuals with a high craving for sweets. However, it is unclear how this might be connected, as craving for sweets is the area least affected by semaglutide, with statistical significance in only one out of twelve questions across all three studies. The craving for sweets actually increased between the start and end of the twelve-week study. The results are contradictory and underscore the need for further research to understand the complex mechanisms behind how semaglutide affects appetite control and to explain why weight loss is greater in individuals with higher initial cravings for sweets despite their cravings not decreasing with semaglutide treatment.

The results show a diminishing effect of semaglutide over time in the reviewed 104-week study, both regarding the management of cravings as well as hunger and satiety, while cravings for sweets were not significantly affected. This raises questions about the drug's effectiveness as a long-term pharmacological solution based on weight loss effects such as reduced hunger, increased satiety, and decreased cravings. Based on the available research in this literature review, it cannot be ruled out that the downward trend continues and more research is needed to understand the long-term effect on these factors (see Table 6).

Further studies are needed to show what happens to cravings, hunger, and satiety feelings when injections are discontinued. The STEP 1 extension study (66) showed that within a year after stopping medication, patients regained two-thirds of the lost weight, indicating that maintenance doses of semaglutide may be needed for life to sustain weight loss.

Diabetes is a lifelong disease requiring treatment. By diagnosing obesity as a chronic disease (67), it is justified to consider that obesity as a chronic disease also requires lifelong medication. The development of tolerance and potentially physiological responses in the form of GLP-1 resistance has been identified by Hertzberg-Schäfer et al. (68) as a risk in type 2 diabetes, and similarly, the development of hyperglycemia during treatment with semaglutide, which over time would mean a poorer response to the use of GLP-1 analogs. Further research is needed to clarify the long-term effect on GLP-1 sensitivity in those injecting GLP-1 analogs weekly year after year.

The questions concerning "craving control," "control of eating," and cravings for dairy products or salty/spicy food were the only questions in the summary of CoEQ (4 out of 19 questions) in Table 5 that showed a consistent positive effect with semaglutide across all three studies and respective periods. Questions related to feelings of hunger, satiety, cravings for sweets, and positive impact on mood showed low significance over time despite titration to the maximum tolerable dose, further supporting H1, that semaglutide does not have a long-term effect on cravings.

The positive weight loss effects of semaglutide may instead be linked to homeostatic control and preventive effects against overeating as the drug, among other things, causes nausea as a side effect during treatment.

According to Farr et al. (39), there are GLP1 receptors in the hypothalamus as well as the brainstem, which can support a hypothesis of homeostatic control. However, GLP-1 receptors are also present in parts of the brain that regulate sensory impressions (17), indicating that there might also be a degree of hedonic regulation with semaglutide.

The BDNF study (52) shows that increased BDNF levels reduce the brain's neural response to visually food-induced cravings and Qi et al. demonstrate (69) that GLP-1 receptor impact in the brain affects BDNF secretion resulting in increased BDNF levels, which suggests that it could be an active mechanism for semaglutide to affect hedonic eating behavior.

Homeostatic hunger regulation is linked to unconscious subcortical areas such as the hypothalamus and brainstem, while hedonic hunger regulation is related to conscious subcortical areas through handling sensory impressions. However, the results from the "Task-dependent" study (53) indicate a more complex relationship. Sensory visual exposure to food initiates neural activities related to craving in the hypothalamus and brainstem without the impact of food via endocrine or vagal signals. This indicates that craving is a complex feeling involving many areas of the brain. It is clear that homeostatic and hedonic hunger and satiety are regulated by a large number of hormones, peptides, and neurotransmitters. Craving, when it arises as a result of interactions between many parts of the brain and complex signaling pathways with many involved signals, should therefore be able to manifest in a highly individual way. See Figures 1 and 2.

The question is whether the hedonic regulation's effectiveness with semaglutide treatment gradually diminishes over time according to homeostatic principles, similar to how craving has been shown to diminish in the habituation study (54). If so, why does this not occur to the same degree for homeostatic regulation?

An important aspect to investigate is whether the intake of high-calorie foods, often consumed during emotional eating, can increase the preventive effect (7). Furthermore, research should focus on understanding whether the side effects summarized in Table 2 create a deterrent against overeating high-calorie foods. These side effects could function similarly to how disulfiram works for alcohol consumption by inducing unpleasant physical reactions (70). Could this be an explanatory model for why those with the greatest craving for sweets at the start of the 104-week intervention (11) also experienced the greatest weight loss despite cravings for sweets not changing proportionately? It would be interesting to see future studies on GLP-1 RAs and analyze whether diet in any way affects perceived side effects and if these side effects can have a preventive effect.

Since craving appears to express itself differently in individuals with addictive behaviors related to food, the question also arises whether food-related addictive behaviors can contribute to individual differences in weight loss with semaglutide, both in terms of actual weight loss, perceived side effects, and effectiveness in reducing cravings. Van Ruiten's secondary analysis of the RCT study "Eating behavior modulates the sensitivity to the central effects of GLP-1 receptor agonist treatment" (71) indicates that emotional eating as a coping strategy for emotion regulation affects GLP-1 sensitivity.

If semaglutide most clearly affects homeostatic hunger over time relative to hedonic regulation, which seems to plateau over time, could this then explain why cravings for savory foods decrease more consistently with semaglutide than cravings for sweets, and why mood is not positively affected in the long term?

As a GLP-1 analog, semaglutide only mimics GLP-1, which is one of many signals involved in the biochemistry of hedonic eating, as summarized in both Figure 2 and Appendix A. Despite significant weight loss benefits for many, its effectiveness is not unequivocal for all participants, as the long-term study shows variance from weight gain to as much as 20% weight loss among participants (11). The variance in weight loss and the lack of long-term sustainable regulation of cravings indicate that semaglutide does not long-term address the underlying causes of overeating, which are often linked to psychological factors and behavior patterns with hedonic connections (71).

This indicates a need for a more integrated treatment strategy that combines pharmacological intervention with psychological support. Such a strategy can effectively manage both the physiological and psychological aspects of, for example, emotional eating and addictive behaviors.

6.1 Weaknesses of the review

In this scientific literature review, an examination of three randomized controlled trials (RCT) that investigated the effect of semaglutide on cravings is presented.
It is worth noting that all three semaglutide studies were funded by Novo Nordisk, which owns the patent for semaglutide, and some of the authors hold shares in the company, which can introduce potential conflicts of interest in interpreting the results (72). This could have influenced the expression in the studies. Interpretations by the authors of the studies have to some extent expressed semaglutide treatment as advantageous for treating obesity without having substance and sufficiently strong evidence in the form of statistically significant results regarding cravings over time, despite the maximum tolerated dose of the drug.

The demographic summary in Table 1 shows small and homogeneous study populations, limiting the ability to generalize the results to a broader population. Furthermore, Table 3 shows that data collection was based on quantitative, questionnaire-based methods, meaning a subjective rather than an objective measurement of cravings. By including fMRI studies that mapped the regions of the brain activated during craving, objective observations related to cravings were added. These observations support the interpretations of data from the studies here that examined the effectiveness of semaglutide as a treatment for weight loss, even though they are not directly comparable.

A significant challenge in these double-blind RCT studies was the risk of unblinding, especially as participants in the semaglutide groups, as illustrated in Table 2, reported a greater number of noticeable gastrointestinal side effects. This circumstance could potentially allow both participants and investigating physicians to identify which intervention group the participants belonged to, thereby changing attitudes towards and interpretations of the questions, both among participants and physicians.

By illustrating the three studies' setups in Table 3, it is clear that two were conducted without any additional intervention, while the third included dietary and exercise interventions. Furthermore, the 12-week study was so short that titration to the maximum dose of 2.4 mg semaglutide was not possible, making them collectively not fully comparable.

Regarding potential confounding factors, despite excluding patients with type 2 diabetes, there was no clarity on whether participants suffered from insulin resistance.

Since one of the active mechanisms of semaglutide is its impact on insulin secretion in the pancreas, insulin resistance (73) could potentially affect the results differently than in metabolically healthy individuals. Furthermore, the dietary and exercise intervention in the long-term study becomes a confounder in comparison with the 12- and 20-week studies.

Finally, it is very unclear to what extent addictive behaviors related to food affect weight loss and the experience of cravings in the participants, as the Yale Food Addiction Scale version 2.0 (YFAS 2.0) was not used to assess these addictive behaviors in the cohorts. According to the study "Food Cue Reactivity in Food Addiction: An fMRI Study" (45), craving has been shown to have different neural expressions in the brain in groups distinguished using YFAS 2.0, based on whether they exhibited clear or no signs of addictive behaviors related to food.

Overall, these observations indicate a need for further research with larger, more heterogeneous populations, objective measurement methods such as fMRI with the primary aim of determining semaglutide's effects on cravings, and clarifying the role nausea and other side effects play in weight loss to better understand semaglutide's mechanisms for weight loss effect.

Future studies should also more closely examine potential confounding factors to clarify the nature and extent of the observed effects.

6.2 Strengths of the review

This work includes a comprehensive review of all available literature that addresses the effect of semaglutide on cravings in people with obesity, without concurrent diabetes. This review is based upon the only known source on PUBMED that examines cravings in connection with GLP-1 receptor agonist treatment for obesity without diabetes, and not just for semaglutide.

One of the main strengths of this review is its use of uniform data collection methods. Specifically, the Control of Eating Questionnaire (CoEQ) was used consistently to collect data, making the results comparable across different studies.

6.3 Conclusion

In summary, this literature review highlights that semaglutide's effects on cravings in general, and cravings for sweets specifically, despite initial good effects on these expressions of craving, do not show statistical significance for any lasting positive impact in the long term. Although semaglutide contributes to weight loss for many, the results from the reviewed studies suggest that the drug's impact on appetite regulation is primarily homeostatic during the two-year period that is overall studied. The hedonic regulation mechanisms, such as cravings for sweets and impact on mood, do not show clear positive results with semaglutide, neither in the short 12-week perspective nor over 20 to 104 weeks.

This literature review highlights that understanding cravings is an important piece and central to sustainable weight management and improving patients' adherence and compliance in obesity treatment.

These observations identify a critical knowledge gap regarding the long-term treatment of overweight individuals and underscore the need for future research focusing on cravings and food desires as a primary endpoint in future studies.

It is important to explore the underlying mechanisms behind weight loss through GLP-1 analogs to understand their true effectiveness. Future studies should therefore include a deeper exploration of hedonic perspectives, such as the impact of emotion regulation linked to food intake. Additionally, the potential impact of the safety profile on long-term weight loss should be investigated by exploring the relationship between dietary choices and side effects, an area not sufficiently explored in current research.

Furthermore, the relationship between addictive behaviors and the effectiveness of semaglutide should be examined to clarify how individual differences can affect treatment outcomes. This type of research is necessary to develop tailored treatment strategies that can offer more comprehensive and sustainable effective solutions for individuals struggling with overweight and obesity.

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Appendixes

Appendix A: Overview of Hormones, Peptides, and Neurotransmitters for Appetite Regulation via Hunger, Satiety, and Craving

Name	Function in Appetite Regulation	Impact	Reference
Adiponectin	Regulates glucose levels and fatty acid breakdown	Improves insulin resistance, reduces inflammation	(16,19,21)
Amylin	Slows digestion and delays gastric emptying	Reduces food intake and can contribute to weight loss	(19,21)
BDNF	Regulates energy balance and neuronal plasticity	Affects eating behavior and possibly stress management	(20)
CART	Appetite-suppressing effect	Reduces appetite and increases energy expenditure	(19,21,22)
CCK	Stimulates the gallbladder, contributes to satiety	Reduces food intake and prolongs satiety after meals	(16,19,21)
CRH	Involved in stress response and appetite regulation	High levels linked to reduced food intake	(19)
Dopamine	Reward-related neurotransmitter	Associated with the pleasure aspects of food intake	(19,21,22,42)
Endocannabinoids	Increase appetite	Increase food intake and can affect the reward system	(19,42)
GABA	Inhibitory neurotransmitter, can affect eating behavior	Regulates stress response and can modulate eating behavior	(19,21,22,42)
Ghrelin	Stimulates appetite and regulates hunger	Increases food intake and can promote fat storage	(16,19,21–23,42)
GIP	Glucose-dependent insulinotropic peptide, regulates insulin secretion	Promotes insulin release post-meal, affects fat storage	(19,23)
GLP1	Stimulates insulin release, reduces glucagon	Reduces food intake, delays gastric emptying	(19,21–23)
Glucagon	Regulates glucose production in the liver	Increases blood sugar levels by breaking down liver glycogen	(16,19,21,23,42)
Glutamate	Major excitatory	Affects many aspects of	(21,22,42)

Name	Function in Appetite Regulation	Impact	Reference
	neurotransmitter	eating behavior and reward	
Insulin	Regulates blood sugar levels by promoting glucose uptake	Lowers blood sugar levels, affects long-term energy storage	(16,19,21–23,42)
Leptin	Signals energy balance to the brain	Reduces hunger, increases energy expenditure	(16,19,21,22,42)
Melanocortins (incl. α-MSH)	Regulates energy balance	Reduces food intake and increases energy expenditure	(16,19,21,22)
Norepinephrine	Affects attention and stress response	Can increase or decrease appetite depending on stress level	(22)
NPY	Strongly appetite-stimulating	Promotes food intake, especially driven by carbohydrates	(19,21,22,24,42)
Orexin	Promotes wakefulness and appetite	Stimulates food intake, also affects sleep-wake cycles	(19,24,42)
Oxintomodulin	Satiety-promoting effects	Reduces food intake and can affect energy expenditure	(21)
Oxytocin	Associated with satiety and social behaviors	Can reduce food intake and is involved in regulating social bonds	(19,42)
POMC	Produces several peptides that regulate food intake	Suppresses hunger and regulates energy expenditure	(19,21,22,42)
PP	Pancreatic polypeptide, promotes satiety	Reduces food intake and can affect gastric emptying	(21,22)
PYY	Released from the gut after meals and contributes to satiety	Reduces food intake and can delay gastric emptying	(19,21–23)
Resistin	Associated with insulin resistance	Can contribute to metabolic disturbances related to obesity and diabetes	(16,21)
Serotonin	Affects mood, satiety, and sleep	Suppresses appetite and is involved in mood regulation	(19,22)
Somatostatin	Inhibits secretion of several hormones including GH and TSH	Regulates digestive enzymes and bile flow, modulates insulin and glucagon	(4,15,18)
Uroguanylin	Stimulates secretion of ions and water in the intestines	Affects gastrointestinal function and possibly satiety	(23)