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Norwegian University of Science and Technology
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Sammendrag

Fedme, appetittregulering, og påfølgende effekter av vekttap med diett og fedmekirurgi

Fedme (BMI≥30kg/m^2) er en sykdom – og karakteriseres som kronisk, progressiv, og med tilbakefall. Likevel blir fedme ofte forbundet med dårlig selvkontroll og mangel på viljestyrke i forhold til matinntak og livsstil. Appetittregulering handler om mye mer enn dette. Kroppen trenger næring for å opprettholde normalfunksjon, og metabolismen spiller dermed en viktig rolle for appetitt. Imidlertid ser det ut til at fedme er assosiert med en dårligere metabolsk (homeostatisk) appetitt kontroll. Økt innsikt om potensielle forskjeller i utskillelsen av gastrointestinale (GI) hormoner og subjektiv appetitt i forbindelse med måltid, vil forbedre vår forståelse av fedme sykdommens patofysiologi. Ettersom at flere og flere utvikler alvorlig fedme, vil det i tillegg være nyttig å undersøke om den antatte forskjellen er mer uttalt med økende alvorlighetsgrad av sykdommen.

En systematisk oversiktstudie og meta-analyse ble gjennomført for å undersøke mulige forskjeller i homeostatisk appetitt kontroll hos personer med- og uten fedme. Resultatene viste at fedme var assosiert med både lavere sult- og metthetssignal fra GI systemet. Videre ble det gjort en tverrsnittstudie for å undersøke potensielle forskjeller i homeostatisk appetitt relatert til alvorlighetsgraden av fedme. Ved å sammenligne de totale verdiene av GI hormoner i tiden etter et måltid, ble det ikke observert noen forskjeller mellom de ulike gradene av fedme. Likevel, var alvorlig fedme (BMI≥35kg/m^2) assosiert med liten, eller ingen, endring i metthetssignal etter et måltid. Resultatene peker dermed på at fedme er assosiert med lavere metthestignaler.

Selv om lavkalori dietter er svært effektive for vekttap på kort sikt, ligger den største utfordringen i det å vedlikeholde vekttapet over tid. Mange komponenter bidrar til dette, men det er helt klart at et misforhold mellom appetitt og fysiologiske behov, spiller en viktig rolle. Dette kan være utfordrende i dagens overflodssamfunn, hvor belønning, følelser og ytre faktorer påvirker matinntak i stor grad (hedonisk appetitt). Fedmekirurgi er den mest effektive behandlingen vi har for vektreduksjon, og gir et mye større og vedvarende vekttap kontra ikke-kirurgiske metoder. Årsakssammenhengene er enda ikke helt forstått, men fedmekirurgi har vist seg å medføre gunstige endringer i appetittregulerings systemene. Disse endringene står i motsetning til hva man kan forvente etter et diett-indusert vekttap. Vi vet imidlertid lite om hvilke komponenter i appetittreguleringssystemet som driver vekttapet (og vedlikeholdet) etter fedmekirurgi - men kunne vi forstå hvorfor fedmeopererte pasienter klarer å holde vekta bedre over tid - i motsetning til de som

gjennomgår konservativ behandling, ville det åpnet for optimalisering og utvikling av flere effektive ikke-kirurgiske behandlingsformer for denne pasientgruppen.

For å undersøke hvordan vekttap i disse gruppene påvirket både hedonisk og homeostatisk appetitt, ble pasienter med alvorlig fedme som hadde fått innvilget fedmekirurgi; Sleeve Gastrectomy (SG) (n=15) og Roux-en-Y Gastric Bypass (RYGB) (n=14), og 15 kontroller (til kun diett-intervensjon) rekruttert. Etter 10 uker med vekttap, hadde pasientene uavhengig av gruppe, oppnådd lik endringer i kroppsvekt og -sammensetning, samt nivå av ketose. Generelt ble subjektiv appetitt redusert etter vekttap, uavhengig av metode. Men, vi kan ikke utelukke at den dempende effekten ketose har på appetitt er en medvirkende faktor. De lave metthetssignalene som sees hos personer med fedme, og spesielt alvorlig fedme, økte kraftig etter fedmekirurgi samtidig med at belønningsrespons for velsmakende mat ble redusert. Dermed var verken objektive mål for appetittkontroll eller belønning og matpreferanser sammenlignbare etter vekttap med diett versus fedmekirurgi. For å lykkes med konservativ vektreduksjon for fedme, behøver vi å utvikle flere strategier for å etterligne de gunstige effektene som er sett i appetittreguleringssystemet etter fedmekirurgi.

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Marthe

Preface

This doctoral thesis is based on four papers and divided into two parts. The first part is an investigation of potential differences in homeostatic appetite markers between individuals with and without obesity, as well as among obesity classes. The second part examines how weight loss induced by dietary restriction alone, or in combination with bariatric surgery, impacts on both the homeostatic and hedonic appetite control systems.

The latter part has been the main component of my PhD. The "Effect of diet-induced weight loss versus Sleeve gastrectomy and Roux-en-Y Gastric bypass on appetite" (DISGAP) study is a three-arm non-randomized control trial, where I have been the project leader and principal investigator. I started my PhD journey in August 2019, originally with the primary aim to investigate changes in three major domains of appetite regulation (homeostatic and hedonic appetite, as well as gut microbiota) following conservative and surgical treatment for obesity. The secondary aims were then to investigate whether initial changes in these domains of appetite regulation could predict 1-year follow-up outcomes, as well as to explore a potential role of ketosis in mediating appetite suppression. However, due to the outbreak of the Covid-19 pandemic in early 2020, with lockdowns and social distancing, my PhD project suffered great delays resulting in data collection being more than 1 year behind schedule.

Considering this, me and my main supervisor, Prof. Catia Martins, had to start thinking of alternatives for my PhD thesis. Therefore, we initiated the first comprehensive systematic review and meta-analysis, together with my co-supervisor Silvia Coutinho, to investigate potential differences in gastrointestinal (GI) hormones and appetite ratings between individuals with and without obesity. Additionally, given the limited evidence about eventual differences on appetite amongst obesity classes, we decided to perform a secondary analysis of previously collected data to compare GI hormones and appetite ratings among obesity classes. In the end, all the hard work has paid off. I am very proud to be able to submit my PhD thesis, with four published manuscripts, despite all the considerable obstacles and challenges along the way.

Abstract

Determining if gastrointestinal (GI) hormones' concentration and appetite ratings differ between individuals with and without obesity, and if this difference is more pronounced with increasing severity of obesity, may improve our understanding of obesity pathophysiology (*Papers 1 and 2*). Further, understanding how both the homeostatic and hedonic appetite control systems are altered with weight-loss (WL) induced by dietary restriction alone or combined with bariatric surgery may help improve obesity treatment outcomes (*Papers 3 and 4*).

A systematic review and meta-analysis of studies assessing the concentrations of GI hormones, as well as appetite ratings, following a test meal, in individuals with and without obesity was undertaken (*Paper 1*). Systematic searches were conducted in the databases MEDLINE, Embase, Cochrane Library, PsycINFO, Web of Science and ClinicalTrials.gov. A total of 7514 unique articles were retrieved, 115 included in the systematic review, and 70 in the meta-analysis. In *Paper 2*, 98 adults with obesity, divided into obesity class I (n= 35), -II (n= 44), and -III (n= 19), together with 45 controls without obesity were included in a cross-sectional analysis. In the "Diet induced weight loss versus sleeve gastrectomy and Roux-en-Y gastric bypass on appetite" (DISGAP) study (*Paper 3 and 4*), patients with severe obesity scheduled for Sleeve Gastrectomy (SG) (n=15) and Roux-en-Y Gastric Bypass (RYGB) (n=14), together with 15 controls (dietary restriction alone) were recruited for a 10-week WL intervention. Body weight/composition, and the plasma concentrations of acylated ghrelin (AG), active and total glucagon-like peptide-1 (GLP-1), total peptide YY (PYY), cholecystokinin (CCK), insulin, and β-hydroxybutyric acid (β-HB), as well as subjective ratings of hunger, fullness, desire to eat (DTE), and prospective food consumption (PFC) were measured pre and postprandially (*Paper 3*). Hedonic hunger was assessed with the Power of Food Scale, and responses on food reward were measured with the Leeds Food Preference Questionnaire before and after the WL intervention (*Paper 4*).

The meta-analysis showed that basal and postprandial total ghrelin concentrations were lower in individuals with obesity compared to controls, and this was reflected by lower postprandial hunger ratings. Individuals with obesity also had a lower postprandial concentration of total PYY compared to controls, but no significant differences were found for GLP-1, CCK, or other appetite ratings. The cross-sectional analysis revealed no differences

in appetite ratings nor in the plasma concentrations of GI hormones among obesity classes, except for insulin in which increased with increasing BMI. However, individuals with obesity had an impaired secretion of GI hormones when compared to individuals without obesity, and this was particularly prominent in the classes of severe obesity. In the DISGAP study, changes in body weight/composition and level of ketosis were similar across WL groups. After SG and RYGB, basal and postprandial AG declined, and postprandial GLP-1 increased significantly more than in controls. Postprandial PYY concentrations increased in all groups. Overall, postprandial hunger decreased, and postprandial fullness increased. However, ratings of DTE and PFC were more favorable after both surgeries compared to controls. Further, similar reductions in hedonic hunger were observed in all groups, and food reward was similarly reduced in SG and RYGB groups, while controls showed little or no change.

In conclusion, obesity is characterized by lower concentrations of basal and postprandial ghrelin, as well as total PYY in the postprandial period, and lower ratings of hunger after a meal. The impaired satiety response seen in individuals with obesity, especially in those with severe obesity, is greatly improved after both RYGB and SG. Despite overall subjective appetite ratings being reduced with all WL modalities, improvements in GI hormones' secretion and food reward were greater post-bariatric surgery compared with diet-induced WL alone. In order to succeed with conservative management of obesity, we likely need to mimic the favorable changes in homeostatic and hedonic appetite seen post bariatric surgery.

List of papers

Paper 1 Aukan, MI, Coutinho, SR, Pedersen, SA, Simpson, MR, Martins, C. Differences in gastrointestinal hormones and appetite ratings between individuals with and without obesity—A systematic review and meta-analysis. Obesity Reviews. 2022;e13531.

Paper 2 Aukan, Marthe Isaksen; Nymo, Siren; Ollestad, Karoline Haagensli; Akersveen Boyesen, Guro; DeBenedictis, Julia Nicole; Rehfeld, Jens Frederik; Coutinho, Silvia; Martins, Catia. Differences in gastrointestinal hormones and appetite ratings among obesity classes. Appetite. vol. 171. (2022)

Paper 3 Aukan MI, Skårvold S, Brandsæter IØ, Rehfeldt JF, Holst JJ, Nymo S, Coutinho SR, Martins C. Gastrointestinal hormones and appetite ratings after weight loss induced by diet or bariatric surgery. Obesity (Silver Spring). 2022;1-13.

Paper 4 Aukan, Marthe Isaksen; Brandsæter, Ingrid Øfsti; Skårvold, Silje; Finlayson, Graham; Nymo, Siren; Coutinho, Silvia; Martins, Catia. Changes in hedonic hunger and food reward after a similar weight loss induced by a very low-energy diet or bariatric surgery. Obesity (Silver Spring). 2022;30(10):1963-1972.

Abbreviations

AcAc - acetoacetate

AG - acylated ghrelin

AgRP - agouti-related peptide

ARC - arcuate nucleus

AUC – area under the curve

BBB – blood-brain-barrier

BL - baseline

β-HB - β-hydroxybutyrate

BMI – body mass index

CART - cocaine- and amphetamine-regulated transcript

CCK - cholecystokinin

CNS - central nervous system

***d*AUC** – decremental area under the curve

DPPIV - dipeptidyl peptidase IV

DTE – desire to eat

EB – energy balance

EE – energy expenditure

EI – energy intake

FFM - fat free mass

FM - fat mass

GI - gastrointestinal

GLP-1 - glucagon-like peptide-1

HFSA - high-fat and savory

HFSW - high-fat and sweet

***i*AUC** – incremental area under the curve

LFPQ - Leeds food Preference Questionnaire

LFSA - low-fat and savory

LFSW - low-fat and sweet

NPY - neuropeptide Y

NTS - nucleus of the solitary tract

PA – physical activity

PFC – prospective food consumption

PFS - Power of Food Scale

POMC - pro-opiomelanocortin

PVN - paraventricular nucleus

PYY - peptide YY

RIA – radioimmunoassay

RYGB - Roux-en-Y gastric bypass

SD – standard deviation

SEM – standard error of the mean

SG - sleeve gastrectomy

***t*AUC** – total area under the curve

VAS – visual analogue scale

W11 – week 11

WL – weight loss

Introduction

Obesity – Definition and prevalence

Obesity is defined by abnormal or excessive fat accumulation that may impair health (1). It is a chronic, progressive, relapsing disease (2), defined by a body mass index (BMI) ≥30 kg/m^2. It is further divided into subclasses according to its degree of severity: class I (BMI: 30.0-34.9 kg/m^2), class II (BMI: 35.0-39.9 kg/m^2), and class III (BMI: ≥40.0 kg/m^2), with the latter two also known as severe obesity (3). The prevalence of obesity has increased dramatically since the late 1970's and reached alarmingly rates worldwide (1). In 2016, more than 1.9 billion adults had overweight, and among those over 650 million had obesity (1) . Reflecting the worldwide trend, the prevalence of obesity in Norway increased from 7.7% to 22.1% and from 13.3% to 23.1% in men and women respectively, in the period 1984/86 – 2006/8 (4). Although the prevalence seems to have stabilized in recent years, it still affects approximately one million Norwegians.

Causes and consequences of obesity

Body weight is considered an heritable trait, with genetic factors accounting for as much as 70% of the variance seen in BMI (5). However, the high and increasing obesity rates observed in the last five decades can be attributed to a complex interplay between susceptible genes, epigenetics, and an obesogenic environment (6, 7). While energy expenditure (EE) has not declined since the 1970's (8, 9), energy intake (EI) has concomitantly increased over time (10). Thus, the current obesity epidemic is most likely a result of a chronic positive energy imbalance driven by excessive food consumption, and it is suggested that increased accessibility to highly palatable foods and increased portion sizes are the main contributors (8).

A recent report from 2019, showed that obesity is one of the most expensive diseases in Norway; with an estimated cost of approximately 70 billion NOK per year (11). Obesity increases morbidity and mortality, due to increased risk of cardio-metabolic diseases, in particular type 2 diabetes (12), but also musculoskeletal disorders and some types of cancers (13-15). Moreover, obesity is associated with functional impairment, depression and anxiety (16, 17), and reduced quality of life (18). In light of the recent Covid-19 pandemic outbreak, obesity was also identified as an independent risk factor for severe Covid-19 disease (19).

Additionally, a BMI ≥40.0 kg/m^2 is associated with approximately 6-14 years shortened life expectancy (20). It is therefore concerning that great increases of prevalence have been observed in classes of severe obesity (up to a fourfold) (20).

A weight loss (WL) of 5-10% of initial body weight can decrease the risk of developing several obesity-related diseases (21, 22). However, even though the majority of individuals with obesity claim they want to lose weight, only a small proportion seek professional help (23). Obesity is stigmatized, and a large proportion of individuals with obesity experience discrimination in social, occupational and educational settings, in media, amongst their families and at health care facilities where (24). It has also been shown that individuals with obesity attend to less preventive health care screenings due to embarrassment or discomfort (24). Further, in the absence of successful non-surgical weight-management strategies, obesity can be thought by many as the simple result of lack of willpower (i.e., eating too much and exercising too little), which might also be a hinder to seek professional help to manage body weight. Nonetheless, energy balance (EB) and appetite are not exclusively controlled by willpower.

Energy balance

Homeostasis is defined as a self-regulating process by which an organism can maintain internal stability while adjusting to changing external conditions (25). The first law of thermodynamics applies to the human body as to any other isolated system; energy cannot be created or destroyed but can only be transformed from one form into another (26). The two sides of the EB equation are EI and EE, which must be matched to achieve EB and keep body weight constant. Thus, any disequilibrium between EI and EE will otherwise lead to changes in body weight. Although humans tend to maintain a relatively constant body weight over longer periods of time, regardless of day-to-day variations in both EI and EE (27-29), mechanisms protecting us from progressive weight gain does not seem to work in modern western conditions (30, 31).

EE is a continuous process, as the body always uses energy, with only physical activity (PA) being a deliberate behavior. Meanwhile, EI is a discontinuous behavior controlled by appetite, and perhaps yield the largest impact on the EB equation (32). Although PA is the most variable component of EE, it has smaller effects on EB than what one would expect,

partly due to compensations in EI (33). Nevertheless, these mechanisms are beyond the scope of this thesis and reviewed elsewhere (34-36).

Appetite regulation

Appetite can be explained as the internal drive to search for, choose and eat food, and under normal circumstances, humans eat in episodes (37). During meals, people usually eat until satiation, and satiety determines the interval elapsed until next meal initiation (38). Although EI is a behavioral trait, eating is essential to fuel metabolism, and it is therefore only reasonable that metabolism controls feeding behavior to some extent.

Homeostatic appetite regulation

The central nervous system (CNS) plays a key role in controlling EI and EE, and regulating EB (39). Homeostatic brain regions, mainly the hypothalamus, receive information regarding both acute and chronic nutritional status and adjust appetite accordingly in order to maintain homeostasis (40). Particularly, the arcuate nucleus (ARC) of the hypothalamus serves a critical role. This is due to the existence of two neuronal populations with opposite effects: the anorexigenic pro-opiomelanocortin (POMC), and cocaine and amphetamine-regulated transcript (CART) neurons, and the orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons (41, 42). These neurons constantly receive information from the periphery via the circulation by crossing the blood-brain-barrier (BBB), via the vagal nerve, and through intensive input from multiple other nuclei in the CNS that modulate their activity. POMC neurons mainly project to second-order neurons in the paraventricular nucleus (PVN), dorsomedial hypothalamus, and the ventromedial hypothalamus (43). The PVN also express receptors for NPY and alpha-melanocyte-stimulating hormone, and other inhibitory peptides, as well as receptors for neurotransmitters that affect eating. The nucleus of the solitary tract (NTS) receives and integrates sensory information related to eating, including taste, vagal and spinal afferents from the viscera, and receptors for various gastrointestinal (GI) hormones (44).

The vagus nerve

The vagus nerve is the longest cranial nerve, providing a path of bidirectional communication between the brain and the periphery (45). The stomach receives the greatest density of vagal afferents, but due to the large surface area, the intestine receives the greatest proportions. The vagal afferents are a combination of mechano- (distension) and chemo- (hormonal) sensitive receptors. The stomach is innervated with mechanoreceptors that respond to gastric filling and signal to the brain via both vagal and spinal afferents. Gastric distention can contribute to the control of eating (satiation), but the stomach has to be markedly stretched for eating to be inhibited (46). Gastric emptying determines the rate at which nutrients reach the small intestine and is controlled by a feedback loop from the rest of the GI tract (47). The entry of nutrients into the distal small intestine stimulates another feedback loop projecting to the proximal GI tract to control motility and secretion, known as the ileal break (37). And in response to nutrients, the stomach and small intestine secrete several GI hormones.

Episodic signals

Episodic/short-term hormonal signals arise mainly from the GI tract and provide information on acute nutritional status. These signals oscillate around meals, are influenced by the macronutrient composition of the meal, and are associated with the signaling of hunger, satiation, and satiety (37, 48, 49).

Ghrelin

One of the key hormones regulating food intake is ghrelin. Ghrelin is an endogenous ligand for the growth hormone secretagogue receptor and is recognized as the only peripheral hormone with orexigenic properties (50-52). Ghrelin exerts wide physiological actions and plays complimentary roles in GI motility, glucose homeostasis and anti-inflammatory functions, among others (53, 54). Mainly produced by oxyntic cells in the gastric mucosa of the fundus, its concentration increases before meals and falls rapidly postprandially (51, 55). The two main isoforms of ghrelin are acylated ghrelin (AG) and de-acylated ghrelin. De-acylated ghrelin represents the major form found in plasma, but AG is the active form that is linked to metabolic actions in the hypothalamus (56). In general, the suppression of ghrelin is greater after larger meals, but it is also influenced by macronutrient composition (57, 58).

Ghrelin reaches the ARC both through crossing the BBB and via vagal activation, and is suggested to play a role in both the short- and long-term regulation of appetite and body weight (59). The appetite stimulating action of ghrelin is mediated though neurons that express growth hormone secretagogue receptor in the ARC. It has been demonstrated that peripheral and central administration of ghrelin suppresses POMC neurons and stimulates NPY/AgRP neurons by an indirect mechanism, acutely increasing food intake and chronically leading to weight gain (50).

Glucagon-like peptide-1

Glucagon-like peptide-1 (GLP-1) is a gut peptide derived from pre-proglucagon and produced in the GI endocrine epithelial L-cells - but is also produced by a small group of neurons in the NTS (60). GLP-1 receptors are expressed in the GI tract, cardiac antrum, vagal afferents and many brain areas. In the circulation, GLP-1 occurs in two active molecular forms: $GLP\text{-}1_{7\text{-}37}$ and $GLP\text{-}1_{7\text{-}36}NH_2$. But, once released, the peptide is quickly degraded by dipeptidyl peptidase IV (DPPIV) to its inactive forms. Due to the short half-life of the molecule, it is important to differentiate between measurements of active GLP-1, responsible for the endocrine actions, and the sum of the intact hormone and its metabolites (total GLP-1) reflecting L-cell secretion and its potential local neural actions (61).

The main actions of GLP-1 are to stimulate insulin secretion from pancreatic beta cells and inhibit glucagon secretion to limit postprandial hyperglycemia, known as the “incretin effect”, as well as to inhibit gastric motility and secretion, as a part of the “ileal break” (37, 61). GLP-1 is also an important physiological regulator of appetite. GLP-1 acts both centrally through hypothalamic actions, particularly in the ARC and PVN, and through the vagal-brainstem signaling pathway leading to satiation and post meal satiety, by reducing food intake in a dose-dependent manner (45, 62). Plasma concentrations of GLP-1 are at the lowest after an overnight fast and its secretion increases rapidly with the presence of nutrients in the lumen (61). After mixed nutrient meals, GLP-1 usually peaks in a biphasic pattern with the first peak around 15-30 minutes, and the second peak between 60-120 minutes (48).

Peptide YY

Most L-cells in the distal small intestine and colon co-express and secrete peptide YY (PYY) (48). PYY is secreted in its inactive form (PYY_{1-36}) following a meal and cleaved by DPPIV to its active form PYY_{3-36} (49). Proteins and lipids stimulate PYY secretion more than carbohydrates, but intraluminal bile acids, gastric acid, and cholecystokinin (CCK) also have an effect (48, 63, 64). PYY slows gastric emptying as part of the "ileal break", while its effects on glycemic control are unclear (65). PYY plasma concentration usually increases within 15-30 minutes after a meal and peaks around 60-90 minutes postprandially.

PYY is thought to be mainly involved in post meal satiety (63) and infusions of PYY_{3-36} at physiological postprandial concentrations have shown to decrease food intake (66). Different forms of PYY have different receptor affinities; the full-length molecule binds with similar affinity to all Y receptors, but PYY_{3-36} has high affinity to Y2 receptors (40). PYY_{3-36} can cross the BBB and act directly or indirectly on the brain. The mechanism by which PYY_{3-36} effects eating is thought to be mainly through an indirect action in the ARC, activating Y2 receptors and reducing NPY signaling, but may also mediate appetite via the vagal nerve (67).

CCK

CCK is a peptide synthesized in the small intestinal endocrine I-cells and cerebral neurons, and expressed in neuroendocrine cells and several endocrine glands, peripheral nerves and in cells of the immune system (68, 69). CCK appears in multiple molecular forms and plays a role in digestion by stimulating pancreatic enzyme secretion and gallbladder contraction, gut motility, satiety, and inhibit acid secretion from the stomach. In addition, CCK also stimulates insulin and glucagon secretion and acts as a growth factor and neurotransmitter in the CNS. CCK is mainly released in response to intraluminal proteins and long-chain fatty acids, with plasma concentrations increasing within 10-15 minutes and peaking between 30-90 minutes postprandially, and then gradually decreasing (48).

CCK is the best established and most important satiation signal, being involved in meal termination and possibly early phase satiety (i.e., reduces meal size and hunger before next meal) (70-72). CCK binds to two receptors: CCK1, which is predominantly expressed in the periphery, and CCK2 which is mostly expressed in both the brain and stomach (68). Acting

primarily through vagal afferent fibers, CCK activates NTS neurons (73, 74), and seems to interact with other gut derived peptides to promote satiety (75).

Tonic signals

Tonic/long-term signals exert a constant pressure on the expression of appetite and regulation of EB. These signals include adipokines (i.e., arising mainly from the adipose tissue) such as leptin, but also insulin secreted from the pancreatic β-cells. The ARC senses information about adiposity status from both leptin and insulin, as their plasma concentrations reflect the size of fat stores (37, 44).

Leptin

Leptin is synthesized in adipose tissue and plasma concentrations correlate positively with fat mass (FM) (27, 37). Leptin is expressed at high levels in the adipose tissue, stomach, and placenta. It is rapidly transported across the BBB, binding to receptors in several brain regions, namely the ARC and other hypothalamic areas. Leptin seems to influence EB through modulation of appetite by suppressing the orexigenic NPY/AgRP neurons and stimulating anorexigenic POMC/CART neurons in a dose-dependent manner (27, 76).

Insulin

Insulin is produced in the pancreatic β-cells and secreted in response to a meal (77), although both basal and postprandial plasma concentrations are proportionally affected by BMI (78). Its main actions are to reduce blood glucose levels by increasing glucose uptake to insulin-sensitive tissues, such as skeletal muscle, adipose tissue, and the heart (79). Insulin receptors are present in hypothalamic areas, such as the ARC, dorsomedial nucleus, and PVN (80). Crossing the BBB, its anorexigenic signals act through the same neuropeptides as leptin (27, 76). Meal-to meal variations in insulin plasma concentrations are conveyed mostly by the NTS, whereas vagal afferent fibers have a central role (81), and deletion of neuron-specific insulin receptors has been shown to induce hyperphagia (82). A brief overview of homeostatic appetite regulation can be seen in **Figure 1**.

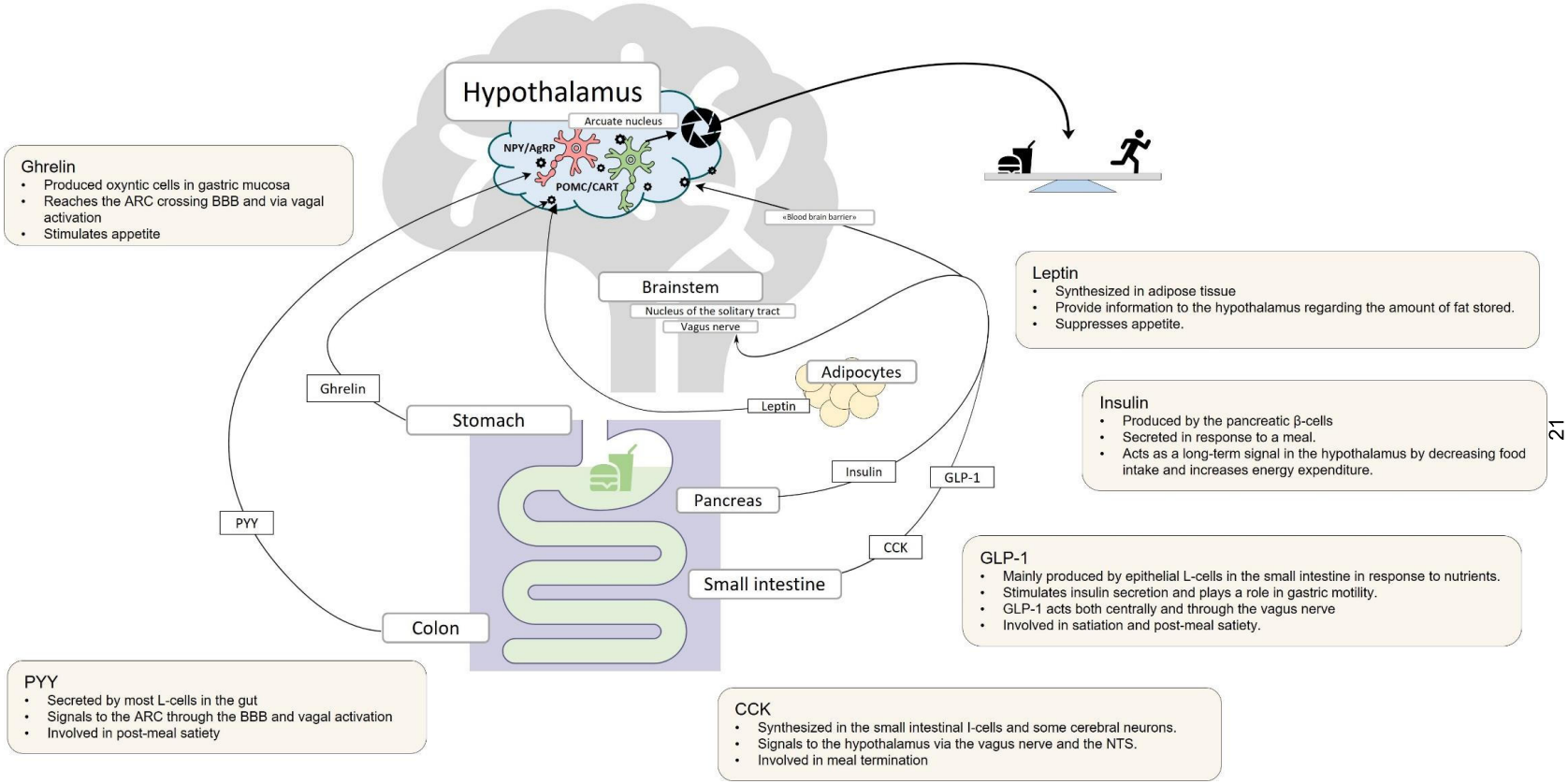

Figure 1. Homeostatic appetite regulation. AgRP: agouti-related peptide. ARC: arcuate nucleus. BBB: blood-brain-barrier. CART: cocaine- and amphetamine-regulated transcript. CCK: cholecystokinin.GLP-1: glucagon-like peptide 1. NPY: neuropeptide Y. POMC: pro-opiomelanocortin. PYY: peptide YY. (Illustrated by M.I. Aukan 2022)

Subjective appetite

Appetite also includes subjective components that are rather conditioned or learned. Hunger can be explained as a conscious sensation, which triggers the motivation to seek and consume food (83), or described as a construct that connotates the drive to eat (38). Hunger can also be linked to physical phenomena described as a dull ache or gnawing sensation from the stomach, that can lead to headache, irritability, feeling of weakness, emptiness, or restlessness (38, 84). Although "hunger" is not required for eating, it is a strong driver for food intake and closely related to feelings of a "desire to eat" (DTE) (85, 86).

On the contrary, John Blundell (first proposed in 1987 as the 'Satiety Cascade') has argued that satiation is a process leading to termination of eating, thereby controlling the meal size, and satiety as a process leading to inhibition of further eating, concomitant with a decline in hunger and increased feelings of "fullness" after meal termination (38). Moreover, meal quality and quantity, i.e., energy density, macronutrient composition, the physical structure of the food, as well as its sensory qualities are all modulators of the processes leading to satiation and satiety (38, 87).

Constructs of subjective appetite can be measured by tracking temporal changes over time, before and after a meal, as well as the duration of the inter-meal interval (38, 86). Visual analogue scales (VAS) have become a popular tool in appetite research, used to measure the motivation of eating, by asking participants to rate their subjective expression of hunger, fullness, DTE and "prospective food consumption" (PFC) on a 100 mm scale (86). Nevertheless, it is important to remember that even though subjective appetite ratings can be quantified with validated tools, are associated with biological signals (72, 88), and have been predictive of EI (89, 90), appetite is also influenced by many other factors (91).

Hedonic appetite regulation

Appetite in humans do not only depend on internal factors to meet homeostatic and physiological needs, but is also highly influenced by external sensory information, emotions, and cognition (92). Hedonic appetite can be described as reward-based eating and the hedonic system can operate independently of homeostatic needs, meaning that when food is highly palatable and easily available it has a major effect on whether the food will be desired and consumed (93-95). A hedonic network of brain regions, including the nucleus accumbens,

cortex, midbrain, and brainstem are thought to play a major role in the reward related drive to eat (96).

By the end of (or after) a meal, the drive to eat is generally low. Despite this, palatable foods (i.e., foods rich in sugar or fats), have been shown to increase food intake by prolonging the eating episode (97). Evidence suggests that endogenous opioid peptides may be involved in mediating both the taste responses and preferences for palatable foods, especially high-fat and sweet foods (98). Moreover, frequent consumption of energy-dense foods may also reduce reward-related neural processes and increase responsiveness to food cues (99, 100). Experiencing frequent thoughts, feelings, and urges for foods in response to cues of palatable foods, even in the absence of energy deficit, has been referred to as ‘‘hedonic hunger’’ (101). Hedonic hunger, as measured by the Power of Food Scale (PFS), is positively related to both oral somatosensory brain responses to cue-triggered anticipation of palatable foods, food reinforcement, appeal for energy-dense foods, and binge eating (102).

In 1996, Berridge (103) characterized food reward by two distinguishing terms: “liking” and “wanting”. *Liking* refers to the hedonic influence of satisfying rewards, which in a state of consciousness can result in subjective pleasure ratings (103, 104). A network of hedonic hotspots in limbic brain structures, such as the nucleus accumbens and ventral pallidum, can intensify the hedonic impact or liking for food rewards (105). *Wanting*, on the other hand, is described as the psychological processes of incentive salience (motivation to eat), which can occur either consciously (explicit) or unconsciously (implicit) and is generated by cue-triggered motivation. When rewards, such as palatable foods, and their predictive cues are strengthened by motivation, those cues, and foods, become attractive, and in conscious form able to induce subjective cravings. The wanting mechanism includes a larger mesocorticolimbic network that extends beyond the hedonic hotspots (105, 106). Neurochemically, the mesocorticolimbic system includes dopamine and glutamate, as well as opioid orexin, and other endocannabinoid neurotransmitters. Meaning that this network is functionally more robust than the hedonic hotspots, and can therefore generate intense incentive motivation and appetite, even without enhancing hedonic liking (106). It is, however, important to note that homeostatic and hedonic appetite control are not isolated systems, but rather interact with each other (107). A brief overview of hedonic appetite regulation can be seen in **Figure 2**.

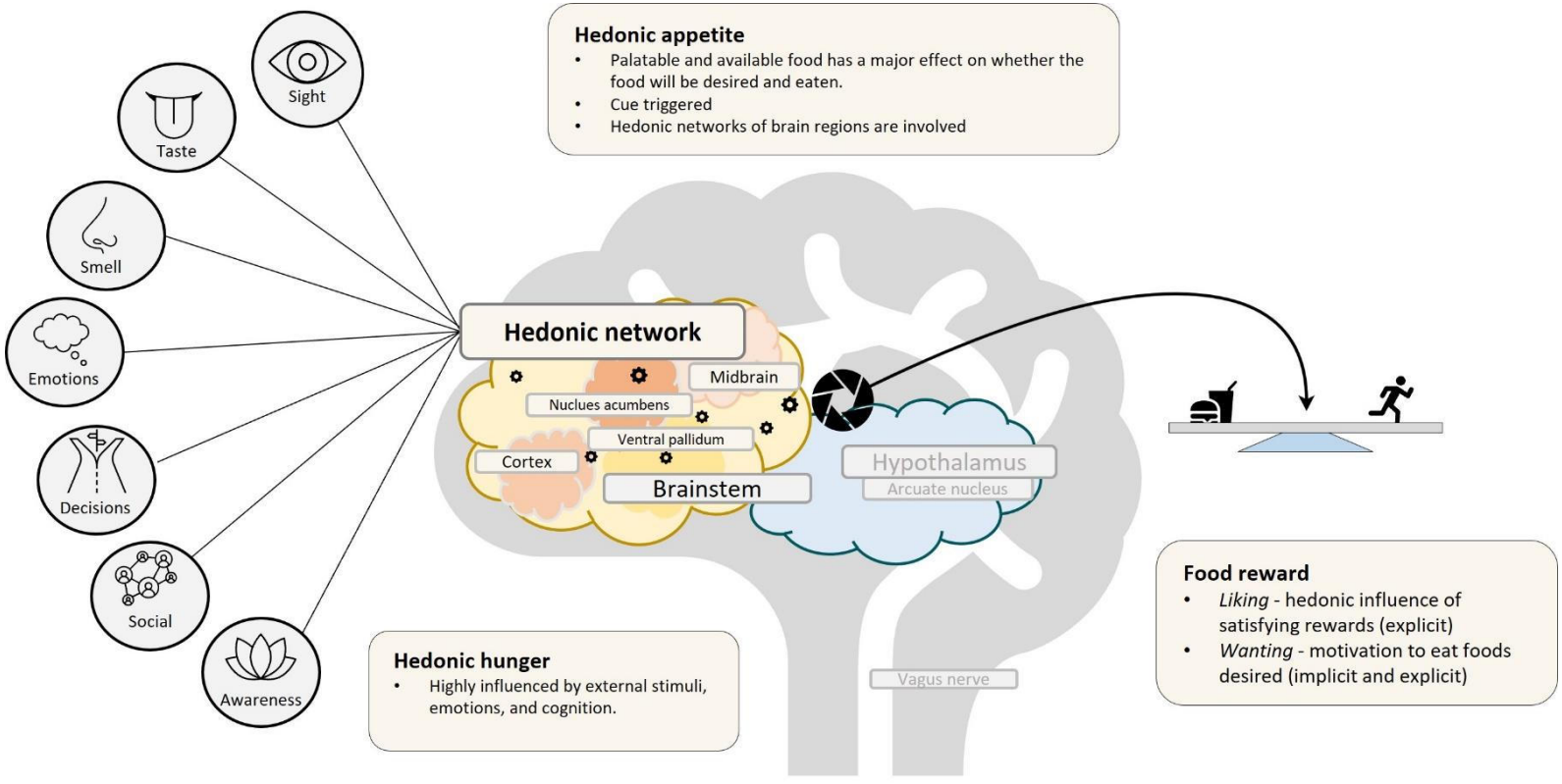

Figure 2. Hedonic appetite regulation. (Illustrated by M.I. Aukan 2022

Obesity and appetite regulation

Homeostatic appetite

Ghrelin

Ghrelin concentrations are negatively correlated with BMI and consistently reported to be lower in individuals with obesity compared to individuals without obesity (108-113). The postprandial decline in ghrelin concentrations normally seen in normal weight subjects is reduced, or even absent, in individuals with obesity (57, 113-118). The lower basal ghrelin concentrations in obesity may be the result of a compensatory mechanism in response to a positive EB. Insulin might also play a role in modulating ghrelin concentrations, as insulin resistance in obesity has been inversely associated with ghrelin concentrations (119). Nevertheless, the lack of meal-related oscillations in ghrelin concentrations may act as a continuous stimulus of appetite (114).

GLP-1

The role of GLP-1 in obesity is unclear (120), but it has been theorized that its actions are impaired (121). It was early suggested that GLP-1 secretion in obesity may be reduced because of impaired responsiveness to carbohydrates (122). And further, in a large cohort study, the postprandial GLP-1 response to an oral glucose load was reduced by up to 20% in individuals with overweight or obesity compared to normal-weight individuals, independently of glucose tolerance status (123). In two other large studies, postprandial concentrations of GLP-1 were found to be inversely proportional to BMI (124, 125). Variations in GLP-1 receptor have been shown to be moderately associated with obesity in European Americans (non-Hispanic white citizens) (126), indicating that defects in GLP-1 signaling may at least contribute to obesity risk in some individuals. Also, leptin resistance (127) and reduced incretin effects (128) in obesity are believed to contribute to reduced GLP-1 levels or sensing defects, respectively. However, the literature is rather inconsistent, with several studies reporting no differences in postprandial GLP-1 concentrations between individuals with and without obesity after either single macronutrient loads or mixed nutrient meals (129-133). Nevertheless, individuals with obesity are sensitive to the effects of GLP-1 receptor agonists with consequent reductions in both appetite and body weight (134).

PYY

Even though several studies have found no differences in PYY plasma concentrations in adults with varying BMIs (135, 136), there is a general agreement that concentrations of PYY are impaired in obesity: Fasting PYY_{3-36} has been shown to correlate negatively with BMI, and postprandial concentrations shown to be lower in individuals with obesity compared to controls (109). Additionally, a meta-analysis conducted in children, reported lower postprandial total PYY concentrations in children with obesity compared to normal weight controls (137). Individuals with overweight or obesity are also reported to have a lower peak PYY concentration compared to normal weight controls, despite requiring a larger volume of a nutrient drink test to reach fullness (108). The inhibitory effect of PYY on eating, however, did not differ between BMI groups in one study, but it was suggested that PYY deficiency might be a contributor to the pathogenesis of obesity (109). Impairment in L-cell function may be one explanation (138), but it remains unknown if altered secretory responses are a cause or consequence of obesity.

CCK

The association between obesity and CCK plasma concentrations remains controversial. Plasma concentrations of CCK in the fasting state have been shown to be reduced in obesity (139), but not all are in agreement (135). Intraduodenal infusion of oleic acid, resulted in a lower postprandial CCK response in individuals with overweight and obesity compared to lean subjects (140). Contrarily, the postprandial concentrations in response to both high-protein, high-fat and high-carbohydrate meals were comparable between BMI groups in another study (135), and obesity has even been associated with greater CCK concentrations after a high-fat meal (141). A recent review by J.F. Rehfeld (142) pointed out that most early CCK measurement assays have been problematic in terms of accuracy. It was further argued that on more recent studies, using accurate “in-house” radioimmunoassay (RIA) methods, fasting and postprandial CCK concentrations were similar in individuals with and without obesity (142). Even so, defects in CCK signaling can contribute to the etiology of obesity, as polymorphism of the CCK1 receptor may affect CCK-induced satiety and is associated with increased risk of eating larger meals, and obesity (143, 144).

Insulin

Insulin plasma concentrations have long been known to be positively correlated with BMI (78). It has been proposed that obesity *per se*, is an independent predictor of fasting hyperinsulinemia (145), and that hyperinsulinemia in obesity is related to increased insulin secretion and decreased insulin clearance (146-148). Insulin plasma concentrations, both in the fasting and postprandial states, have been shown to be inversely correlated with *ad libitum* EI in lean subjects, but not in individuals with obesity (131, 149), and a meta-analysis suggested that insulin plasma concentrations are associated with short-term appetite regulation in normal weight subjects, but that this association is weakened or absent in obesity (150). This impairment is thought to be mediated through the excessive body fat gain and consequently impaired glucose homeostasis, which decreases insulin sensitivity in the CNS and might also account for signaling defects (151).

Subjective appetite ratings

Obesity has been associated with lower satiation (measured as a higher volume intake of a liquid mixed meal to reach fullness) (108) and greater EI (152). Despite this, most studies in this field report no differences in fasting or postprandial appetite ratings (hunger, fullness, DTE or PFC) (113, 132, 153-155). Interestingly, many individuals with obesity claim to detect no relationship between their eating habits and sensations of hunger and fullness, and this has been associated with higher scores on disinhibition and hunger measured by the Three-Factor Eating Questionnaire (156).

Hedonic appetite

Although it can happen to everyone, eating in the absence of physiological needs, or metabolic requirements, has long been suggested as a prototypical trait in individuals with obesity (157). Research has consistently shown that individuals with obesity have greater food reinforcement (157-160), greater hedonic hunger (161), stronger liking for sweetness (162), and higher wanting for food in general (163) compared to individuals without obesity. Moreover, BMI has been found to predict implicit wanting for high-fat relative to low-fat

foods (163). Neuro-imaging studies have demonstrated that alterations in functional connectivity in mesolimbic brain regions may indicate a fundamental difference in food seeking and motivational behavior between individuals with and without obesity (164). Higher sensitivity to food reward and food reinforcement have also been associated with greater EI (152), and it has been suggested that polymorphisms of dopamine receptor and transporter genes in obesity are related to greater food reinforcement, which again influences EI (159). However, it remains unknown if the differences observed, in both the homeostatic and hedonic appetite systems, between individuals with and without obesity are a cause or consequence of excess adiposity.

Obesity management

The aims of obesity management may vary, including weight reduction or stabilization, management of co-morbidities or improvement of overall health and quality of life. It should be emphasized that obesity is a chronic disease that requires a lifelong approach. The first choice of obesity treatment should be lifestyle interventions, including behavioral treatment, dietary modifications, and increased PA. It is important to include realistic WL goals aimed at maintaining WL and preventing weight regain (165). Even a modest WL of 5-10% of initial body weight, through lifestyle modifications, has been shown to lead to significant clinical benefits, by reducing metabolic risk factors and co-morbidities associated with obesity in several patient groups, as well as decreasing all-cause mortality (165-168). Individuals with obesity may consult primary health care for help, but referrals to obesity outpatient clinics are usually not offered before the disease becomes severe: BMI ≥40.0 kg/m^2, or BMI: ≥35.0 with co-morbidities (165, 169).

Lifestyle interventions

Behavioral treatments are usually provided on a weekly basis for an initial period of 4-6 months, and some programs even continue treatment after this, focusing on developing WL maintenance skills (170). These treatments are often provided in groups and generally emphasize principles like goal setting, self-monitoring, and stimulus control (170).

Dietary modification is the cornerstone of weight control in obesity treatment. Most dietary interventions prescribed for WL include some form of energy restriction and can either be continuous, by applying a fixed energy deficit per day, or intermittent, by alternating between fasting and unrestricted eating periods (171). Balanced energy restricted diets are designed to meet traditional macronutrient recommendations, providing a balanced distribution of protein (10-35%), carbohydrate (45-65%), and fats (25-35%) (171). Alternatively, a macronutrient focused diet can be prescribed. Most commonly, these types of diets manipulate macronutrient composition to be either low-fat, high-protein, or low-carbohydrate (can also be ketogenic). Also, it is possible to focus on the quality and nature of the foods, rather than the quantity, as in the Mediterranean diet. However, these types of dietary patterns usually result in only modest WL, unless combined with energy restriction (172).

Greater energy restriction is associated with a larger WL in the short-term (173). Low-energy diets usually restrict EI to 800-1200 kcal/day (165), or alternatively provide an energy deficit of 500-750 kcal/day from estimated energy requirements (174), while very-low-energy diets (VLEDs) restrict EI to < 800 kcal/day (175). VLEDs are effective in inducing a large WL over a short period of time, and are usually applied for 8-16 weeks, leading to a WL of 1.5-2.5 kg per week (175). Due to the very low EI in VLEDs, total meal replacement products are generally used to ensure that nutritional intake adequately meets dietary recommendations, for both macro- and micronutrients. VLEDs are considered a safe WL approach, have minimal and transient side effects (175, 176), and do not seem to exacerbate loss of lean tissue or weight regain (177). However, due to the large and rapid WL there is an increased risk of gallstone formation with VLEDs (178).

Furthermore, when glucose is not available or is below a certain threshold, due to fasting, starvation, low energy and/or low carbohydrate intake, ketogenesis in hepatic mitochondrial matrix is stimulated as a normal physiological response to provide an alternative source of energy (179). The ketone bodies (β-hydroxybutyrate (βHB), acetoacetate (AcAc), and acetone) are produced in liver from acetyl-CoA derived primarily from fatty acid oxidation. βHB is the product of spontaneous reduction of AcAc, it is the predominant circulating ketone body, and, within physiological levels, elevated βHB circulating plasma concentrations is a metabolic state known as nutritional-induced ketosis.

Although, ketogenic diets seem to induce a greater WL at 3-6 months compared to low-fat diets, the difference is usually no longer apparent at 12 month follow up (180).

Moreover, a 10% WL might not be sufficient for an individual with obesity to reduce their BMI to <30 kg/m^2, but as previously reviewed, the impact of WL on health is well documented. Several studies have shown that it is possible to maintain a clinically significant WL at 1-year follow-up, despite partial weight regain (177, 181). However, it appears that only approximately 20% of weight losers are successful at maintaining a WL of at least 10% at 1-year follow-up (182), and, long-term WL maintenance results after lifestyle interventions are rather discouraging (183). For example, participants who had lost an average of 8 kg during a VLED protocol, regained 114% of the lost weight at 2 years follow-up (184). Similarly, a VLED in combination with behavioral treatment resulted in an initial 13.5% WL, but the mean weight change at 5 years follow-up was 2% above baseline (BL) weight (185).

Bariatric surgery

Bariatric surgery can be offered to individuals with severe obesity who have not succeeded with other WL strategies, and who are eligible for the respective and appropriate surgical procedure. The first surgical treatment for obesity was performed in 1953 as a jejunoileal bypass with ileocolostomy (186). Since then, bariatric surgery has advanced to become the most effective treatment for obesity, with nadir WL of 50-70% of excess body weight, and results being sustained for up to at least 10 years (187).

Sleeve Gastrectomy (SG) and Roux-en-Y Gastric Bypass (RYGB) are the most commonly performed procedures resulting in higher rates of successful WL outcomes that are not yet achievable with lifestyle modification alone (187). Both procedures also reduce the risk of existing co-morbidities, and in some instances remission of type 2 diabetes (188), as well as improved health-related quality of life (189). However, bariatric surgery is invasive, and not everybody wishes to undergo surgical treatment. In addition, it may be medically contraindicated for some individuals (190), it requires lifelong nutritional management (191), post-operative complications can occur at any time of the patients life (192), and both socioeconomic and geographic disparities can affect accessibility to treatment (193, 194). Moreover, it should be noted that most patients experience some weight regain after

reaching nadir WL (195), and approximately 30% of patients also struggle with suboptimal WL and/or excessive weight regain, post bariatric surgery (195-198).

As described above, there is a large gap between lifestyle interventions and bariatric surgery regarding their long-term WL success (187). It has been suggested that diverging changes in appetite regulatory systems and feeding behavior that follow dieting and bariatric surgery explain, at least partially, the differences seen in long-term WL maintenance after both treatment modalities (199-201). Furthermore, disinhibited eating, binge eating and eating in response to negative emotions or stress may also be a risk for weight regain (201). The next section summarizes the current evidence on how weight loss, induced by dietary restriction alone or bariatric surgery impacts both the homeostatic and hedonic appetite regulatory systems.

Responses to weight loss interventions

Homeostatic appetite

Dietary restriction

Diet-induced WL has consistently been reported to increase plasma concentrations of ghrelin, and result in increased ratings of hunger, DTE, and PFC (177, 181, 202-204). Moreover, several of these changes seem to be sustained at one year follow-up (177, 202), even with partial weight regain (181). However, the impact of diet-induced WL on postprandial concentrations of satiety peptides and subjective ratings of fullness remains controversial (131, 177, 181, 202). Some studies report increased postprandial concentrations of total GLP-1 (131, 202) and PYY_{3-36} (202), while decreases in total PYY and no changes in active GLP-1 have also been shown (177, 202). Further, even though most studies find that diet-induced WL leads to no changes in postprandial fullness (181, 203-205), the largest study to date (n=100) reported an increase in postprandial ratings of fullness (177).

Nutritional-induced ketosis seen during VLEDs (or with ketogenic low-carbohydrate diets) has been shown to prevent the increase in hunger feelings and ghrelin secretion otherwise seen with diet-induced WL (206-208). In addition, ketosis seem to prevent a reduction in postprandial GLP-1 and CCK concentrations, and possibly increase fullness (208, 209). Even though the mechanisms are not completely understood, βHB is believed to be the

main driver for appetite suppression observed during nutritional-induced ketosis (207, 210-214).

Bariatric surgery

The success of bariatric surgery was initially thought to be a result of the malabsorptive and restrictive nature of the procedures, or a combination of the two. However, the discovery of several metabolic alterations at the level of the homeostatic appetite regulatory system changed this view. Plasma concentrations of ghrelin have consistently been shown to decline following SG (215, 216), and to remain low up to 1 year follow-up (217). However, less consensus exists regarding the impact of RYGB on ghrelin concentrations, with some studies showing a decrease (218), and others no change (219). Postprandial concentrations of GLP-1, PYY, and CCK, have consistently been reported to increase shortly after bariatric surgery in general, and to be sustained for up to 10 years (220-222).

It should also be noted that many studies find a more pronounced increase in satiety peptides post-RYGB compared to SG (215, 218, 221). Nevertheless, patients who have undergone both SG and RYGB show decreases in appetite, and report feeling less hungry and more satiated than their non-surgical counterparts (111, 220, 223, 224). Furthermore, patients who develop ketosis post-SG have shown greater WL at 6 and 12 months (225), however, the role of ketosis on appetite regulation post-bariatric surgery is under-investigated.

Hedonic appetite

Dietary restriction

Even though an increased drive to eat is commonly seen following diet-induced WL (181, 203), as well as an increase in the reward value of food during energy deficit (226), food reward has been described to decrease following WL induced by different lifestyle modifications (227). Food reinforcement and food hedonics may influence eating behavior differently (226), but limited studies have measured the effect of diet-induced WL on constructs of hedonic appetite in individuals with obesity, and the results are rather conflicting (228-231).

Bariatric surgery

Bariatric surgery has consistently been shown to induce favorable changes in hedonic appetite. Following SG and RYGB, patients experience decreases in measures of hedonic eating, including reductions on food addiction scales, lower preference for energy dense foods (161, 232-238), and the palatability of foods seems altered along with a development of an aversion to "sweetness" similar to that seen in healthy controls (239, 240). In addition, these patients report lower frequency of food cravings and decreased influence of emotions and external food cues on eating behavior (236, 239, 241).

A case-control analysis demonstrated that successful WL, 1-year post-bariatric surgery, was associated with improvements or alterations in taste and flavor perception, and that patterns of liking were associated with healthier diets, especially when coupled with less hunger (242). However, some patients may also experience a gradual increase in appetite, cravings and portion sizes after initial favorable changes, along with feelings of loss of control and emotional distress (195).

Overall remarks

The current obesity epidemic seems to have emerged from factors disrupting the appetite regulatory mechanisms, which allow for a positive energy imbalance when in presence of an obesogenic environment. Obesity has been associated with poor homeostatic appetite control, but despite extensive efforts in this research field, methodological differences seem to produce rather conflicting results on this matter. Given that individuals with obesity eat larger meals and need to eat more than their normal weight counterparts to reach fullness, the hypothesis that individuals with obesity present poor homeostatic satiety control needs to be confirmed. Moreover, considering the great increases in prevalence of classes of severe obesity, together with the disappointing results in non-surgical treatments for obesity, another hypothesis that warrants further investigation is whether the homeostatic appetite regulatory system deteriorates with increasing BMI in obesity.

Bariatric surgery is the most effective treatment for severe obesity, leading to a much larger and sustained weight loss, not yet achievable with lifestyle interventions. It can be hypothesized that bariatric surgery's success can be partially explained by beneficial changes in appetite control systems, opposite to what is normally seen after dietary restriction alone. Despite this, no studies have previously compared how a similar weight loss, induced by diet alone or combined with bariatric surgery impacts on both homeostatic and hedonic appetite.

Aims, part 1

Primary

The primary aim was to investigate if there were differences in homeostatic appetite regulation, namely GI hormones' secretion, and subjective appetite ratings, between individuals with and without obesity.

Secondary

The secondary aim was to investigate if there were differences in these constructs of homeostatic appetite regulation among obesity classes.

Aims, part 2

Primary

The primary aim was to investigate how a similar WL induced by a VLED alone or combined with bariatric surgery impacts on homeostatic appetite regulation.

Secondary

The secondary aim was to investigate how a similar WL induced by a VLED alone or combined with bariatric surgery impacts on hedonic constructs of appetite, namely hedonic hunger, and food reward.

Methods

Systematic review and meta-analysis (*Paper 1*)

Literature search

A structured database search was conducted in MEDLINE, Embase, Cochrane Library, PsycINFO, Web of Science, and ClinicalTrials.gov. The query involved a combination of thesaurus- and free-text terms optimized to capture studies comparing appetite markers between individuals with and without obesity. The search strategies excluded studies focusing exclusively on children, or animals, and publication types like comments, editorials, or news. The searches were also restricted to studies written in English, Norwegian, Swedish, Danish, Portuguese, French or Spanish (see ***Appendix 1, Supplementary file, Paper 1*** for a detailed description of the search strategies adopted in the different databases).

Study selection

Two reviewers (MIA, SRC) independently screened titles and abstracts of the identified articles based on the predefined inclusion and exclusion criteria. Results from each reviewer were compared to ensure that exclusions were made on the same basis before screening full text articles. Any disagreements between the reviewers were discussed, and a third reviewer (CM) involved if needed. Full text articles were screened and assessment of risk of bias was performed for all the included articles in the meta-analysis.

Eligibility criteria

The database search was conducted based on the following inclusion criteria: a study population of adults with obesity (BMI ≥ 30 kg/m^2) and a control group without obesity (BMI 18.5-29.9 kg/m^2), assessing one or several of the following variables in the fasting state and/or after a test meal (using total area under the curve (AUC) as a measure of postprandial response): plasma or serum concentrations of total or active ghrelin, total or active GLP-1, total or active PYY, or CCK, and/or appetite ratings of hunger, fullness, DTE, or PFC measured with VAS (243). Postprandial data was not included if appetite measures were taken under infusion of pharmacological agents or hormonal infusion. Exclusion criteria included diabetes or other endocrine disorders known to affect appetite, previous bariatric surgery, and current

or recent use of medications known to affect appetite or body weight. Since ketosis is known to affect appetite (212), studies were excluded if the appetite measurements were taken while participants were ketotic (defined as a plasma βHB concentration >0.3 mmol/L (207)).

Data extraction

The two reviewers (MIA, SCR) extracted the data of all included articles. General characteristics of the participants (i.e., age, sex, BMI, body composition) were extracted from each article along with energy and macronutrient composition of the test meal used, duration of postprandial period, and frequency of blood sampling/appetite ratings assessment.

Risk of bias assessments

Depending on the study designs, the risk of bias in the articles included in the meta-analysis was assessed using the Cochrane tools ROB-2 (244) and ROBINS-1 (245) for randomized and non-randomized studies, respectively (***Appendix 1, Supplementary file, Paper 1***). The tools identified to what extent studies addressed the possibility of bias in their design, conduct, and analysis. Any disagreements that arose between the reviewers were resolved through discussion and assistance of a third reviewer when required.

Original papers (*Papers 2, 3 and 4*)

Study-design and participants

Paper 2

The second manuscript reports a secondary cross-sectional case-control analysis of the *"Weight loss maintenance and compensatory mechanisms activated with a very-low energy diet (VLED)"* study. The study was approved by the Norwegian regional ethics committee (Ref., 2012/1901), registered in clinicaltrials.gov (NCT01834859), and conducted according to the guidelines laid down in the Declaration of Helsinki. The main findings have previously been published (177, 203). Adults (18–65 year) with obesity (BMI: ≥30 kg/m^2) and a control group without obesity (BMI: 18.5-29.9 kg/m^2) were recruited via newspaper advertising serving the community of Trondheim, Norway. All participants provided written informed consent before

commencement. At recruitment, all participants were required to be weight stable (<2 kg body weight change over the past 3 months), not currently dieting to lose weight, and have a sedentary lifestyle (engaging in <150 minutes/week of PA of at least moderate intensity) (246). The study excluded pregnant or breastfeeding women and those with clinically significant illnesses, including diabetes, previous bariatric surgery, and/or taking medications known to affect appetite or induce WL. Supplementary material for *Paper 2* can be seen in ***Appendix 2, Supplementary file – Paper 2.***

Papers 3 and 4

The "effect of *DIet-induced weight loss versus Sleeve gastrectomy and Gastric bypass on APpetite"* (DISGAP) study is a three-armed prospective non-randomized controlled trial, comparing how a similar WL induced by diet or bariatric surgery impacts constructs of homeostatic and hedonic appetite, both in the short- and long-term (1 year). An outline of the short-term study design implemented in *Papers 3 and 4* can be seen in Figure 3.

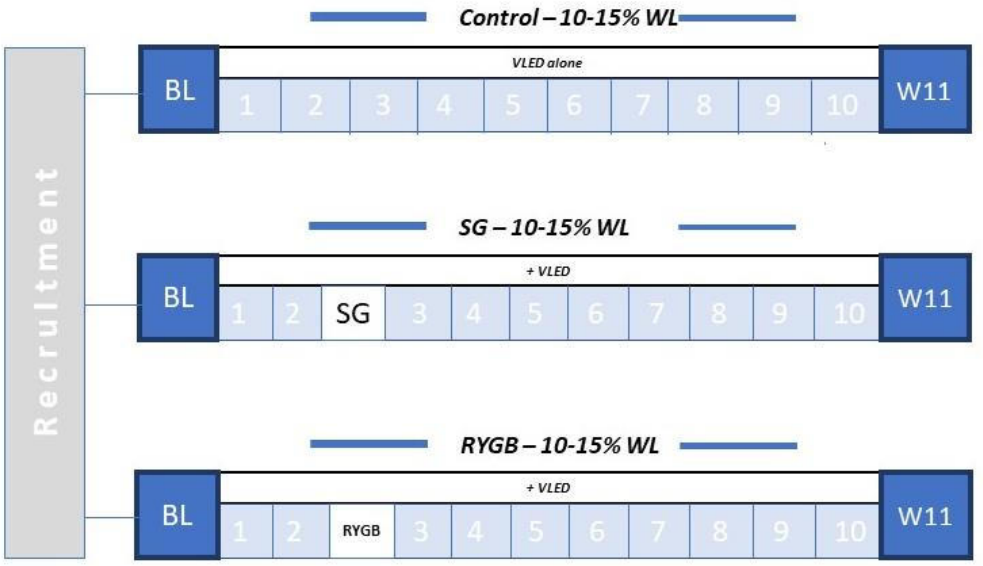

Figure 3. Study design of the DISGAP study. BL: baseline. SG: Sleeve Gastrectomy. RYGB: Roux-en-Y Gastric Bypass. VLED: very-low energy diet. W11: week 11. WL: weight loss. (Aukan et.al 2022)

Adults with severe obesity scheduled for SG or RYGB at two local hospitals in the Central Norway Health Region were recruited for this study. The control group (VLED intervention alone) comprised of patients on a waiting list for bariatric surgery, patients who declined or were not eligible for surgery, as well as individuals with severe obesity from the local community motivated to lose weight (recruited through advertisements at St. Olav's University Hospital and the Norwegian University of Science and Technology (NTNU) intranet). The control group was matched for pre-operative BMI, age, and sex distribution of the surgical groups. Recruitment and data collection took place between September 2019 and January 2022. A flow diagram of the DISGAP study can be seen in Figure 4.

The study was approved by the regional ethics committee (REK) (Ref: 2019/252), registered in Clinicaltrials.gov (NCT04051190), and conducted according to the guidelines laid down in the Declaration of Helsinki. All participants provided written informed consent before enrollment in the study (***Appendix 3, Written consent - DISGAP***). Participants had to be weight stable (self-reported; <2 kg body weight change over the last three months) and not enrolled in any other obesity treatment or behavioral program. Patients who had previously undergone bariatric surgery, were using medication known to affect energy metabolism or appetite, had a current cancer diagnosis, substance abuse, as well as present a psychiatric diagnose that precluded bariatric surgery (such as eating disorders) were excluded from the study.

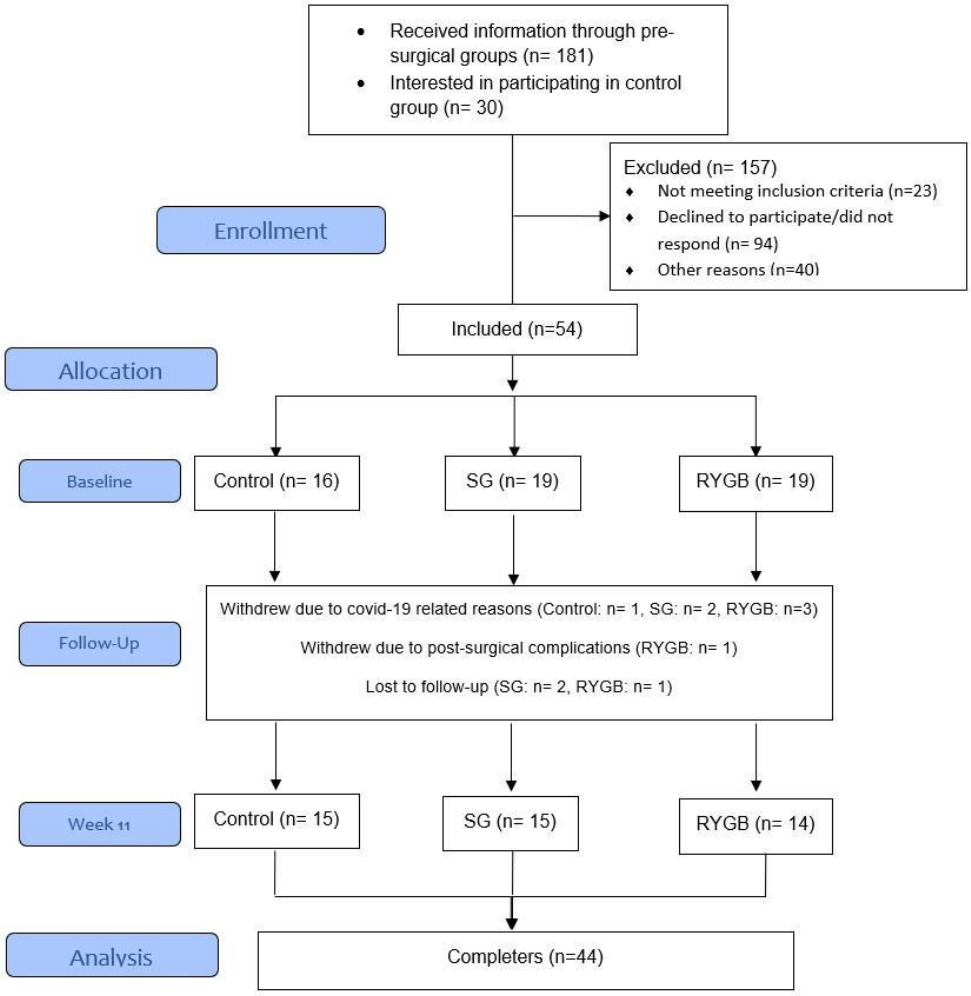

Figure 4. Flow diagram of the DISGAP study. SG: Sleeve Gastrectomy. RYGB: Roux-en-Y Gastric Bypass. (Aukan et.al 2022).

Weight loss interventions in the DISGAP study (Papers 3 and 4)

VLED

Participants from all groups were asked to follow a formula-based VLED using commercial food products (Lighter Life, Harlow, Essex, United Kingdom) for 10 weeks under the guidance of a dietitian. The average daily macronutrient composition of the VLED was 750 kcal, 26 E% fat, 36 E% carbohydrates, 5 E% fiber, and 33 E% protein. The products consisted of different shakes, soups, textured meals, porridge, and bars with approximately 150 kcal/meal. Participants could choose any combination of five products per day. In addition, they were encouraged to consume a maximum of 100 g low-starch vegetables per day, as well as 2.5 L water daily. Alcohol consumption was not allowed during the 10-week intervention. Non-caloric beverages were allowed, in addition to a maximum of 500 ml of low energy drinks (< 3 kcal/100ml).

Patients scheduled for SG and RYGB started the VLED 2 weeks prior to surgery, as standard procedure, and continued the diet for another 8 weeks post-operatively. The first weeks after surgery, SG and RYGB patients were instructed to consume only food packs in liquid form (shakes and soups) and then gradually increase the texture of the products. All participants were asked to fill out a self-reported food diary. At weekly scheduled follow-ups, food diaries were discussed, side effects recorded, body weight monitored, and AcAc was measured in urine with ketostix (Bayer Ketostix 2880 Urine Reagent Test Strip, Ascensia Diabetes Care) as a measure of dietary compliance.

Bariatric surgery

Bariatric surgeries were performed at St. Olavs University Hospital in Trondheim and in the Hospital of Namsos, both in central Norway, using standard laparoscopic procedures. The SG involved dividing the gastrocolic ligament, initiating the gastrectomy 4 cm proximal to the pylorus along the greater curvature, and creating the sleeve along the lesser curvature using a 36 French Bougie. The RYGB procedure involved creating a small (~20-30 mL) proximal gastric pouch and a stapled gastrojejunostomy. A 75–150 cm Roux-Y limb was constructed by transecting the jejunum 60-100 cm distal to the ligament of Treitz and performing a stapled jejunostomy at this site. Figure 5 illustrates the anatomical rearrangement of the GI system following SG and RYGB, respectively.

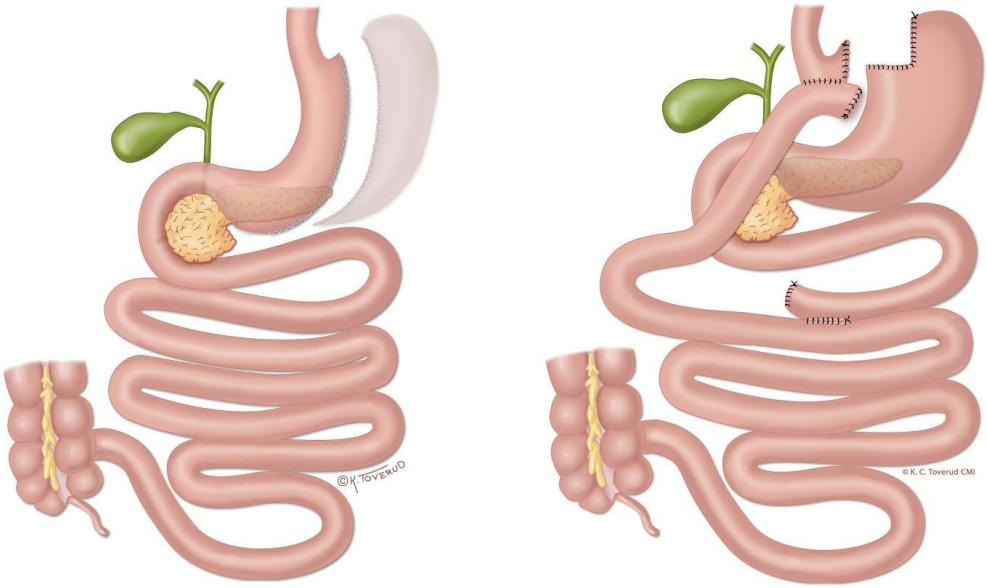

Figure 5. Anatomical rearrangements of the gastrointestinal tract following Sleeve Gastrectomy (left) and Roux-en-Y Gastric Bypass (right), illustrated by Kari C. Toverud CMI.

Outcome variables, *Papers 2, 3, and 4*

The following variables were measured once (cross-sectional design) in *Paper 2* and twice as repeated measures at BL and week 11 (W11) in the DISGAP study for *Papers 3 and 4*:

Body composition

Air-displacement plethysmography (BodPod, COSMED, Rome, Italy) was used to measure body weight, FM, and fat free mass (FFM).

Gastrointestinal hormones

Blood samples were collected in 4 ml EDTA-coated tubes and drawn in fasting, and every 15 minutes for the first hour after a standardized breakfast, and then at 30-minute intervals until 150 minutes. In *Paper 2*, the standardized breakfast consisted of a solid mixed meal (600 kcal, 17% protein, 35% fat, and 48% carbohydrates). In *Papers 3 and 4*, the standardized breakfast consisted of a 200 ml commercial low glycemic drink (Diben Drink, Fresenius Kabi Norge AS) (300 kcal, 20% protein, 42% fat, 35% carbohydrates, including 3% fiber). Participants were asked to drink it slowly over a 15-minute period, to avoid dumping syndrome (247).

For acylated ghrelin, total PYY, active GLP-1, and insulin, one milliliter of whole blood was transferred into a micro tube and a 20 µL mixture of inhibitor (10 µL of Pefabloc [Roche Diagnostic, Germany] + 10 µL dipeptidyl-peptidase IV inhibitor [Merck Millipore, Germany]) was added. For total GLP-1 and CCK, 500 KIU aprotinin (DSM, Coatech AB, Kaiseraugst, Switzerland) /mL whole blood was added to the EDTA tube. Samples were then centrifuged at 2106 RCF for 10 minutes at 18°C and the plasma frozen at −80°C until further analysis. Plasma samples for acylated ghrelin, total PYY, active GLP-1, and insulin were analyzed using a Human Metabolic Hormone Magnetic Bead Panel (HMHEMAG-34K, Merck KGaA, Darmstadt, Germany). The cross-reactivity between antibodies and any of the other analytes in this panel is non-detectable or negligible. Total GLP-1 and CCK were analyzed using “in-house” RIA methods (248, 249). Intra- and inter-assays CV were <10% and <20% for acylated ghrelin, total PYY and active GLP-1, and <5% and <15% for insulin, total GLP-1 and CCK, respectively. All the samples from the same participant were analyzed in the same plate. The analyses of acylated ghrelin, total PYY, active GLP-1, and insulin were performed by the same

technician at NTNU's lab. Total GLP-1 and CCK were both analyzed at the University of Copenhagen, Denmark.

Ketosis

A ketone body assay kit was used to analyze fasting plasma concentrations of βHB (MAK134, Sigma-Aldrich, St.Louis, MO, USA), at NTNU´s lab for the DISGAP study (*Papers 3 and 4*). All samples from each participant were analyzed in the same plate.

Subjective appetite ratings

In *Papers 2 and 3*, subjective appetite ratings (hunger, fullness, DTE, and PFC) were measured using a 10-cm VAS (243) in the fasted state, immediately after the standardized breakfast, and every 30 minutes for a period of 2.5 hours.

Hedonic hunger

In *Paper 4,* hedonic hunger was assessed by the PFS (250). This questionnaire consists of 15 questions, comprising of an aggregated score and divided into three subcategories: "food available" - readily attainable food, but not physically present; "food present"- the food both available and physically present, but not tasted; and last "food tasted" - food physically present and tasted or about to be tasted. A Likert scale with five levels was used (1= "I don't agree at all", to 5= "I strongly agree"). The higher the PFS-score, the higher the hedonic hunger. The questionnaire was handed out 60 minutes after initiating the breakfast.

Food reward

In *Paper 4,* food preferences and food reward were assessed using the Leeds Food Preference Questionnaire (LFPQ) (251). The LFPQ is a computerized behavioral task that provides measures of 'explicit liking' and 'explicit-' and 'implicit wanting' using images of food. The food pictures in the LFPQ are divided into four food categories: high-fat and sweet (HFSW), low-fat and sweet (LFSW), high-fat and savory (HFSA), and low-fat and savory (LFSA). For this study, participants were presented with pictures of foods common in the Norwegian diet. Individual food images were randomly presented to the participants who were required to

rate them according to “How pleasant would it be to taste some of this food now?” (explicit liking) and “How much do you want some of this food now?” (explicit wanting) with the scale ranging from “not at all” to “extremely”. Next, a forced choice task presented participants with a series of food image pairs and the instruction “Which food do you most want to eat now?”. A score was calculated according to how often a food category was chosen over another category, how often it was not selected, and the reaction time of the trial (implicit wanting). LFPQ was performed in the fasted state and immediately after breakfast.

Physical activity

General PA levels were assessed once for participants in *Paper 2*, and in the DISGAP study *(Papers 3 and 4*), participants were asked to maintain their PA levels during the 10-week intervention. PA levels and compliance with the latter recommendation was assessed by asking participants to wear SenseWear armbands (BodyMedia, Pittsburgh, PO, USA) for 7-days prior to BL and at W11, measuring average steps per day, PA level, metabolic equivalents, and total PA duration. Data was considered valid if participants wore the device for ≥ 4 days, including at least 1 weekend day, on more than 95% (22.8 hours/day) of the time (252).

Sample size calculation

Paper 2

Several studies have shown that individuals with obesity have a lower postprandial total GLP-1 response compared to those with normal weight (118, 253, 254). However, no studies have compared GLP-1 AUC among classes of obesity. Here, we hypothesized that individuals with obesity class I, -II, and -III would display a 10%, 20%, and 30% lower GLP-1 AUC, respectively, compared to controls without obesity (1533, 1226 and 858 min*pmol/l, respectively) (113). Power calculation was performed in Stata16 (StataCorp LLC, Collage Station, Texas, USA). For a power of 80%, a significance level of 0.05, and assuming a within group variance of 640 000 min*pmol/l (202), 87 participants would be required (29 in each group).

Papers 3 and 4

Given that WL with RYGB has been shown to induce a larger increase in total GLP-1 AUC compared to SG (215), and to dietary restriction alone (255), for the DISGAP study (an exploratory study) we hypothesized that bariatric surgery would induce a two (SG) and three (RYGB) times larger increase in total GLP-1 postprandial concentrations (AUC) compared to diet-induced weight loss alone (~600 pmol/ml*min) (202). For a power of 80%, a significance level of 0.05 and assuming a standard deviation (SD) of 1000 min*pmol/L, and a within group variance of 640 000 min*pmol/L, 45 participants would be required (15 in each group).

Statistical analysis

Paper 1

The mean and standard deviation for hormone concentrations and appetite ratings in the fasting and postprandial state (AUC) were extracted. Articles with extreme values (more than 10-fold larger than the average) were excluded from the meta-analysis. Articles reporting incremental AUC or calculating total AUC using "0" as basal value were also excluded. When not reported, the standard deviation was calculated from the provided standard error or confidence intervals. Data reported as medians and interquartile range were converted to means and SDs (256). If hormonal concentrations were reported in metric units, data were converted to SI units as follows: ghrelin pg/mL × 0.3 = pmol/L, GLP-1 pg/mL x 0.33 = pmol/L, PYY pg/mL × 0.25 = pmol/L. All values for subjective appetite ratings were converted to millimeters. AUC data were converted to minutes whenever necessary. Some studies reported data on subgroups within the obesity and controls groups, for example for men and women separately. Prior to inclusion in the meta-analysis, outcomes for these subgroups were pooled to obtain a single pooled mean and standard deviation within the obesity and control groups separately. For studies including more than one test meal, the meal closest to the dietary recommendations in terms of macronutrient composition was selected. For studies including more than one basal measure, before different infusions of nutrients, a basal value was chosen at random. When two basal values were given before infusion of saline or a hormone, the basal value measured before hormone infusion was selected.

The corresponding authors of the respective articles were contacted for further information or clarification when needed. If the missing data was not obtained, the respective

article was included in the systematic review, but not in the meta-analysis. Meta-analyses were conducted to compare the obesity and control groups for each outcome variable, when there were at least three studies with data. Pooled estimates of standardized mean differences (SMDs) were obtained using a random-effects model. Statistical heterogeneity was investigated using the I^2 statistic and a threshold of 75% was considered to represent high heterogeneity (257). Evidence of publication bias was assessed by visual inspection of funnel plots and Egger's test. Analyses were performed using Stata version 16.1 (Stata Corp., College Station, Texas, USA).

Paper 2

The statistical analysis was carried out using SPSS, version 26 (SPSS Inc., Chicago, IL). Data are presented as estimated marginal means ± standard error of the mean (SEM), unless otherwise stated. Due to the large number of tests, the significance level was reduced to $P<0.01$, to account for increased risk of type-1 error. Two separate general linear models were performed to compare GI hormones and subjective appetite ratings among different BMI classes, presented as estimated marginal means. One model compared obesity class I, -II, and -III, and a second model compared individuals with obesity (and its subclasses) with controls (a total of six comparisons). Residuals were checked for normality with Shapiro Wilk test and did not deviate significantly from normality.

A conversion from metric to SI units was made whenever required, as previously described, and as well for insulin; pg/mL x 6 = pmol/L. Plasma concentrations of GI hormones and appetite ratings were analyzed as dependent variables, with BMI group as a fixed factor. Potential covariates that could affect appetite (age, sex, and PA levels) were added to both models, and Bonferroni correction was used for post-hoc pairwise comparisons. The trapezoidal rule was applied to calculate total AUC (tAUC) or incremental AUC (iAUC) from 0 to 150 minutes. A linear mixed model was run to look at changes in plasma concentrations of GI hormones over the sampling period (0, 30, 60, 90, 120 and 150 min) in each group, using Bonferroni correction for post-hoc pairwise comparisons. Spearman correlation was used to investigate the association between BMI and the different appetite variables.

Papers 3 and 4

The statistical analyses for *Papers 3 and 4* were carried out using SPSS, version 27 (SPSS Inc., Chicago, IL). Residuals were checked for normality using Shapiro Wilk test and visual inspection of QQ plots, and histograms and did not deviate significantly from normality. Data are presented as means ± SEM, unless otherwise stated. Due to the large number of tests in *Paper 4*, the significance level was reduced to $P<0.01$ to avoid type-I errors. All data (anthropometrics, GI hormones, βHB, subjective appetite ratings, hedonic hunger, and food reward) were analyzed using linear mixed-effects models with restricted maximum likelihood estimation, including fixed effects for time, group, and their interactions. Bonferroni correction was used for post-hoc pairwise group comparisons. Blood samples from two participants could not be collected at BL (one control, one RYGB), and these were therefore excluded from the analysis of GI hormones. Total and incremental (or decremental) area under the curves (*t*AUC, *i*AUC, and *d*AUC, respectively) for GI hormone concentrations and appetite ratings were calculated using the trapezoid rule.

Summary of results

A summary of the main findings is given below and described in detail in their respective papers attached (*Papers 1-4*).

Paper 1

The systematic review and meta-analysis represent the first comprehensive effort to investigate if the plasma concentrations of GI hormones and subjective appetite ratings differ between adults with and without obesity. The systematic review indicated a trend towards an attenuated hormonal response to nutrient ingestion in individuals with obesity. The meta-analysis showed that individuals with obesity indeed presented with statistically significantly lower basal and postprandial total ghrelin concentrations compared to controls, lower postprandial concentrations of total PYY, and lower postprandial hunger ratings. No convincing differences were found for GLP-1, CCK, or fullness, DTE or PFC ratings. However, there was a large methodological and statistical heterogeneity among studies. Figure 6 shows the overall results of the meta-analysis.

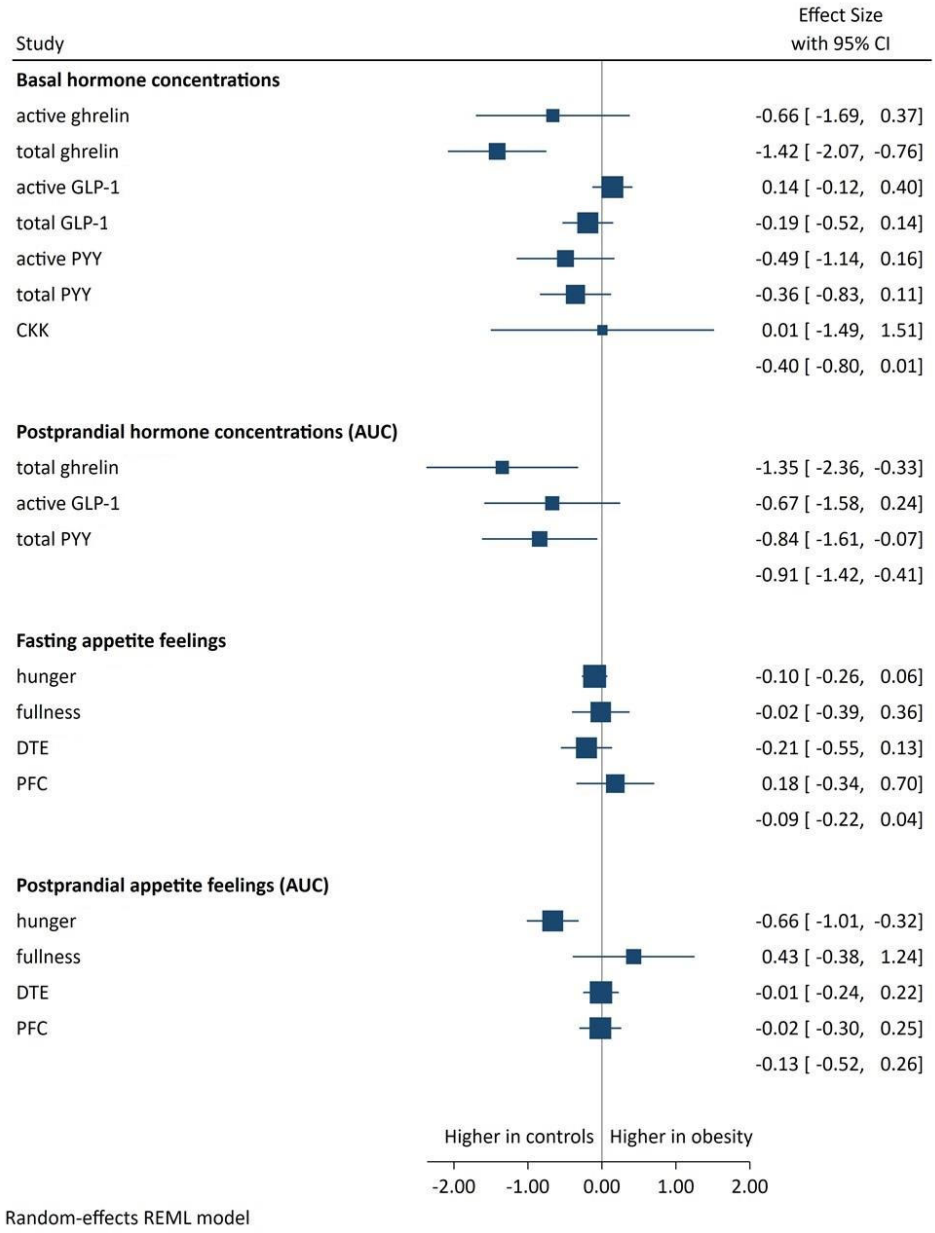

Figure 6. Overall results from the meta-analysis (Aukan et. al 2022).

Paper 2

No significant differences were seen for plasma concentrations of GI hormones (either basal or postprandial values) among obesity classes, except for insulin. But, in general, obesity was associated with impaired secretion of GI hormones compared to controls and ghrelin concentrations did not decline postprandially in obesity class-III. Moreover, the GLP-1 peak for obesity class-I and -II was early and lower compared to controls, while class-III showed no postprandial GLP-1 response. Postprandial PYY responses in obesity class-II and -III were absent. In addition, obesity class-III showed a delayed and shortened postprandial CCK response compared to controls. Basal and postprandial concentrations of insulin increased progressively across obesity classes.

These findings were supported by correlational analyses, showing inverse associations between BMI and basal and postprandial concentrations of ghrelin and PYY, postprandial GLP-1, as well as positive associations between BMI and basal and postprandial insulin. No differences were found for subjective appetite ratings among obesity classes. Figure 7 shows mean ± SD postprandial concentrations over time for GI hormones.

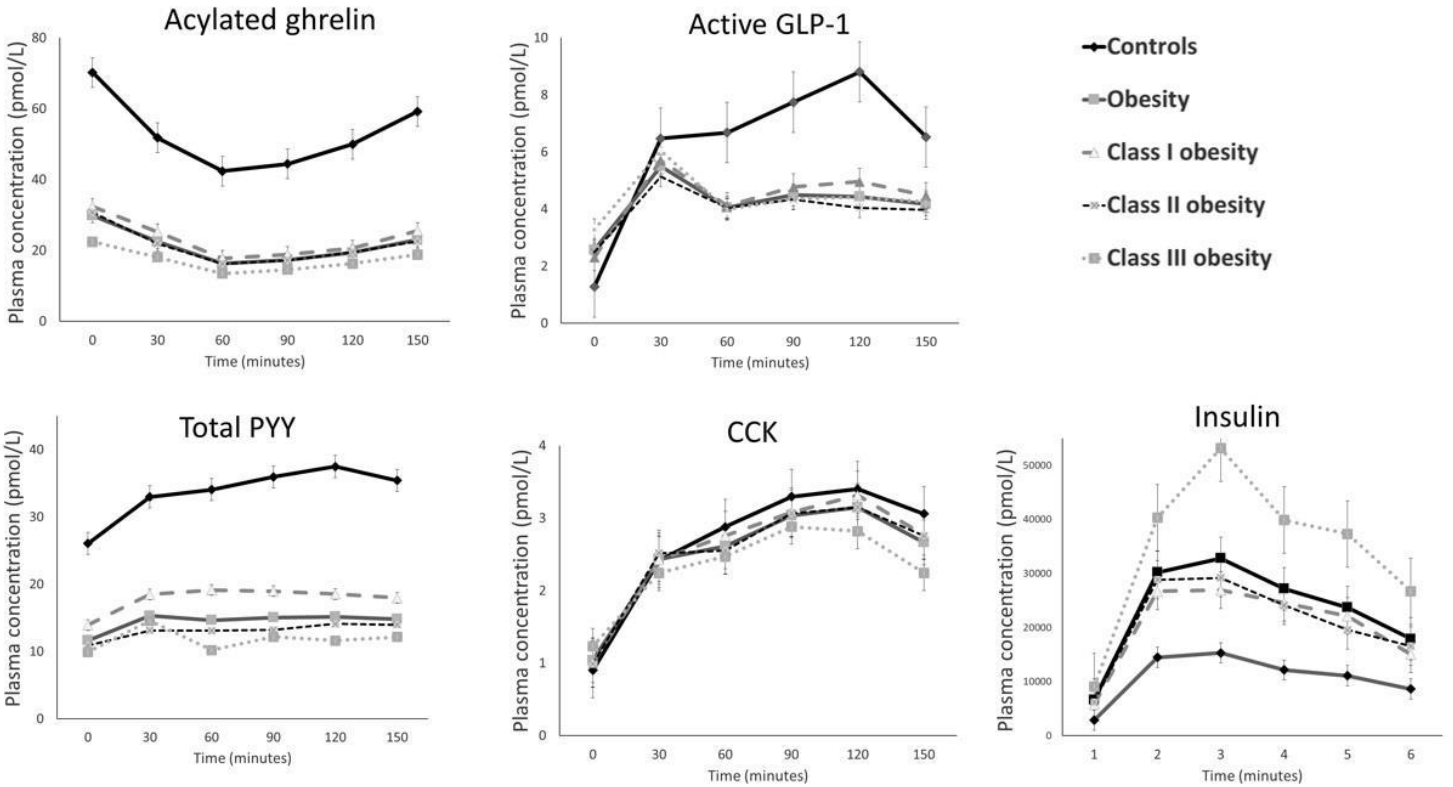

Figure 7. Mean basal and postprandial plasma concentrations of GI hormones shown in subgroups of obesity and controls. AG: acylated ghrelin. CCK: cholecystokinin. GLP-1: glucagon-like peptide-1. PYY: peptide YY. Conversion from metric to SI units has been made in table 2 and figure 1 and is as follows: ghrelin pg/mL × 0.3 = pmol/L, GLP-1 pg/mL x 0.33 = pmol/L, PYY pg/mL × 0.25 = pmol/L, and insulin pg/mL x 6 = pmol/L. (Aukan et. al 2022)

Paper 3

After 10 weeks on a VLED alone or combined with either SG or RYGB the magnitude of WL achieved (18.3 ± 0.6 kg), as well as the changes in body composition and level of ketosis, were comparable across groups. SG and RYGB experienced a decrease in both basal and postprandial AG concentrations and an increase in postprandial total GLP-1 concentrations. All groups experienced an increase in postprandial concentrations of total PYY. At W11, RYGB obtained the greatest postprandial concentrations of both total GLP-1 and total PYY. Overall, postprandial CCK concentrations remained unchanged. Figure 8 shows mean ± SD concentrations of GI hormones over time at BL and W11.

Overall, postprandial hunger decreased, and postprandial fullness increased. However, larger decreases in fasting and postprandial DTE and PFC were seen after both bariatric procedures, and at W11 ratings tended to be overall lower in SG and RYGB compared to controls. **Figure 9** shows mean ± SD appetite ratings over time at BL and W11.

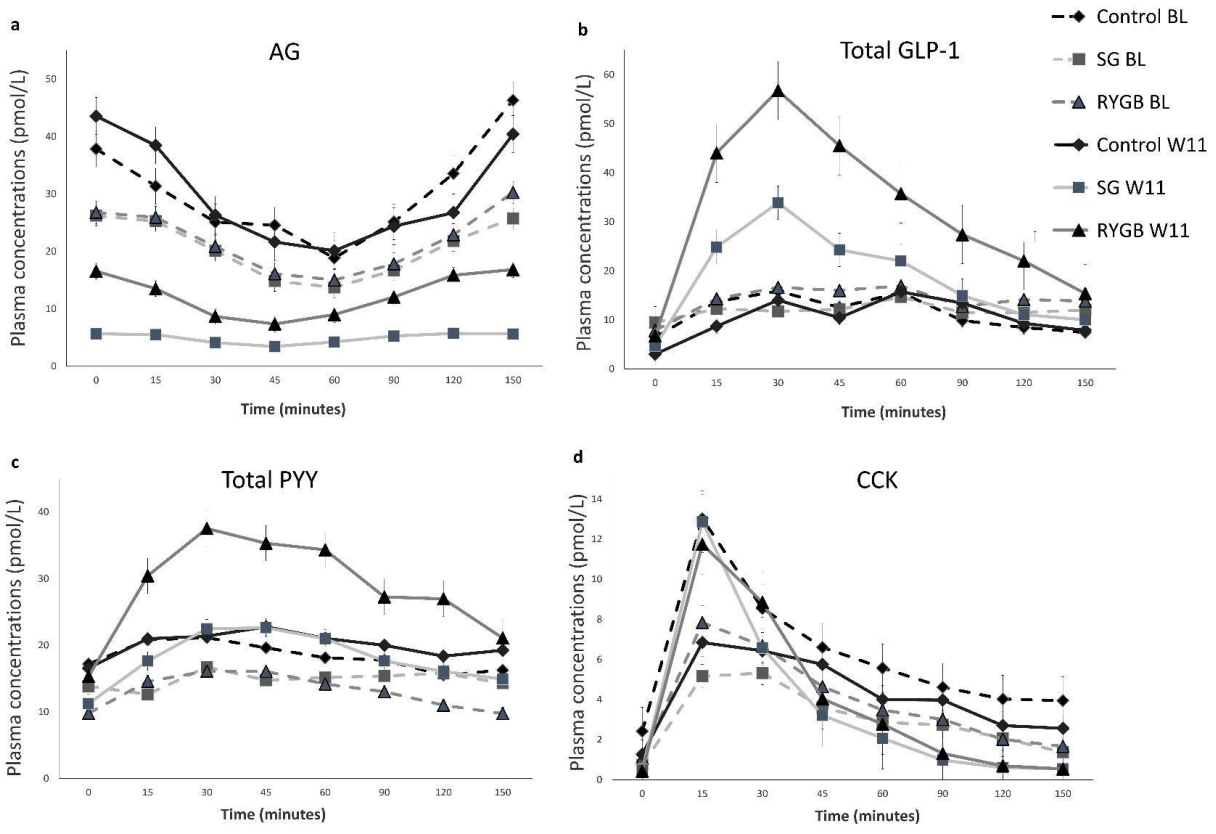

Figure 8. Mean postprandial concentrations of gastrointestinal hormones at baseline and week 11. Dotted lines indicate baseline concentrations, solid lines indicate week 11 concentrations. AG: acylated ghrelin. BL: baseline. CCK: cholecystokinin. GLP-1: glucagon-like peptide 1. PYY: peptide YY. RYGB: Roux-en-Y Gastric Bypass. SG: Sleeve Gastrectomy. W11: week 11. (Aukan et. al 2022)

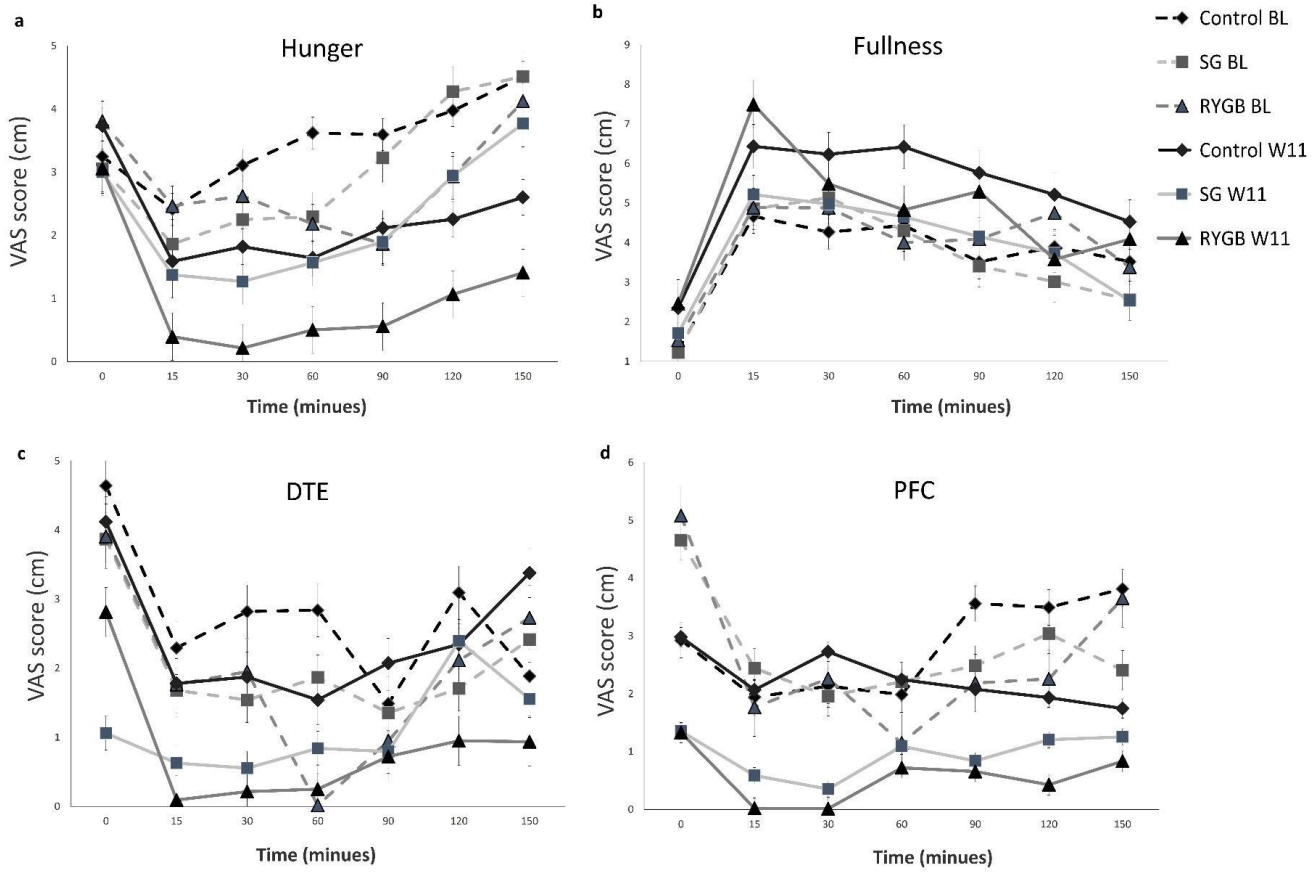

Figure 9. Mean postprandial ratings of appetite at baseline and week 11. Solid lines indicate baseline ratings, dotted lines indicate week 11 ratings. BL: baseline. DTE: desire to eat. PFC: prospective food consumption. RYGB: roux-en-Y Gastric Bypass. SG: Sleeve Gastrectomy. VAS: visual analogue scale. W11: week 11. (Aukan et. al 2022)

Paper 4

BL characteristics and changes in body weight and composition overtime, and level of nutritional-induced ketosis were comparable across groups. This was paralleled by similar reductions in hedonic hunger, both the aggregated score and the subcategories from the PFS, across groups. When measuring food reward by the LFPQ, both SG and RYGB showed decreased liking for most food categories, while controls experienced no changes. Moreover, liking for foods was overall greater in controls compared to RYGB after WL. The explicit motivation to eat (for all food categories) was generally reduced in SG and RYGB, and lower compared to controls at W11. A reduction in the motivation to eat HFSW foods in controls was seen in both states of consciousness (explicit and implicit), but their implicit motivation for LFSA foods increased. The mean scores for the PFS can be seen in Figure 10 and overall changes across groups for the LFPQ in Figure 11.

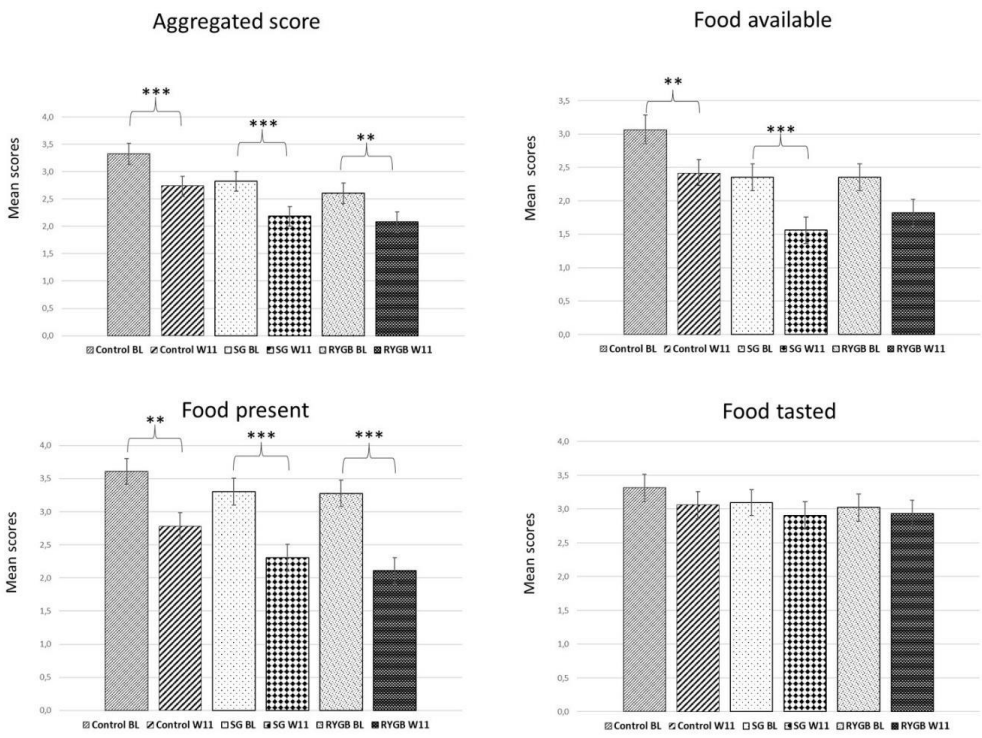

*Figure 10. Mean scores from the Power of Food scale, before and after a 16% weight loss. BL; baseline. RYGB; Roux-en Y Gastric Bypass. SG; Sleeve Gastrectomy. W11; week 11. Stars denote significant differences over time (***P<0.001, **P<0.01.). (Aukan et. al 2022)*

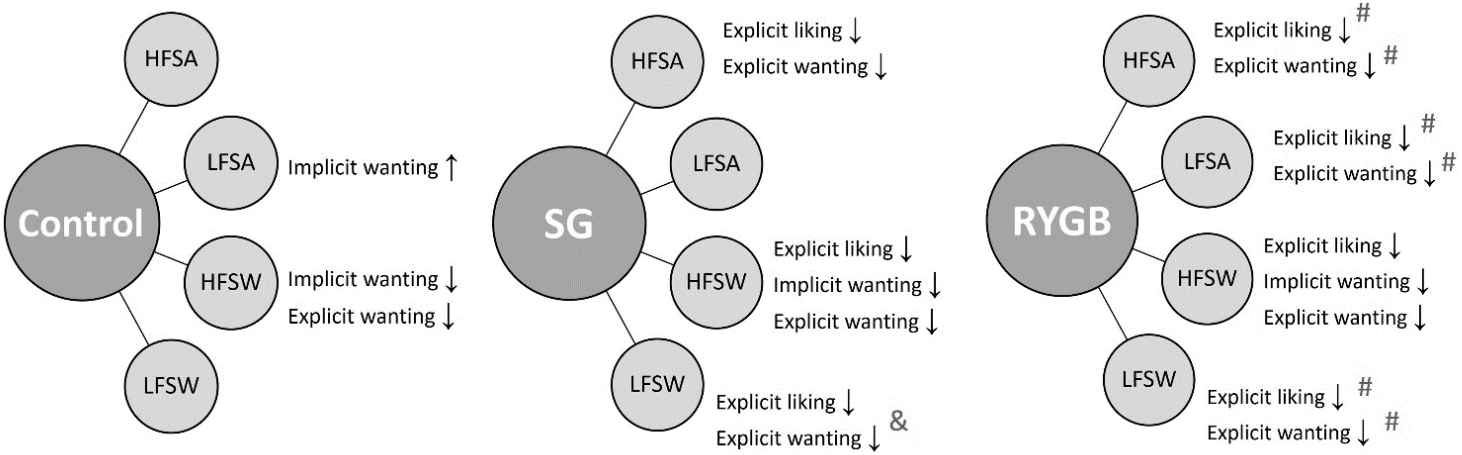

Figure 11. Overview of changes in liking and wanting for palatable foods across groups. HFSA: high-fat savory. HFSW: high-fat sweet. LFSA: low-fat savory. LFSW: low-fat sweet. RYGB: Roux-en Y Gastric Bypass. SG: Sleeve Gastrectomy. Arrows denote significant changes over time for each category, within groups (P<0.01). Superscript letters denote significantly lower scores in SG and RYGB compared to controls at week 11 (&#, P<0.01). (Illustrated by M.I. Aukan, 2022)

Discussion

The overall aim of this PhD thesis was to investigate if, and how, homeostatic appetite regulation is different in individuals with- and without obesity, and how WL induced by dietary restriction alone or in combination with bariatric surgery, impact on constructs of both homeostatic and hedonic appetite. An overview of the main findings can be seen in **Figure 12.**

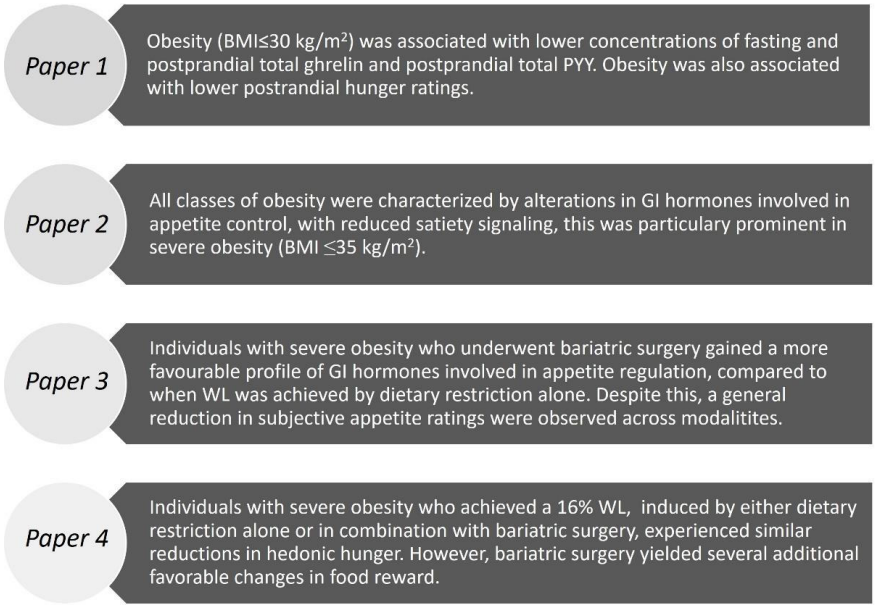

Figure 12. Overview of the results of Papers 1-4. BMI: body mass index. GI: gastrointestinal. PYY: peptide YY. WL: weight loss. (Aukan, 2022).

Papers 1 and 2

Irregularities in homeostatic appetite regulation and eating behavior compared to normal weight subjects, specifically eating in the absence of physiological needs, have been suggested to be a challenging trait of obesity. However, little consensus exists on how homeostatic appetite regulation may be altered in the first place, and if it becomes worse with increasing severity of the disease. In both *Papers 1* and 2 it was observed that basal and

postprandial ghrelin concentrations were lower in individuals with obesity compared to controls. In addition, *Paper 2* replicated well established results about the positive relationship between BMI and both basal and postprandial insulin secretion (78). Interestingly, it has been suggested that the relationship between obesity and ghrelin is mediated through insulin resistance and/or compensatory hyperinsulinemia, and that it is not the adiposity *per se* that affects ghrelin concentrations (119). However, in the latter study it was not possible to distinguish whether it was resistance to insulin, hyperinsulinemia, or an unmeasured associated factor contributing to low ghrelin concentrations. Nevertheless, it seems reasonable that insulin would decrease ghrelin concentrations as part of a complex feedback loop to decrease hunger in obesity. Moreover, associations between the inter-meal-interval between breakfast and lunch have been associated with AUC ghrelin responses in normal weight men, but not in men with obesity, suggesting that individuals with obesity are less sensitive to the effects of ghrelin (258). *Paper 1* also showed that postprandial total PYY were statistically significantly lower in individuals with obesity compared to controls. In *Paper 2*, the postprandial PYY response was shown to be completely absent in obesity class II and -III, and BMI was negatively correlated with postprandial PYY concentrations (259). Interestingly, it has been suggested that the lower postprandial PYY concentrations measured in obesity would result in increased food intake to achieve the same degree of fullness as that seen in normal weight individuals (88).

Regarding both GLP-1 and CCK, the findings in *Paper 1* were associated with a large degree of uncertainty due to high heterogeneity, altogether preventing conclusions to be drawn. In *Paper 2,* a weaker and earlier postprandial GLP-1 peak in individuals with obesity (and absence in obesity class III), as well as an inverse association between BMI and postprandial GLP-1, were found. Even though these findings can be supported by several large cohorts (123-125), discrepancies in the literature have been observed in both human and animal studies (120). For example, a higher GLP-1 peak has been reported in both individuals with overweight, and obesity class I, -II and -III compared to subjects with normal weight (108). However, in the latter study, individuals with obesity drank more of a liquid test meal to reach fullness. It has been suggested that if all subjects were given a test-meal corresponding to their body weight, GLP-1 response might not be reduced in individuals with obesity compared to normal weight subjects (120), which might explain the conflicting

findings in the literature. Nevertheless, individual variability seems to be high, and reductions in GLP-1 responses are suggested to occur before both diabetes and obesity (123), thus the role of GLP-1 at normal physiological levels in obesity remains to be determined (120). Although CCK is the best-established GI satiation signal (70-72), few studies have investigated differences in postprandial CCK concentrations between individuals with and without obesity. Obesity has been associated with both lower (113) and greater postprandial concentration of CCK (141) compared to controls. However, and in line with the results of *Paper 2*, most studies report no differences between these groups (135, 260, 261).

It needs to be emphasized that even if no true differences in GLP-1 or CCK plasma concentrations exist between individuals with and without obesity, one cannot rule out the importance of the vagus nerve or other signaling pathways in regulating appetite. For example, chronic ingestion of energy-rich diets has been shown to reduce the sensitivity of vagal afferent neurons to peripheral signals, which would be sufficient to drive both hyperphagia and obesity (262).

Since obesity is also associated with greater EI (152), it is somewhat surprising that individuals with obesity obtained lower postprandial hunger ratings compared to controls in *Paper 1*, and no differences being found among classes of obesity in *Paper 2*. Yet, in the latter, obesity was associated with greater postprandial PFC, implying that individuals with obesity thought they could eat more food after the standardized breakfast meal compared to controls. However, it was early demonstrated that subjective appetite ratings in individuals with, and without obesity, have similar sensitivity to macronutrients (263) and dietary manipulations (264). Additionally, in laboratorial settings, infusion of GI hormones has been shown to affect eating behavior in both individuals with normal-weight and obesity (37, 66, 88, 265, 266). The associations between these variables are, nonetheless, highly complex and the evidence for their influence on food intake at normal physiological levels is less clear (267). In a longitudinal study, appetite, and especially disinhibition, was shown to be a key characteristic for adults with high obesity risk and associated with higher BMI (268). One hypothesis is that obesity, through distinctive processes (i.e., reduced vagal sensitivity as previously discussed, or other central mechanisms), dysregulates the sensing of appetite. As briefly mentioned before, many individuals with obesity report no relationship between their sensations of hunger and fullness in conjunction with their actual eating habits (156). In this

study, it was further suggested that the process underlying disinhibition, which probably also includes biological components, might be associated with recognition of satiety or satiation (156). Maier and colleagues (2008) found that in individuals with a normal weight, ghrelin and PYY concentrations correlated with hunger and fullness ratings, respectively, while no association was found in individuals with obesity (269), suggesting a discrepancy between biological signals and sensing of appetite. It may be challenging to determine the role of GI hormones in obesity, especially in a state of weight stability. But the lower ghrelin plasma concentrations - both in the fasting and postprandial states, lower ratings of postprandial hunger, greater postprandial ratings of PFC, and lower (or absent) postprandial PYY and GLP-1 responses seen in individuals with obesity in *Papers 1 and 2*, asks for more research on this matter.

Even though establishing a direction of causality is difficult, and out of the scope of this thesis, the previously discussed findings point to obesity being a cause, not a consequence, of the differences observed in the homeostatic appetite control system. However, the greatest challenge in obesity weight management is not achieving clinically significant WL, but maintaining the WL in the long-term, whereas consequent changes in appetite regulatory systems might play a contributing role.

Paper 3

Interestingly, our research group has recently demonstrated that the increased orexigenic drive to eat seen after WL likely reflects a normalization towards a lower body weight, given that no differences were seen between reduced-obese individuals and FM matched controls (113). In *Paper 3*, individuals with severe obesity following a VLED alone showed no changes in AG concentrations, despite a substantial WL. Ketosis has previously been shown to prevent the expected increase in ghrelin plasma concentrations otherwise seen following diet-induced WL (206, 208, 270), which might explain these findings. The main production site of ghrelin is the fundus of the stomach, which is removed during the SG procedure, and in line with several others (215, 216, 221), the findings of lower AG concentrations post-SG were therefore not surprising. Similarly, ghrelin has previously been shown to decrease post-RYGB (221, 223, 255, 271), and that concentrations are lower when compared to diet-induced WL (223, 255). However, not all studies are in agreement (220, 272), and an increase in ghrelin

concentrations has also been reported post-RYGB (273). A systematic review and meta-analysis showed that at least fasting total ghrelin concentrations decrease in the short-term post-RYGB (<3 months) but increase again after 3 months (274). These conflicting findings might, however, result from differences in the surgical technique, namely, size of the remaining pouch, the magnitude of WL achieved across groups, as well as dynamic adaptions in the GI tract (275).

The impact of diet-induced WL on postprandial concentrations of GLP-1 and PYY remains controversial (177, 181, 202). A previously published paper by our research group demonstrated that higher levels of ketosis after a VLED were associated with smaller reductions in active GLP-1 (208). This might explain why no significant reductions were seen in controls for postprandial total GLP-1 concentrations in *Paper 3*. Some have reported a decrease in postprandial PYY concentrations with WL, both with- (203, 206), and without ketosis (206), while others found an increase in fasting total PYY (276) and postprandial concentrations of PYY_{3-36} (202). The findings of an increase in postprandial total PYY concentrations following VLED alone, in *Paper 3,* were, therefore, contrary to the hypothesis of poor satiety control, but combined with the latter two abovementioned studies – results are in line with the normalization theory (113).

Nevertheless, larger increases in the postprandial concentrations of both GLP-1 and PYY were seen after bariatric surgery in *Paper 3*, particularly post-RYGB, where concentrations were significantly greater compared to controls, and to some extent SG. Several other studies have reported increased postprandial concentrations of both GLP-1 and PYY following SG and RYGB, and also demonstrated that RYGB results in a greater postprandial concentration of these gut hormones compared to SG (and controls) (215, 216, 218, 221, 222, 255, 272, 277). Alterations in the plasma concentration of the satiety peptides in general, post-bariatric surgery are in accordance with the hindgut hypothesis - and the distinctive anatomical rearrangements following the two procedures. The amplified response may be due to accelerated gastric emptying, caused by the surgical alterations of the stomach, leading to an exaggerated secretion of satiety hormones post-SG (215), and with the anatomical shortcuts following RYGB - the nutrients are rapidly delivered to the distal small intestine (215, 221, 278). Also, the anatomical rearrangement that follows bariatric surgery, especially RYGB,

seems to lead to the proliferation of GI hormones' secreting cells, at least in the longer term (279), but this is an under-investigated phenomenon.

In *Paper 3,* basal CCK plasma concentrations, were greater in controls at BL compared with patients scheduled for SG and RYGB. The difference was unexpected, but, nevertheless unlikely to play a significant role in appetite regulation, especially satiety. Moreover, controls experienced a reduction in basal CCK concentrations over time, resulting in no differences among groups at W11. Diet-induced WL has previously been shown to decrease postprandial CCK concentrations in individuals with obesity, but not when participants were ketotic (209), and higher levels of ketosis have been associated with smaller reductions in CCK postprandial concentrations (208). This is in line with the findings of *Paper 3* showing no changes over time in postprandial CCK concentrations under nutritional induced ketosis. Previous literature on the impact of SG and RYGB on CCK concentrations are, however, inconsistent. Peterli at al. (221) reported an increase in postprandial CCK response following SG, but not post RYGB. On the other hand, Schmidt et al, (255) reported a marked increase in postprandial CCK, along with GLP-1 and PYY response, post-RYGB.

Furthermore, successful long-term WL after dietary restriction alone has been suggested to be dependent on increases in both postprandial GLP-1 and PYY responses (202), and greater GLP-1 concentrations at 1 year follow-up have been associated with greater WL post-RYGB (280). In line with this, GLP-1 agonists have shown great success in the management of both obesity and type 2 diabetes, by reducing food intake and producing significant WL (281, 282). Altogether, this suggests an important role for GI hormones (and their agonists) in appetite control and weight management in obesity, without the risks associated with bariatric surgery.

Despite supposedly less beneficial alterations in GI hormones' concentrations after WL induced by VLED alone in *Paper 3,* overall ratings of postprandial hunger were reduced, and postprandial feelings of fullness increased across groups. In line with this, it has previously been shown that the expected increase in hunger feelings that follows WL is prevented, and postprandial fullness sometimes increased, when participants are ketotic (206, 209). Even though ketosis has been associated with greater WL 1 year post-SG (225), the impact of ketosis on appetite in the context of bariatric surgery is under-investigated, but nevertheless likely to play a role (225, 283). *Paper 3* showed that all participants were in nutritional-induced

ketosis at W11, with no differences among groups. SG also experienced a reduction in ratings of DTE in fasting at W11, and both fasting and postprandial DTE ratings were lower in SG and in RYGB, respectively, compared to controls. Moreover, fasting, and postprandial PFC decreased more after bariatric surgery in general, while they remained unchanged and increased, respectively, in controls. Overall, the decrease in appetite ratings seen across groups in *Paper 3* was not unexpected given that participants were in nutritional-induced ketosis and experienced no changes, or even a decrease in ghrelin concentration, as well as increases in postprandial PYY and/or GLP-1 concentrations.

Although, the overall changes were more favorable post bariatric surgery, several aspects may help explain the somewhat lack of alignment between changes in the plasma concentrations of GI hormones and hunger-, and fullness ratings seen in *Paper 3*. In addition to the previously discussed question of appetite sensing in obesity, an important issue to consider is that subjective appetite ratings do not provide the full spectrum of either appetite control/behaviors or actual food intake. Rather, they are likely to reflect individual factors, such as learned behaviors throughout the lifespan (83). Also, it is debatable to what degree subjective hunger ratings can reflect actual physiological needs. While hunger ratings in the fasting state are most likely a reflection of energy depletion, hunger ratings in the fed state may also be impacted by hedonic traits (91). Hedonic appetite can easily override homeostatic signals when food is readily available and highly palatable, even in the absent of physiological hunger (93). This is particularly important considering the obesogenic environment that has emerged over the past decades. Hedonic characteristics might, therefore, offer an additional construct to help reflect an individual's subjective appetite, motivation to eat, and subsequent food intake.

Paper 4

To my knowledge, no study had previously compared how a similar WL induced by VLED alone or in combination with bariatric surgery impacts on hedonic constructs of appetite. Although hedonic hunger has not been predictive of weight gain in individuals without obesity, those with a high score, as measured by the PFS, are likely to have increased neural responses to palatable food cues, increased motivation to consume those foods, as well as a greater risk of binge eating (102). Furthermore, patients with severe obesity present with higher hedonic

hunger compared to controls without obesity (161), but it has been less clear how diet-induced WL impacts on this construct of appetite.

A 10% increase in hedonic liking of food was reported after eight weeks of caloric deprivation, independently of WL (228). Alternatively, hedonic hunger has been found to decrease after a 12-week WL program, and this decrease was inversely associated with improvements in reported weight-control behaviors (229). The results in *Paper 4* showed that a 16% WL, over the course of 10 weeks, decreased hedonic hunger (measured in the fed state) comparably across all groups. These results might also reflect the overall reduction in postprandial subjective appetite scores seen in *Paper 3.* Interestingly, reductions in hedonic hunger post-RYGB (measured at 15 months) seem to be accompanied by more favorable changes in dietary habits, such as increased intake of protein-rich foods and vegetables, as well as reduced consumption of sugary foods, snacks, and beverages (284). A recent publication (285) demonstrated that reductions in hedonic hunger, both post-SG and -RYGB, could predict WL outcomes at 12- and 24 months post-operatively. Moreover, sub-optimal WL, 13 years post-RYGB, has been associated with increased hedonic hunger, when compared to their counterparts who had experienced an optimal WL in the same period (196). Even though decreased hedonic hunger has been associated with better WL after a 12-week commercial WL program (229), there seems, however, to be little or no evidence constituting this issue on long- term WL outcomes after diet-induced WL.

A 5% WL, induced by continuous or intermittent energy restriction, have been reported to improve dietary restraint, craving control, susceptibility to hunger and binge eating in women with overweight or obesity, but elicited no changes in liking and wanting (food reward and preferences) for high-fat foods relative to low-fat foods (230). However, in another study with the same sample of participants, decreased liking for all food categories with diet-induced WL was reported (231). *Paper 4* showed little or no changes in liking and wanting for controls, but the same magnitude of WL induced by SG and RYGB (at least in the initial stages) yielded several additional favorable changes in food reward compared WL with the VLED alone. This could have implications for the motivation that triggers actual food seeking behavior, as well as consumption of the foods desired. Moreover, the results in *Paper 3* indicated that bariatric surgery (SG and RYGB) decreases the motivation to eat (DTE), as well as the amount of food desired (PFC), a phenomenon that was not seen with diet-induced WL

in the DISGAP study. In line with these findings, a similar WL induced by either SG or RYGB have previously been shown to lead to comparable changes on key factors involved in the regulation of eating behavior and hedonic components, such as frequency of food cravings, influence of emotions and external food cues, and favorable shifts in the pleasantness of sweets (239). Altough, dumping syndrome is a common side effect after bariatric surgery, especially post-RYGB, and suggested to alter the pleasantness of foods, especially carbohydrate- and fat-rich foods (247), which might explain some of the differences seen between WL induced by bariatric surgery and VLED alone.

Nevertheless, it has been argued that these changes in eating behavior post-bariatric surgery are largely driven by increased postprandial concentrations of satiety peptides (285). For example, intravenous infusion of PYY has been shown to modulate responses to visual food cue stimuli (286), and the use of GLP-1 receptor agonists is associated with decreased activation of key brain regions involved in hedonic control of appetite in responses to palatable food cues (287, 288). This might also explain why SG and RYGB were associated with a more favorable hedonic appetite profile in *Paper 4* (as well as DTE and PFC in *Paper 3*) compared to controls. Decreased dopamine receptor availability has been reported in individuals with obesity (289), and bariatric surgery seems to be able to reverse this pattern (290). This could also serve as a possible mechanism for the additional improvements in food reward seen after bariatric surgery, compared with the control group. Continuing to optimize medical treatment of obesity as an additional tool to lifestyle treatments, or bariatric surgery, may therefore be necessary to manage obesity as a disease and the current obesity epidemic.

Strengths and limitations

Paper 1

The systematic review and meta-analysis have several strengths. It represents the first attempt to compare GI hormones and appetite ratings between adults with, and without obesity. Second, the analysis was conducted following the PRISMA statement guidelines, and used well established tools during the whole selection process. Third, its comprehensiveness provides a warranted descriptive picture of the topic of interest. Unfortunately, this analysis also has some limitations. First, several studies were not included in the meta-analysis due to

missing data. This might have affected the results and contributed to the lack of significant differences between groups for some of the outcome variables. Second, the heterogeneity in most meta-analyses conducted in this study was relatively high and, as such, conclusions should be made with caution. When interpreting the present results, it is critical to consider the timing, nature, and structure of the test-meal, important aspects in modulating the outcome variables of this review. The statistical heterogeneity seen in this meta-analysis, particularly for the GI hormone comparisons, is likely to be the result of differences in the underlying study populations, test-meals used, sample processing, and heterogenicity in the hormonal fractions measured and methods of analysis. For example, GLP-1 is rapidly degraded, and accurate methods are crucial to obtain precise measures. Also, the adequate measure of L-cell secretion is total GLP-1, while active GLP-1 provides information about the endocrine part of the peptide's actions (291). Thus, developing an optimized standardized method to assess hormonal responses and subjective appetite is needed. Third, transparent research and reporting of results should be encouraged, as there is some indication of an overall publication bias with an apparent small study effect among the published results for basal hormone concentrations. Fourth, different GI hormones are stimulated by specific nutrients in the lumen (48). This means that the mixed meals used (liquid or solid), with different macronutrient composition, or even single macronutrient meals, might not have been the best to maximize the inhibition of ghrelin, or the release of the different satiety peptides. For example, among the included studies in the analysis for active GLP-1 (AUC), higher concentrations were seen in controls, versus individuals with obesity, after a 750 kcal liquid meal (118), while no differences were reported between groups after a 450-650 kcal solid meal (113, 130, 155). Another important aspect to take into consideration is if the energy content of the tests meals was similar in the obesity and control groups, or if they were adjusted for body weight. Most of the studies have used the same test meal in both groups. This controls for that the stimuli are given to each subject but does not account for individual nutritional needs. Lastly, even though all efforts were made to ensure that measures were comparable, the length of the postprandial period was not uniform and could have affected the results.

Paper 2

The strengths of *Paper 2* include its novel study design, which allowed for the evaluation of alterations in GI hormones and appetite ratings among obesity classes, as well as between obesity classes and controls, an issue that is under-investigated. Moreover, variables known to affect appetite were added to the models as covariates, the significance level adjusted for multi-comparisons (Bonferroni), as well as the large number of variables tested. However, this study also has some limitations. First, a multiplex kit was used to measure hormonal concentrations, except for CCK. This method is likely to result in less accurate and precise measures compared to optimized assays for each hormone. Second, also here, the energy load of the test meal was kept constant regardless of body weight. This ensures that the same nutritional stimulus was provided to all participants but did not account for individual energy needs. Third, participants in this study were not equally distributed among groups, the class-III obesity was small, and controls included both subjects with normal weight and overweight. Last, this is a cross-sectional analysis comparing groups with different BMI's and, as such, a cause-effect relationship cannot be established.

Papers 3 and 4

The DISGAP study (*Papers 3 and 4*) has several strengths. First, groups were matched for baseline BMI, age, and sex distribution, and changes in body weight and composition, level of ketosis, PA and dietary regime were comparable across groups. Therefore, these factors were unlikely to have affected the outcome variables, allowing for identification of the impact of SG and RYGB alone on the outcome variables. Second, the significance level was adjusted for multi-comparisons (Bonferroni) and in *Paper 4* significance level was reduced to take into account the large number of variables tested. However, these studies also have some limitations. First, as the intervention period was 10 weeks, we could not ensure that measurements were taken in the same phase of menstrual cycle, which is known to impact appetite (292). However, the distribution was likely to occur at random, so there is no strong indication that this constitutes an issue. Although the DISGAP study obtained enough power to detect significant differences among groups for the main outcome variable (GLP-1 AUC), we cannot rule out the possibility that the study was underpowered to detect true differences in the other variables. Additionally, the small number of participants in each group might have

increased the possibility of type II error and prevented the detection of true differences among groups, despite almost reaching the desired sample size. Third, a milliplex kit was used also in the DISGAP study to analyze AG and total PYY, which is expected to result in less accurate measures than specific assays for each hormone. Fourth, validated questionnaires were used to measure subjective appetite, hedonic hunger, and food reward, but only one instrument was used to measure each construct. Other instruments measuring different constructs might be differently impacted by WL and possibly provide different results. Fifth, even though the standardization of the diet across groups is a strength, we cannot rule out that some of the differences found among groups, especially bariatric surgery groups versus controls, is due to transitory changes in postoperative physiology, including fluid shifts and changes in absorption and metabolism. Sixth, the nature of the dietary regime and the test-meal used might also play a role. The test meal was standardized for all participants on both assessment days, but the meal contained twice the number of calories compared to each of the food packs participants consumed per meal during the 10-week intervention period. Last, but not least, stress is a potential mediator of homeostatic appetite regulation, food cravings and eating behavior (293, 294). Given that this study was carried out under unusual circumstances (Covid-19 pandemic), stress could also have had some influence on the outcome variables.

Practical implications

Together with the current literature, the findings of this thesis have important clinical implications for obesity management. As demonstrated in *Paper 1*, individuals with obesity show lower postprandial hunger ratings in line with lower ghrelin concentrations, but also lower postprandial PYY concentrations. This suggests that individuals with obesity do not have an exaggerated perceived hunger, but might obtain a weaker satiety response, which theoretically can cause overeating. As discussed previously, many individuals with obesity claim to detect no relationship between hunger/fullness ratings and their habitual eating patterns, and in addition, the term hunger may have a different meaning for different people. For example, in *Paper 2*, no differences in postprandial hunger ratings between individuals with and without obesity were seen, but obesity was associated with higher postprandial PFC, indicating that they thought they could eat more food compared to controls without obesity after the standardized breakfast. Thus, weaker satiation and satiety signaling (and possibly disinhibition), and not increased hunger, seem to be the main challenges in obesity. Identifying the direction of causality, however, remains to be established. But considering the previously discussed literature and findings of this thesis, obesity points towards being a cause, and not a consequence, of potential differences in the homeostatic appetite control system.

The DISGAP study (*Papers 3 and 4*) demonstrated that a controlled VLED is equally effective in inducing WL as bariatric surgery in the short-term, but SG and RYGB resulted in a more favorable profile of GI hormones involved in appetite control and seemed to induce several additional favorable changes in hedonic constructs of appetite. However, the literature reveals large gaps between these WL modalities and long-term WL outcomes. And evidently, successful WL maintenance seems to be dependent on maintenance of these initial and favorable changes. The overall reduction in subjective appetite and hedonic hunger after WL seen across groups in the DISGAP study, were very positive. But one cannot rule out the impact of ketosis on dampening appetite. A growing body of evidence points towards a lower drive to eat during WL interventions when participants are ketotic, thus representing one promising approach to manage excessive appetite during WL and WL maintenance. However, the drive to eat would likely increase after refeeding, when βHB plasma concentrations return to normal physiological levels - and little knowledge exists on how ketosis impacts appetite in

the longer term - or for how long patients are in nutritional induced ketosis post-bariatric surgery.

From a public health perspective, stronger and effective approaches – not only general recommendations - should be used to emphasize, and facilitate, a healthy and balanced diet throughout the lifespan along with healthy PA levels for the general population. Given the large impact of obesity, both on an individual and societal level, it is important that obesity is ultimately accepted as a disease (and not as an individual responsibility) by the public, as well as at political arenas. Further, implementing dietary strategies with a goal of achieving adequate satiety/satiation signaling from the GI tract could be a start to help individuals with obesity to manage their appetite behavior. Additionally, managing the reward aspects of food, through intensive follow-up programs, perhaps including cognitive behavioral therapy, might be necessary to maintain WL in the long-term for those who receive conservative weight management (or those who fail with weight management after bariatric surgery). Also, reducing palatable food cues in the environment (commercials, supermarkets, billboards etc.) could be preventive of general weight gain in the population. And finally, obtaining a healthy diet and lifestyle should not compromise an individual, or family's economy or vice versa.

Such strategies should first be used preventively, and in the early stages of obesity. This could avoid further weight gain and/or development of co-morbidities of a disease that require lifelong management and may help the many who already struggle to manage the disease by themselves or even with professional help.

Future research

The preliminary findings from the DISGAP study need to be confirmed and future research should also investigate potential differences in the long-term impact of diet-induced WL and bariatric surgery on GI hormones, subjective appetite ratings, hedonic hunger, and food reward. More importantly, it needs to be investigated if, and how, initial changes in these constructs of appetite might modulate long-term WL outcomes. As previously mentioned, our research group recently showed in a cross-sectional case-control study that sub-optimal WL 10 years after RYGB was associated with dysfunctional eating behaviors, increased hedonic hunger, and food reward (196). In the DISGAP study, the largest increases in the

concentrations of the satiety hormones GLP-1 and PYY were observed post-RYGB, and food reward was often lower post-RYGB compared to WL achieved by dietary restriction alone. Growing evidence points towards an integrated appetite control system including both homeostatic and hedonic circuits (295). As such, investigating possible associations between concentrations of GI hormones and hedonic appetite following WL and WL maintenance, after both lifestyle treatments and bariatric surgery, should be encouraged. In this way, we might also come closer to a more personalized approach for obesity management, concurrent with overall higher success rates.

Conclusions

This PhD thesis shows that the lower satiety response seen in individuals with obesity, and especially in the classes of severe obesity, is greatly improved after bariatric surgery. Even though WL induced by a VLED alone does not lead to any unfavorable changes in the appetite measures assessed (at least under ketogenic conditions), GI hormones' concentration and food reward was less improved compared with WL after bariatric surgery. In order to succeed with conservative management of obesity, we likely need to mimic the favorable changes in homeostatic and hedonic appetite seen post-bariatric surgery.

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Paper I

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REVIEW

OBESITY Reviews WILEY

Differences in gastrointestinal hormones and appetite ratings between individuals with and without obesity—A systematic review and meta-analysis

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Summary

Determining if gastrointestinal (GI) hormone response to food intake differs between individuals with, and without, obesity may improve our understanding of obesity pathophysiology. A systematic review and meta-analysis of studies assessing the concentrations of GI hormones, as well as appetite ratings, following a test meal, in individuals with and without obesity was undertaken. Systematic searches were conducted in the databases MEDLINE, Embase, Cochrane Library, PsycINFO, Web of Science, and ClinicalTrials.gov. A total of 7514 unique articles were retrieved, 115 included in the systematic review, and 70 in the meta-analysis. The meta-analysis compared estimated standardized mean difference in GI hormones' concentration, as well as appetite ratings, between individuals with and without obesity. Basal and postprandial total ghrelin concentrations were lower in individuals with obesity compared with controls, and this was reflected by lower postprandial hunger ratings in the former. Individuals with obesity had a lower postprandial concentration of total peptide YY compared with controls, but no significant differences were found for glucagon-like peptide 1, cholecystokinin, or other appetite ratings. A large methodological and statistical heterogeneity among studies was found. More comprehensive studies are needed to understand if the differences observed are a cause or a consequence of obesity.

KEYWORDS
appetite, ghrelin, obesity, PYY

Abbreviations:: AUC, area under the curve; BMI, body mass index; CCK, cholecystokinin; DTE, desire to eat; GI, gastrointestinal; GLP-1, glucagon-like peptide 1; PFC, prospective food consumption; PYY, peptide YY.

1 | INTRODUCTION

Obesity is a chronic relapsing disease,[1] characterized by excessive fat accumulation and defined as a body mass index (BMI) ≥ 30 kg/m^2 (with cutoffs varying among ethnicities).[2] The prevalence of obesity has increased dramatically over the past five decades resulting in socioeconomic challenges and public health issues. Obesity is associated with reduced quality of life and poorer mental health, increased risk of noncommunicable diseases, and shortened life expectancy.[3] Thus, obesity represents one of the greatest global health problems of our times.

The causes of obesity are multifactorial, and genetics play an important role.[4] The contribution of the gut–brain axis and the underpinnings of homeostatic body weight regulation have been frequently investigated in the context of obesity pathophysiology.[5] Ingestion of food leads to the stimulation, or inhibition, of the secretion of different hormones from distinctive sites of the gastrointestinal (GI) tract.[6] These peripheral signals have the potential to modulate food intake and long-term body weight homeostasis, both via hormonal and vagal pathways.[7] Ghrelin is the only known peripheral hormone with orexigenic properties.[8] Its plasma concentration peaks during fasting and in anticipation of the upcoming meal and declines in the postprandial period.[9] On the other hand, as macronutrients interact with receptors of enteroendocrine cells, several anorexic peptides, including glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK), are secreted from the GI tract, promoting satiation and satiety.[10–12]

Obesity has been shown to be associated with alterations in the secretion of several GI hormones, increased fasting gastric volume, accelerated gastric emptying, and decreased satiety.[13–15] Many studies have measured the basal and postprandial plasma concentrations of GI hormones in individuals with obesity, and the majority reports lower basal and postprandial plasma concentrations of ghrelin compared with individuals without obesity.[15–17] However, results regarding satiety peptides are inconclusive, most likely due to different hormonal fractions being measured.[14,16,18] Understanding if obesity is, or not, associated with alterations in the secretion of GI hormones, and subjective appetite feelings, will improve our knowledge on the pathophysiology of this chronic disease. Therefore, this systematic review and meta-analysis aimed to compare basal and postprandial plasma concentrations of GI hormones, as well as subjective appetite ratings, between individuals with and without obesity.

2 | METHODS

This systematic review and meta-analysis is registered in PROSPERO (PROSPERO 2020 CRD42020161552) (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020161552). The PRISMA statement for systematic reviews and meta-analyses was followed.[19]

2.1 | Literature search

A structured database search was conducted in MEDLINE, Embase, Cochrane Library, PsycINFO, Web of Science, and ClinicalTrials.gov. The query involved a combination of thesaurus- and free-text terms optimized to capture studies comparing appetite/appetite markers between individuals with and without obesity. The search strategies excluded studies focusing exclusively on nonadults, or animals, and publication types like comments, editorials, or news. The searches were also restricted to studies written in English, Norwegian, Swedish, Danish, Portuguese, French, or Spanish (see Supporting Information for a detailed description of the search strategies adopted in the different databases).

2.2 | Study selection

Two reviewers (MIA, SC) independently screened titles and abstracts of the identified articles based on the predefined inclusion and exclusion criteria. Results from each reviewer were compared to ensure that exclusions were made on the same basis before screening full text articles. Any disagreements between the reviewers were discussed, and a third reviewer (CM) involved if needed. Full text articles were screened, and assessment of risk of bias was performed for all the included articles in the meta-analysis.

2.3 | Eligibility criteria

The database search was conducted based on the following inclusion criteria: A study population of adults with obesity (BMI ≥ 30 kg/m^2) and a control group without obesity (BMI 18.5–29.9 kg/m^2); assessing one or several of the following variables in the fasting state and/or after a test meal (using total area under the curve (AUC) as a measure of postprandial response): Plasma or serum concentrations of total or active ghrelin, total or active GLP-1, total or active PYY, or CCK, and/or appetite ratings of hunger, fullness, desire to eat (DTE), or prospective food consumption (PFC) measured with a visual analog scale.[20] Postprandial data were not included if appetite measures were taken under infusion of pharmacological agents or hormonal infusion. Exclusion criteria included diabetes or other endocrine disorders known to affect appetite, previous bariatric surgery, and current or recent use of medications known to affect appetite or body weight. Because ketosis is known to affect appetite,[21] studies were excluded if the appetite measurements were taken while participants were ketotic (defined as a plasma ßeta-hydroxybutyrate concentration >0.3 mmol/L).

2.4 | Data extraction

The two reviewers (MIA, SC) extracted the data of all included articles. General characteristics of the participants (i.e., age, sex, BMI, and body composition) were extracted from each article along with energy

and macronutrient composition of the test meal used, duration of postprandial period, and frequency of blood sampling/appetite ratings assessment.

2.5 | Risk of bias assessments

Depending on the study designs, the risk of bias in the articles included in the meta-analysis was assessed using the Cochrane tools ROB-2[22] and ROBINS-1[23] for randomized and nonrandomized studies, respectively (Supporting Information). The tools identified to what extent studies addressed the possibility of bias in their design, conduct, and analysis. Any disagreements that arose between the reviewers were resolved through discussion and assistance of a third reviewer when required.

2.6 | Statistical analysis

The mean and standard deviation for hormone concentrations and appetite ratings in the fasting, and postprandial state (AUC) were extracted. Articles with extreme values (more than 10-fold larger than the average) were excluded from the meta-analysis. Articles reporting incremental AUC or calculating total AUC using "0" as basal value were also excluded. When not reported, the standard deviation was calculated from the provided standard error or confidence intervals. Data reported as medians and interquartile range were converted to means and standard deviations (SDs).[24] If hormonal concentrations were reported in metric units, data were converted to SI units as follows: ghrelin pg/ml $\times$ 0.3 = pmol/L, GLP-1 pg/ml $\times$ 0.33 = pmol/L, PYY pg/ml $\times$ 0.25 = pmol/L. All values for subjective appetite ratings were converted to millimeters. AUC data were converted to minutes whenever necessary. Some studies reported data on subgroups within the obesity and controls groups, for example, for men and women separately. Prior to inclusion in the meta-analysis, outcomes for these subgroups were pooled to obtain a single pooled mean and standard deviation within the obesity and control groups separately. For studies including more than one test meal, the meal closest to the balanced dietary recommendations in terms of macronutrient composition was selected. For studies including more than one basal measure, before different infusions of nutrients, a basal value was chosen at random. When two basal values were given before infusion of saline or a hormone, the basal value measured before hormone infusion was selected. The corresponding authors of the respective articles were contacted for further information or clarification when needed. If the missing data were not obtained, the respective article was included in the systematic review, but not in the meta-analysis.

Meta-analyses were conducted to compare the obesity and control groups for each outcome, when there were at least three studies. Pooled estimates of standardized mean differences (SMDs) were obtained using a random-effects model. Statistical heterogeneity was investigated using the I^2 statistic and a threshold of 75% was considered to represent high heterogeneity.[25] Evidence of publication bias was assessed by visual inspection of Funnel plots and Egger's test. Analyses were performed using Stata version 16.1 (Stata Corp., College Station, Texas, USA).

3 | RESULTS

3.1 | Search result

A total of 13,273 records were obtained by collecting the results from the different databases into a common library. After removing duplicates, 7514 unique records remained. Manual screening of the records, based on title and abstract, identified 163 potentially relevant records. Further full-text screening of these records identified 115 studies relevant for inclusion. A flow chart of the search results and selection process can be seen in the Supporting Information.

3.2 | Systematic review

A systematic review comparing concentrations of GI hormones, as well as appetite ratings, between individuals with and without obesity was conducted. A total of 115 articles were included, resulting in the comparison of 22 variables.

3.2.1 | Concentrations of GI hormones in the fasting state

Basal active ghrelin

Twenty-four articles compared basal active ghrelin between individuals with obesity and controls. Fifteen studies reported higher basal active ghrelin concentrations in controls,[16,26–39] whereas seven articles found no differences between groups,[40–46] and two reported higher concentrations in individuals with obesity.[43,47]

Basal total ghrelin

Fifty-one articles compared basal total ghrelin between individuals with obesity and controls. Forty articles reported higher basal total ghrelin concentrations in the control group,[14,15,26,31,34,45,48–81] whereas 11 articles found no differences between groups.[82–92]

Basal active GLP-1

Sixteen articles compared basal concentrations of active GLP-1 between individuals with obesity and controls. One study found individuals with obesity to have lower basal concentrations,[93] 14 studies found no significant differences between groups,[40,43,55,66,94–103] and one study found higher basal active GLP-1 concentrations in individuals with obesity.[52]

Basal total GLP-1

Eighteen studies compared basal total GLP-1 concentration between individuals with obesity and controls. One study reported lower basal

concentrations in individuals with obesity,[104] 15 studies found no significant differences between groups,[35,42,58,89,102,105–114] and two studies reported higher basal total GLP-1 in individuals with obesity.[103,115]

Basal active PYY

Fourteen studies compared basal concentrations of active PYY between individuals with obesity and controls. Four studies reported lower basal active PYY concentrations in individuals with obesity,[45,49,71,116] and 10 studies found no significant differences between groups.[67,78,83,89,100,104,107,117–119]

Basal total PYY

Ten studies compared basal concentrations of total PYY between individuals with obesity and controls. Three studies reported lower basal total PYY concentrations in individuals with obesity,[120–122] and seven studies found no significant differences between groups.[42,84,90,117,120,123,124]

Basal CCK

Twelve articles assessed basal CCK concentrations. One study reported individuals with obesity to have lower basal CCK concentrations compared with controls,[125] nine articles found no differences between groups,[52,66,104,107,118,119,126–128] and two studies reported greater basal CCK concentrations in individuals with obesity.[18,101]

3.2.2 | Concentrations of GI hormones in the postprandial state

Active ghrelin (AUC)

Ten articles assessed postprandial active ghrelin. Five articles reported lower concentrations in individuals with obesity,[16,26,27,35,38] three articles found no differences between groups,[40,42,116] and two articles reported individuals with obesity to have higher concentrations.[47,129]

Total ghrelin (AUC)

Sixteen articles assessed postprandial total ghrelin. Thirteen articles reported lower concentrations in individuals with obesity[15,17,26,53,54,57,59,63,67,71,78,100,129] and three articles found no differences between groups.[82,88,130]

Active GLP-1 (AUC)

Nine studies assessed postprandial concentrations of active GLP-1. Four studies reported lower postprandial concentrations in individuals with obesity[15,16,94,101] and five studies found no significant differences between groups.[40,97,99,100,131]

Total GLP-1(AUC)

Eight studies measured postprandial concentrations of total GLP-1. Four studies reported individuals with obesity to have lower postprandial concentrations of total GLP-1,[102,105,114,122] and four studies found no significant differences between groups.[42,103,113,115]

Active PYY (AUC)

Five articles assessed postprandial concentrations of active PYY. Two studies found that individuals with obesity had lower postprandial concentrations of active PYY compared with controls,[71,116] whereas three studies found no differences between groups.[67,78,100]

Total PYY (AUC)

Seven studies measured postprandial concentrations of total PYY. Four studies reported postprandial total PYY concentrations to be lower in individuals with obesity compared with controls,[14–16,121] whereas three found no differences between groups.[42,130,131]

CCK (AUC)

Five studies assessed postprandial concentrations of CCK. One article reported individuals with obesity to have lower postprandial CCK concentrations compared with controls,[16] three studies found no differences between groups,[101,128,130] whereas one study reported individuals with obesity to have greater postprandial concentration of CCK.[18]

3.2.3 | Appetite ratings in the fasting state

Hunger

Eighteen articles assessed hunger ratings in the fasted state. Three studies showed that individuals with obesity reported lower hunger ratings compared with controls,[114,116,132] whereas 15 studies found no differences between groups.[16,18,31,42,47,58,88,90,103,104,107,113,133–135]

Fullness

Eighteen articles reported ratings of fullness in the fasted state. Fourteen found no differences between groups,[18,29,42,58,88,90,94,103,104,107,113,133–135] whereas four studies reported greater fullness in individuals with obesity compared with controls.[107,114,116,132]

DTE

Nine articles measured DTE in the fasted state. One study reported that individuals with obesity had lower DTE compared with controls[132] and eight studies found no differences between groups.[16,18,47,88,94,133–135]

PFC

Nine articles assessed PFC in the fasted state. One study reported individuals with obesity to have a lower PFC compared with controls,[132] whereas eight studies found no differences between groups.[16,42,58,88,103,113,133,135]

3.2.4 | Appetite ratings in the postprandial state

Hunger (AUC)

Postprandial hunger ratings were assessed in 16 articles. Two studies reported individuals with obesity to have lower postprandial ratings of

TABLE 1 Overall meta-analysis results

Outcome	No. of studies	Reference nr.	SMD (95% CI)	*p* value	I^2	Egger's test (*p* value)
Basal hormone concentrations						
Active ghrelin	16	14,24,25,27–32,38–41,43–45	−0.66 (−1.69 to 0.37)	0.21	97.98	0.33
Total ghrelin	33	12,15,24,26,30,41,43,47,49–53, 55–58,60–63,65–68,82–89	−1.42 (−2.07 to −0.76)	<0.001	96.96	0.03
Active GLP-1	7	14,38,50,92,93,96,101	0.14 (−0.12 to 0.40)	0.29	32.81	0.53
Total GLP-1	13	40,53,56,87,94,101–104,106–108,111	−0.19 (−0.52 to 0.14)	0.26	62.35	0.06
Active PYY	8	43,47,65,87,88,102,105,115	−0.49 (−1.14 to 0.16)	0.14	85.12	0.35
Total PYY	7	14,40,82,115,118,121,122	−0.36 (−0.83 to 0.11)	0.14	90.09	0.60
CKK	7	14,16,50,102,123,125,134	0.01 (−1.49 to 1.51)	0.99	96.29	0.16
Postprandial (AUC) hormone concentrations						
Total ghrelin	5	13,15,51,65,86	−1.35 (−2.36 to −0.33)	0.01	86.16	0.06
Active GLP-1	4	13,14,92,95	−0.67 (−1.58 to 0.24)	0.15	88.92	0.48
Total PYY	3	13,14,118	−0.84 (−1.61 to −0.07)	0.03	80.08	0.88
Fasting appetite ratings						
Hunger	11	14,27,29,45,56,88,101,102,105,130,133	−0.10 (−0.26 to 0.06)	0.23	0.00	0.40
Fullness	9	14,27,56,88,101,102,105,130,133	−0.02 (−0.39 to 0.36)	0.94	71.80	0.36
DTE	4	14,45,130,133	−0.21 (−0.55 to 0.13)	0.22	54.70	0.95
PFC	5	14,56,101,130,133	0.18 (−0.34 to 0.70)	0.49	81.42	0.32
Postprandial (AUC) appetite ratings						
Hunger	5	14,45,86,101,133	−0.66 (−1.01 to −0.32)	<0.001	41.82	0.08
Fullness	4	14,86,101,133	0.43 (−0.38 to 1.24)	0.30	87.63	0.38
DTE	4	14,86,101,133	−0.01 (−0.24 to 0.22)	0.91	0.00	0.48
PFC	4	14,86,101,133	−0.02 (−0.30 to 0.25)	0.88	13.94	0.46

Abbreviations: AUC, area under the curve; CCK, cholecystokinin: DTE, desire to eat; GLP-1, glucagon-like peptide 1; PFC, prospective food consumption; PYY, peptide YY; SMD, standardized mean difference.

hunger compared with controls,[18,88] whereas 14 studies found no differences between groups.[16,42,47,66,90,103,113,114,116,121,130,133–135]

Fullness (AUC)

Postprandial fullness ratings were assessed in 16 studies. One article showed that individuals with obesity had lower postprandial ratings of fullness,[114] whereas 15 studies found no differences between groups.[18,42,66,88,90,94,103,113,114,116,121,130,133–135]

DTE and PFC (AUC)

Eight studies measured postprandial DTE,[16,18,47,88,94,133–135] and seven studies measured postprandial PFC.[16,42,88,103,113,133,135] All studies reported no differences in DTE or PFC between individuals with obesity and controls.

3.3 | Meta-analysis

A total of 70 articles were included in the meta-analysis, resulting in the comparison of 18 variables. An overview of the meta-analysis results can be seen in Table 1, and the pooled results in Figure 1.

Twenty-eight studies were randomized control trials, whereas the remaining had a cross sectional design with a control group. The average BMI of the obesity groups ranged from 29.1 to 57.6 kg/m^2, whereas control groups had an average BMI range of between 18.5 and 27.6 kg/m^2. The average age of the obesity groups ranged from 20.8 to 68.5 years, and controls from 20.1 to 68.5 years. The smallest study comprised five individuals with obesity and seven controls,[88] whereas the largest study comprised 779 individuals with obesity and 1315 controls.[123] Fourteen studies included only females,[31,41,43,46,55,57,62–64,70,90,117,125,136] 12 studies included only males,[30,47,52,58,84,91,103–105,107,113,124] three studies did not report on sex distribution,[15,69,127] whereas the remaining studies included a combination of both sexes. When reported, test meals had a varied macronutrient composition and its energy content ranged between 260–632 kcal. Only one study used a single macronutrient loading (75 g glucose).[67] The AUC period after the test meal varied between 60 and 330 min. For active ghrelin, total GLP-1, active PYY, and CCK, there were not enough studies (two or less) reporting total AUC concentrations to run the meta-analysis. Study characteristics and a summary of contributing articles can be seen in the Supporting Information.

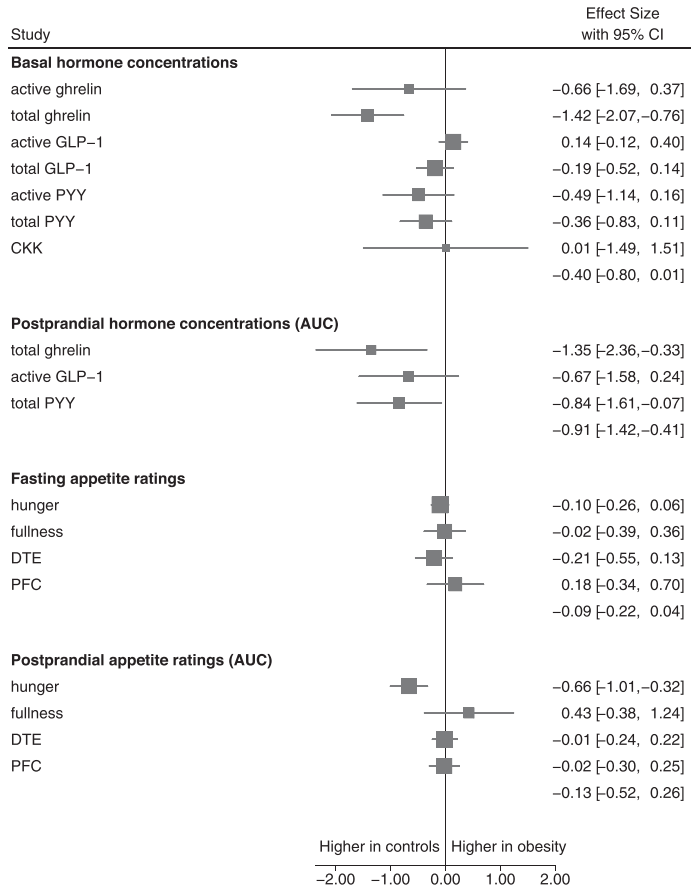


FIGURE 1 Pooled results from each meta-analysis for each outcome

3.3.1 | Concentrations of GI hormones in the fasting and postprandial states

Overall, we observed a high degree of statistical heterogeneity between studies investigating the concentration of GI hormones in the fasting and postprandial state. The I^2 statistic was over 80% for all GI hormones, both in the fasting and postprandial states, except for active and total GLP-1 with I^2 statistic of 32.8 and 62.4%, respectively (Table 1). Forrest plots for meta-analyses of basal concentrations of GI hormones are presented in Figure 2A–G and postprandial concentrations (AUC) in Figure 3A–C. In the comparison of basal concentrations, the pooled SMDs were observed to be lower in obesity for basal active and total ghrelin, total GLP-1, active PYY, and total PYY, although this was only statistically significant for basal total ghrelin (SMD: −1.42, 95% CI −2.07 to −0.76, $I^2 = 96.96\%$, $p < 0.001$) (Figure 2B). In the comparison of AUC, the pooled SMDs for total ghrelin, active GLP-1 and total PYY also indicated lower postprandial concentrations in the obesity group, with the AUCs for both total ghrelin and total PYY being statistically significantly smaller in obesity (Figure 3A and Figure 3C, respectively). For the other GI hormones, the pooled SMD was associated with a large degree of uncertainty, such that it is not possible to conclude whether these hormones differ been individuals with and without obesity. In particular, the confidence intervals for basal active ghrelin, active GLP-1, total GLP-1, active PYY, total PYY, and CKK were consistent with there being between a substantially lower concentration in obesity, no difference, or even a moderately to substantially higher concentration in obesity. In contrast, the pooled results from the seven studies reporting on basal active GLP-1 indicated that any difference between the obesity and control group is likely to be small (SMD: 0.14, 95% CI −0.12 to 0.40, $p = 0.29$, $I^2 = 32.8\%$).

Visually, the funnel plots for active- and total ghrelin and total GLP-1 are suggestive of some publication bias, with the smaller published studies reporting large effect sizes. Furthermore, Egger's test also implied that there may be a small study effects for total ghrelin and total GLP-1 (Table 1). The funnel plots and Egger's test for other GI hormones, in the fasting and postprandial states, should be interpreted cautiously given that there are fewer studies in these comparisons.

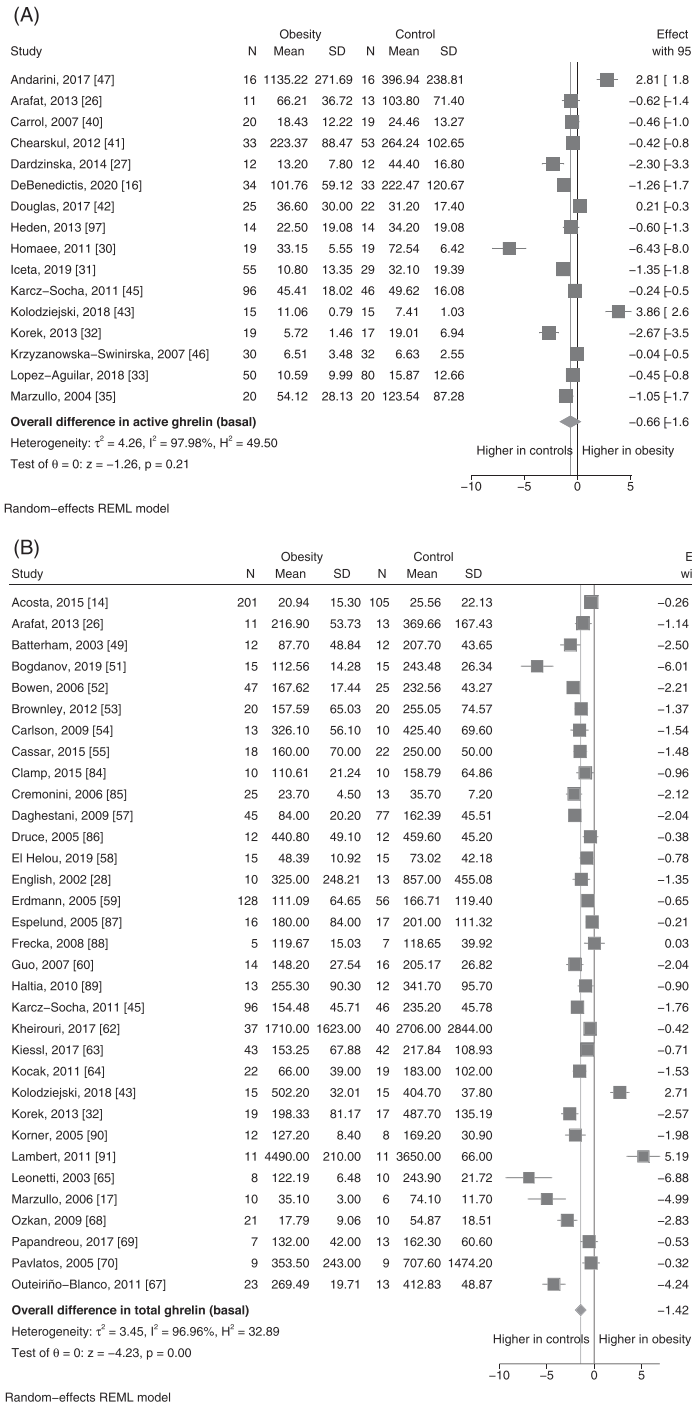


FIGURE 2 (A–G) Meta-analysis results for basal concentrations of gastrointestinal hormones

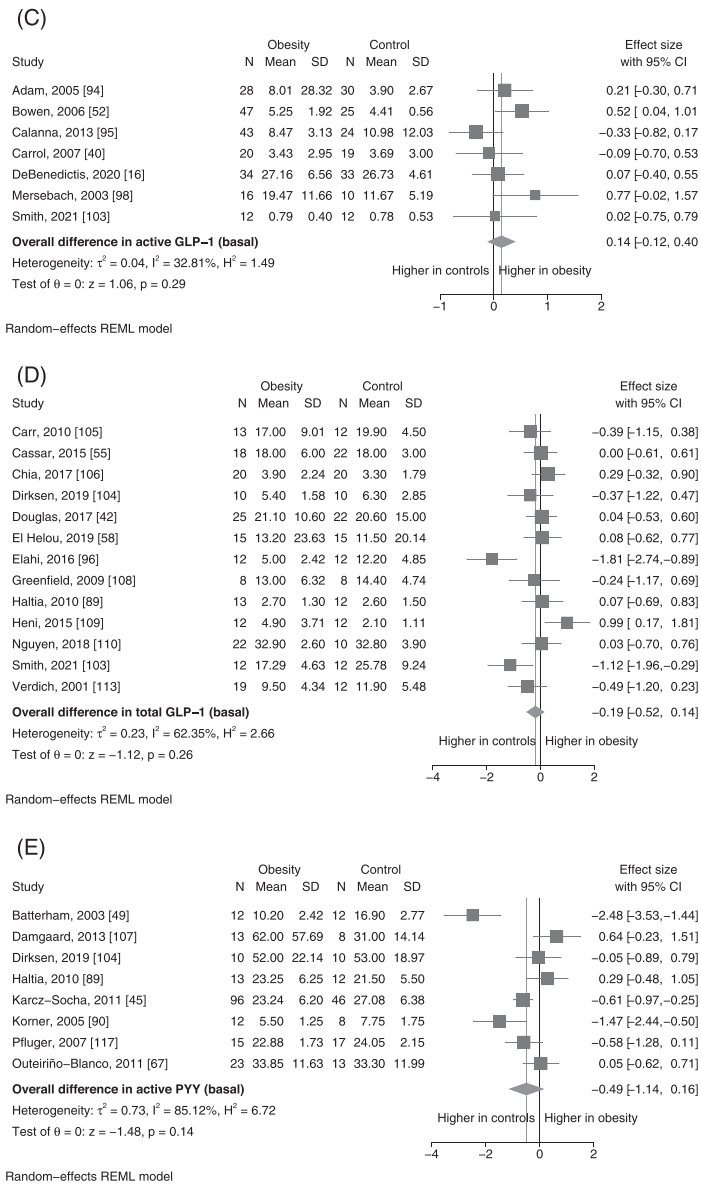


FIGURE 2 (Continued)

3.3.2 | Appetite ratings in the fasting and postprandial state

Compared with the GI hormone concentrations, there was less statistical heterogeneity in the comparison of appetite ratings, although still high for fullness, both in the fasting and postprandial state, and fasting PFC (Table 1). The pooled SMD for fasting appetite ratings was small and not statistically significant (Figure 4A–D). In the comparison of postprandial hunger, the pooled SMD indicated lower hunger AUC in the obesity group (SMD: −0.66, 95% CI −1.01 to −0.32, $p < 0.001$, $I^2 = 41.8$) (Figure 5A). Postprandial fullness was observed to be higher in obesity, although this was associated with a high degree of statistical uncertainty and heterogeneity, and was not statistically significant (SMD: 0.43, 95% −0.38 to 1.24, $p = 0.30$,

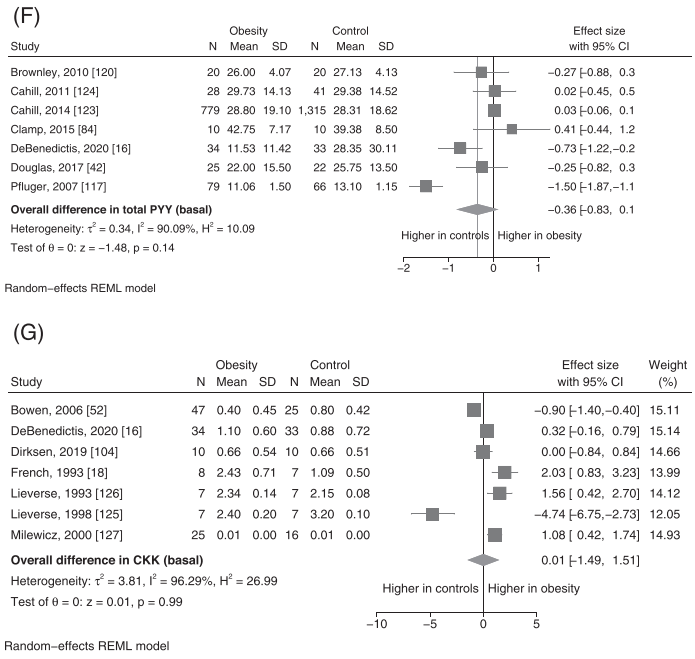


FIGURE 2 (Continued)

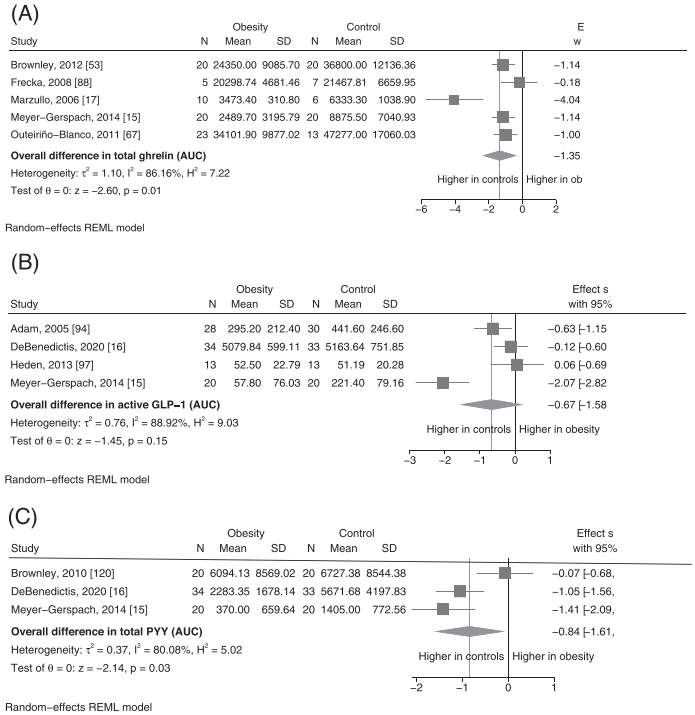


FIGURE 3 (A–C) Meta-analysis results for postprandial concentrations of gastrointestinal hormones

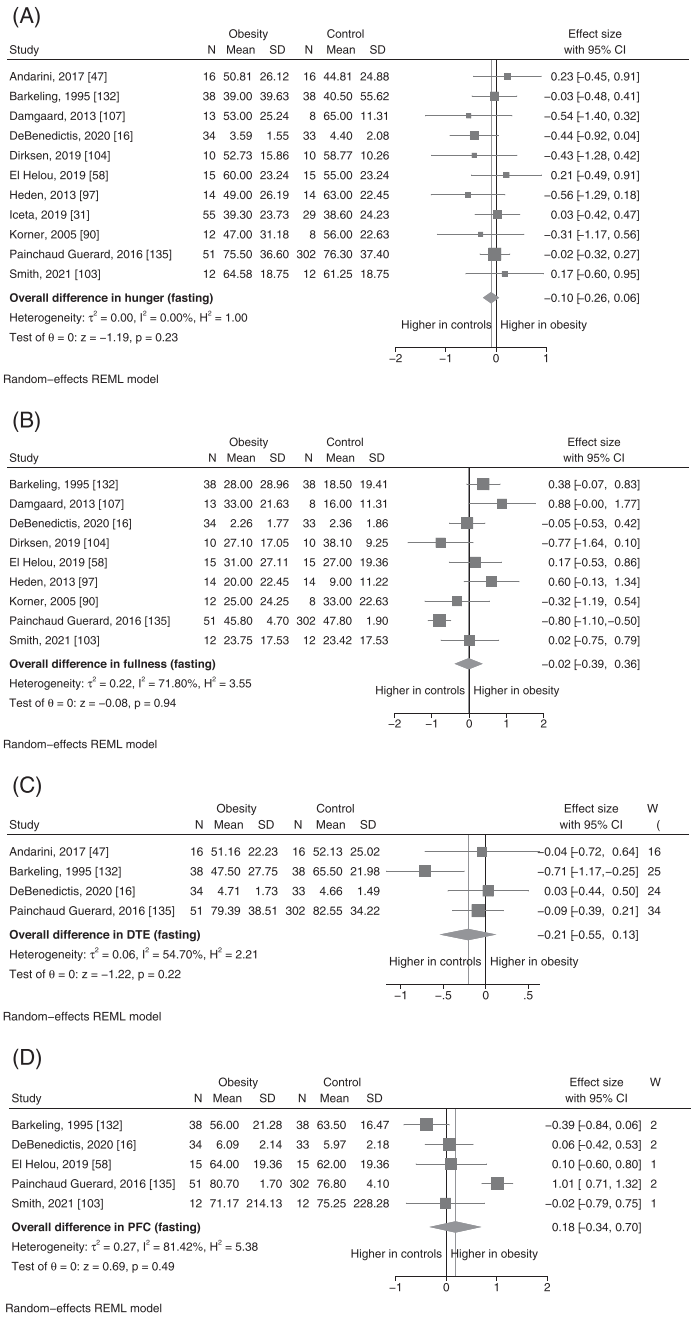


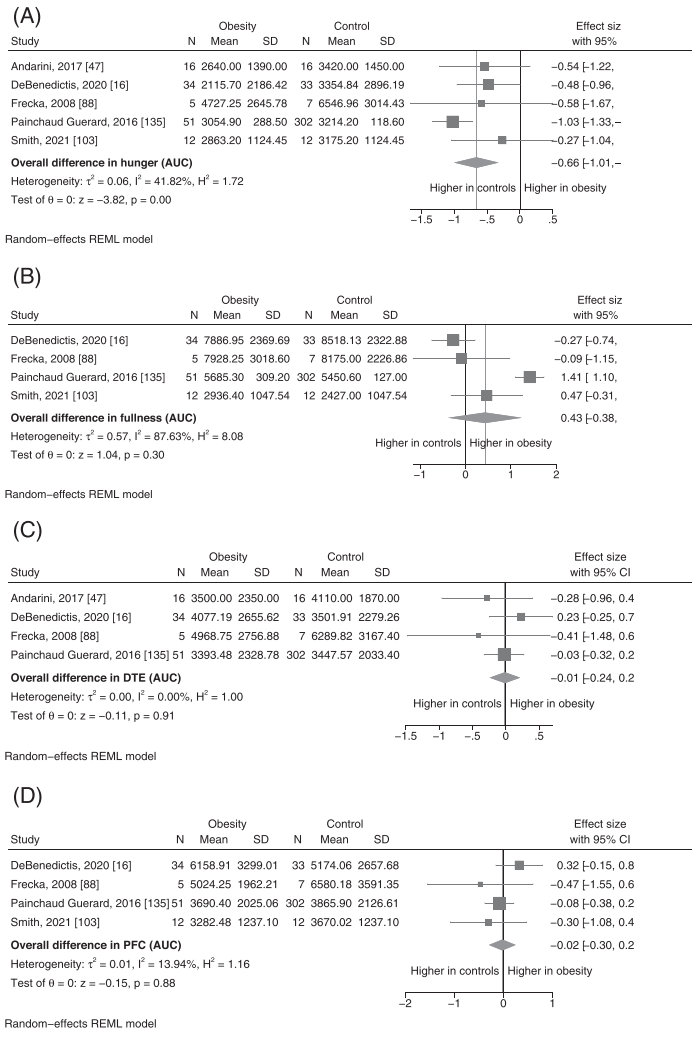
FIGURE 4 (A–D) Meta-analysis results for fasting appetite ratings

$I^2 = 87.6\%$) (Figure 5B). The estimated SMD and associated confidence intervals for meta-analyses of postprandial DTE and PFC indicate that it is unlikely to be any substantial difference in these appetite feelings between individuals with obesity and controls (Figure 5C and Figure 5D, respectively).

4 | DISCUSSION

This systematic review and meta-analysis represent the first comprehensive effort to investigate if the plasma concentration of GI hormones and subjective appetite ratings differ between adults with, and

FIGURE 5 (A–D) Meta-analysis results for postprandial appetite ratings



without, obesity. The systematic review showed a trend toward an attenuated hormonal response to nutrient ingestion in individuals with obesity. The meta-analysis showed that individuals with obesity indeed present with statistical significantly lower basal and postprandial total ghrelin concentrations compared with controls, lower postprandial concentrations of total PYY, and lower postprandial hunger ratings. No convincing differences were found for GLP-1, CCK, or fullness, DTE or PFC ratings. However, there was a large methodological and statistical heterogeneity among studies. Interestingly, a similar systematic review and meta-analysis previously conducted in children reported the same results, with an attenuated postprandial total ghrelin and total PYY response in children with obesity, despite large heterogeneity.[137]

Ghrelin is produced in the fundus of the stomach and stimulates appetite. Its concentration peaks during fasting, and in anticipation of the upcoming meal, and declines in the postprandial period.[8,9] It has long been reported that individuals with obesity have a lower basal and postprandial concentration of ghrelin compared with controls.[28] This meta-analysis confirmed these findings. However, for active ghrelin, the differences were associated with a large degree of uncertainty, preventing conclusions to be drawn.

As macronutrients interact with receptors in enteroendocrine cells, satiety peptides are secreted from the GI tract.[10–12,138] It is generally accepted that obesity is associated with lower postprandial concentrations of satiety peptides and a weaker satiation/satiety.[13,14,94,114,139] Centrally, through hypothalamic actions and the vagal-brainstem signaling pathway, GLP-1 promotes satiation and post meal satiety by reducing food intake in a dose-dependent manner.[140,141] The present meta-analysis, however, found no conclusive evidence of a difference in the plasma concentration of active or total

GLP-1 between individuals with and without obesity. There was an overall trend for a higher postprandial concentration of active GLP-1 in controls, but this was not statistically significant, and with a high degree of statistical heterogeneity among the studies. Discrepancies in the literature have previously been observed in both human and animal studies.[142] And as such, it may be difficult to determine the role of GLP-1 in common obesity, especially in a state of weight stability.

PYY is thought to be involved in post meal satiety[143] and thereby decrease food intake.[12] Its plasma concentrations increase within 15–30 min after a meal and peak around 60–90 min postprandially. The quantitative analysis demonstrated that postprandial total PYY concentrations were statistically significantly lower in individuals with obesity compared with controls. This is in line with a previously published paper from our group showing that PYY postprandial response is poor in class I obesity compared with individuals without obesity, and completely absent in class II and III obesity.[13] It has been suggested that the lower postprandial PYY concentrations measured in obesity would result in increased food intake in order to achieve the same degree of fullness as that seen normal weight individuals.[139]

CCK is the best established and most important satiation signal, being involved in meal termination, and possibly also early phase satiety,[144–147] and acts primarily through vagal afferent fibers.[148,149] Unfortunately, few studies have assessed concentrations of CCK in individuals with and without obesity, and we were therefore unable to run a meta-analysis on this hormone. Based on the systematic review alone, results were rather inconclusive. Even if no true differences in CCK (or GLP-1) plasma concentrations exist between individuals with and without obesity, one cannot rule out the importance of the vagus nerve in regulating appetite. The chronic ingestion of energy-rich diets has been shown to reduce the sensitivity of vagal afferent neurons to peripheral signals, which would be sufficient to drive both hyperphagia and obesity.[150]

In laboratorial settings, infusion of GI hormones has been shown to affect eating behavior in both individuals with normal-weight and obesity.[12,86,138,139,151] However, the association between plasma concentration of GI hormones and appetite ratings is highly complex and the evidence for their influence on food intake at normal physiological levels less clear.[152] An important aspect to consider is that subjective appetite ratings do not provide the full spectrum of either appetite control/behaviors or actual food intake. Subjective appetite ratings may merely represent an individual's interpretation of his/her feelings and motivations to eat, rather than direct measures of the underlying physiological processes controlling eating.[40,153,154] It was early reported that subjective appetite ratings in individuals with and without obesity showed similar sensitivity to macronutrients[155] and dietary manipulations.[156] However, because obesity is associated with greater energy intake,[157] it was somewhat surprising that in the present meta-analysis, individuals with obesity presented with lower postprandial hunger ratings compared with controls. One hypothesis is that obesity, through distinctive processes (i.e., reduced vagal sensitivity as previously discussed, or other central mechanisms), dysregulates the sensing of appetite. For example, in individuals with a normal weight, ghrelin and PYY concentrations are correlated with hunger and fullness ratings, respectively, whereas no association has been found in individuals with obesity.[158] A second alternative hypothesis is that once an individual reaches his/her genetically determined weight, no differences in appetite markers are seen between individuals with normal-weight and obesity. However, the lower ghrelin plasma concentrations, both in the fasting and postprandial states, and lower postprandially PYY secretion seen in individuals with obesity, questions this hypothesis and asks for more research. Finally, it is also possible that food intake in individuals with obesity is driven by the hedonic system. There is evidence that GI hormones also mediate the hedonic appetite system.[159] Hedonic appetite can easily override homeostatic signals when food is easily available and highly palatable, even in the absent of physiological hunger.[160] This is particularly important considering the obesogenic environment that has emerged over the past decades. Hedonic characteristics might, therefore, offer an additional proxy to help reflect motivation to eat and actual food intake.

Diet-induced weight loss has consistently been shown to modulate the plasma concentration of GI hormones, and appetite ratings, including increases in ghrelin plasma concentrations, as well as hunger and fullness ratings,[16,161,162] despite inconsistent findings regarding satiety peptides.[14,16,18] Interestingly, our research group has recently demonstrated that the increased orexigenic drive to eat seen after weight loss likely reflects a normalization toward a lower body weight, given that no differences were seen between reduced-obese individuals and fat mass matched controls.[16] Moreover, maintaining weight loss after dietary restriction has been suggested to be dependent on increases in postprandial GLP-1 and PYY responses.[163] Even though establishing a direction of causality if difficult, and out of the scope of this review, the previously discussed findings point to obesity being a cause, not a consequence, of potential abnormalities in the homeostatic appetite control system.

This review has several strengths. It is the first systematic review and meta-analysis comparing GI hormones and appetite ratings between adults with obesity and controls. Second, the analysis was conducted following the PRISMA statement guidelines, and used well established tools during the whole selection process. Third, its comprehensiveness provides a warranted descriptive picture of the topic of interest. Unfortunately, this analysis also has some limitations. First, several studies were not included in the meta-analysis due to missing data. This might have affected the results and contributed to the lack of significant differences between groups for some of the outcome variables. Second, the heterogeneity in most meta-analyses conducted in this study was also relatively high and, as such, conclusions should be made with caution. When interpreting the present results, it is critical to consider timing, nature, and structure of the test-meal, important aspects in modulating the outcome variables of this review. The statistical heterogeneity seen in this meta-analysis, particularly for the GI hormone comparisons, is likely to be the result of differences in the underlying study populations, test-meals used, and sample processing. For example, GLP-1 is rapidly degraded, and accurate methods are crucial to obtain precise measures. Also, the adequate measure of L-cell secretion is total GLP-1, whereas active GLP-1 provides information about the endocrine part of the peptide's actions.[164] Thus,

developing an optimized standardized method to assess hormonal responses and subjective appetite is needed. Third, transparent research and reporting of results should be encouraged, as there is some indication of publication bias with an apparent small study effect among the published results for basal hormone concentration. Fourth, different GI hormones are stimulated by specific nutrients in the lumen.[5] This means that the mixed meals used (liquid or solid), with different macronutrient composition, or even single macronutrient meals, might not have been the best to maximize the inhibition of ghrelin, or the release of the different satiety peptides. For example, among the included studies in the analysis for active GLP-1 (AUC), higher concentrations were seen in controls, versus individuals with obesity, after a 750 kcal liquid meal,[15] whereas no differences were reported between groups after a 450–650 kcal solid meal.[16,94,97] Another important aspect to take into consideration is if the tests meals were similar in the obesity and control groups, or if they were adjusted for body weight. Most of the studies have used the same test meal in both groups. This ensures that the same stimuli is given to each subject but does not account for individual nutritional needs. Lastly, although all efforts were made to ensure that measures were comparable, the length of the postprandial period could affect the results.

5 | CONCLUSION

Obesity is associated with lower basal and postprandial concentrations of total ghrelin, lower postprandial concentration of total PYY, and lower postprandial hunger ratings, but large variations exist. More studies are needed to better understand the implications of these findings and to determine if they are a cause or a consequence of obesity. Further, it is important to establish if an association exists between the alterations in GI hormones seen in individuals with obesity and their actual food intake. This will provide a better understanding of the pathophysiology of this chronic disease.

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CONFLICT OF INTEREST

The authors have no conflict of interest to disclosure.

AUTHOR CONTRIBUTIONS

Catia Martins and Marthe Isaksen Aukan formulated the research questions and designed the study. Marthe Isaksen Aukan and Silvia Coutinho conducted the reviewer process. Sindre Andre Pedersen conducted the literature search. Melanie Rae Simpson conducted the statistical analysis. All authors were involved in the writing of the manuscript.

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SUPPORTING INFORMATION

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Paper II

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Differences in gastrointestinal hormones and appetite ratings among obesity classes

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ABSTRACT

The aim of this study was to compare gastrointestinal (GI) hormones and subjective ratings of appetite among obesity classes, and between classes of obesity and controls. Ninety-eight adult individuals with obesity, divided into class I (n = 35), II (n = 44) and III (n = 19), together with 45 controls without obesity were included in this cross-sectional analysis. Body weight/composition, and basal and postprandial (after a 600 kcal fixed breakfast) plasma concentrations of acylated ghrelin, active glucagon-like peptide 1 (GLP-1), total peptide YY (PYY), cholecystokinin (CCK) and insulin, as well as subjective ratings of hunger, fullness, desire to eat (DTE) and prospective food consumption (PFC) were measured. There were no differences in the plasma concentration of GI hormones (either basal or postprandial) among obesity classes, except for insulin. In general, obesity was associated with impaired secretion of GI hormones. Ghrelin secretion did not decline postprandially in class-III obesity. GLP-1 peak for obesity class I and II was early and lower, while class III showed no postprandial GLP-1 response. Postprandial PYY response for obesity class II and III was absent, and class III showed a delayed and shortened postprandial CCK response. Obesity class II and III had greater basal insulin concentration compared to controls and postprandial insulin was greater in obesity class III versus class II, class I and controls. No differences were found for appetite ratings among obesity classes. In conclusion, obesity is characterized by impaired secretion of GI hormones, with reduced postprandial satiety, particularly in individuals with obesity class III. This abnormal pattern may lead to overeating.

1. Introduction

Obesity is a chronic, progressive, and relapsing disease (Bray, Kim, & Wilding, 2017) classified by body mass index (BMI) ≥30 kg/m^2. It is further divided into subclasses according to the degree of severity: class I (BMI: 30.0–34.9 kg/m^2), class II (BMI: 35.0–39.9 kg/m^2), and class III (BMI: ≥40.0 kg/m^2), with the latter two defined as severe obesity ((WHO), 2000).

Obesity results from a chronic positive energy imbalance (Hall & Guo, 2017), and the rising prevalence is most likely driven by increased accessibility to highly palatable foods and increased portion sizes (Westerterp & Speakman, 2008). Adverse health outcomes increase with BMI, and a BMI ≥40.0 kg/m^2 is associated with approximately 6–14 years shortened life expectancy (Walls et al., 2010). It is therefore concerning that the greatest increases in prevalence have been seen in the classes of severe obesity (Walls et al., 2010).

In normal conditions, the appetite control system senses both acute and chronic changes in nutritional status, and gastrointestinal (GI) hormones have been hypothesized to act as physiological signals. Food ingestion is followed by the suppression of ghrelin, thought to signal

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hunger, and the secretion of glucagon-like peptide 1 (GLP-1), peptide YY (PYY) and cholecystokinin (CCK) involved in both meal-termination (or satiation) and inter-meal interval (or satiety) (Steinert et al., 2017). Individuals with obesity seem to have a dysregulated appetite control. We (DeBenedictis et al., 2020) and others (Daghestani, Ozand, Al-Himadi, & Al-Odaib, 2007; El Helou, Obeid, & Olabi, 2019; le Roux, Aylwin, et al., 2006; Mans, Serra-Prat, Palomera, Sunol, & Clave, 2015) have previously shown that individuals with obesity present with lower fasting plasma concentrations of ghrelin and lower postprandial secretion of GLP-1 (Dirksen et al., 2019; le Roux, Aylwin, et al., 2006), PYY and CCK (Batterham et al., 2003; Clamp, Hehir, Lambert, Beglinger, & Goedecke, 2015; le Roux, Aylwin, et al., 2006; Mans et al., 2015) compared to controls, although results are inconsistent (Brennan et al., 2012; Dirksen et al., 2019; El Helou et al., 2019; Federico et al., 2016; Rahat-Rozenbloom, Fernandes, Cheng, & Wolever, 2017). Moreover, basal and postprandial secretion of insulin has long been shown to be positively correlated with BMI (Bagdade, Bierman, & Porte, 1967). Even though no association between BMI and subjective ratings of appetite has been found (Gregersen et al., 2011; Painchaud Guerard et al., 2016), individuals with obesity report lower ratings of hunger in the fasted state (Wikarek, Chudek, Owczarek, & Olszanecka-Glinianowicz, 2014), reduced postprandial fullness (Adam & Westerterp-Plantenga, 2005; le Roux, Batterham, et al., 2006) and eat larger meals (Acosta et al., 2015; Meyer-Gerspach et al., 2014) compared to controls. Alterations in GI hormones may therefore play a key role in feeding behavior and obesity pathophysiology (Hansen, Andersen, Astrup, Blundell, & Sjodin, 2019; le; Roux, Batterham, et al., 2006; Steinert et al., 2017).

Considering this, little is known regarding potential alterations in the appetite control system among obesity classes, and if the secretion of GI hormones changes with increasing BMI. To our knowledge, few studies (Acosta et al., 2015; Zwirska-Korczala et al., 2007) have looked into this and results are so far inconclusive. Therefore, the main aim of this analysis was to compare GI hormones and subjective appetite ratings among obesity classes. A secondary aim was to compare obesity classes with controls without obesity.

2. Materials and methods

2.1. Study design

This is a cross sectional case control study, where individuals with different obesity classes were compared among themselves, and then against a control group without obesity.

2.2. Participants

This manuscript reports a secondary analysis of the "Weight loss maintenance and compensatory mechanisms activated with a very-low energy diet (VLED)" study, approved by the Norwegian regional ethics committee (Ref., 2012/1901), registered in clinicaltrials.gov (NCT01834859), and conducted according to the guidelines laid down in the Declaration of Helsinki. The main findings have already been published (Nymo et al., 2017, 2018). Adults (18–65 year) with obesity (BMI: $\geq$30 kg/m^2), and a control group (BMI: 18.5–29.9 kg/m^2) were recruited via newspaper advertising serving the community of Trondheim, Norway. All participants provided written informed consent before commencement. At recruitment, all participants were required to be weight stable (<2 kg body weight change over the past 3 months), not currently dieting to lose weight, and have a sedentary lifestyle (engaging in <150 min/week of physical activity of at least moderate intensity) (Haskell et al., 2007). The study excluded pregnant or breastfeeding women and those with clinically significant illnesses, including diabetes, previous weight loss surgery, and/or taking medication known to affect appetite or induce weight loss.

2.3. Outcome variables

The following measurements were performed:

2.3.1. Body weight and composition

Body weight- and composition (fat mass (FM) and fat free mass (FFM)) were measured in the fasted state with air-displacement plethysmography (BodPod, COSMED, Rome, Italy).

2.3.2. Appetite measures

Subjective appetite ratings (hunger, fullness, desire to eat (DTE), and prospective food consumption (PFC)), were measured using a 100-mm visual analog scale (VAS) (Stubbs et al., 2000). VAS and blood samples were collected in the fasting state, immediately after a fixed breakfast meal (VAS only), (2512 kJ [600 kcal]: 17% protein, 35% fat, and 48% carbohydrates) and every 30 min for a period of 2.5 h. Plasma samples were analyzed for acylated ghrelin, active GLP-1, total PYY and insulin using a Human Metabolic Hormone Magnetic Bead Panel (LINCOplex Kit, Millipore, St Louis, MO). The cross-reactivity between antibodies and any of the other analytes in this panel is non-detectable or negligible. CCK was analyzed using an "in-house" radioimmunoassay (Rehfeld, 1998). Intra- and inter-assays CV were <10% and <20% for acylated ghrelin, GLP-1 and PYY; <10% and <15% for insulin and <5% and <15% for CCK, respectively. Blood samples were collected in 4 ml EDTA-coated tubes. One milliliter of whole blood was then transferred into a micro tube and a 20 μL mixture of inhibitor (10 μL of Pefabloc [Roche Diagnostic, Germany] + 10 μL dipeptidyl-peptidase IV inhibitor [Merck Millipore, Germany]) was added. For CCK, 500 KIU aprotinin (DSM, Coatech AB, Kaiseraugst, Switzerland)/mL whole blood was added to the EDTA tube. Samples were then centrifuged at 2106 RCF for 10 min at 18 °C and the plasma frozen at −80 °C until further analysis. All the samples from the same participant were analyzed in the same plate. The analyses were performed by the same technician, except for CCK, which was analyzed at the University of Copenhagen, Denmark.

2.3.3. Physical activity

Habitual physical activity levels were measured with SenseWear armbands (BodyMedia, Pittsburgh, PO, USA) for 7-days prior to the assessments. Data was considered valid if participants wore the device for $\geq$4 days, including at least 1 weekend day, on more than 95% (22.8 h/day) of the time (Jakicic et al., 2004). Total physical activity was defined as time (minutes/day) spent on activities >1.5 metabolic equivalents.

2.4. Power calculation

Several studies have shown that individuals with obesity have a lower postprandial GLP-1 response compared to those with normal weight (Dirksen et al., 2019; le Roux, Aylwin, et al., 2006; Meyer-Gerspach et al., 2014). However, there are no studies comparing GLP-1 AUC among obesity classes. We hypothesized that individuals with obesity class I, –II and –III would have a 10, 20 and 30% lower GLP-1 AUC, respectively, compared to controls without obesity (1533, 1226 and 858 min*pmol/l, respectively) (DeBenedictis et al., 2020). For a power of 80%, a significance level of 0.05, and assuming a within group variance of 640,000 min*pmol/l, 87 participants (29 in each group) would be required.

2.5. Statistical analysis

The statistical analysis was carried out using SPSS, version 26 (SPSS Inc., Chicago, IL). Data are presented as estimated marginal means ± SEM, unless otherwise stated. Due to the large number of tests, the significance level was reduced to $P < 0.01$, in order to account for increased risk of type-1 error. Two separate general linear models were performed to compare GI hormones and subjective appetite ratings

among different BMI classes, presented as estimated marginal means. One model compared individuals with obesity class I, II, and III, and a second model compared individuals with obesity (and its subclasses) with controls (a total of 6 comparisons). Residuals were checked for normality with Shapiro Wilk test and did not deviate significantly from normality. Plasma concentration of GI hormones and appetite ratings were analyzed as dependent variables, with BMI group as a fixed factor. Covariates known to affect appetite (age, sex and physical activity) were added to both models, and Bonferroni correction was used for post-hoc pairwise comparisons. The trapezoidal rule was applied to calculate total area under the curve (tAUC) and incremental area under the curve (iAUC) from 0 to 150 min. A linear mixed model was run to look at changes in plasma concentrations of GI hormones over the sampling time period (0, 30, 60, 90, 120 and 150 min) in each group, using Bonferroni correction for post-hoc pairwise comparisons. Spearman correlation was used to investigate the association between BMI and the different appetite variables.

3. Results

The general characteristics of the participants are presented in Table 1. 143 participants were included in the analysis; 98 individuals with obesity (OB), further divided into class I (OBI), –II (OBII) and –III (OBIII) (BMI: 32.9 ± 0.3 kg/m^2, 37.2 ± 0.3 kg/m^2 and 43.1 ± 0.4 kg/m^2, respectively) and 45 control individuals without obesity (BMI: 24.6 ± 0.6 kg/m^2). There were no significant differences in age or sex distribution between groups. FM (kg) differed between all groups, with FM increasing with BMI category ($P < 0.001$, for all). FFM (kg) was greater in the obesity group compared to controls ($P < 0.001$). Obesity class III had a greater FFM (kg) compared to the other two classes ($P < 0.001$, $P = 0.003$ and $P = 0.006$, for controls, OBI and OBII respectively). OBII had borderline higher FFM (kg) compared to controls ($P = 0.011$). FFM (%) decreased with increasing BMI and was lower in all obesity classes compared to controls ($P < 0.01$, for all). There was no difference in total physical activity duration among obesity classes, but the obesity group had a lower total physical activity duration compared to controls ($P = 0.005$), and borderline lower in OBII compared to controls ($P = 0.011$).

Table 2 shows mean basal and postprandial concentrations of GI hormones, and plasma concentrations over time can be seen in Fig. 1. No differences were found among classes of obesity in either basal or postprandial plasma ghrelin concentrations. However, the postprandial suppression in ghrelin secretion was absent in obesity class III. All obesity classes presented with lower basal ($P < 0.001$, for all) and postprandial (tAUC; $P < 0.001$, for all) (borderline for iAUC in OB, $P = 0.013$) ghrelin concentration compared controls.

No differences were found for basal or postprandial concentrations of GLP-1 among obesity classes. Compared to basal values, postprandial secretion of GLP-1 was only elevated at minute 30 and 90 in OBII, and at no postprandial timepoint in OBIII. GLP-1 iAUC was lower in all obesity classes, and the obesity group, compared to controls ($P < 0.001$, for all). All obesity classes reached peak GLP-1 concentrations after 30 min whilst, controls reached their peak at 120 min after the fixed meal.

There were no differences among obesity classes in basal or postprandial secretion of PYY. PYY returned to basal concentrations at 150 min in OBI, while OBII and OBIII did not experience any postprandial increase in PYY. Individuals with obesity had lower PYY concentrations throughout the postprandial period compared to controls. Basal concentration of PYY was lower in the obesity group ($P = 0.006$) compared to controls. tAUC for PYY was lower in OBI, OBII and OBIII ($P = 0.009$, $P < 0.001$ and $P < 0.001$, respectively) and the obesity group ($P < 0.001$), as well as iAUC for OBII and the obesity group compared to controls ($P = 0.001$ and $P < 0.001$, respectively). The different obesity classes reached peak PYY concentrations at minute 60, whilst controls reached their peak 120 min after the fixed meal.

No differences were found for basal or postprandial CCK concentration among obesity classes, or between obesity classes and controls. All groups experienced a similar postprandial curve, with the exception of OBIII where the CCK response was delayed and shortened (only greater than basal concentrations between 60 and 120 min after the fixed meal).

OBII and OBIII had greater basal insulin concentration compared to controls ($P = 0.007$ and $P < 0.001$, respectively). Postprandial insulin (iAUC and tAUC) was greater in OBIII versus OBII, OBI and controls ($P < 0.001$, $P < 0.01$ and $P < 0.01$, respectively). Compared to basal concentrations, insulin was elevated throughout all sample timepoints in all obesity classes, while controls returned to basal concentrations 2.5 h after the fixed meal.

Fasting and postprandial ratings of appetite are shown in Table 3 and postprandial ratings over time can be seen in Fig. 2. There were no differences among obesity classes in fasting or postprandial ratings of hunger, fullness, DTE or PFC. Postprandial PFC (iAUC) was greater in the obesity group compared to controls ($P = 0.001$).

Associations between BMI, plasma concentration of GI hormones, and appetite ratings can be seen in Table 4. Significant inverse associations with BMI were found for basal and postprandial ghrelin ($P < 0.001$, for both), postprandial GLP-1 plasma concentration ($P < 0.001$)

Table 1
General characteristics of the participants.

n	Control	OB	OB I	OB II	OB III
	45	98	35	44	19
Age (years)	39.1 ± 11.1	42.4 ± 9.8	43.2 ± 9.9	42.8 ± 9.9	40.1 ± 9.4
Females (%)	58	55	49	66	42
BMI (kg/m2)	24.6 ± 2.7	36.8 ± 4.1	32.9 ± 1.4	37.2 ± 1.5	43.1 ± 3.2
FM (%)	30.1 ± 7.1 [abcd]	44.3 ± 6.3 [a]	40.9 ± 6.6 [bef]	45.8 ± 5.5 [ce]	46.9 ± 5.1 [df]
(females)	(33.2 ± 0.9)	(48.1 ± 0.6)	(46.2 ± 1.1)	(48.5 ± 0.8)	(50.7 ± 1.6)
(males)	(25.9 ± 1.2)	(39.5 ± 0.9)	(35.8 ± 1.2)	(40.4 ± 1.3)	(44.2 ± 1.4)
FM (kg)	22.5 ± 6.7 [abcd]	48.8 ± 11.1 [a]	40.1 ± 6.3 [bef]	50.1 ± 6.4 [ceg]	61.8 ± 12.3 [dfg]
(females)	(23.1 ± 1.6)	(49.6 ± 1.1)	(42.2 ± 1.6)	(51.1 ± 1.2)	(59.8 ± 2.4)
(males)	(22.1 ± 2.9)	(47.7 ± 1.8)	(38.0 ± 2.1)	(47.9 ± 2.3)	(63.3 ± 2.5)
FFM (%)	69.9 ± 7.1 [abcd]	55.7 ± 6.3 [a]	59.1 ± 6.6 [bef]	54.1 ± 5.5 [ce]	53.1 ± 5.1 [df]
(females)	(66.7 ± 0.9)	(51.9 ± 0.6)	(53.8 ± 1.1)	(51.5 ± 0.8)	(49.3 ± 1.6)
(males)	(74.1 ± 1.2)	(60.5 ± 0.9)	(64.1 ± 1.2)	(59.6 ± 1.3)	(55.8 ± 1.5)
FFM (kg)	52.2 ± 10.7 [ad]	61.3 ± 11.6 [a]	58.7 ± 11.4 [f]	59.6 ± 10.2 [g]	69.7 ± 11.7 [dfg]
(females)	(44.9 ± 1.0)	(53.0 ± 0.7)	(48.9 ± 1.1)	(54.0 ± 0.8)	(57.9 ± 1.5)
(males)	(62.2 ± 2.1)	(71.6 ± 1.3)	(67.9 ± 1.9)	(71.1 ± 2.1)	(78.4 ± 2.4)
Total PA (min/day)	342 ± 126 [a]	276 ± 103 [a]	301 ± 118	257 ± 97	271 ± 77

Data presented as estimated marginal means ± SEM. BMI = body mass index. FM = fat mass. FFM = fat free mass. OB = obesity. PA = physical activity. Mean values with equal superscript letters denote significant differences between groups ($P < 0.01$) after Bonferroni adjustment.

Table 2
Mean basal and postprandial concentrations of GI hormones.

	Controls	OB	OB I	OB II	OB III
Basal ghrelin (pmol/l)	72 ± 6 [abcd]	30 ± 4 [a]	33 ± 6 [b]	31 ± 5 [c]	25 ± 9 [d]
Ghrelin tAUC (pmol/l *min)	8054 ± 590 [abcd]	3095 ± 379 [a]	3453 ± 618 [b]	2938 ± 578 [c]	2708 ± 912 [d]
Ghrelin iAUC (pmol/l *min)	−2712 ± 400 [a]	−1494 ± 257 [a]	−1424 ± 419	−1721 ± 392	−1067 ± 618
Basal GLP-1 (pmol/l)	1 ± 1	3 ± 1	2 ± 1	3 ± 1	3 ± 2
GLP-1 tAUC (pmol/l *min)	1028 ± 151	691 ± 97	736 ± 158	633 ± 148	742 ± 233
GLP-1 iAUC (pmol/l *min)	839 ± 69 [abcd]	270 ± 45 [a]	372 ± 72 [b]	198 ± 67 [c]	227 ± 106 [d]
Basal PYY (pmol/l)	21 ± 3 [a]	11 ± 2 [a]	12 ± 3	11 ± 3	8 ± 5
PYY tAUC (pmol/l *min)	4522 ± 408 [abcd]	2011 ± 275 [a]	2525 ± 445 [b]	1807 ± 421 [c]	1447 ± 622 [d]
PYY iAUC (pmol/l *min)	1383 ± 200 [acd]	386 ± 134 [a]	616 ± 218	203 ± 207 [c]	340 ± 305 [d]
Basal CCK (pmol/l)	1 ± 0	1 ± 0	1 ± 0	1 ± 0	1 ± 0
CCK tAUC (pmol/l*min)	408 ± 29	400 ± 19	409 ± 30	403 ± 28	370 ± 45
CCK iAUC (pmol/l*min)	284 ± 23	242 ± 15	257 ± 24	257 ± 23	170 ± 36
Basal insulin (pmol/l)	3389 ± 597 [acd]	6351 ± 396 [a]	5524 ± 625	6219 ± 584 [c]	8526 ± 922 [d]
Insulin tAUC (pmol/l *min)	2,043,605 ± 344,834 [abcd]	3,677,969 ± 239,476 [a]	3,275,226 ± 360,896 [bf]	3,238,669 ± 337,605 [cg]	5,696,987 ± 532,872 [dfg]
Insulin iAUC (pmol/l *min)	1,543,046 ± 294,514 [ad]	2,679,982 ± 204,741 [a]	2,443,018 ± 308,231 [f]	2,211,975 ± 288,994 [g]	4,405,207 ± 455,112 [dfg]

Data presented as estimated marginal means ± SEM and adjusted for age, sex and total physical activity duration, and pairwise comparisons for the general mixed model. Accounting for multiplicity, significance level was set to P < 0.01. Conversion from metric to SI units has been made in Table 2 and Fig. 1 and is as follows: ghrelin pg/ml × 0.3 = pmol/l, GLP-1 pg/ml x 0.33 = pmol/l, PYY pg/ml × 0.25 = pmol/l, and insulin pg/ml x 6 = pmol/l. CCK: cholecystokinin. GLP-1: glucagon-like peptide-1. iAUC: incremental area under the curve. OB: obesity. PYY: peptide YY. tAUC: total area under the curve. Mean values with equal superscript letter denote significant differences between groups (P <0.01) after Bonferroni adjustment.

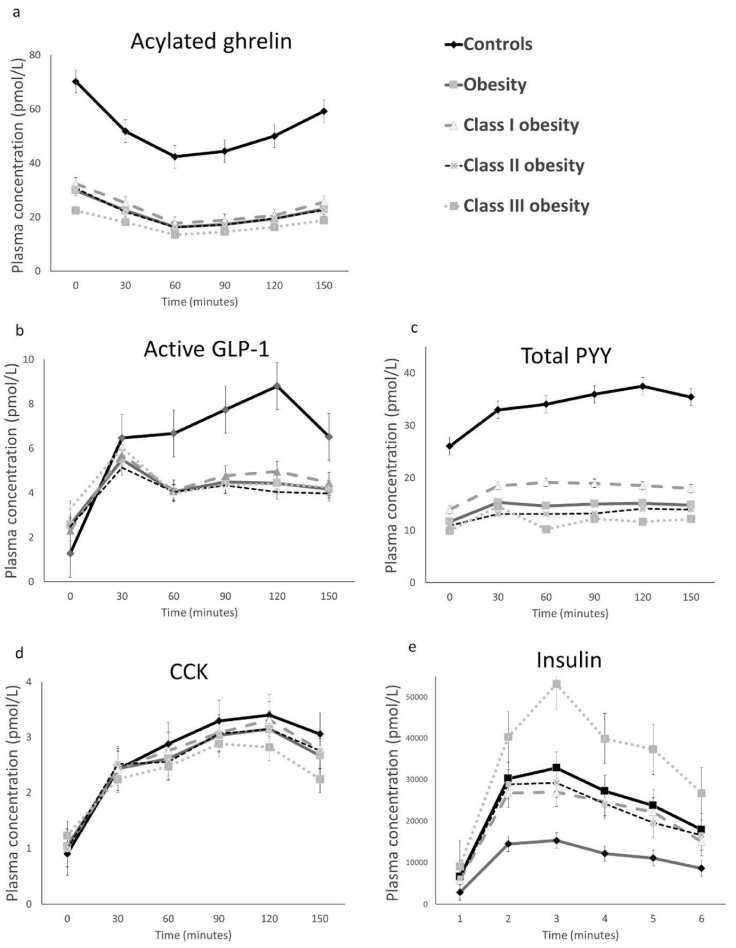

Fig. 1. a–e. Mean basal and postprandial plasma concentrations of gastrointestinal hormones over time.
Data presented as estimated marginal means ± SEM and adjusted for age, sex and total physical activity duration. AG: acylated ghrelin. CCK: cholecystokinin. GLP-1: glucagon-like peptide-1. PYY: peptide YY. Mean basal and postprandial plasma concentrations of GI hormones are shown in subgroups of obesity and controls. Conversion from metric to SI units has been made in Table 2 and Fig. 1 and is as follows: ghrelin pg/mL × 0.3 = pmol/L, GLP-1 pg/mL x 0.33 = pmol/L, PYY pg/mL × 0.25 = pmol/L, and insulin pg/mL x 6 = pmol/L.

Table 3
Mean fasting and postprandial scores for appetite ratings.

	Controls	OB	OB I	OB II	OB III
Fasting hunger (mm)	45 ± 4	39 ± 2	40 ± 4	39 ± 4	37 ± 6
Hunger tAUC (mm*min)	2829 ± 413	3436 ± 259	3995 ± 421	3153 ± 391	2959 ± 600
Hunger iAUC (mm*min)	−3870 ± 540	−2451 ± 336	−2060 ± 550	−2760 ± 512	−2515 ± 784
Fasting fullness (mm)	22 ± 3	21 ± 2	18 ± 3	24 ± 3	18 ± 5
Fullness tAUC (mm*min)	8597 ± 471	8969 ± 293	8552 ± 480	9125 ± 446	9458 ± 684
Fullness iAUC (mm*min)	5336 ± 570	5830 ± 356	5796 ± 581	5490 ± 540	6713 ± 828
Fasting DTE (mm)	46 ± 4	47 ± 2	49 ± 4	48 ± 4	41 ± 5
DTE tAUC (mm*min)	2955 ± 447	4229 ± 280	4759 ± 447	3959 ± 424	3783 ± 650
DTE iAUC (mm*min)	−3893 ± 472	−2811 ± 294	−2532 ± 481	−3210 ± 447	−2433 ± 685
Fasting PFC (mm)	64 ± 4	59 ± 2	63 ± 4	56 ± 3	61 ± 5
PFC tAUC (mm*min)	5187 ± 576	6623 ± 360	7043 ± 587	6046 ± 546	7137 ± 837
PFC iAUC (mm*min)	−4382 ± 499 [a]	2278 ± 310 [a]	−2440 ± 509	−2267 ± 473	−1967 ± 725

Data presented as estimated marginal means ± SEM and adjusted for age, sex and total physical activity duration, and pairwise comparisons for the general mixed model. Accounting for multiplicity, significance level was set to $P < 0.01$. DTE: desire to eat. iAUC: incremental area under the curve. OB: obesity. PFC: prospective food consumption. tAUC: total area under the curve. Mean values with equal superscript letter denote significant differences between groups ($P < 0.01$) after Bonferroni adjustment.

as well as basal and postprandial PYY ($P = 0.003$, $P < 0.001$ and $P = 0.002$, respectively). Basal and postprandial insulin secretion were also positively associated with BMI ($P < 0.001$, for all).

4. Discussion

The aim of this study was to compare plasma concentrations of GI hormones and subjective appetite ratings among obesity classes, as well as between obesity classes and controls. Our results show that GI hormones and subjective ratings of appetite generally do not differ among classes of obesity (with the exception of insulin), but some obesity classes display an abnormal postprandial secretion of GI hormones compared to controls, and postprandial curves are somewhat dissimilar. Basal and postprandial secretion of ghrelin was lower in all obesity classes compared to controls, with no postprandial ghrelin suppression, from basal values, in obesity class III. Postprandial GLP-1, PYY and CCK responses were lower, or to some extent absent, in some obesity classes compared to controls. Basal and postprandial concentrations of insulin increased progressively across obesity classes. These findings were supported by correlational analyses, which showed inverse associations between BMI and basal and postprandial ghrelin, postprandial GLP-1, and basal and postprandial PYY, as well as positive associations between BMI and basal and postprandial insulin.

Studies looking at potential differences among obesity classes are few. We are aware of only two studies who have addressed this issue. Acosta and colleagues (Acosta et al., 2015) examined associations of GI traits with obesity before and after a nutrient drink test and reported a borderline inverse association between BMI and fasting ghrelin plasma concentrations ($P = 0.063$). However, ghrelin was only measured in overweight subjects and individuals with obesity class I and II/III obesity, and not in subjects with normal weight. Zwirska-Korczala and colleagues (Zwirska-Korczala et al., 2007) analyzed GI hormones in lean control women, women with moderate obesity and severe obesity (BMI: 23.2 ± 0.7, 34.9 ± 0.9 and 46.9 ± 1.6 kg/m^2, respectively). They reported lower fasting total ghrelin in both obesity groups compared to controls. After a standard mixed meal (527 kcal), ghrelin concentration did not change in either obesity group, while values dropped and remained low in controls. Further, postprandial ghrelin concentration was lower in women with moderate obesity compared to women with severe obesity. This is in line with the present analysis showing no postprandial change in ghrelin plasma concentration in obesity class III,

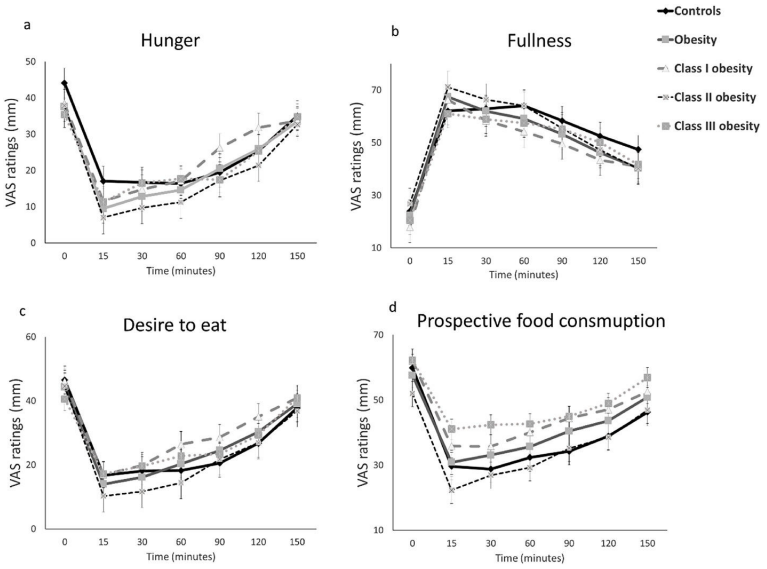

Fig. 2. a–d. Mean fasting and postprandial appetite ratings over time.
Data presented as estimated marginal means ± SEM and adjusted for age, sex and total physical activity duration. Mean fasting and postprandial ratings of appetite in subgroups of obesity and controls. VAS: visual analogue scale.

Table 4
Correlation analysis between BMI and plasma concentration of GI hormones, and BMI and appetite ratings.

	BMI	
	Spearman correlation coefficient (rho)	P
Basal ghrelin	**−0.531**	**<0.001**
Ghrelin tAUC	**−0.536**	**<0.001**
Ghrelin iAUC	**0.376**	**<0.001**
Basal GLP-1	−0.222	0.011
GLP-1 tAUC	**−0.388**	**<0.001**
GLP-1 iAUC	**−0.570**	**<0.001**
Basal PYY	**−0.294**	**0.003**
PYY tAUC	**−0.462**	**<0.001**
PYY iAUC	**−0.308**	**0.002**
Basal CCK	0.142	0.104
CCK tAUC	−0.119	0.175
CCK iAUC	−0.222	0.011
Basal insulin	**0.570**	**<0.001**
Insulin tAUC	**0.622**	**<0.001**
Insulin iAUC	**0.546**	**<0.001**
Fasting hunger	−0.183	0.029
Hunger tAUC	−0.102	0.606
Hunger iAUC	0.135	0.108
Fasting fullness	0.019	0.819
Fullness tAUC	0.113	0.178
Fullness iAUC	0.016	0.853
Fasting DTE	−0.112	0.182
DTE tAUC	0.041	0.659
DTE iAUC	0.142	0.092
Fasting PFC	−0.076	0.369
PFC tAUC	0.061	0.472
PFC iAUC	0.206	0.014

Correlation is significant at the level 0.01. BMI: body mass index. CCK: cholecystokinin. DTE: desire to eat. GLP-1: glucagon-like peptide 1. iAUC: incremental area under the curve. P: p-value. PFC: prospective food consumption. PYY: peptide YY. tAUC: total area under the curve.

and an inverse relationship between BMI and both basal and postprandial plasma acylated ghrelin.

The findings of a weaker and earlier postprandial GLP-1 peak in individuals with obesity (and absence in obesity class III), as well as an inverse association between BMI and postprandial GLP-1 found in the present study are in contrast with those of Acosta and colleagues. They reported a higher GLP-1 peak in overweight, and obesity class I and class II/III compared to subjects with normal weight (Acosta et al., 2015). It is interesting to note that, the present study, and others (le Roux, Aylwin, et al., 2006; Toft-Nielsen et al., 2001), have measured responses of GI hormones after a standardized solid fixed meal and found similar results, while in Acosta and colleagues' study subjects drank a liquid meal until satiation (Acosta et al., 2015). The fact that obesity was associated with decreased satiation (measured by consumption of a higher volume (and kcal) of the nutrient drink to reach fullness) in addition to accelerated gastric emptying of liquids (Acosta et al., 2015), may explain why obesity was associated with higher GLP-1 peak in that study. Both the present and the forementioned studies measured the active form of GLP-1, but methodological differences still make it difficult to make direct comparisons (Heijboer, Frans, Lomecky, & Blankenstein, 2011).

Overall, individuals with obesity had lower basal and postprandial secretion of total PYY compared to controls in the present analysis. Zwirska-Korczala and colleagues (Zwirska-Korczala et al., 2007) reported basal PYY_{3-36} to be reduced in obesity, particularly in those with severe obesity, compared to controls. Similarly, Acosta and colleagues (Acosta et al., 2015) found lower PYY postprandial peak in individuals with overweight and obesity class I, but not class II/III, when compared to subjects with normal weight. Given that individuals with class II/III obesity needed a larger volume of the nutrient drink test to reach fullness, it is surprising that their PYY postprandial peak concentrations did not differ from individuals with a normal weight. In another study by Meyer-Gerspach and collaborators, no postprandial increase in total PYY was seen in participants with severe obesity after a liquid meal, (Meyer-Gerspach et al., 2014). This is in line with the present analysis showing no postprandial total PYY response in individuals with obesity class II and III after the fixed breakfast meal. BMI was also negatively correlated with postprandial PYY concentrations. The absence of significant findings among obesity classes in the present analysis might result of lack of power, given that we did not have enough participants with obesity class III to reach the desired power. Also, differences in the hormonal fractions measured might affect results, and thus limit comparisons among studies. Total PYY is a measure of secretion, whereas PYY_{3-36} results from dipeptidyl peptidase-4 metabolism and has been shown to inhibit food intake (Kuhre, WewerAlbrechtsen, Hartmann, Deacon, & Holst, 2015; Sloth, Davidsen, Holst, Flint, & Astrup, 2007).

Women with severe obesity have been shown to have lower basal and postprandial CCK secretion compared to both women with moderate obesity and lean (Zwirska-Korczala et al., 2007). The present analysis found a delayed and shortened postprandial CCK response in individuals with obesity class III, which deviated from the other groups. Contrarily, in the study of Acosta and colleagues (Acosta et al., 2015), BMI was associated with borderline higher peak CCK concentrations in overweight and obesity. However, CCK was not assessed in subjects with normal weight in that study. Thus conclusions regarding CCK secretion remain controversial, likely due to methodological issues (Rehfeld, 2020).

Conflicting results among studies could be due to differences in energy- and macronutrient loads, gastric emptying, or other factors. For example, the energy, macronutrient composition, and physical form (solid versus liquid) of the test meal, as well as the proportion of the individual energy requirements covered by the test meal, are likely to affect the postprandial secretion of the different GI hormones (Mourao, Bressan, Campbell, & Mattes, 2007; Tischmann et al., 2019). Also, it needs to be acknowledged that individuals with obesity need to eat larger meals than individuals with a normal weight, under conditions of weight stability. It remains, therefore, to be determined if the impaired satiety response in individuals with obesity, particularly in those with obesity class III, seen in the present study, and others (le Roux, Aylwin, et al., 2006; Toft-Nielsen et al., 2001; Zwirska-Korczala et al., 2007) which use a fixed test meal across BMI groups, remains when participants are allowed to eat/drink until satiation, as in Acosta et al. study (Acosta et al., 2015).

Positive relationships between BMI and both basal and postprandial insulin secretion are well established (Bagdade et al., 1967), and the present analysis replicated this. Contrarily, Zwirska-Korczala and colleagues (Zwirska-Korczala et al., 2007) found no differences in basal concentrations of insulin between groups. However, and similar to the present analysis, insulin concentrations remained elevated throughout the postprandial period in both women with moderate and severe obesity, while in controls they returned to basal values at the end of the 2 h period. Of note, this study was carried out in women with obesity and the metabolic syndrome.

Even though infusions of GI hormones have been shown to affect eating behavior in both individuals with obesity and normal weight in laboratorial settings (Batterham et al., 2002; de Graaf, Blom, Smeets, Stafleu, & Hendriks, 2004; Druce et al., 2005; Flint, Raben, Astrup, & Holst, 1998; le Roux, Batterham, et al., 2006), it needs to be emphasized that the relationship between plasma concentration of GI hormones and subjective appetite ratings is highly complex (Crum, Corbin, Brownell, & Salovey, 2011). Individuals with obesity class II and III in the present sample seemed to have a more dysregulated hormonal response, but no differences in appetite ratings were seen. It is important to note in this connection that subjective appetite ratings represent an individual's interpretation of his/her feelings and motivations to eat rather than direct measures of the underlying physiological processes controlling eating (Blundell, 1979; Carroll, Kaiser, Franks, Deere, & Caffrey, 2007; Stubbs et al., 2000). Yet, obesity was associated with greater postprandial DTE in the present analysis. Also, Le Roux and colleagues (le

Roux, Aylwin, et al., 2006) reported that individuals with obesity exhibited a lower postprandial GLP-1 response, no postprandial rise in PYY, and lower ratings of fullness after a fixed meal compared to controls. In another study by the same group (le Roux, Batterham, et al., 2006), attenuated postprandial PYY response was matched by a lower perception of postprandial fullness in individuals with obesity. In line with this, Acosta and colleagues (Acosta et al., 2015) showed that obesity was associated with decreased satiation and lower PYY peak (Acosta et al., 2015). Altogether, these results indicate reduced satiety and stronger drive to eat in individuals with obesity. Further, a study by Maier and colleagues (Maier et al., 2008) showed that changes in ghrelin and PYY plasma concentrations were correlated with hunger and fullness ratings, respectively, but only in individuals with a normal weight.

Strengths of the present analysis include its study design, which allowed for the evaluation of alterations in GI hormones and appetite ratings among obesity classes, as well as between obesity classes and controls, an issue that is under-investigated. Moreover, variables known to affect appetite were added to the models as covariates, and the significance level adjusted for multi-comparisons (Bonferroni) and the large number of variables tested. However, this study also has some limitations. First, a multiplex kit was used to measure hormonal concentrations, except for CCK. This method is likely to result in less accurate and precise measures compared to optimized assays for each hormone. Second, a classical 100 mm VAS were used to assess appetite ratings. This method is known to be less sensitive than generalized labeled magnitude scales when comparing differences between groups of individuals with healthy weight versus obesity (Bartoshuk, Duffy, Hayes, Moskowitz, & Snyder, 2006). Third, the energy load of the test meal was kept constant regardless of body weight. This ensured that the same nutritional stimulus was provided to all participants but did not account for individual energy needs. Fourth, participants in this study were not equally distributed among groups, the group of obesity class III was small, and controls included both subjects with normal weight and overweight. Last, this is a cross-sectional analysis comparing groups with different BMIs and, as such, a cause-effect relationship cannot be established.

5. Conclusions

In conclusion, the present analysis confirms that meal-stimulated secretion of GI hormones is impaired in individuals with obesity, especially those with obesity class III (and to some extent class II), where no postprandial decline in ghrelin concentration or increase in GLP-1 and PYY were seen. Additionally, obesity was associated with greater PFC. Altogether, this may strengthen the drive to eat and lead to overeating.

Disclosure summary

The authors have no conflict of interest to disclosure.

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Ethical statement

This manuscript reports a secondary analysis of the “Weight loss maintenance and compensatory mechanisms activated with a very-low energy diet (VLED)” study, approved by the Norwegian regional ethics committee (Ref., 2012/1901), registered in clinicaltrials.gov (NCT01834859), and conducted according to the guidelines laid down in the Declaration of Helsinki.

Author contributions

C.M and M.I.A formulated the research questions and designed the study. J.N.D, S.N, K.H.O, and G.A.B carried out the study. J.F.R analyzed CCK. M.I.A analyzed the data. All authors were involved in the writing of the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.appet.2022.105940.

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Paper III

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ORIGINAL ARTICLE

Clinical Trials and Investigations

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Gastrointestinal hormones and appetite ratings after weight loss induced by diet or bariatric surgery

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Abstract

Objective: The aim of this study was to compare changes in gastrointestinal hormones and appetite ratings after a similar weight loss induced by a very low-energy diet alone or in combination with sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB).

Methods: Patients with severe obesity scheduled for SG ($n = 15$) and RYGB ($n = 14$) and 15 controls (very low-energy diet alone) were recruited. Body weight/composition, plasma concentrations of ß-hydroxybutyric acid, acylated ghrelin, total glucagon-like peptide-1, total peptide YY, cholecystokinin, and ratings of hunger, fullness, desire to eat, and prospective food consumption were measured pre- and postprandially, before and after 10 weeks of intervention.

Results: Changes in body weight/composition and level of ketosis were similar across groups. In SG and RYGB, basal and postprandial acylated ghrelin declined, and postprandial glucagon-like peptide-1 increased, both significantly more compared with controls. Postprandial peptide YY increased in all groups. Overall, postprandial hunger decreased, and postprandial fullness increased. But ratings of desire to eat and prospective food consumption were more favorable after both surgeries compared with controls.

Conclusions: Weight loss with SG and RYGB leads to more favorable changes in gastrointestinal hormones compared with diet alone, although ratings of appetite were reduced across all groups.

INTRODUCTION

Bariatric surgery is the most effective treatment for obesity, inducing a greater and more sustained weight loss compared with nonsurgical approaches [1]. It is hypothesized that bariatric surgery's success can be partially explained by beneficial changes in the secretion of gastrointestinal (GI) hormones, key regulators of eating behavior and homeostatic appetite control [2].

Patients who have undergone sleeve gastrectomy (SG) report feeling less hungry and more satiated than their nonsurgical counterparts [3], and several studies have shown decreases in appetite also following Roux-en-Y gastric bypass (RYGB) [4, 5]. Plasma concentrations of ghrelin, the only known orexigenic gut-derived signal, have consistently been shown to decline following SG [6, 7]. However, less consensus exists regarding the impact of RYGB on ghrelin plasma concentrations, with some studies showing a decrease [8], while others show no change [9]. The plasma concentrations of glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin (CCK), collectively known as satiety peptides, have been consistently reported to increase shortly after bariatric surgery and to be sustained for up to 10 years postoperatively [4, 10, 11].

Diet-induced weight loss, on the other hand, has consistently been shown to lead to increased basal ghrelin plasma concentrations and hunger ratings [12, 13]. Moreover, these changes seem to be sustained at 1-year follow-up [13, 14], even with partial weight regain [12]. However, the impact of diet-induced weight loss on the postprandial concentrations of satiety peptides and appetite ratings remains controversial [12–14].

Few studies have compared how weight loss induced by diet versus bariatric surgery impacts the secretion of GI hormones and subjective appetite ratings. RYGB, in combination with a low-calorie diet, was reported to induce a greater weight loss along with decreased motivation to eat and lower basal and postprandial total ghrelin concentrations, as well as greater postprandial concentrations of total GLP-1, PYY_{3-36}, and CCK, compared with dietary restriction alone [15]. However, in another study, a 10-kg weight loss induced by RYGB was reported to decrease total ghrelin plasma concentrations, whereas the same magnitude of weight loss induced by dietary restriction alone had the opposite effect [16]. Moreover, RYGB resulted in more favorable changes in appetite ratings (hunger, satiety, prospective food consumption [PFC], and cravings), despite no changes in total GLP-1 or total PYY concentrations in the postprandial state in either group [16].

Nutritional-induced ketosis has been shown to modulate the concentrations of GI hormones, particularly ghrelin [17, 18], with the increased drive to eat otherwise seen with diet-induced weight loss being attenuated, or even absent, under ketogenic conditions [17, 19, 20]. Interestingly, it has been reported that patients who undergo bariatric surgery develop mild ketosis shortly after surgery [21]. Studies comparing the impact of weight loss induced by diet alone versus bariatric surgery on appetite are limited given that they have not controlled for ketosis, the magnitude of weight loss, or the overall energy deficit and macronutrient composition of the diet. A study controlling for these variables would be useful for elucidating the mechanisms behind the effectiveness of bariatric surgery. Therefore, the aim of this study was to compare how a similar weight loss induced by a very low-energy diet (VLED) alone, or VLED combined with SG or RYGB, impacts GI hormone plasma concentrations and subjective appetite ratings.

Study Importance

What is already known?

- Bariatric surgery leads to substantial and sustained weight loss, concomitant with beneficial changes in gastrointestinal (GI) hormones toward reduced hunger and increased satiety.
- Very low-energy diets (VLED) are effective for weight loss in the short term but are usually followed by an increased drive to eat, and long-term weight loss maintenance is poor.

What does this study add?

- When diet and weight loss are similar, bariatric surgery (both Roux-en-Y gastric bypass and sleeve gastrectomy) leads to a more favorable profile in the concentration of GI hormones, compared with diet-induced weight loss.
- However, an overall reduction in appetite ratings is seen after both diet-induced weight loss and bariatric surgery, likely because participants were under nutritional-induced ketosis.

How might these results change the direction of research or the focus of clinical practice?

- For patients with severe obesity who cannot, or choose not to, undergo bariatric surgery, VLED seem to be a good alternative, at least in the short term, to induce significant weight loss concomitant with an overall reduction in appetite ratings like what is seen after bariatric surgery.
- Long-term studies are needed to determine whether these initial changes in GI hormones and appetite ratings modulate long-term weight loss outcomes after both diet-induced weight loss and bariatric surgery.

METHODS

Study design

The Effect of Dlet-induced weight loss versus Sleeve gastrectomy and Gastric bypass on Appetite (DISGAP) study is a three-arm, nonrandomized controlled trial, comparing how a similar weight loss induced by VLED alone, or VLED in combination with SG or RYGB, impacts different domains of appetite regulation. This paper reports the initial changes in GI hormones and appetite ratings after a similar weight loss achieved across groups. An outline of the study can be seen in Figure 1.

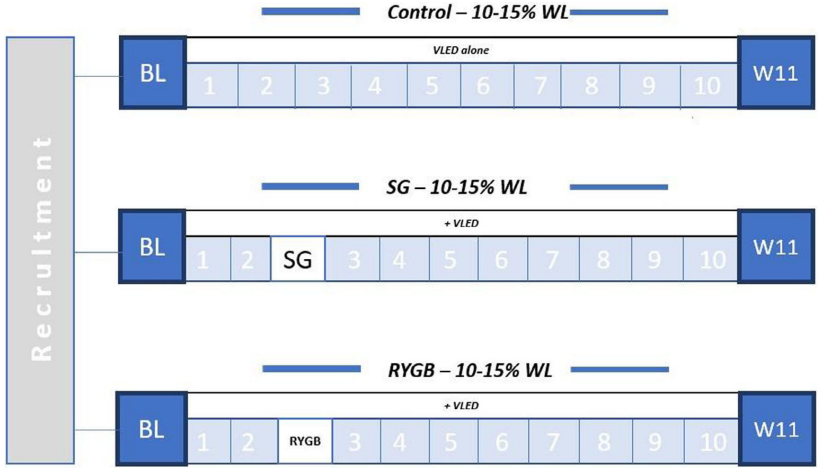

FIGURE 1 Study design. BL, baseline; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VLED, very low-energy diet; W11, week 11; WL, weight loss [Color figure can be viewed at wileyonlinelibrary.com]

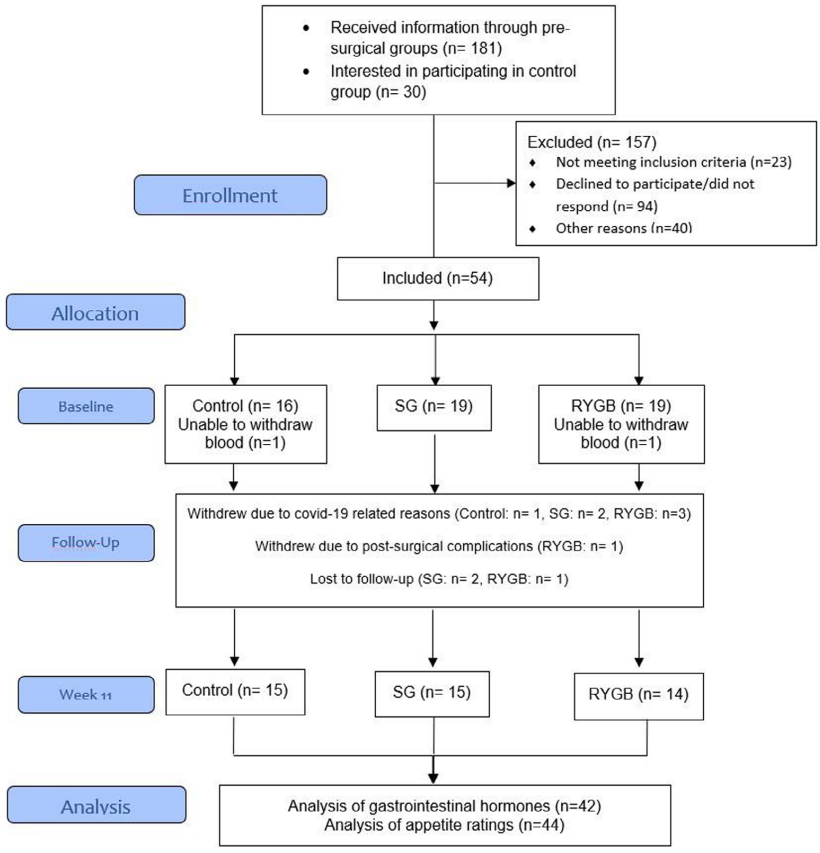

FIGURE 2 Flow diagram of the study. RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy [Color figure can be viewed at wileyonlinelibrary.com]

Participants

Adults with severe obesity scheduled for SG or RYGB at two local hospitals in the Central Norway Health Region were recruited for this study. The control group (VLED intervention alone) was composed of patients on a waiting list for bariatric surgery, patients who declined or were not eligible for surgery, as well as individuals with severe obesity from the local community (recruited through advertisements at St. Olav's University Hospital and the Norwegian University of Science and Technology intranet). The control group was recruited aiming to match the preoperative body mass index (BMI), age, and sex of the surgical groups. Recruitment and data collection took place between September 2019 and January 2022. A flow diagram of the study can be seen in Figure 2.

The study was approved by the regional ethics committee (Regional etisk komite [REK], Ref: 2019/252), registered in ClinicalTrials.gov (NCT04051190), and conducted according to the guidelines laid down in the Declaration of Helsinki. All participants provided written informed consent before enrolling in the study. Participants had to be weight stable (self-reported) (< 2-kg body weight change over the last 3 months) and not enrolled in any other obesity treatment or behavioral program. Patients who had previously undergone bariatric surgery, were using medication known to affect metabolism or appetite, or had a current cancer diagnosis, substance abuse, or a psychiatric diagnosis that precluded bariatric surgery (such as eating disorders) were excluded from the study.

Interventions

Surgical procedures

Bariatric surgeries were performed using standard laparoscopic procedures. The SG involved dividing the gastrocolic ligament, initiating the gastrectomy 4 cm proximal to the pylorus along the greater curvature, and creating the sleeve along the lesser curvature using a 36-French bougie. The RYGB procedure involved creating a small (~20–30 mL) proximal gastric pouch and a stapled gastrojejunostomy. A 75– to 150-cm Roux-Y limb was constructed by transecting the jejunum 60 to 100 cm distal to the ligament of Treitz and performing a stapled jejunostomy at this site.

Diet

All participants followed a formula-based VLED, using commercial food packs (Lighter Life, Harlow), for 10 weeks under the guidance of a registered dietitian. The average daily macronutrient composition of the VLED was 750 kcal, and percent energy (E%) was 26 E% fat, 36 E% carbohydrates, 5 E% fiber, and 33 E% protein. The products consisted of shakes, soups, textured meals, porridge, and bars with approximately 150 kcal/product. Participants could choose any combination of five products per day. They were encouraged to consume a maximum of 100 g of low-starch vegetables and 2.5 L of water daily. Alcohol consumption was not allowed during the 10-week intervention. Noncaloric beverages were allowed, in addition to a maximum of 500 mL of low-energy drinks (< 3 kcal/100 mL).

Patients scheduled for SG and RYGB initiated the VLED 2 weeks prior to surgery and continued for another 8 weeks afterward. The surgical groups were instructed to consume only fluid food packs the first weeks postoperatively, gradually increasing the texture of the food. All participants were asked to fill out a self-reported food diary. At weekly scheduled follow-ups, food diaries were discussed, side effects recorded, body weight monitored, and acetoacetate (a ketone body) measured in urine with ketostix (Bayer Ketostix 2880 Urine Reagent Test Strip, Ascensia Diabetes Care), as a measure of dietary compliance.

Physical activity

Participants were asked to maintain their physical activity (PA) levels during the 10-week intervention. Compliance with this recommendation was assessed by asking participants to wear SenseWear armbands (BodyMedia) for 7 days prior to baseline (BL) and on the last week of the study (W10). Data were considered valid if participants wore the device for ≥ 4 days, including at least 1 weekend day, on more than 95% (22.8 h/d) of the time [22]. Average steps per day, PA levels, metabolic equivalents, and total PA duration were included in the analysis.

Outcome variables

After an overnight fast (at least 10 hours), participants came to the obesity outpatient clinic at St. Olav's University Hospital on two occasions: before start of the dietary intervention (BL) and after 10 weeks (W11), to measure body weight and composition, plasma concentrations of GI hormones, and appetite ratings.

Air-displacement plethysmography (BodPod, COSMED) was used to measure body weight, fat mass (FM), and fat free mass (FFM).

Blood samples were collected in 4-mL EDTA-coated tubes and drawn at fasting, every 15 minutes for the first hour after a standardized breakfast, and then at 30-minute intervals until 150 minutes. The breakfast consisted of a 200-mL commercial low-glycemic drink (Diben Drink, Fresenius Kabi Norge AS) (300 kcal, 42 E% fat, 35 E% carbohydrates, 3 E% fiber, and 20 E% protein), and participants were asked to drink it slowly over a 15-minute period, to avoid dumping syndrome.

For acylated ghrelin (AG) and total PYY, 1 mL of whole blood was transferred into a microtube and a 20-μL mixture of inhibitor (10 μL of Pefabloc [Roche Diagnostic] + 10 μL of dipeptidyl-peptidase IV inhibitor [Merck Millipore]) was added. For CCK and total GLP-1, 500 KIU of aprotinin (DSM, Coatech AB) per milliliter of whole blood was added to the EDTA tubes. Samples were then centrifuged at 2106 relative centrifugal force (RCF) for 10 minutes

at 18 °C and the plasma frozen at −80 °C until further analysis. Plasma samples were analyzed for AG and total PYY using a Human Metabolic Hormone Magnetic Bead Panel (HMHEMAG-34 K, Merck KGaA). Cross-reactivity between antibodies and any of the other analytes in this panel is nondetectable or negligible. CCK and total GLP-1 were analyzed using "in-house" radioimmunoassay (RIA) methods [23, 24]. Intra- and inter-assay coefficients of variation were < 10% and < 20% for AG and total PYY; and < 5% and < 15% for total GLP-1 and CCK, respectively. All the samples from the same participant were analyzed in the same plate. The analyses of AG and total PYY were performed by the same technician at NTNU's lab. CCK and total GLP-1 were both analyzed at the University of Copenhagen, Denmark. A ketone body assay kit (MAK134, Sigma-Aldrich) was used to measure ß-hydroxybutyric acid (ßHB) plasma concentrations.

Appetite ratings (hunger, fullness, desire to eat [DTE], and PFC) were assessed using a 10-cm visual analog scale [25] at fasting, immediately after the standardized breakfast, and every 30 minutes for a period of 2.5 hours.

Sample size calculation

Given that RYGB has been shown to induce a larger increase in GLP-1 area under the curve (AUC) compared with SG [6] and dietary restriction alone [15], for this exploratory study, we hypothesized that bariatric surgery would induce a two (SG) and three (RYGB) times larger increase in total GLP-1 postprandial concentrations (AUC) compared with diet-induced weight loss alone (~600 pmoL/mL × min) [13]. For a power of 80%, a significance level of 0.05, and assuming a standard deviation of 1000 min × pmol/L, and a within-group variance of 640,000 min × pmol/L, 45 participants would be required (15 in each group).

Statistical analysis

The statistical analysis was carried out using SPSS Statistics, version 27 (IBM Corp.). Residuals were checked for normality using the Shapiro–Wilk test and visual inspection of QQ plots and histograms and they did not deviate significantly from normality. Data are presented as means ± standard errors of the mean (SEM), unless otherwise stated. All data (anthropometrics, GI hormones, appetite ratings, and ßHB) were analyzed using a linear mixed-effects model with restricted maximum likelihood estimation, including fixed effects for time, group, and their interaction. Bonferroni correction was used for post hoc pairwise group comparisons. We were unable to collect blood samples from two participants at BL (one control, one RYGB), and these were therefore excluded from the analysis of GI hormones. Total and incremental (or decremental) area under the curve (*t*AUC, *i*AUC, and *d*AUC, respectively) for GI hormone concentrations and appetite ratings was calculated using the trapezoid rule.

RESULTS

Participants

Table 1 shows mean characteristics of the groups at baseline and week 11. A total of 44 participants completed BL and W11 assessments ($n = 15$ VLED, $n = 15$ SG, and $n = 14$ RYGB). A main effect of time was seen for all anthropometric variables ($p < 0.001$, for all). Post hoc analysis showed no differences in any anthropometric variables between groups at BL or W11 or in changes over time. Participants lost on average 18.3 ± 0.6 kg (16%), and BMI was reduced by 6.3 ± 0.8 kg/m^2, FM decreased by 13.5 ± 0.5 kg (24%), and FFM decreased by 4.8 ± 0.3 kg (8%) ($p < 0.001$, for all). All participants were in nutritional-induced ketosis at W11, with no significant differences in ßHB plasma concentrations between groups. No changes over time or differences between groups were seen for any of the PA variables assessed (data not shown).

Gastrointestinal hormones

Mean basal and postprandial plasma concentrations of GI hormones at BL and W11 can be seen in Table 2, and the postprandial curves over time can be seen in Figure 3A–D.

An overall reduction in basal and postprandial ghrelin concentrations was seen

A main effect of time, group, and time × group interaction was seen for basal AG concentrations ($p < 0.001$, for all). Post hoc analysis showed that SG and RYGB experienced a decrease in basal AG concentrations ($p < 0.001$ and $p = 0.13$, respectively), whereas controls showed no change over time and had higher basal concentrations compared with SG and RYGB at W11 ($p < 0.001$, for both). A main effect of time ($p < 0.001$, for both) and group ($p = 0.002$, and $p = 0.003$, respectively) was also seen for AG *t*AUC and *d*AUC. Controls had significantly greater postprandial concentrations (tAUC and iAUC) at W11 compared with SG ($p = 0.003$, for both) and RYGB ($p = 0.013$ and $p = 0.014$).

There was an overall reduction in basal and postprandial concentrations of total GLP-1

A main effect of time was seen for basal GLP-1 ($p = 0.002$) and a main effect of time, group, and time × group interaction for GLP-1 *t*AUC and *i*AUC ($p < 0.001$, for all). Post hoc analysis showed no differences between groups in postprandial GLP-1 concentrations at BL. An increase was seen for GLP-1 (*t*AUC and *i*AUC) after both surgical procedures (SG: $p = 0.02$, for both, RYGB: $p < 0.001$, for both), whereas no changes were seen for controls. At W11, postprandial GLP-1 (*t*AUC and *i*AUC) had increased significantly more after both bariatric

TABLE 1 Demographic and anthropometric variables by group at baseline and week 11

	Baseline			Week 11			Main effects		
	Control	SG	RYGB	Control	SG	RYGB	Time	Group	Time × group interaction
n	15	15	14	15	15	14			
Age (y)	45.5 ± 2.6	39.6 ± 2.4	46.7 ± 2.5					NS	
Females, %	69	79	61					NS	
Body weight (kg)	115.4 ± 3.9[a]	117.6 ± 3.6[b]	120.4 ± 3.7[c]	98.1 ± 3.9[a]	98.6 ± 3.6[b]	101.6 ± 3.7[c]	$p < 0.001$	NS	NS
Weight loss (kg)				−17.3 ± 1.0	−19.0 ± 1.0	−18.8 ± 1.0			
BMI (kg/m^2)	39.7 ± 0.9[a]	40.2 ± 0.7[b]	41.6 ± 1.1[c]	33.7 ± 0.9[a]	34.1 ± 0.8[b]	35.0 ± 1.3[c]	$p < 0.001$	NS	NS
FM (%)	46.6 ± 1.5[a]	47.9 ± 1.4[b]	47.0 ± 1.4[c]	41.0 ± 1.5[a]	43.0 ± 1.4[b]	42.7 ± 1.4[c]	$p < 0.001$	NS	NS
FM (kg)	53.7 ± 2.6[a]	56.5 ± 2.4[b]	56.5 ± 2.4[c]	40.4 ± 2.6[a]	42.4 ± 2.4[b]	43.6 ± 2.4[c]	$p < 0.001$	NS	NS
FFM (%)	53.0 ± 1.5[a]	52.1 ± 1.4[b]	53.0 ± 1.4[c]	59.1 ± 1.5[a]	57.0 ± 1.4[b]	57.3 ± 1.4[c]	$p < 0.001$	NS	NS
FFM (kg)	61.7 ± 2.6	61.1 ± 2.4[b]	63.8 ± 2.4[c]	57.8 ± 2.5[a]	56.2 ± 2.4[b]	58.1 ± 2.4[c]	$p < 0.001$	NS	NS
βHB (mM)	0.1 ± 0.2[a]	0.1 ± 0.2[b]	0.0 ± 0.2[c]	0.7 ± 0.2[a]	1.1 ± 0.2[b]	0.5 ± 0.2[c]	$p < 0.001$	NS	NS

Note: Data presented as estimated marginal means ± SEM. Means sharing the same superscript letter denote significant changes over time ($p < 0.001$ for all).
Abbreviations: βHB, beta-hydroxybutyric acid; FFM, fat free mass; FM, fat mass; NS, not significant; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

procedures compared with controls, and concentrations were greater in RYGB compared with both SG and controls ($p < 0.001$, for all).

All groups experienced an increase in total PYY in the postprandial state

No main effects were seen for basal PYY concentrations. A main effect of time and time × group interaction was seen for PYY *t*AUC ($p = 0.005$, and $p = 0.034$, respectively), and a main effect of time was seen for PYY *i*AUC ($p < 0.005$). Post hoc analysis showed that all groups experienced an increase in PYY *t*AUC and *i*AUC over time ($p = 0.008$ and $p = 0.005$ for all). At W11, RYGB had greater PYY *t*AUC compared with SG ($p = 0.034$).

An overall reduction in basal CCK was seen

A main effect of time and group was seen for basal CCK plasma concentrations ($p < 0.001$, for both). Post hoc analysis showed that controls had higher basal CCK concentrations compared with SG ($p < 0.001$) and RYGB ($p = 0.003$) at BL. Basal CCK concentrations declined overall ($p < 0.001$), and at W11, no differences between groups were seen. No main effects were seen for postprandial CCK concentrations.

Appetite ratings

Mean scores for appetite ratings, fasting and postprandially, at BL and W11 can be seen in Table 3. Postprandial curves over time can be seen in Figure 4A–D.

An overall reduction in postprandial hunger and an increase in postprandial fullness ratings were seen across WL modalities

No main effects were seen for fasting hunger ratings. A main effect of time was seen for postprandial (*t*AUC and *d*AUC) hunger ratings ($p = 0.001$ and $p = 0.032$, respectively), with no differences between groups.

An overall increase in postprandial fullness ratings was seen at W11, with a main effect of time for postprandial (*t*AUC) fullness ($p = 0.011$).

Overall decreases in DTE in the fasting and postprandial state were seen

A main effect of time ($p = 0.005$) was seen for fasting DTE, whereas a main effect of time and group ($p = 0.017$ and $p = 0.006$, respectively) was observed for DTE *t*AUC and a time × group interaction ($p = 0.035$) for DTE *d*AUC. Post hoc analysis showed that DTE ratings

TABLE 2 Plasma concentration of gastrointestinal hormones at baseline and week 11 by group

	Baseline			Week 11			Main effects		
	Control	SG	RYGB	Control	SG	RYGB	Time	Group	Time × group interaction
Basal AG (pmol/L)	40.1 ± 4.6	27.6 ± 4.3^{b}	26.1 ± 4.7^{c}	45.1 ± 4.7 $^{*\&\ \Omega\ ¤}$	6.6 ± 4.4$^{b\ *\Omega}$	16.1 ± 4.8$^{c\ \&\ ¤}$	$p < 0.001$	$p < 0.001$	$p < 0.001$
AG *t*AUC (pmol/mL *min)	521.9 ± 83.1	237.8 ± 78.0	331.0 ± 85.9	432.1 ± 85.5 $^{*\&}$	21.5 ± 82.1 *	70.5 ± 88.6$^{\&}$	$p < 0.001$	$p = 0.002$	NS
AG *d*AUC (pmol/mL *min)	515.9 ± 82.6	233.6 ± 77.6	327.1 ± 85.5	425.4 ± 84.5 $^{*\&}$	20.5 ± 81.7 *	68.2 ± 88.1$^{\&}$	$p < 0.001$	$p = 0.003$	NS
Basal GLP-1^{total} (pmol/L)	6.4 ± 1.2	8.6 ± 1.1	7.8 ± 1.3	3.0 ± 1.2	4.5 ± 1.2	6.8 ± 1.3	$p = 0.002$	NS	NS
GLP-1 *t*AUC (pmol/mL *min)	58.6 ± 46.7	43.3 ± 42.3^{b}	66.2 ± 48.4^{c}	52.3 ± 48.4$^{\&\ \Omega\ ¤}$	189.4 ± 44.7$^{b\ \#\ \Omega}$	548.0 ± 48.4$^{c\ \&\ \#\ ¤}$	$p < 0.001$	$p < 0.001$	$p < 0.001$
GLP-1 *i*AUC (pmol/mL *min)	57.6 ± 46.2	42.0 ± 41.9^{b}	65.0 ± 48.0^{c}	51.9 ± 46.2$^{\&}$	188.7 ± 44.6$^{b\ \#}$	547.0 ± 47.9$^{c\ \&\ \#}$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Basal PYY^{total} (pmol/L)	19.1 ± 3.0	14.6 ± 2.8	11.6 ± 3.1	17.1 ± 3.1	11.8 ± 2.9	16.6 ± 3.2	NS	NS	NS
PYY *t*AUC (pmol/mL *min)	292.6 ± 164.7^{a}	154.3 ± 156.4^{b}	691.3 ± 169.3^{c}	725.6 ± 167.4^{a}	587.3 ± 156.4$^{b\ \#}$	1124.3 ± 172.2$^{c\ \#}$	$p = 0.005$	NS	$p = 0.034$
PYY *i*AUC (pmol/mL *min)	275.5 ± 166.5	176.7 ± 158.9	674.8 ± 171.2	739.4 ± 169.3	640.6 ± 164.1	1138.7 ± 174.1	$p = 0.005$	NS	NS
Basal CCK (pmol/L)	2.4 ± 0.3 $^{*\&}$	0.8 ± 0.3 *	1.1 ± 0.3$^{\&}$	1.3 ± 0.3	0.5 ± 0.3	0.4 ± 0.3	$p < 0.001$	$p < 0.001$	NS
CCK *t*AUC (pmol/mL *min)	11.7 ± 1.8	6.1 ± 1.7	7.1 ± 1.9	7.5 ± 1.8	5.6 ± 1.8	6.4 ± 1.9	NS	NS	NS
CCK *i*AUC (pmol/mL *min)	11.3 ± 1.8	6.0 ± 1.6	6.9 ± 1.9	7.3 ± 1.8	5.6 ± 1.7	6.3 ± 1.9	NS	NS	NS

Note: Data are presented as estimated marginal means ± SEM. Conversion from metric to SI units has been applied as follows: ghrelin pg/mL × 0.3 = pmol/L, PYY pg/mL × 0.25 = pmol/L. Post hoc pairwise comparisons corrected with Bonferroni adjustment. Averages sharing the same superscript letter denote a significant change over time ($p < 0.05$). Averages sharing the same superscript symbol denote significant differences between groups ($^{*\&\#}$, $p < 0.05$) or significant differences in the changes over time between groups at week 11 ($^{\Omega¤}$, $p < 0.05$).

Abbreviations: AG, acylated ghrelin; CCK, cholecystokinin; *d*AUC, decremental area under the curve; GLP-1, glucagon-like peptide-1; *i*AUC, incremental area under the curve; NS, not significant; PYY, peptide YY; RYGB, Roux-en Y gastric bypass; SG, sleeve gastrectomy; *t*AUC, total area under the curve.

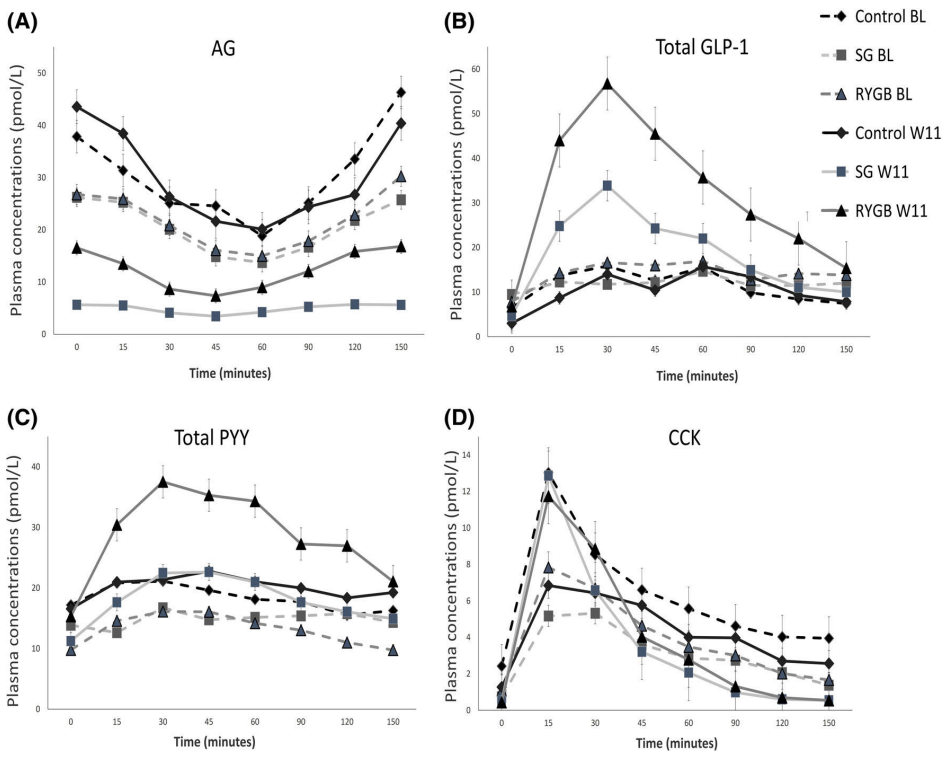

FIGURE 3 Mean postprandial concentrations of gastrointestinal hormones at baseline (BL) and week 11 (W11). Dotted lines indicate baseline concentrations, and solid lines indicate week 11 concentrations. AG, acylated ghrelin; CCK, cholecystokinin; GLP-1, glucagon-like peptide 1; PYY, peptide YY; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy [Color figure can be viewed at wileyonlinelibrary.com]

at W11 were lower in SG compared with controls ($p = 0.029$), and postprandial ratings (*t*AUC) were lower in RYGB compared with controls ($p = 0.019$).

An overall decrease in ratings of PFC, both fasting and postprandially, was seen

A main effect of time and time × group interaction was seen for PFC in the fasting state ($p < 0.001$, for both), and a main effect of time ($p < 0.001$) and group ($p = 0.028$) was seen for PFC tAUC. Post hoc analysis showed that RYGB presented with greater PFC ratings in fasting at BL compared with controls ($p = 0.017$). At W11, SG and RYGB had lower fasting (for both) and *t*AUC (RYGB) PFC ratings, compared with controls ($p < 0.001$ for both and $p = 0.015$, respectively).

DISCUSSION

This study aimed to compare changes in GI hormone concentrations and subjective appetite ratings in individuals with severe obesity achieving a similar weight loss with VLED alone or in combination with SG or RYGB. It represents the first attempt to perform such comparisons when changes in body weight and composition, as well as magnitude of nutritional-induced ketosis, are similar across groups. SG and RYGB groups experienced a decrease in both basal and postprandial AG concentrations and an increase in postprandial total GLP-1 concentrations. All groups experienced an increase in postprandial concentrations of total PYY. At W11, RYGB obtained the greatest postprandial concentrations of both total GLP-1 and total PYY. Postprandial CCK concentrations remained unchanged over time for all groups. Overall, postprandial hunger decreased, and postprandial fullness increased. Moreover, larger decreases in fasting and postprandial DTE and PFC were seen after both bariatric procedures, and at W11, ratings tended to be overall lower in SG and RYGB compared with controls.

It is generally accepted that individuals with obesity present with lower basal and postprandial ghrelin concentrations compared with individuals without obesity [26–28], and that diet-induced weight loss leads to an increase in ghrelin concentrations [13, 15, 16]. In the present study, controls showed no changes in AG concentrations, despite substantial weight loss. Ketosis was shown to prevent the increase in ghrelin plasma concentrations otherwise seen following diet-induced

TABLE 3 Subjective appetite ratings at baseline and week 11 by group

	Baseline			Week 11			Main effects		
	Control	SG	RYGB	Control	SG	RYGB	Time	Group	Time × group interaction
Hunger in fasting (cm)	3.2 ± 0.8	2.7 ± 0.7	3.9 ± 0.7	3.7 ± 0.8	2.9 ± 0.8	3.1 ± 0.8	NS	NS	NS
Hunger *t*AUC (cm × min)	524.3 ± 72.1	415.9 ± 66.2	404.2 ± 68.0	311.9 ± 74.5	320.1 ± 74.5	118.4 ± 77.1	$p = 0.001$	NS	NS
Hunger *d*AUC (cm × min)	2.1 ± 118.2	−2.0 ± 108.5	−83.5 ± 114.7	−248.1 ± 122.1	−129.9 ± 122.1	−340.2 ± 126.4	$p = 0.032$	NS	NS
Fullness in fasting (cm)	1.7 ± 0.6	1.0 ±. 0.5	1.4 ± 0.6	2.4 ± 0.6	1.7 ± 0.6	2.5 ± 0.6	NS	NS	NS
Fullness *t*AUC (cm × min)	577.3 ± 85.8	610.5 ± 78.8	584.7 ± 80.9	841.4 ± 88.1	641.9 ± 86.6	705.2 ± 89.5	$p = 0.011$	NS	NS
Fullness *i*AUC (cm × min)	269.4 ± 102.8	445.6 ± 94.3	396.6 ± 99.7	491.3 ± 106.2	360.1 ± 106.2	357.9 ± 109.9	NS	NS	NS
DTE in fasting (cm)	4.8 ± 0.8	4.0 ± 0.7	4.0 ± 0.8	4.2 ± 0.8*	1.1 ± 0.8 *	2.9 ± 0.8	$p = 0.005$	NS	NS
DTE *t*AUC (cm × min)	399.7 ± 55.5.	289.3 ± 50.9	241.5 ± 52.3	330.5 ± 57.3$^{\&}$	175.2 ± 57.3	99.7 ± 59.3$^{\&}$	$p = 0.017$	$p = 0.006$	NS
DTE *d*AUC (cm × min)	−314.2 ± 107.1	−375.4 ± 98.2	−215.7 ± 103.7	−289.5 ± 110.4	13.9 ± 110.0	−318.1 ± 113.8	NS	NS	$p = 0.035$
PFC in fasting (cm)	2.7 ± 0.7$^{\&}$	4.6 ± 0.6	5.3 ± 0.6$^{\&}$	2.9 ± 0.7$^{\#\,¤}$	1.3 ± 0.6.8$^{\#}$	1.4 ± 0.7$^{¤}$	$p < 0.001$	NS	$p < 0.001$
PFC *t*AUC (cm × min)	422.7 ± 59.4	358.5.4 ± 54.5	325.2 ± 56.0	327.8 ± 61.3$^{\&}$	135.2 ± 61.1	74.9 ± 63.2$^{\&}$	$p < 0.001$	$p = 0.028$	NS
PFC *d*AUC (cm × min)	−70.8 ± 108.8	−289.3 ± 99.8	−401.5 ± 105.5	−118.3 ± 112.3	−63.1 ± 112.3	−142.3 ± 125.6	NS	NS	NS

Note: Data are presented as estimated marginal means ± SEM. Conversion from metric to SI units has been applied as follows: ghrelin pg/mL × 0.3 = pmol/L, PYY pg/mL × 0.25 = pmol/L. Post hoc pairwise comparisons corrected with Bonferroni adjustment. Averages sharing the same superscript letter denote a significant change over time ($p < 0.05$). Averages sharing the same superscript symbol denote significant differences between groups ($^{*\&\#}$, $p < 0.05$) or significant differences in the changes over time between groups at week 11 ($^{\Omega¤}$, $p < 0.05$).

Abbreviations: CCK, cholecystokinin; *d*AUC, decremental area under the curve; DTE, desire to eat; GLP-1, glucagon-like peptide-1; iAUC, incremental area under the curve; NS, not significant. PFC, prospective food consumption; PYY, peptide YY; RYGB, Roux-en Y gastric bypass; SG, sleeve gastrectomy; *t*AUC, total area under the curve.

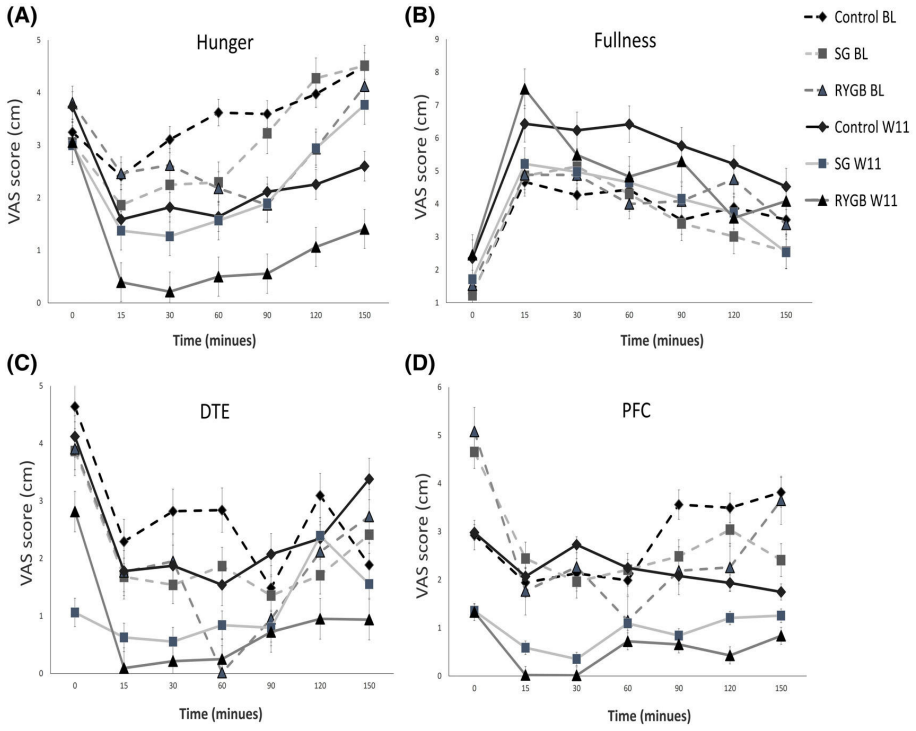

FIGURE 4 Mean postprandial ratings of appetite at baseline (BL) and week 11 (W11). Dotted lines indicate baseline ratings, and solid lines indicate week 11 ratings. DTE, desire to eat; PFC, prospective food consumption; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VAS, visual analog scale [Color figure can be viewed at wileyonlinelibrary.com]

weight loss [17, 18, 20], which might explain these findings. The main production site of ghrelin is the fundus of the stomach, which is removed during the SG procedure. It is therefore not surprising that the present, as well as several other studies [6, 7, 10], report a reduction in AG concentrations post SG. The present study also confirmed previous findings that ghrelin decreases post RYGB [10, 15, 16, 29], and that concentrations are lower when compared with dietary restriction alone [15, 16]. However, not all are in agreement [4, 28], and an increase in both total ghrelin and AG concentrations has also been reported post RYGB [27]. These conflicting findings likely result from differences in the surgical technique, namely the size of the remaining pouch.

The impact of diet-induced weight loss on postprandial concentrations of the satiety peptides GLP-1 and PYY remains controversial [12–14]. Based on previous literature, we hypothesized that WL with SG and RYGB would induce a two- and threefold larger increase in GLP-1 AUC compared with VLED alone [13]. The present study showed no changes in postprandial total GLP-1 concentrations after weight loss induced by VLED alone, whereas the magnitude of increase seen after SG and RYGB was larger than hypothesized. Although increased postprandial total PYY concentrations were seen across all groups, the increases were larger following RYGB. Several other studies report increased postprandial concentrations of both GLP-1 and PYY following both surgical procedures and also demonstrate that RYGB results in larger postprandial concentrations of these gut hormones compared with SG (as well as controls) [6–8, 10, 11, 15, 28, 30]. Alterations in the plasma concentrations of these satiety peptides post bariatric surgery may be due to accelerated gastric emptying, caused by the surgical alterations of the stomach, leading to an exaggerated secretion of satiety hormones after SG [6], and possibly by faster nutrient contact with the distal gut due to anatomical shortcuts following RYGB [31]. In addition, the anatomical rearrangement that follows bariatric surgery, especially RYGB, seems to lead to the proliferation of GI hormone-secreting cells [32]. Postprandial GLP-1 concentrations at 1-year follow-up have been associated with greater weight loss post RYGB [33], and increased postprandial responses of both GLP-1 and PYY were shown to be sustained for up to 10 years post bariatric surgery [4, 10, 11]. As a result, GLP-1 analogs have become increasingly popular in the management of obesity by increasing satiety and reducing food intake and body weight [34]. Interestingly, with the second-generation GLP-1 receptor agonists, it is possible to obtain weight losses approaching those observed after bariatric surgery [35].

Diet-induced weight loss has previously been shown to decrease postprandial CCK concentrations in individuals with obesity but not when participants are ketotic [36]. This is in line with the present

findings showing no changes over time in postprandial CCK concentrations across groups under nutritional-induced ketosis. With RYGB, the duodenum is excluded from contact with nutrients, which could explain why an increased CCK response was not seen after this bariatric procedure. However, previous literature on this issue is inconsistent. Peterli et al. [10] reported an increase in postprandial CCK response following SG but not RYGB. On the other hand, Schmidt et al. [15] reported a marked increase in postprandial CCK, along with GLP-1 and PYY response, post RYGB.

Despite supposedly less beneficial alterations in GI hormonal concentrations with weight loss induced by diet alone, an overall reduction in ratings of postprandial hunger, as well as an overall increase in postprandial fullness, was seen in the present study. It has previously been demonstrated that the expected increase in hunger that follows weight loss is prevented and postprandial fullness sometimes increased when participants are ketotic [20, 36]. Even though ketosis has been associated with a greater weight loss 1 year post SG [37], the impact of ketosis on appetite in the context of bariatric surgery is underinvestigated [21, 37]. Moreover, SG reduced ratings of DTE in the fasting state at W11, and both fasting and postprandial DTE ratings were lower in SG and RYGB groups, respectively, compared with controls. In addition, fasting and postprandial PFC ratings decreased more so after bariatric surgery, and ratings were significantly lower compared with controls at W11. Even though the association between plasma concentrations of GI hormones and subjective appetite ratings is complex [38], the lower drive to eat seen across groups in the present study is not unexpected, given that participants experienced no changes (or even a decrease) in ghrelin concentrations as well as increases in postprandial PYY and/or GLP-1 concentrations.

Several aspects may help explain the lack of alignment between the plasma concentrations of GI hormones and appetite feelings seen in the present study. Subjective appetite ratings are likely to reflect individual factors, such as learned behaviors throughout the life-span [39]. Also, dumping syndrome is a common side effect of bariatric surgery, especially post RYGB, that is suggested to alter the pleasantness of foods, specifically foods rich in carbohydrates and fats [40]. The nature of the dietary regime and the test meal used might also play a role. Although the test meal was standardized for all participants on both assessment days, the meal contained twice the number of calories compared with each of the food packs participants consumed during the 10-week intervention period. Moreover, it is debatable to what degree subjective hunger ratings can reflect actual physiological needs. For example, although hunger ratings in the fasting state are most likely a reflection of energy depletion, hunger ratings in the fed state may also be impacted by the hedonic properties of food [41]. In light of this, our group recently showed, in these same participants, an overall reduction in hedonic hunger (measured postprandially) after both diet-induced weight loss and bariatric surgery [42]. Emerging evidence also has shown that GI hormones also act in mesolimbic pathways [43], and as such, GI hormones might play a role both in homeostatic and hedonic appetite control. In our previous analysis and compared with controls, additional favorable changes in food reward (measured both pre- and postprandially) were seen both after SG and RYGB [42], and this might reflect the present findings of favorable DTE and PFC ratings post bariatric surgery.

This study has several strengths. First, weight loss, diet composition, and ketosis level were similar across groups, allowing for the identification of the impact of SG and RYGB alone on the outcome variables. Second, sex distribution, age, baseline anthropometric variables, and PA levels were similar in all groups and therefore unlikely to have affected the variables of interest. Finally, the significance level was adjusted for multicomparisons, using Bonferroni adjustment. However, this study also suffers from some limitations. First, with this study design, we cannot establish a cause–effect relationship. Second, we could not ensure that pre- and postintervention measurements were taken in the same phase of menstrual cycle, as the intervention period was 10 weeks. This is important, as phase of menstrual cycle is known to impact on appetite [44]. However, the distribution was likely to occur at random, so there is no strong indication that this constitutes a major issue in our analysis. Third, although this study obtained enough power to detect significant differences among groups for the main outcome variable (GLP-1 AUC), we cannot rule out the possibility that the study was underpowered to detect true differences in the other variables. Fourth, even though the standardization of the diet and test meal is a strength, we cannot rule out that some of the differences found among groups, especially bariatric groups versus controls, is due to transitory changes in postoperative physiology, including fluid shifts and changes in absorption and metabolism. Also, because of the low-glycemic-index nature of the test meal, its macronutrient composition was not in line with nutritional guidelines. Fifth, a Milliplex kit was used to analyze AG and total PYY, which is expected to result in less accurate measures than specific assays for each hormone. Last, but not least, stress is a potential mediator of appetite and eating behavior [45]. Given that this study was carried out under unusual circumstances (COVID-19 pandemic), stress could have had some influence on both GI hormone concentrations and subjective appetite measures.

CONCLUSION

Changes in GI hormones, which are involved in homeostatic appetite regulation, following RYGB and SG seem to be more favorable compared with when weight loss is induced by dietary restriction alone. However, weight loss, independently of modality, seems to be associated with an overall appetite reduction. This might reflect the fact that the magnitude of weight loss and the level of nutritional-induced ketosis, as well as the dietary intervention, were similar across groups. Larger studies with a longer duration are needed to determine whether these initial changes in GI hormone concentration and subjective appetite ratings modulate long-term weight loss outcomes after both diet and bariatric surgery.

AUTHOR CONTRIBUTIONS

Catia Martins and Marthe Isaksen Aukan formulated the research questions and designed the study. Marthe Isaksen Aukan, Silje

Skårvold, and Ingrid Øfsti Brandsæter carried out the study. Jens Frederik Rehfeld and Jens Juul Holst measured CCK and GLP-1 concentrations, respectively. Marthe Isaksen Aukan analyzed the data. All authors were involved in the writing of the manuscript.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

CLINICAL TRIALS REGISTRATION

Clinicaltrials.gov identifier NCT04051190.

DATA AVAILABILITY STATEMENT

Data described in the manuscript will be made available upon request pending.

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Paper IV

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ORIGINAL ARTICLE

Clinical Trials and Investigations

Changes in hedonic hunger and food reward after a similar weight loss induced by a very low-energy diet or bariatric surgery

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Abstract

Objective: The aim of this study was to compare changes in hedonic hunger and food reward in individuals with severe obesity achieving 10% to 15% weight loss with a very low-energy diet (VLED) alone or VLED and bariatric surgery.

Methods: Patients scheduled for sleeve gastrectomy (SG) or Roux-en-Y gastric bypass (RYGB) initiated a VLED 2 weeks prior to surgery and continued the diet for 8 weeks postoperatively. BMI-matched controls underwent a VLED for 10 weeks. Hedonic hunger was assessed with the Power of Food Scale, and food reward with the Leeds Food Preference Questionnaire, pre and post intervention.

Results: A total of 44 participants completed the study: 15 SG, 14 RYGB, and 15 controls (61%, 79% and 69% females, respectively; BMI: 40.5 ± 0.5 kg/m^2; age: 43.9 ± 1.4 years). Average weight loss was 18.3 ± 0.6 kg (16%), comprising 13.5 ± 0.5 kg fat mass, with no significant differences between groups. Similar reductions in hedonic hunger were observed in all groups. Overall, food reward was similarly reduced in SG and RYGB groups, whereas controls showed little or no change.

Conclusions: Independent of modality, weight loss seems to reduce hedonic hunger, but bariatric surgery leads to several additional favorable changes in food reward and preferences.

INTRODUCTION

Lifestyle treatments of obesity have had limited success. Even though most individuals with obesity can achieve a clinically significant weight loss (5%–10% of initial body weight), the majority experience weight regain and some relapse to or above baseline weight [1]. To date, bariatric surgery is the most effective treatment, leading to sustained lower body weight in the long term, which is not yet achievable with conservative approaches [2]. The mechanisms behind the long-term weight loss success after bariatric surgery are still not clearly understood, but beneficial changes in appetite behavior are seen [3].

Appetite behavior is highly complex, and the brain plays a key role controlling energy intake. Homeostatic brain regions, mainly the

hypothalamus, receive information from the periphery regarding both acute and chronic nutritional status and adjust appetite accordingly in order to maintain homeostasis [4]. However, advances in research have led to the integration of hedonic brain regions in appetite control [5]. Hedonic hunger refers to appetite for palatable foods and is driven by external sensory information, feelings, and emotions [6]. Food reward can be characterized by "liking" (pleasurable response to food) and "wanting" (motivation to eat palatable foods that provided pleasure in the past) [7]. Exposure to palatable foods trigger dopamine release and is associated with wanting for food [8]. Thus, the hedonic system can operate independently of homeostatic signals when food is highly palatable and easily available [9]. Moreover, individuals with obesity have shown greater food reinforcement [10] and hedonic hunger [11], stronger liking for sweetness [12], and higher wanting for food [13], compared with individuals without obesity. Higher sensitivity to food reward and food reinforcement has also been associated with greater energy intake [14]. This might compromise adherence to dietary interventions.

Even though an increased drive to eat is commonly seen following diet-induced weight loss [15,16], food reward has been described to decrease following different lifestyle interventions [17]. Following sleeve gastrectomy (SG) and Roux-en-Y gastric bypass (RYGB), patients experience decreases in measures of hedonic eating, lower preference for energy dense foods [11,18–24], development of an aversion to sweetness [25,26], lower frequency of food cravings, and decreased influence of emotions and external food cues on food intake [22,25]. However, knowledge on the effect of dietary restriction alone on hedonic hunger is limited, and no studies have compared diet alone with bariatric surgery. Moreover, it remains to be elucidated whether the beneficial effects of bariatric surgery on hedonic hunger and food reward are mediated by the bariatric procedure, weight loss, the inherent changes in the diet, or a combination of those.

Therefore, we aimed to compare how a similar weight loss achieved by a very low-energy diet (VLED) alone or VLED in combination with one of the two most performed bariatric procedures (SG and RYGB) impacts hedonic hunger and food reward in individuals with severe obesity.

Study Importance

What is already known?

- Hedonic appetite can easily override homeostatic signals.
- Individuals with obesity have a greater hedonic appetite compared with individuals without obesity.
- Following bariatric surgery, patients experience decreased hedonic eating behavior and improved appetite control, but the effect of weight loss induced by dietary restriction alone is unclear.

What does this study add?

- Hedonic hunger decreases regardless of weight loss modality when weight loss is matched.
- However, bariatric surgery is superior compared with dietary restriction alone on the effect of food reward.

How might these results change the direction of research or the focus of clinical practice?

- Comprehensive behavioral interventions might be needed to control hedonic hunger and food reward after weight loss with dietary restriction alone.
- Future research should investigate potential relationships between hedonic hunger and food reward and long-term weight loss maintenance after both lifestyle treatment and bariatric surgery.

METHODS

The effect of DIet-induced weight loss versus Sleeve gastrectomy and Gastric bypass on APpetite (DISGAP) study is a three-armed prospective nonrandomized controlled trial, comparing how a similar weight loss induced by diet or bariatric surgery impacts homeostatic and hedonic appetite markers and gut microbiota, both in the short and long term. The present paper reports the initial changes in hedonic hunger and food reward after a similar weight loss induced by diet alone, diet plus SG, or diet + RYGB. An outline of the present study can be seen in Figure 1.

Adults with severe obesity scheduled for SG or RYGB at two local hospitals in the Central Norway Health Region were recruited. The control group (VLED intervention alone) was composed of patients on a waiting list for bariatric surgery and patients who declined or were not eligible for surgery, as well as individuals from the local community (advertised at St. Olav's and the Norwegian University of Science and Technology [NTNU] intranet). The control group was matched for preoperative body mass index (BMI), age, and sex of the surgical groups. Recruitment and data collection took place between September 2019 and January 2022. A flowchart of the study can be seen in Figure 2. The study was approved by the regional ethics committee (REK 2019/252), registered in ClinicalTrials.gov (NCT04051190), and conducted according to the guidelines laid down in the Declaration of Helsinki. All participants provided written informed consent before enrollment in the study.

Participants had to be weight stable (self-reported) (< 2-kg body weight change over the last 3 months) and not enrolled in any other obesity treatment or behavioral program. Patients who had previously undergone bariatric surgery, who used medication known to affect energy metabolism or appetite, and who had a current cancer diagnosis or substance abuse, as well as those presenting with a psychiatric diagnosis that precluded bariatric surgery (such as eating disorders), were excluded from the study.

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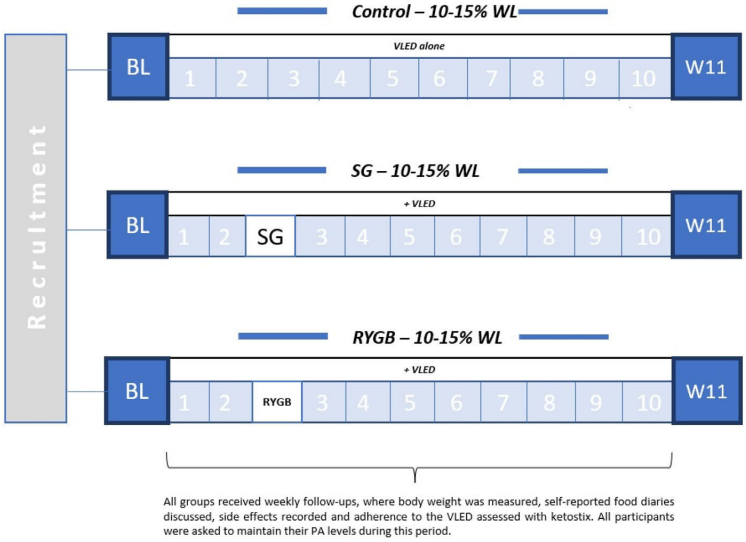

FIGURE 1 Study design. BL, baseline; PA, physical activity; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy; VLED, very low-energy diet; W11, week 11; WL, weight loss.

Bariatric surgeries were performed at St. Olav University Hospital in Trondheim and the Namsos Hospital, both in Norway, using standard laparoscopic procedures. The SG involved dividing the gastrocolic ligament, initiating the gastrectomy 4 cm proximal to the pylorus along the greater curvature, and creating the sleeve along the lesser curvature using a 36 French Bougie. The RYGB procedure involved creating a small (∼20–30 mL) proximal gastric pouch and a stapled gastrojejunostomy. A 75– to 150-cm Roux-Y limb was constructed by transecting the jejunum 60 to 100 cm distal to the ligament of Treitz and performing a stapled jejunostomy at this site.

Participants from all groups were asked to follow a formula-based VLED using a variety of commercial food packs (Lighter Life) composed of different soups, shakes, pasta dishes, bars, and porridge for 10 weeks under the guidance of a registered dietitian. The average daily nutritional composition of the VLED used in this study was 750 kcal; energy percentages (E%) were 26 E% fat, 36 E% carbohydrates, 5 E% fiber, and 33 E% protein. In addition, participants were encouraged to consume a maximum of 100 g of low-starch vegetables per day, as well as 2.5 L of water daily. Alcohol consumption was not allowed during the 10-week intervention. Noncaloric beverages were allowed, and a maximum of 500 mL of low-energy drinks (<3 kcal/100 mL) and four sugar−/calorie-free chewing gum, artificial sweeteners, or mints per day. Patients scheduled for bariatric surgery initiated the diet 2 weeks prior to surgery as standard procedure and continued the VLED for another 8 weeks postoperatively. The first weeks after surgery, SG and RYGB patients were instructed to consume only fluids (food packs in liquid form as soups and shakes) and then gradually increase the texture of the commercial food packs provided. All participants were asked to fill out a self-reported food diary. At weekly follow-ups, food diaries were discussed, side effects recorded, body weight monitored, and ketone bodies (acetoacetate) measured in urine with ketostix (Bayer Ketostix 2880 Urine Reagent Test Strip, Ascensia Diabetes Care), as a measure of dietary compliance. The plasma concentration of beta-hydroxybutyric acid (ßHB), another ketone body, was also measured pre and post intervention as an additional measure of compliance (MAK134, Sigma-Aldrich). Because of COVID-19 restrictions, most participants were followed up by phone.

Participants were asked to maintain their physical activity (PA) level during the 10-week intervention. Compliance with this recommendation was assessed by asking participants to wear SenseWear armbands (BodyMedia) for 7 days prior to baseline (BL) and at week 10. The data were considered valid if participants wore the device for ≥ 4 days, including at least one weekend day, for more than 95% (22.8 h/d) of the time [27]. The following variables were analyzed: average daily steps, PA level, metabolic equivalents (METs), and total PA duration.

After an overnight fast (at least 10 hours) at BL and week 11 (W11), air-displacement plethysmography (BodPod, COSMED) was used to measure body weight, fat mass, and fat-free mass. The test meal consisted of a 200-mL commercial low-glycemic drink (Diben Drink, Fresenius Kabi Norge AS) (300 kcal, 42 E% fat, 35 E% carbohydrates, 3 E% fiber, and 20 E% protein), which was consumed slowly over a 15-minute period, to avoid dumping syndrome.

Hedonic hunger was assessed by the Power of Food Scale (PFS) [28]. This questionnaire consists of 15 questions, comprising an aggregated score and divided into three subcategories: "food available," readily attainable food, but not physically present; "food present," the food both available and physically present, but not tasted; and "food tasted," food physically present and tasted or about to be tasted. A

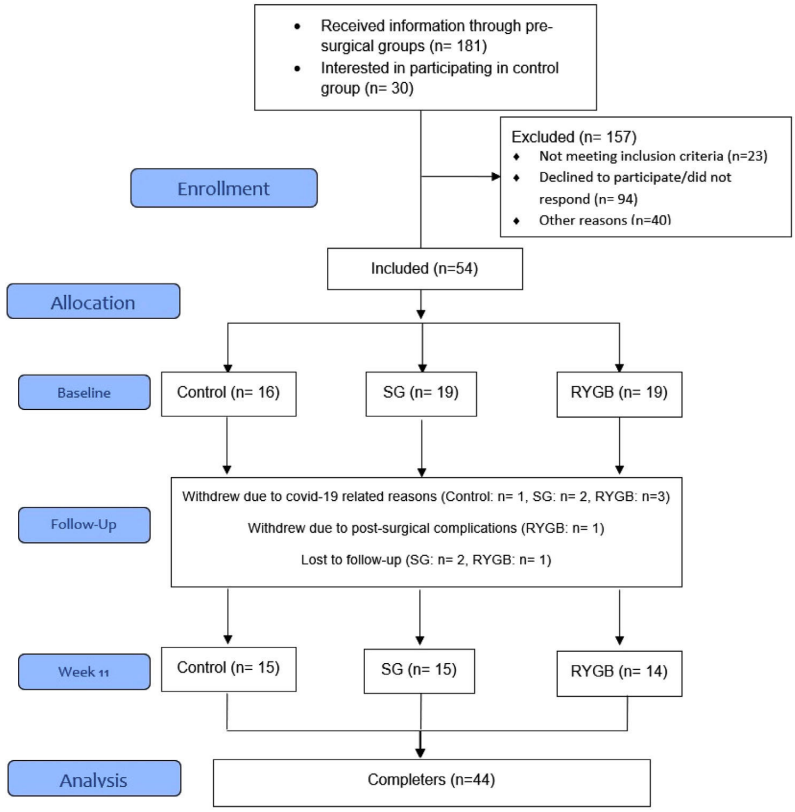

FIGURE 2 Flow diagram of the study. RYGB, Roux-en-Y Gastric bypass; SG, sleeve gastrectomy.

TABLE 1 Mean characteristics of the participants at baseline and week 11

	Baseline			Week 11		
	Control	SG	RYGB	Control	SG	RYGB
n	15	15	14			
Age	45.5 ± 2.6	39.6 ± 2.4	46.7 ± 2.5			
Females, %	69	79	61			
Body weight (kg)	115.4 ± 3.9^{a}	117.6 ± 3.6^{b}	120.4 ± 3.7^{c}	98.1 ± 3.9^{a}	98.6 ± 3.6^{b}	101.6 ± 3.7^{c}
Weight loss (kg)				−17.3 ± 1.0	−19.0 ± 1.0	−18.8 ± 1.0
BMI (kg/m^2)	39.7 ± 0.9^{a}	40.2 ± 0.7^{b}	41.6 ± 1.1^{c}	33.7 ± 0.9^{a}	34.1 ± 0.8^{b}	35.0 ± 1.3^{c}
FM (%)	46.6 ± 1.5^{a}	47.9 ± 1.4^{b}	47.0 ± 1.4^{c}	41.0 ± 1.5^{a}	43.0 ± 1.4^{b}	42.7 ± 1.4^{c}
FM (kg)	53.7 ± 2.6^{a}	56.5 ± 2.4^{b}	56.5 ± 2.4^{c}	40.4 ± 2.6^{a}	42.4 ± 2.4^{b}	43.6 ± 2.4^{c}
FFM (%)	53.0 ± 1.5^{a}	52.1 ± 1.4^{b}	53.0 ± 1.4^{c}	59.1 ± 1.5^{a}	57.0 ± 1.4^{b}	57.3 ± 1.4^{c}
FFM (kg)	61.7 ± 2.6^{a}	61.1 ± 2.4^{b}	63.8 ± 2.4^{c}	57.8 ± 2.5^{a}	56.2 ± 2.4^{b}	58.1 ± 2.4^{c}

Note: Data presented as estimated marginal mean ± SEM. Mean values sharing the same superscript letter denote significant changes over time ($p < 0.001$ for all).
Abbreviations: FFM, fat-free mass; FM, fat mass; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Likert scale with five levels was used (1 = "I don't agree at all" to 5 = "I strongly agree"). The higher the PFS score, the higher the hedonic hunger. The questionnaire was handed out 60 minutes after initiating the breakfast.

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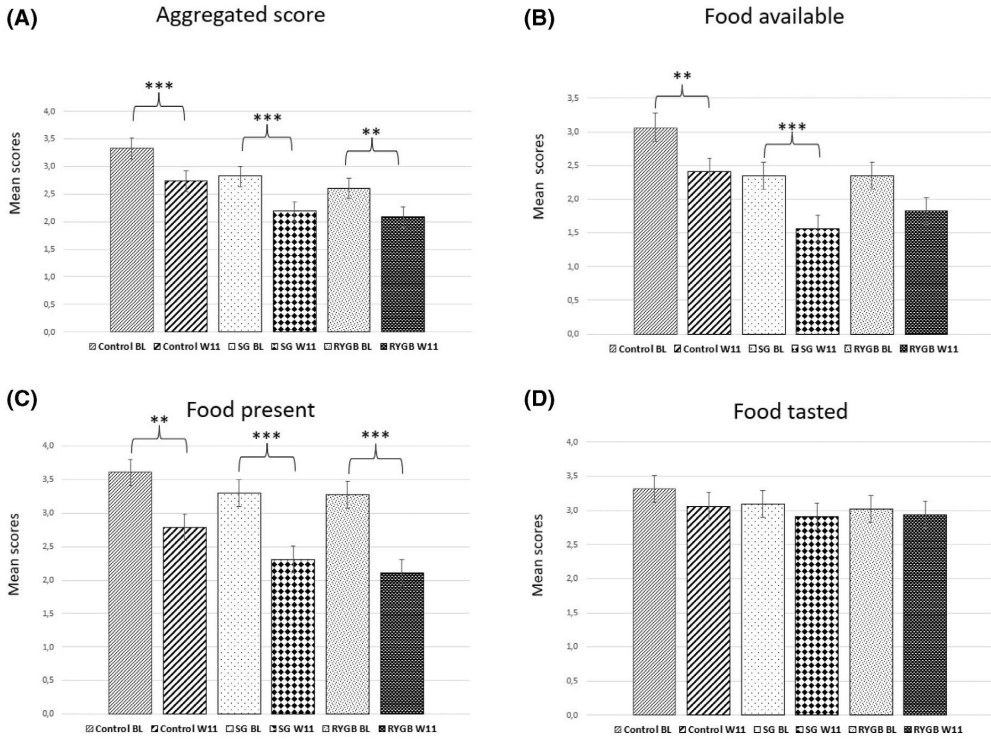

FIGURE 3 Power of Food Scale scores. Data presented as mean ± SE. Asterisks denote significant differences over time (***$p < 0.001$, **$p < 0.01$) BL, baseline; RYGB, Roux-en Y gastric bypass; SG, sleeve gastrectomy; W11, week 11.

Food preferences and reward were assessed using the Leeds Food Preference Questionnaire (LFPQ) [29]. The LFPQ is a computerized behavioral task that provides measures of "explicit liking" and "explicit and implicit wanting" using images of food. The food pictures in the LFPQ are divided into four categories: high-fat and sweet (HFSW), low-fat and sweet (LFSW), high-fat and savory (HFSA), and low-fat and savory (LFSA). For this study, participants were presented with pictures of foods common in the Norwegian diet. Individual food images were randomly presented to the participants who were required to rate them according to "How pleasant would it be to taste some of this food now?" (explicit liking) and "How much do you want some of this food now?" (explicit wanting) with the scale ranging from "not at all" to "extremely." Next, a forced choice task presented participants with a series of food image pairs and the instruction "Which food do you most want to eat now?" A score was calculated according to how often a food category was chosen over another category, how often it was not selected, and the reaction time of the trial (implicit wanting). The LFPQ was performed in the fasted state and immediately after breakfast.

This paper reports a secondary analysis of the main study powered to detect differences in postprandial plasma concentrations of glucagon-like peptide-1 (GLP-1) between groups. Power calculation was performed assuming that bariatric surgery would induce a postprandial increase in GLP-1 that was two (SG) and three times (RYGB) larger compared with diet-induced weight loss. For a power of 80% and 0.05 significance level and assuming an SD of 1000 min*pmol/L and a within group variance of 640,000 min*pmol/L [30], 45 participants would be required (15 in each group).

Statistical analysis was carried out using SPSS Statistics version 27 (IBM Corp.). Data are presented as mean ± SEM, unless otherwise stated. Because of the large number of tests, the significance level was reduced to $p < 0.01$ to avoid type I errors. Residuals were checked and they did not deviate significantly from normality. All data were analyzed using a linear mixed-effects model with restricted maximum likelihood estimation, including fixed effects for group, time, and their interaction. Bonferroni correction was used for post hoc pairwise comparisons.

RESULTS

Table 1 shows anthropometrics at BL and W11. Forty-four participants completed BL and W11 assessments ($n = 15$ VLED, $n = 15$ SG, and $n = 14$ RYGB). There were no significant differences in any anthropometric variables between groups at either time point. Overall, participants lost 18.3 ± 0.6 kg (∼16%) from BL to W11. BMI

TABLE 2 Mean scores from the Leeds Food Preference Questionnaire

		Baseline			Week 11		
		Control	SG	RYGB	Control	SG	RYGB
Explicit liking							
Fasting	HFSA	48.7 ± 5.7	39.4 ± 5.3	33.8 ± 5.4	43.9 ± 5.2	25.9 ± 5.2	28.1 ± 5.4
	LFSA	52.9 ± 5.6	43.6 ± 5.1	43.5 ± 5.3	57.9 ± 5.2	36.1 ± 5.2	41.4 ± 5.4
	HFSW	43.6 ± 5.8*	34.1 ± 5.3[b]	17.4 ± 5.5*	32.9 ± 4.3	16.8 ± 4.3[b]	12.7 ± 4.3
	LFSW	52.3 ± 5.5	47.4 ± 5.1	47.5 ± 5.2	51.8 ± 4.8	39.9 ± 4.8	45.0 ± 4.9
Postprandial	HFSA	43.5 ± 5.7	40.1 ± 5.3[b]	23.4 ± 5.4[c]	30.4 ± 5.2*	14.8 ± 5.2[b]	2.3 ± 5.4[c*]
	LFSA	43.5 ± 5.6	31.5 ± 5.1	28.5 ± 5.3[c]	35.3 ± 5.2*	16.2 ± 5.2	5.7 ± 5.4[c*]
	HFSW	35.9 ± 5.8	32.5 ± 5.3[b]	17.6 ± 5.5[c]	21.3 ± 4.3	7.7 ± 4.3[b]	1.8 ± 4.3[c]
	LFSW	48.1 ± 5.5	43.8 ± 5.1[b]	38.2 ± 5.2[c]	37.8 ± 4.8*	22.3 ± 4.8[b]	7.2 ± 4.9[c*]
Implicit wanting							
Fasting	HFSA	12.1 ± 5.8	1.0 ± 5.3	−0.5 ± 5.4	5.8 ± 4.8	1.2 ± 4.8	−1.5 ± 4.9
	LFSA	−5.1 ± 7.9[a]	−5.5 ± 7.3	4.9 ± 7.5	16.5 ± 7.3[a]	0.4 ± 7.2	15.7 ± 6.9
	HFSW	−11.0 ± 6.9[a]	−11.4 ± 6.4	−23.9 ± 6.5	−34.0 ± 5.6[a]	−24.5 ± 5.6	−38.6 ± 5.8
	LFSW	4.1 ± 4.5	15.9 ± 4.1	19.4 ± 4.2	11.7 ± 4.6	23.1 ± 4.6	24.4 ± 4.7
Postprandial	HFSA	9.6 ± 5.8	2.5 ± 5.3	0.7 ± 5.4	2.3 ± 4.8	7.2 ± 4.8	0.2 ± 4.9
	LFSA	−9.9 ± 7.9[a]	−5.7 ± 7.3	−1.8 ± 7.5	8.2 ± 7.3[a]	−2.8 ± 7.2	6.9 ± 7.5
	HFSW	−10.8 ± 6.9[a]	−12.7 ± 6.3[b]	−24.7 ± 6.5	−28.9 ± 5.6[a]	−27.9 ± 5.6[b]	−38.8 ± 5.8
	LFSW	11.2 ± 4.5	16.0 ± 4.1	25.8 ± 4.2	18.5 ± 4.6	23.6 ± 4.6	31.8 ± 4.8
Explicit wanting							
Fasting	HFSA	49.2 ± 5.6	38.7 ± 5.1[b]	33.9 ± 5.3	44.8 ± 5.1	23.2 ± 5.1[b]	23.7 ± 5.3
	LFSA	53.5 ± 5.4	42.4 ± 4.9	42.4 ± 5.1	56.4 ± 5.4	35.5 ± 5.4	40.7 ± 5.5
	HFSW	44.6 ± 5.4*	33.4 ± 4.9[b]	17.4 ± 5.1*	32.0 ± 4.1	15.5 ± 4.1[b]	12.1 ± 4.3
	LFSW	52.9 ± 5.4	47.9 ± 4.9	45.3 ± 5.1	52.6 ± 5.0	38.8 ± 5.0	44.1 ± 5.2
Postprandial	HFSA	42.6 ± 5.6	36.1 ± 5.1[b]	22.7 ± 5.3[c]	26.4 ± 5.1*	14.3 ± 5.1[b]	2.7 ± 5.2[c*]
	LFSA	44.2 ± 5.4	30.7 ± 4.9	30.6 ± 5.1[c]	38.2 ± 5.4*[#]	16.5 ± 5.4*	5.7 ± 5.4[c#]
	HFSW	36.4 ± 5.4[a*]	28.6 ± 4.9[b]	15.5 ± 5.1[c*]	19.9 ± 4.1[a]	7.1 ± 4.1[b]	1.7 ± 4.2[c]
	LFSW	46.6 ± 5.4	40.1 ± 4.9[b]	40.0 ± 5.1[c]	35.9 ± 5.0*	22.2 ± 5.0[b]	6.5 ± 5.2[c*]

Note: Data presented as estimated marginal mean ± SEM. Averages sharing the same superscript letter denote a significant change over time ($p < 0.01$). Averages sharing the same superscript symbol denote significant differences between groups (*#, $p < 0.01$).
Abbreviations: HFSA, high-fat savory; HFSW, high-fat sweet; LFSA, low-fat savory; LFSW, low-fat sweet; RYGB, Roux-en Y gastric bypass; SG, sleeve gastrectomy.

dropped by 6.3 ± 0.8 kg/m^2, fat mass decreased by 13.5 ± 0.5 kg (24% change), and fat-free mass decreased by 4.8 ± 0.3 kg (8% change) ($p < 0.001$, for all). Participants were not ketotic at baseline (ßHB plasma concentration: 0.1 ± 0.07 mM), but all were in nutritional-induced ketosis at W11 (ßHB plasma concentration: 0.7 ± 0.07 mM), with no differences between groups. No significant differences between groups or changes over time were seen for any of the PA variables assessed (data not shown).

Hedonic hunger

Mean scores of the PFS can be seen in Figure 3A–D. At baseline, no differences were seen between groups, but there was a tendency for the control group to have a higher aggregated score compared with RYGB ($p = 0.024$). All groups experienced similar reductions in the aggregated score over time ($p = 0.001$, $p < 0.001$, and $p = 0.003$, for controls, SG, and RYGB, respectively). There was a decrease in the subcategory "food available" in controls and SG ($p = 0.003$ and $p < 0.001$, respectively) and a tendency toward a decrease in RYGB ($p = 0.013$). For the category "food present," all groups experienced similar reductions from baseline to W11 ($p = 0.002$, $p < 0.001$, and $p < 0.001$, for controls, SG and RYGB, respectively). There was an overall reduction in the category "food tasted" from baseline to W11 but this was not significant at group level.

Table 2 presents mean scores from the LFPQ.

Explicit liking

At BL, controls had greater fasting HFSW compared with RYGB ($p = 0.003$) (Table 2). SG experienced reductions in fasting for HFSW

from BL to W11 ($p = 0.004$). Overall, there was a reduction over time for postprandial liking for all food categories but not at the group level. HFSA was reduced for SG and RYGB ($p < 0.001$ for both). At W11, controls had greater postprandial liking for HFSA compared with RYGB ($p = 0.001$). Postprandial LFSA decreased only for RYGB ($p = 0.001$), and scores were lower compared with controls ($p < 0.001$). Postprandial HFSW and LFSW were reduced for SG and RYGB ($p = 0.001$ and $p < 0.001$, respectively). At W11, RYGB had lower liking for LFSW compared with controls ($p < 0.001$).

Implicit wanting

For LFSA, there was an overall increase, but this was significant only for the control group ($p < 0.001$, both fasting and postprandially). Overall, implicit wanting for HFSW was reduced at W11 but this was significant only for controls ($p < 0.001$, both the fasted and fed state) and postprandially in SG ($p = 0.001$).

Explicit wanting

Controls had greater explicit wanting for HFSW in the fasting state compared with RYGB at BL ($p = 0.001$). At W11, SG showed reduced explicit wanting for HFSA and HFSW in the fasted state ($p = 0.008$ and $p = 0.001$, respectively). At BL, controls had higher postprandial explicit wanting for HFSW ($p = 0.002$) and for LFSA and LFSW at W11 compared with RYGB ($p = 0.001$ and $p = 0.004$, respectively). At W11, SG showed a postprandial reduction in explicit wanting for HFSA ($p = 0.001$), HFSW ($p = 0.001$), and LFSW ($p = 0.007$) and RYGB for HFSA ($p = 0.001$), LFSA ($p < 0.001$), HFSW ($p = 0.01$), and LFSW ($p < 0.001$), whereas the control group showed reductions only for HFSW ($p = 0.002$).

DISCUSSION

The aim of this study was to compare how a similar weight loss achieved by a VLED alone or VLED in combination with the two most common bariatric procedures (SG and RYGB) impacted hedonic hunger and food reward in individuals with severe obesity. Baseline characteristics and changes in body weight and composition were matched among groups and paralleled by similar reductions in hedonic hunger. However, weight loss induced by SG and RYGB yielded several additional and favorable changes in food reward.

Few studies have investigated the impact of diet-induced weight loss on hedonic hunger in individuals with obesity. Cameron and colleagues [31] reported that a 5% weight loss induced by a low-energy diet did not change the reinforcing value of palatable snacks, but food "liking" increased by 10%, independently of the magnitude of weight loss. However, this was a small study ($n = 15$), and liking was measured as a global evaluation of a meal. A much larger study ($n = 111$) by O'Neil et al. [32] found that a 4% weight loss induced by a 12-week commercial weight loss program, consisting of caloric restriction, encouragement of physical activity, and regular meetings, led to decreases in hedonic hunger. Similarly, a study by Ross et al. [33] reported that a 3-month behavioral weight loss program resulted in reduced food reward sensitivity and impulsivity after an average 6-kg (7%) weight loss. The two latter studies measured hedonic hunger with the PFS, and as such, results are similar and comparable with ours.

Ross et al. [33] reported that a greater food reward sensitivity (from PFS) was associated with greater body weight but not with weight loss. Contrarily, O'Neil and colleagues [32] showed that a decrease in the aggregated PFS score was associated with a greater percentage of weight loss and with improvements in reported weight control behaviors determined by the Eating Behavior Inventory.

To our knowledge, no studies have addressed the impact of SG on hedonic hunger. But several studies [11,18,34,35], including the present one, suggest that bariatric surgery in general leads to reductions in hedonic hunger. Moreover, significantly reduced hedonic hunger post RYGB was shown to be parallel with more favorable changes in dietary habits, such as increased intake of protein-rich foods and vegetables, as well as reduced consumption of sugary foods, snacks, and beverages [35]. Patients with severe obesity were shown to have higher hedonic hunger (aggregated score) compared with controls without obesity [11]. Furthermore, this difference was not seen between controls and patients who had already undergone RYGB ≥1 year ago [11]. Similarly, another study showed that hedonic hunger ("food available" and "food present") was not different in patients who had undergone gastric banding 7 years ago (with BMI between 25 and 52 kg/m^2) compared with individuals with a normal weight, and their scores were lower compared with individuals with severe obesity [18]. These two last studies suggest a "normalization" of hedonic hunger post bariatric surgery.

An overall improvement in food reward after weight loss was seen in the present analysis, but the results are not completely in line with previous findings. A 5% weight loss, induced by continuous or intermittent energy restriction, was reported to improve dietary restraint, craving control, and susceptibility to hunger and binge eating in women with overweight or obesity, despite no changes in liking and wanting for high-fat foods relative to low-fat foods, as measured by the LFPQ [36]. However, a recent study from the same group comparing absolute changes for each food category showed that weight loss decreased liking across all foods [37]. In the present study, only the surgical groups experienced reductions in both liking and wanting for all food categories, whereas the control group showed an increase in wanting for LFSA and a decrease in wanting for HFSW. Even though the changes in controls were overall favorable, food reward was still greater in several food categories post weight loss compared with the surgical groups, especially RYGB. Several aspects may account for the inconsistencies seen among the previously discussed studies. In the present study, weight loss (%) was larger and energy intake significantly lower (almost half) compared with the Oustric et al. study [36].

Martin and colleagues showed in a long-term follow-up study that a low-carbohydrate diet decreased preferences for high-carbohydrate/sugary foods, whereas a low-fat diet decreased cravings for

high-fat foods, despite no differences in weight loss at 24 months between diets [38]. In this study, participants from both groups received a comprehensive treatment program to foster daily adherence [38]. This is in contrast to the study by Oustric et al. [37], in which no contact was made until the 1-year follow-up, wherein participants regained half of the weight initially lost, and food reward was no longer different from baseline. Martin et al. (2011) also reported that greater weight loss was associated with larger reductions in cravings for sweets and high-fat foods, at 3 and 24 months, respectively, but in line with the present analysis, changes in food preferences did not correlate with weight loss [38].

Both SG [20,21] and RYGB [21] patients have shown positive alterations in food reward and appetite behaviors post bariatric surgery. Comparing the two procedures, one study [21] showed that SG led to more favorable changes, with decreased preference for high-sugar foods, whereas RYGB did not. Contrarily, we found RYGB to induce additional changes in liking and wanting for the different food categories but with no overall differences between the two. In line with this, a similar weight loss induced by either SG or RYGB was shown to lead to comparable changes on key factors involved in the regulation of eating behavior and hedonic components, such as frequency of food cravings, influence of emotions and external food cues, and favorable shifts in the pleasantness of sweets [25]. Dumping syndrome is a common side effect after bariatric surgery, especially post RYGB, and it was suggested to alter the pleasantness of foods, especially carbohydrate- and fat-rich foods [39]. This might explain some of the differences seen between bariatric surgery and diet-induced weight loss in the present and previously discussed studies. Moreover, individuals with obesity were reported to have decreased dopamine receptor availability [40], but bariatric surgery seemed to reverse this [41]. This could also serve as a possible mechanism for the additional improvements in food reward seen after bariatric surgery, compared with the control group.

Together with the current literature, the present findings have clinical implications for weight management. Overall, bariatric surgery seems to induce favorable (and sustained) changes in hedonic hunger, food reward, and weight control behavior toward a "normalization." To some extent, this appears to be possible to manipulate, which is especially important for those receiving conservative treatment, as comprehensive behavioral interventions seem to play a key role in ameliorating hedonic hunger and food reward after weight loss with dietary restriction. Moreover, adding pharmacotherapy, namely the recently approved GLP-1 receptor agonist [42], to lifestyle interventions might provide benefits on appetite behaviors and body weight, without the risks associated with bariatric surgery.

This study has several strengths. First, weight loss and diet were matched across groups, as well as sex distribution, age, and anthropometric variables, allowing for identification of the impact of SG and RYGB alone. Second, the significance level was adjusted for multicomparisons (Bonferroni) and for the large number of variables tested. This study also has some limitations. First, as the intervention period was 10 weeks, we could not ensure that measurements were taken in the same phase of the menstrual cycle, which is known to have an impact on appetite [43]. However, the distribution was likely to occur at random, so there is no strong indication that this constitutes an issue. Secondly, this was a secondary analysis of a trial powered to detect differences in postprandial GLP-1 secretion between groups, and therefore, this study might be underpowered to look at hedonic appetite and food reward. Additionally, the small number of participants in each group might have increased the possibility of type II error and prevented the detection of true differences among groups. Third, even though validated questionnaires were used to measure hedonic eating and food reward, only one instrument was used to measure each construct, and other instruments measuring different constructs, which might be differently impacted by bariatric surgery, might provide different results. Fourth, the strict significance level imposed might have affected the results and prevented the identification of significant findings. Fifth, even though the standardization of the diet across groups is a strength, we cannot rule out that some of the differences found among groups, especially bariatric groups versus controls, is due to transitory changes in postoperative physiology, including fluid shifts and changes in absorption and metabolism. Finally, stress is a potential mediator for appetite and food cravings [44], and given that this study was carried out under unusual circumstances (COVID-19 pandemic), stress could have affected our outcome variables.

CONCLUSION

Initial weight loss seems to reduce hedonic hunger, independent of modality. However, SG and RYGB led to several additional favorable changes in food reward. These preliminary findings need to be confirmed, and future research should also investigate the long-term impact of both diet-induced weight loss and bariatric surgery on hedonic hunger and food reward and how initial changes in these constructs might modulate long-term weight loss outcomes.O

AUTHOR CONTRIBUTION

CM and MIA formulated the research questions and designed the study. MIA, IØB, and SS carried out the study. GF analyzed data from the LFPQ. MIA analyzed the data. All authors were involved in the writing of the manuscript.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

CLINICAL TRIAL REGISTRATION

ClinicalTrials.gov identifier NCT04051190.

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Appendix I

Supplementary file

Differences in gastrointestinal hormones and appetite ratings between individuals with and without obesity – A systematic review and meta-analysis

Authors: Marthe Isaksen Aukan [1,2], Silvia Coutinho [1,3], Sindre Andre Pedersen [4], Melanie Rae Simpson[5,6] and Catia Martins [1,2,7]

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Contents

Search strategy:

MEDLINE

Ovid MEDLINE(R) ALL <1946 to September 01, 2021>

#	Searches
1	exp Obesity/
2	exp Obesity, Morbid/
3	exp Obesity, Abdominal/
4	exp Overweight/
5	adipos*.ti,ab,kw.
6	obes*.ti,ab,kw.
7	overweight*.ti,ab,kw.
8	over-weight*.ti,ab,kw.
9	((high* or unhealthy) adj3 (body-mass-ind* or BMI?)).ti,ab,kw.
10	or/1-9 [Combined thesaurus and text words for overweight/obesity concept]
11	exp Ideal Body Weight/
12	normal-weight*.ti,ab,kw.
13	normal-body-weight*.ti,ab,kw.
14	normal-body-mass*.ti,ab,kw.
15	healthy-weight*.ti,ab,kw.
16	healthy-body-weight*.ti,ab,kw.
17	healthy-body-mass*.ti,ab,kw.
18	non-obese.ti,ab,kw.
19	nonobese.ti,ab,kw.
20	non-overweight*.ti,ab,kw.
21	slim.ti,ab,kw.
22	lean.ti,ab,kw.
23	((normal or control? or healthy or low*) adj3 (overweight or over-weight or obese* or men or women or subject* or person* or body-mass-ind* or BMI? or volunteer*)).ti,ab,kw.
24	or/11-23 [Combined thesaurus and text words for healthy weight concept]
25	exp Hunger/
26	exp Appetite/
27	exp Appetite Regulation/
28	exp Satiation/
29	appetite?.ti,ab,kw.
30	apetite?.ti,ab,kw.
31	hunger.ti,ab,kw.

32 fullness.ti,ab,kw.
33 satiation.ti,ab,kw.
34 satiety.ti,ab,kw.
35 prospective-food-consumption*.ti,ab,kw.
36 ((desire or craving*) adj3 (eat* or food or feed*)).ti,ab,kw.
37 exp Ghrelin/
38 ghrelin.ti,ab,kw.
39 GHRL.ti,ab,kw.
40 appetite-regulating-hormone.ti,ab,kw.
41 exp Cholecystokinin/
42 cholecystokinin.ti,ab,kw.
43 CCK.ti,ab,kw.
44 uropancreozymin.ti,ab,kw.
45 pancreozymin.ti,ab,kw.
46 exp Peptide-YY/
47 peptide-YY.ti,ab,kw.
48 PYY.ti,ab,kw.
49 PYY3-36.ti,ab,kw.
50 peptide-tyrosine-tyrosine.ti,ab,kw.
51 exp Glucagon-Like Peptide 1/
52 glucagon-like-peptide-1.ti,ab,kw.
53 GLP-1.ti,ab,kw.
54 GLP1.ti,ab,kw.
55 or/25-54 [Combined thesaurus and text words for appetite/appetite markers concept]
56 and/10,24,55
57 56 not (comment or editorial or news or newspaper article).pt. [Excluded publication types]
58 (Animals/ or Models, Animal/ or Disease Models, Animal/) not Humans/
59 ((animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rat or rats or rodent* or sheep* or veterinar*) not (human* or patient*)).ti,kf,jw.
60 57 not (58 or 59) [Animal-only studies excluded]
61 (exp infant/ or exp child/ or exp adolescent/) not exp adult/
62 ((child* or stepchild* or step-child* or kid or kids or girl or girls or boy or boys or teen* or youth* or youngster* or adolescent* or adolescence or preschool* or pre-school* or kindergarten* or school* or juvenile* or minors or p?ediatric* or PICU) not adult*).ti,ab.
63 60 not (61 or 62) [Non-adults only studies excluded]
64 limit 63 to (english or norwegian or swedish or danish or portuguese or french or spanish) [Limiting results to English, Norwegian, Swedish, Danish, Portugese, French or Spanish language]

Embase

Embase <1974 to 2021 September 01>

#	Searches
1	exp Obesity/
2	exp Morbid Obesity/
3	exp Abdominal Obesity/
4	exp Obesity Management/
5	exp Maternal Obesity/
6	adipos*.ti,ab,kw.
7	obes*.ti,ab,kw.
8	overweight*.ti,ab,kw.
9	over-weight*.ti,ab,kw.
10	((high* or unhealthy) adj3 (body-mass-ind* or BMI?)).ti,ab,kw.
11	or/1-10 [Combined thesaurus and text words for overweight/obesity concept]
12	exp Ideal Body Weight/
13	normal-weight*.ti,ab,kw.
14	normal-body-weight*.ti,ab,kw.
15	normal-body-mass*.ti,ab,kw.
16	healthy-weight*.ti,ab,kw.
17	healthy-body-weight*.ti,ab,kw.
18	healthy-body-mass*.ti,ab,kw.
19	non-obese.ti,ab,kw.
20	nonobese.ti,ab,kw.
21	non-overweight*.ti,ab,kw.
22	slim.ti,ab,kw.
23	lean.ti,ab,kw.
24	((normal or control? or healthy or low*) adj3 (overweight or over-weight or obese* or men or women or subject* or person* or body-mass-ind* or BMI? or volunteer*)).ti,ab,kw.
25	or/12-24
26	or/12-24 [Combined thesaurus and text words for healthy weight concept]
27	exp Hunger/
28	exp Appetite/
29	exp Decreased Appetite/
30	exp "Loss Of Appetite"/
31	exp Appetite Disorder/
32	exp Appetite Stimulant/
33	exp Increased Appetite/
34	exp Satiety/
35	appetite?.ti,ab,kw.

36 apetite?.ti,ab,kw.
37 hunger.ti,ab,kw.
38 fullness.ti,ab,kw.
39 satiation.ti,ab,kw.
40 satiety.ti,ab,kw.
41 prospective-food-consumption*.ti,ab,kw.
42 ((desire or craving*) adj3 (eat* or food or feed*)).ti,ab,kw.
43 exp Ghrelin/
44 ghrelin.ti,ab,kw.
45 GHRL.ti,ab,kw.
46 appetite-regulating-hormone.ti,ab,kw.
47 exp Cholecystokinin/
48 cholecystokinin.ti,ab,kw.
49 CCK.ti,ab,kw.
50 uropancreozymin.ti,ab,kw.
51 pancreozymin.ti,ab,kw.
52 exp Peptide-YY/
53 peptide-YY.ti,ab,kw.
54 PYY.ti,ab,kw.
55 PYY3-36.ti,ab,kw.
56 peptide-tyrosine-tyrosine.ti,ab,kw.
57 exp Glucagon-Like Peptide 1/
58 glucagon-like-peptide-1.ti,ab,kw.
59 GLP-1.ti,ab,kw.
60 GLP1.ti,ab,kw.
61 or/27-60 [Combined Combined thesaurus and text words for appetite/appetite markers concept]
62 and/11,26,61
63 62 not (comment or editorial or news or newspaper article).pt. [Exluded publication types]
64 (exp Animal/ or exp Juvenile Animal/ or Adult Animal/ or Animal Cell/ or Animal Tissue/ or Nonhuman/ or Animal Experiment/ or Animal Model/) not Human/
65 (animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rat or rats or rodent* or sheep* or veterinar*).ti,kw,dq,jx. not (human* or patient*).mp.
66 63 not (64 or 65) [Animal-only studies excluded]
67 (exp Infant/ or exp Child/ or exp Adolescent/) not exp Adult/
68 ((child* or stepchild* or step-child* or kid or kids or girl or girls or boy or boys or teen* or youth* or youngster* or adolescent* or adolescence or preschool* or pre-school* or kindergarten* or school* or juvenile* or minors or p?ediatric* or PICU) not adult*).ti,ab.
69 66 not (67 or 68) [non-adults only studies excluded]

70	limit 69 to (english or norwegian or swedish or danish or portuguese or french or spanish) [Limiting results to English, Norwegian, Swedish, Danish, Portugese, French or Spanish language]
71	limit 70 to medline
72	70 not (medline or "pubmed not medline").ns. [Excluding MEDLINE and PubMed not MEDLINE records]

PsycINFO

APA PsycInfo <1806 to August Week 4 2021>

#	Searches
1	exp Obesity/
2	exp Overweight/
3	adipos*.tw.
4	obes*.tw.
5	overweight*.tw.
6	over-weight*.tw.
7	((high* or unhealthy) adj3 (body-mass-ind* or BMI?)).tw.
8	or/1-7 [Combined thesaurus and text words for overweight/obesity concept]
9	normal-weight*.tw.
10	normal-body-weight*.tw.
11	normal-body-mass*.tw.
12	healthy-weight*.tw.
13	healthy-body-weight*.tw.
14	healthy-body-mass*.tw.
15	non-obese.tw.
16	nonobese.tw.
17	non-overweight*.tw.
18	slim.tw.
19	lean.tw.
20	((normal or control? or healthy or low*) adj3 (overweight or over-weight or obese* or men or women or subject* or person* or body-mass-ind* or BMI? or volunteer*)).tw.
21	or/9-20 [Combined thesaurus and text words for healthy weight concept]
22	exp Hunger/
23	exp Appetite/
24	exp Satiation/
25	appetite?.tw.
26	apetite?.tw.
27	hunger.tw.
28	fullness.tw.

29	satiation.tw.
30	satiety.tw.
31	prospective-food-consumption*.tw.
32	((desire or craving*) adj3 (eat* or food or feed*)).tw.
33	exp Ghrelin/
34	ghrelin.tw.
35	GHRL.tw.
36	appetite-regulating-hormone.tw.
37	exp Cholecystokinin/
38	cholecystokinin.tw.
39	CCK.tw.
40	uropancreozymin.tw.
41	pancreozymin.tw.
42	peptide-YY.tw.
43	PYY.tw.
44	PYY3-36.tw.
45	peptide-tyrosine-tyrosine.tw.
46	glucagon-like-peptide-1.tw.
47	GLP-1.tw.
48	GLP1.tw.
49	or/22-48 [Combined thesaurus and text words for appetite/appetite markers]
50	and/8,21,49
51	50 not ("column opinion" or "comment reply" or "Editorial").dt. [Excluded document types]
52	((human or animal) not human).po.
53	(animal or animals or canine* or dog or dogs or feline or hamster* or lamb or lambs or mice or monkey or monkeys or mouse or murine or pig or pigs or piglet* or porcine or primate* or rabbit* or rat or rats or rodent* or sheep* or veterinar*).ti,ab. not (human* or patient*).mp.
54	51 not (52 or 53) [Animal-only studies excluded]
55	((adolescence 13 17 yrs or adulthood 18 yrs older or childhood birth 12 yrs) not adulthood 18 yrs older).ag.
56	((child* or stepchild* or step-child* or kid or kids or girl or girls or boy or boys or teen* or youth* or youngster* or adolescent* or adolescence or preschool* or pre-school* or kindergarten* or school* or juvenile* or minors or p?ediatric* or PICU) not adult*).ti,ab.
57	54 not (55 or 56) [non-adult studies excluded]
58	limit 57 to (english or norwegian or swedish or danish or portuguese or french or spanish) [Limiting results to English, Norwegian, Swedish, Danish, Portugese, French or Spanish language]

Cochrane Library

ID	Search	Hits

#1 (adipos*):ti,ab,kw
#2 (obes*):ti,ab,kw
#3 (overweight*):ti,ab,kw
#4 (over-weight*):ti,ab,kw
#5 ((high* or unhealthy) NEAR/3 (body-mass-ind* or BMI?)):ti,ab,kw
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 (normal-weight*):ti,ab,kw
#8 (normal-body-weight*):ti,ab,kw
#9 (normal-body-mass*):ti,ab,kw
#10 (healthy-weight*):ti,ab,kw
#11 (healthy-body-weight*):ti,ab,kw
#12 (healthy-body-mass*):ti,ab,kw
#13 (non-obese):ti,ab,kw
#14 (nonobese):ti,ab,kw
#15 (non-overweight*):ti,ab,kw
#16 (slim):ti,ab,kw
#17 (lean):ti,ab,kw
#18 ((normal or control? or healthy or low*) NEAR/3 (overweight or over-weight or obese* or men or women or subject* or person* or body-mass-ind* or BMI? or volunteer*)):ti,ab,kw
#19 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
#20 (appetite?):ti,ab,kw
#21 (apetite?):ti,ab,kw
#22 (hunger):ti,ab,kw
#23 (fullness):ti,ab,kw
#24 (satiation):ti,ab,kw
#25 (satiety):ti,ab,kw
#26 (prospective-food-consumption*):ti,ab,kw
#27 ((desire or craving*) NEAR/3 (eat* or food or feed*)):ti,ab,kw
#28 (ghrelin):ti,ab,kw
#29 (GHRL):ti,ab,kw
#30 (appetite-regulating-hormone):ti,ab,kw
#31 (cholecystokinin):ti,ab,kw
#32 (CCK):ti,ab,kw
#33 (uropancreozymin):ti,ab,kw
#34 (pancreozymin):ti,ab,kw
#35 (peptide-YY):ti,ab,kw
#36 (PYY):ti,ab,kw
#37 ("PYY3-36"):ti,ab,kw
#38 (peptide-tyrosine-tyrosine):ti,ab,kw
#39 (glucagon-like-peptide-1):ti,ab,kw
#40 (GLP-1):ti,ab,kw
#41 (GLP1):ti,ab,kw
#42 #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41
#43 #6 AND #19 AND #42
#44 ((child* OR stepchild* OR step-child* OR kid OR kids OR girl OR girls OR boy OR boys OR teen* OR youth* OR youngster* OR adolescent* OR adolescence OR preschool* OR pre-school* OR kindergarten* OR school* OR juvenile* OR minors OR p?ediatric* OR PICU) NOT adult*):ti,ab,kw

#45 #43 NOT #44

Web of Science

Web of Science Core Collection

16	#13 not #14 and Editorial Materials (Exclude – Document Types)
15	#13 not #14
14	TS=(("child*" or "stepchild*" or "step-child*" or "kid" or "kids" or "girl" or "girls" or "boy" or "boys" or "teen*" or "youth*" or "youngster*" or "adolescent*" or "adolescence" or "preschool*" or "pre-school*" or "kindergarten*" or "school*" or "juvenile*" or "minors" or "p?ediatric*" or "PICU") not "adult*")
13	#11 not #12
12	TS=(("animal" or "animals" or "canine*" or "dog" or "dogs" or "feline" or "hamster*" or "lamb" or "lambs" or "mice" or "monkey" or "monkeys" or "mouse" or "murine" or "pig" or "pigs" or "piglet*" or "porcine" or "primate*" or "rabbit*" or "rat" or "rats" or "rodent*" or "sheep*" or "veterinar*") not ("human*" or "patient*"))
11	#10 AND #6 AND #3
10	#9 OR #8 OR #7
9	TS=("ghrelin" or "GHRL" or "appetite-regulating-hormone" or "cholecystokinin" or "CCK" or "uropancreozymin" or "pancreozymin" or "peptide-YY" or "PYY" or "PYY3-36" or "peptide-tyrosine-tyrosine" or "glucagon-like-peptide-1" or "GLP-1" or "GLP1")
8	TS=(("desire" or "craving*") NEAR/3 ("eat*" or "food" or "feed*"))
7	TS=("appetite?" or "apetite?" or "hunger" or "fullness" or "satiation" or "satiety" or "prospective-food-consumption*")
6	#4 OR #5
5	TS=((normal or control? or healthy or low*) NEAR/3 (overweight or over-weight or obese* or men or women or subject* or person* or body-mass-ind* or BMI? or volunteer*))
4	TS=("normal-weight*" or "normal-body-weight*" or "normal-body-mass*" or "healthy-weight*" or "healthy-body-weight*" or "healthy-body-mass*" or "non-obese" or "nonobese" or "non-overweight*" or "slim" or "lean")
3	#2 OR #1
2	TS=(("high*" or "unhealthy") NEAR/3 ("body-mass-ind*" or "BMI?"))
1	TS=("adipos*" or "obes*" or "overweight*" or "over-weight*")

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(hunger OR appetite OR fullness OR satiation OR satiety OR prospective-food-consumption OR desire OR craving OR cravings OR ghrelin OR GHRL OR appetite-regulating-hormone OR cholecystokinin OR PYY OR PYY3-36 OR GLP-1 OR GLP1) AND (obese OR obesity OR overweight OR over-weight OR body-mass-index OR BMI OR overweight) AND (normal-weight OR normal-body-weight OR normal-body-mass OR healthy-weight OR healthy-body-weight OR healthy-body-mass OR non-obese OR nonobese OR lean OR slim) AND (Adult OR Older Adult)

Flow diagram

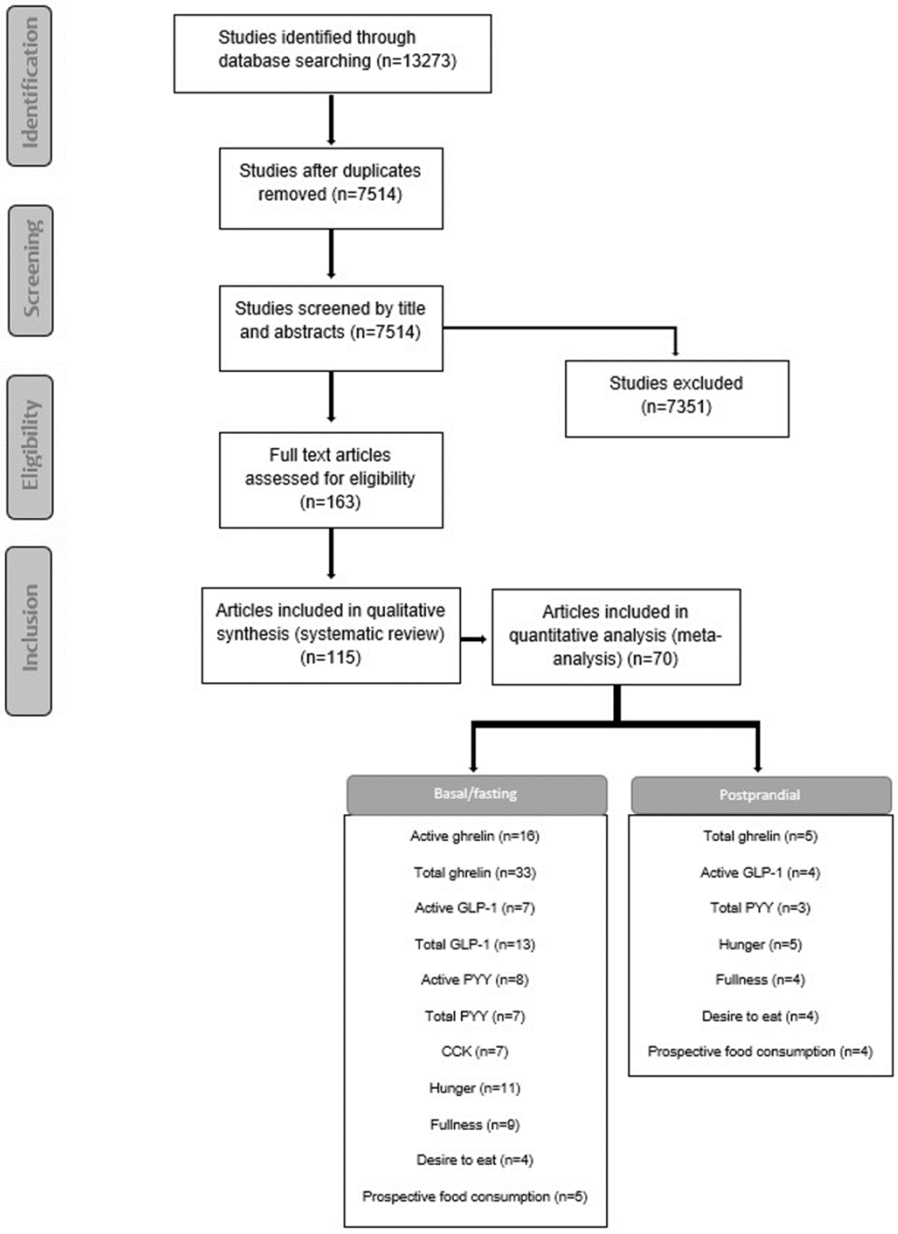

Figure 1: Flow diagram of the selection process.

Summary of contributing articles

Basal hormone concentrations

Active ghrelin (basal)

Table 1: Summary of contributing articles for active ghrelin (basal)

		Obesity group				Control group			
Author (year)	**Study design**	**n**	**% female**	**Age (years)**	**BMI (kg/m²)**	**n**	**% female**	**Age (years)**	**BMI (kg/m²)**
Andarini, 2017 [47]	Cross-sectional	16	0.0	21.4 (1.9)	33.6 (4.8)	16	0.0	20.6 (1.1)	21.3 (1.1)
Arafat, 2013 [26]	Parallel RCT	11	55.0	28.4 (8.6)	34.4 (5.6)	13	54.0	25.1 (2.2)	21.7 (2.2)
Carrol, 2007 [40]	Cross-sectional	20	55.0	47.2 (11.0)	36.8 (4.8)	19	47.0	39.2 (10.3)	22.6 (1.2)
Chearskul, 2012 [41]	Cross-sectional	33	100.0	33.6 (6.3)	29.4 (3.6)	53	100.0	30.1 (5.8)	20.7 (2.2)
Dardzinska, 2014 [27]	.	12	71.0	35.4 (9.1)	43.8 (6.8)	12	92.0	37.2 (9.4)	23.0 (3.5)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Douglas, 2017 [42]	Crossover	25	50.0	45.0 (12.4)	29.2 (2.9)	22	44.0	37.5 (15.2)	22.4 (1.5)
Heden, 2013 [97]	Crossover	14	57.0	25.1 (5.0)	34.8 (4.4)	14	43.0	26.0 (6.0)	22.9 (1.7)
Homaee, 2011 [30]	Cross-sectional	19	0.0	27.5 (5.8)	31.0 (3.6)	19	0.0	26.9 (5.6)	18.5 (2.2)
Iceta, 2019 [31]	Cross-sectional	55	100.0	38.0 (11.1)	41.5 (5.9)	29	100.0	37.0 (10.8)	21.5 (2.2)
Karcz-Socha, 2011 [45]	Cross-sectional	96	50.0	51.5 (6.5)	35.3 (2.9)	46	52.0	51.2 (6.5)	23.4 (1.5)
Kolodziejski, 2018 [43]	Cross-sectional	15	100.0	53.0 (8.5)	39.8 (1.0)	15	100.0	58.6 (10.3)	22.3 (0.5)
Korek, 2013 [32]	Cross-sectional	19	90.0	42.2 (3.3)	34.7 (4.9)	17	89.0	42.9 (5.3)	21.1 (1.9)
Krzyzanowska-Swinirska, 2007 [46]	Cross-sectional	30	100.0	44.3 (4.3)	34.4 (4.1)	32	100.0	30.6 (3.6)	21.3 (1.7)
Lopez-Aguilar, 2018 [33]	Cross-sectional	50	52.0	29.2 (6.3)	34.5 (5.2)	80	67.0	26.4 (5.6)	22.7 (1.5)
Marzullo, 2004 [35]	Cross-sectional	20	50.0	31.8 (2.5)	41.3 (1.1)	20	50.0	33.5 (2.4)	22.4 (0.6)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

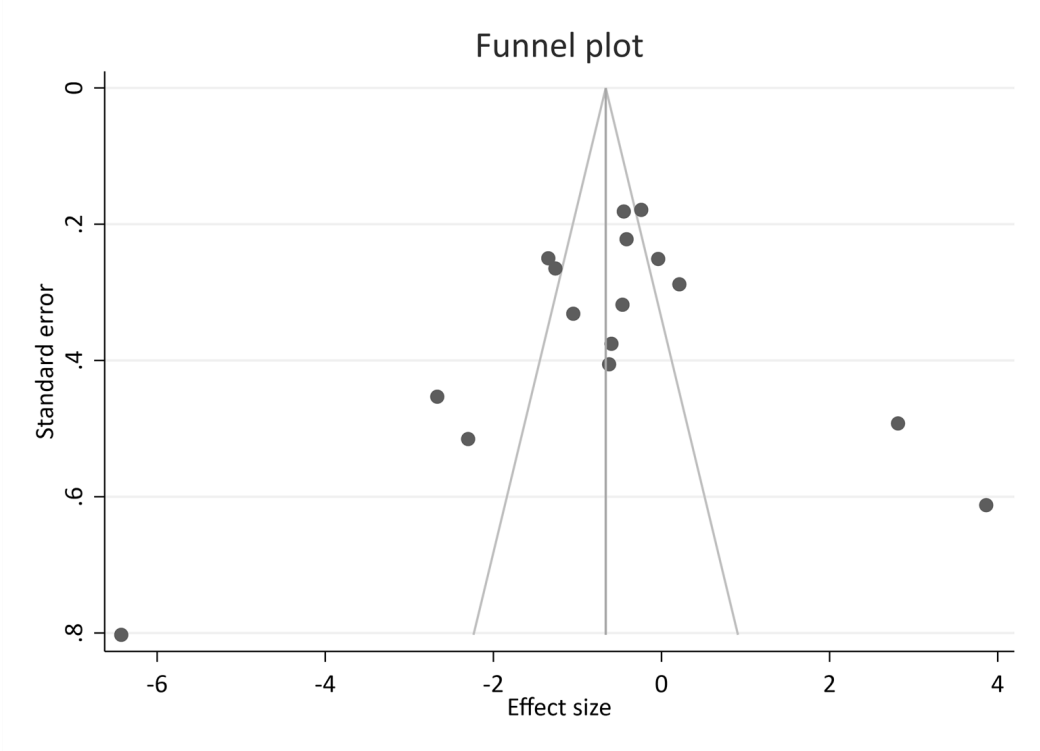

Figure 2: Funnel plot for active ghrelin (basal).

Total ghrelin (basal)

Table 2: Summary of contributing articles for total ghrelin (basal)

Author (year)	Study design	Obesity group n	Obesity group % female	Obesity group Age (years)	Obesity group BMI (kg/m^2)	Control group n	Control group % female	Control group Age (years)	Control group BMI (kg/m^2)
Acosta, 2015 [14]	Cross-sectional	201	72.0	37.8 (12.1)	35.4 (3.9)	105	61.0	37.3 (12.0)	27.6 (0.1)
Arafat, 2013 [26]	Parallel RCT	11	55.0	28.4 (8.6)	34.4 (5.6)	13	54.0	25.1 (2.2)	21.7 (2.2)
Batterham, 2003 [49]	Crossover	12	50.0	29.0 (8.3)	33.0 (3.1)	12	50.0	27.3 (1.4)	20.5 (0.3)
Bogdanov, 2019 [51]	Cross-sectional	15	80.0	38.7 (9.4)	41.2 (2.1)	15	87.0	37.0 (7.1)	21.8 (2.6)
Bowen, 2006 [52]	Crossover	47	0.0	56.8 (7.5)	30.1 (3.4)	25	0.0	50.5 (12.0)	23.3 (1.0)
Brownley, 2012 [53]	Crossover	20	50.0	34.9 (9.0)	34.7 (2.8)	20	50.0	27.9 (7.0)	22.9 (1.4)
Carlson, 2009 [54]	Cross-sectional	13	100.0	35.6 (9.7)	44.5 (7.1)	10	100.0	32.2 (8.6)	23.1 (1.3)
Cassar, 2015 [55]	Cross-sectional	18	100.0	35.0 (5.0)	31.0 (3.0)	22	100.0	28.0 (6.0)	22.0 (2.0)
Clamp, 2015 [84]	Cross-sectional	10	0.0	30.0 (6.0)	33.2 (3.0)	10	0.0	25.0 (5.0)	22.3 (1.6)
Cremonini, 2006 [85]	Parallel RCT	25	80.0	35.0 (8.0)	36.0 (4.0)	13	100.0	34.0 (12.0)	22.0 (2.0)
Daghestani, 2009 [57]	Cross-sectional	45	100.0	26.5 (6.4)	35.9 (6.2)	77	100.0	23.5 (4.5)	22.3 (3.3)
Druce, 2005 [86]	Parallel RCT	12	67.0	33.4 (6.9)	31.9 (3.5)	12	67.0	24.7 (4.6)	20.5 (0.6)
El Helou, 2019 [58]	Crossover	15	0.0	21.7 (3.5)	35.1 (3.9)	15	0.0	20.1 (1.5)	22.0 (1.9)
English, 2002 [28]	Cross-sectional	10	30.0	42.8 (7.0)	42.8 (6.4)	13	60.0	32.0 (8.3)	22.5 (1.9)
Erdmann, 2005 [59]	Cross-sectional	128	36.0	45.0 (13.6)	33.8 (5.7)	56	80.0	30.0 (10.5)	22.0 (2.2)
Espelund, 2005 [87]	Cross-sectional	16	56.0	39.7 (12.4)	29.5 (4.0)	17	47.0	33.7 (14.0)	23.4 (2.5)
Frecka, 2008 [88]	Cross-sectional	5	40.0	32.0 (9.6)	32.2 (1.6)	7	57.0	24.3 (4.2)	23.3 (1.6)
Guo, 2007 [60]	Cross-sectional	14	50.0	59.4 (7.3)	30.1 (1.9)	16	50.0	54.4 (4.5)	21.6 (1.7)
Haltia, 2010 [89]	Crossover	13	38.0	27.0 (6.0)	33.0 (4.5)	12	50.0	26.0 (5.0)	21.7 (1.3)
Karcz-Socha, 2011 [45]	Cross-sectional	96	50.0	51.5 (6.5)	35.3 (2.9)	46	52.0	51.2 (6.5)	23.4 (1.5)
Kheirouri, 2017 [62]	Cross-sectional	37	100.0	37.2 (7.5)	23.1 (0.8)	40	100.0	35.2 (7.9)	31.4 (0.7)
Kiessl, 2017 [63]	Crossover	43	100.0	37.2 (7.5)	31.5 (1.8)	42	100.0	35.2 (7.9)	21.7 (2.0)
Kocak, 2011 [64]	Cross-sectional	22	100.0	NR	34.1 (4.0)	19	100.0	NR	25.2 (1.7)
Kolodziejski, 2018 [43]	Cross-sectional	15	100.0	53.0 (8.5)	39.8 (1.0)	15	100.0	58.6 (10.3)	22.3 (0.5)
Korek, 2013 [32]	Cross-sectional	19	90.0	42.2 (3.3)	34.7 (4.9)	17	89.0	42.9 (5.3)	21.1 (1.9)
Korner, 2005 [90]	Cross-sectional	12	100.0	NR	34.1 (1.8)	8	100.0	NR	21.6 (0.7)
Lambert, 2011 [91]	Crossover	11	NR	32.5 (6.5)	29.3 (0.6)	11	NR	28.8 (4.8)	21.3 (0.6)
Leonetti, 2003 [65]	Cross-sectional	8	70.0	20.8 (0.6)	35.9 (2.5)	10	50.0	21.5 (0.5)	23.0 (3.6)
Marzullo, 2006 [17]	Cross-sectional	10	50.0	32.4 (1.6)	43.0 (0.9)	6	50.0	31.7 (1.3)	21.8 (1.4)
Outeiriño-Blanco, 2011 [67]	Cross-sectional	23	100.0	39.8 (2.9)	38.8 (1.2)	13	100.0	34.4 (3.6)	22.3 (0.7)
Ozkan, 2009 [68]	Parallel RCT	21	71.0	37.4 (12.4)	24.8 (3.1)	10	60.0	36.1 (9.8)	37.0 (3.6)
Papandreou, 2017 [69]	Cross-sectional	7	NR	21.0 (2.1)	31.3 (2.1)	13	NR	21.0 (0.8)	20.6 (3.0)
Pavlatos, 2005 [70]	Parallel RCT	9	100.0	39.5 (14.5)	37.2 (8.4)	9	100.0	38.7 (14.1)	23.0 (2.1)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

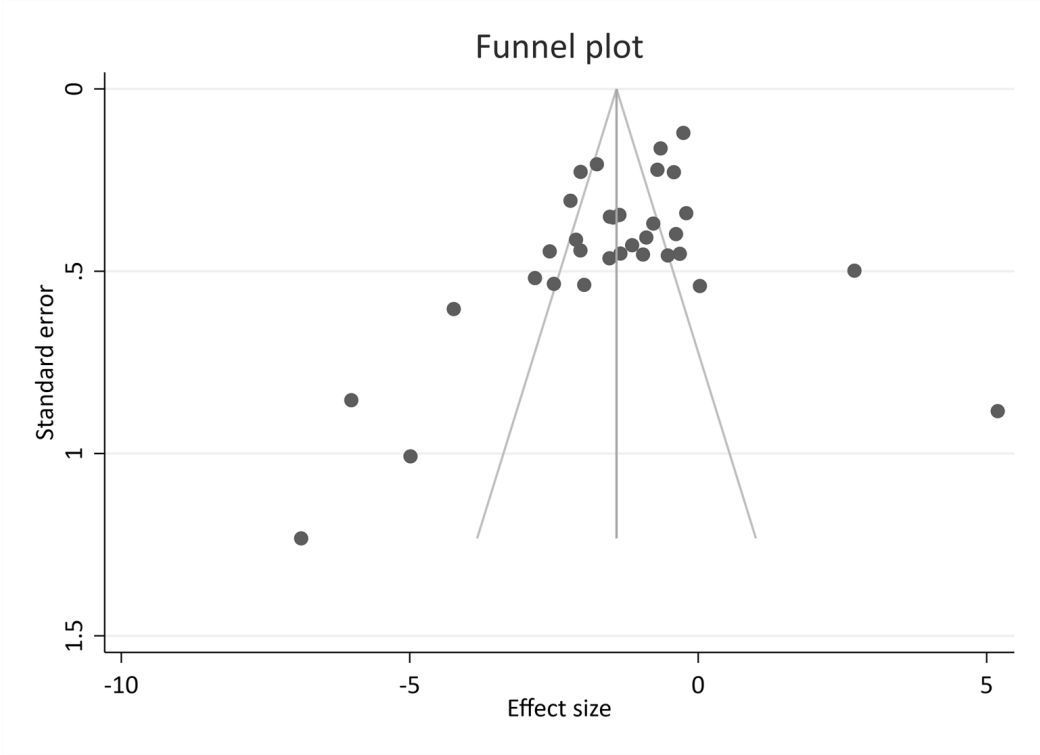

Figure 3: Funnel plot for total ghrelin (basal).

Active GLP-1 (basal)

Table 3: Summary of contributing articles for active GLP-1 (basal)

Author (year)	Study design	Obesity group n	% female	Age (years)	BMI (kg/m²)	Control group n	% female	Age (years)	BMI (kg/m²)
Adam, 2005 [94]	Crossover	28	68.0	44.4 (9.8)	30.4 (2.7)	30	50.0	31.6 (12.8)	22.9 (1.5)
Bowen, 2006 [52]	Crossover	47	0.0	56.8 (7.5)	30.1 (3.4)	25	0.0	50.5 (12.0)	23.3 (1.0)
Calanna, 2013 [95]	Cross-sectional	43	67.0	42.8 (13.1)	34.6 (3.9)	24	83.0	38.3 (9.8)	22.1 (2.0)
Carrol, 2007 [40]	Cross-sectional	20	55.0	47.2 (11.0)	36.8 (4.8)	19	47.0	39.2 (10.3)	22.6 (1.2)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Mersebach, 2003 [98]	Cross-sectional	16	75.0	39.3 (3.5)	36.1 (2.4)	10	70.0	37.9 (5.9)	21.5 (1.3)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

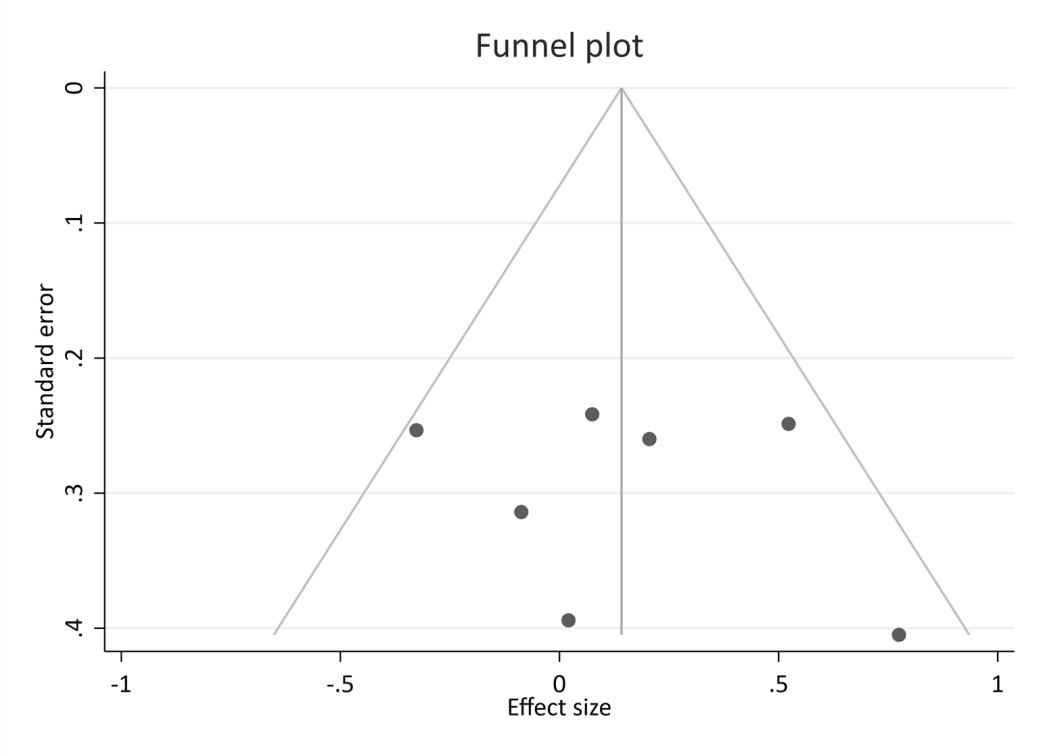

Figure 4: Funnel plot for active GLP-1 (basal).

Total GLP-1 (basal)

Table 4: Summary of contributing articles for total GLP-1 (basal)

Author (year)	Study design	Obesity group n	Obesity group % female	Obesity group Age (years)	Obesity group BMI (kg/m^2)	Control group n	Control group % female	Control group Age (years)	Control group BMI (kg/m^2)
Carr, 2010 [105]	Crossover	13	0.0	25.6 (4.0)	33.8 (0.6)	12	0.0	22.0 (1.8)	22.3 (0.3)
Cassar, 2015 [55]	Cross-sectional	18	100.0	35.0 (5.0)	31.0 (3.0)	22	100.0	28.0 (6.0)	22.0 (2.0)
Chia, 2017 [106]	Cross-sectional	20	50.0	68.5 (13.0)	35.6 (4.0)	20	50.0	68.5 (13.0)	23.6 (1.3)
Dirksen, 2019 [104]	Crossover	10	0.0	42.1 (9.8)	57.6 (17.2)	10	0.0	43.1 (8.9)	24.1 (3.8)
Douglas, 2017 [42]	Crossover	25	50.0	45.0 (12.4)	29.2 (2.9)	22	44.0	37.5 (15.2)	22.4 (1.5)
El Helou, 2019 [58]	Crossover	15	0.0	21.7 (3.5)	35.1 (3.9)	15	0.0	20.1 (1.5)	22.0 (1.9)
Elahi, 2016 [96]	Cross-sectional	12	50.0	42.0 (6.9)	37.2 (5.2)	12	50.0	29.0 (6.4)	22.3 (1.4)
Greenfield, 2009 [108]	Crossover	8	14.0	39.0 (9.8)	34.5 (4.4)	8	33.0	30.0 (5.8)	21.9 (2.2)
Haltia, 2010 [89]	Crossover	13	38.0	27.0 (6.0)	33.0 (4.5)	12	50.0	26.0 (5.0)	21.7 (1.3)
Heni, 2015 [109]	Cross-sectional	12	50.0	25.0 (6.9)	30.5 (6.2)	12	50.0	23.0 (6.9)	21.2 (3.8)
Nguyen, 2018 [110]	Cross-sectional	22	50.0	50.2 (2.5)	48.6 (1.8)	10	59.0	38.6 (8.4)	23.9 (0.7)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)
Verdich, 2001 [113]	.	19	0.0	35.0 (10.9)	38.1 (3.1)	12	0.0	24.2 (9.6)	23.1 (1.4)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

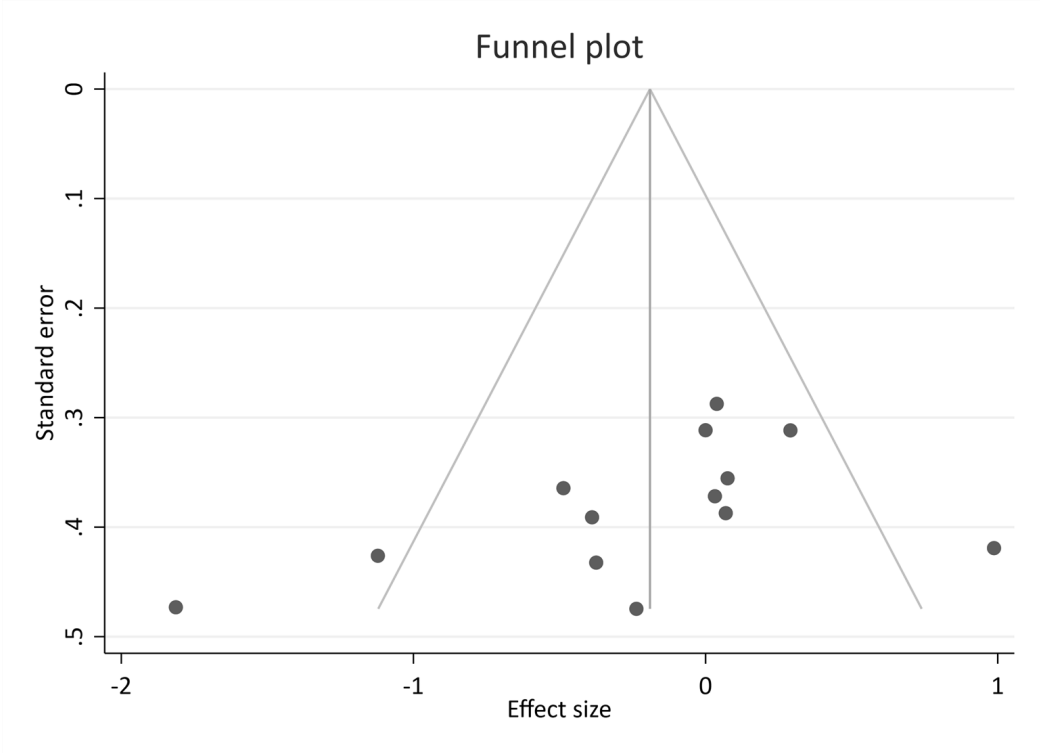

Figure 5: Funnel plot for total GLP-1 (basal).

Active PYY (basal)

Table 5: Summary of contributing articles for active PYY (basal)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m^2)	n	% female	Age (years)	BMI (kg/m^2)
Batterham, 2003 [49]	Crossover	12	50.0	29.0 (8.3)	33.0 (3.1)	12	50.0	27.3 (1.4)	20.5 (0.3)
Damgaard, 2013 [107]	Crossover	13	0.0	32.3 (7.7)	30.6 (3.5)	8	0.0	27.1 (6.1)	22.1 (2.3)
Dirksen, 2019 [104]	Crossover	10	0.0	42.1 (9.8)	57.6 (17.2)	10	0.0	43.1 (8.9)	24.1 (3.8)
Haltia, 2010 [89]	Crossover	13	38.0	27.0 (6.0)	33.0 (4.5)	12	50.0	26.0 (5.0)	21.7 (1.3)
Karcz-Socha, 2011 [45]	Cross-sectional	96	50.0	51.5 (6.5)	35.3 (2.9)	46	52.0	51.2 (6.5)	23.4 (1.5)
Korner, 2005 [90]	Cross-sectional	12	100.0	NR	34.1 (1.8)	8	100.0	NR	21.6 (0.7)
Outeiriño-Blanco, 2011 [67]	Cross-sectional	23	100.0	39.8 (2.9)	38.8 (1.2)	13	100.0	34.4 (3.6)	22.3 (0.7)
Pfluger, 2007 [117]	Crossover	15	100.0	52.0 (2.0)	31.1 (0.5)	17	100.0	51.6 (1.9)	22.0 (0.5)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

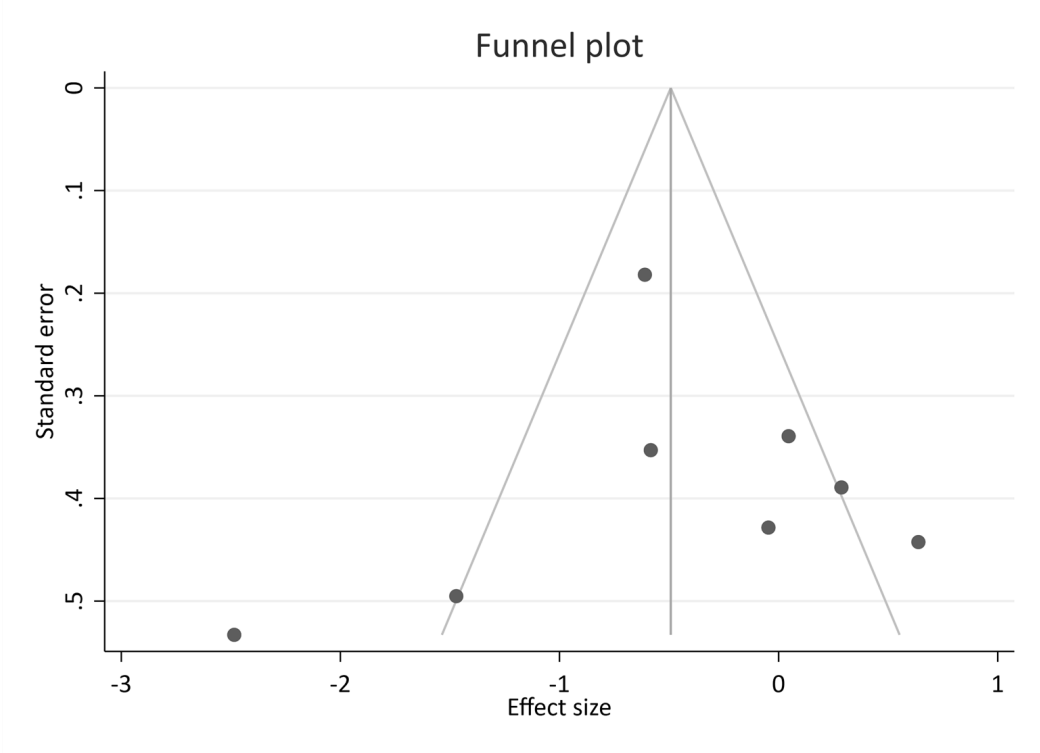

Figure 6: Funnel plot for active PYY (basal).

Total PYY (basal)

Table 6: Summary of contributing articles for total PYY (basal)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m²)	n	% female	Age (years)	BMI (kg/m²)
Brownley, 2010 [120]	Crossover	20	50.0	34.9 (9.0)	34.7 (2.8)	20	50.0	27.9 (7.0)	22.9 (1.4)
Cahill, 2011 [124]	Cross-sectional	28	0.0	23.2 (2.6)	29.1 (4.9)	41	0.0	23.1 (3.5)	23.1 (2.3)
Cahill, 2014 [123]	Cross-sectional	779	74.0	43.8 (12.1)	30.6 (4.8)	1315	76.0	42.1 (13.2)	24.4 (3.1)
Clamp, 2015 [84]	Cross-sectional	10	0.0	30.0 (6.0)	33.2 (3.0)	10	0.0	25.0 (5.0)	22.3 (1.6)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Douglas, 2017 [42]	Crossover	25	50.0	45.0 (12.4)	29.2 (2.9)	22	44.0	37.5 (15.2)	22.4 (1.5)
Pfluger, 2007 [117]	Crossover	79	73.0	47.6 (2.9)	35.1 (4.8)	66	70.0	41.5 (2.2)	22.1 (0.2)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

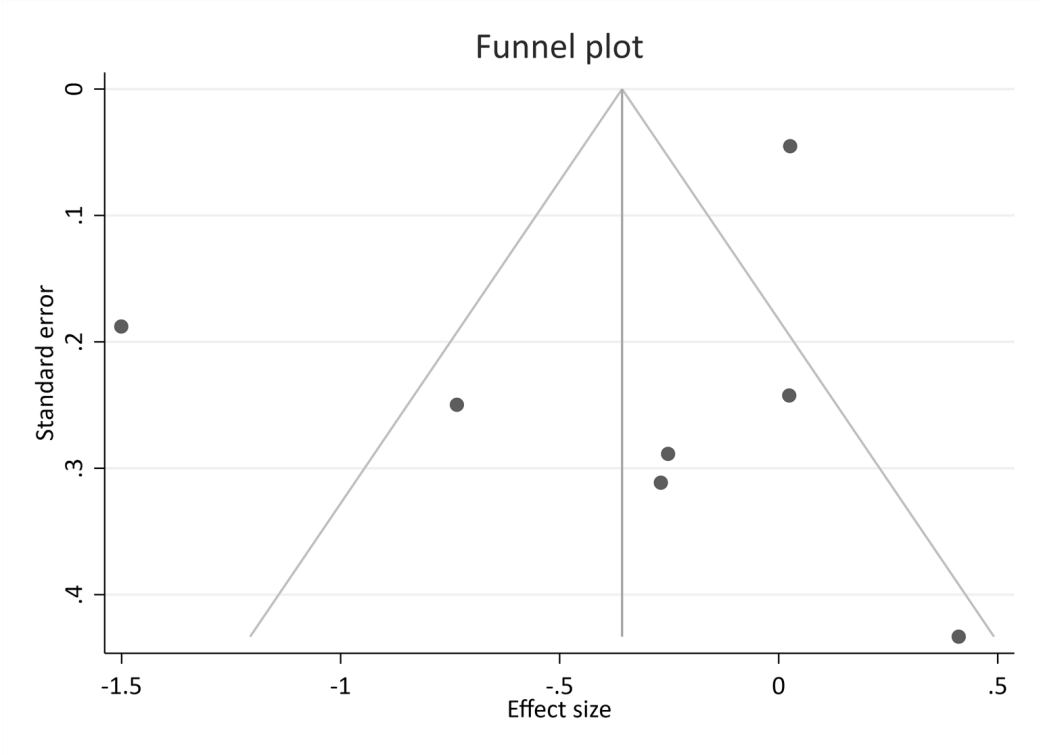

Figure 7: Funnel plot for total PYY (basal).

CKK (basal)

Table 7: Summary of contributing articles for CKK (basal)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m²)	n	% female	Age (years)	BMI (kg/m²)
Bowen, 2006 [52]	Crossover	47	0.0	56.8 (7.5)	30.1 (3.4)	25	0.0	50.5 (12.0)	23.3 (1.0)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Dirksen, 2019 [104]	Crossover	10	0.0	42.1 (9.8)	57.6 (17.2)	10	0.0	43.1 (8.9)	24.1 (3.8)
French, 1993 [18]	Crossover	8	63.0	NR	NR	7	57.0	NR	NR
Lieverse, 1993 [126]	Parallel RCT	7	100.0	40.2 (10.6)	40.7 (6.7)	7	100.0	41.2 (11.6)	22.3 (2.1)
Lieverse, 1998 [125]	Parallel RCT	7	100.0	NR	39.0 (2.0)	7	100.0	NR	22.0 (0.3)
Milewicz, 2000 [127]	Cross-sectional	25	NR	NR	34.6 (1.4)	16	NR	NR	21.2 (0.4)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

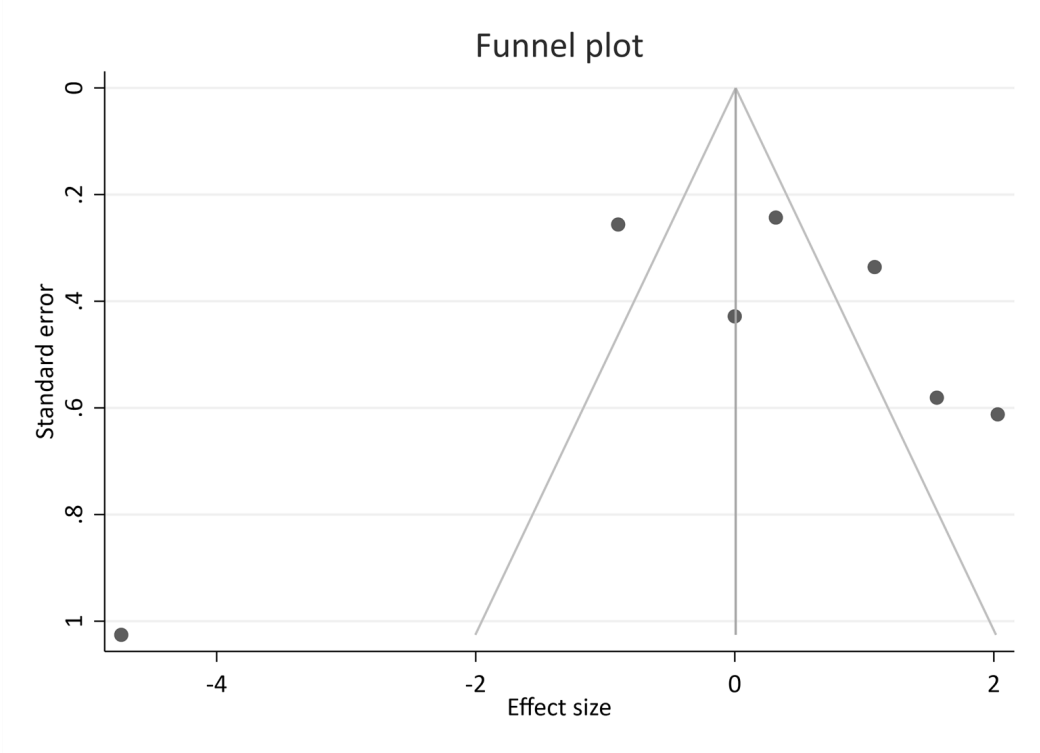

Figure 8: Funnel plot for CKK (basal)

Postprandial hormone concentrations

Total ghrelin (AUC)

Table 8: Summary of contributing articles for total ghrelin (AUC)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m²)	n	% female	Age (years)	BMI (kg/m²)
Brownley, 2012 [53]	Crossover	20	50.0	34.9 (9.0)	34.7 (2.8)	20	50.0	27.9 (7.0)	22.9 (1.4)
Frecka, 2008 [88]	Cross-sectional	5	40.0	32.0 (9.6)	32.2 (1.6)	7	57.0	24.3 (4.2)	23.3 (1.6)
Marzullo, 2006 [17]	Cross-sectional	10	50.0	32.4 (1.6)	43.0 (0.9)	6	50.0	31.7 (1.3)	21.8 (1.4)
Meyer-Gerspach, 2014 [15]	Cross-sectional	20	NR	29.8 (1.9)	39.3 (1.9)	20	NR	24.1 (0.6)	21.8 (0.4)
Outeiriño-Blanco, 2011 [67]	Cross-sectional	23	100.0	39.8 (2.9)	38.8 (1.2)	13	100.0	34.4 (3.6)	22.3 (0.7)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

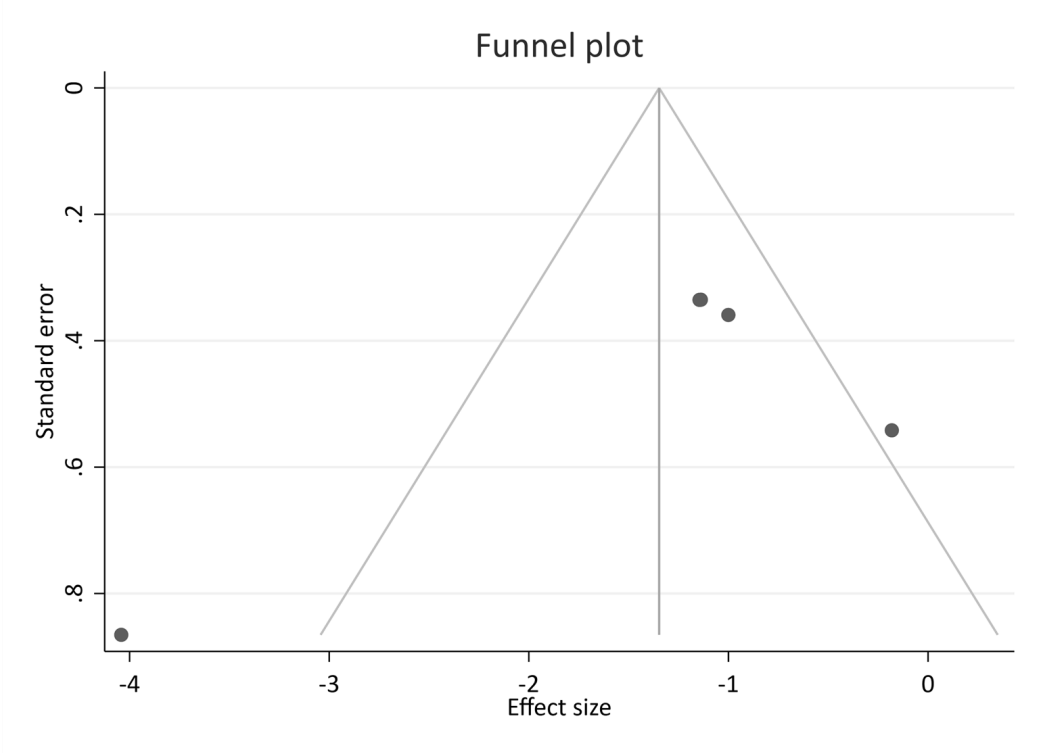

Figure 9: Funnel plot for total ghrelin (AUC).

Active GLP-1 (AUC)

Table 9: Summary of contributing articles for active GLP-1 (AUC)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m²)	n	% female	Age (years)	BMI (kg/m²)
Adam, 2005 [94]	Crossover	28	68.0	44.4 (9.8)	30.4 (2.7)	30	50.0	31.6 (12.8)	22.9 (1.5)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Heden, 2013 [97]	Crossover	13	54.0	25.4 (3.6)	34.6 (3.6)	13	46.0	26.0 (7.2)	23.0 (1.8)
Meyer-Gerspach, 2014 [15]	Cross-sectional	20	NR	29.8 (1.9)	39.3 (1.9)	20	NR	24.1 (0.6)	21.8 (0.4)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

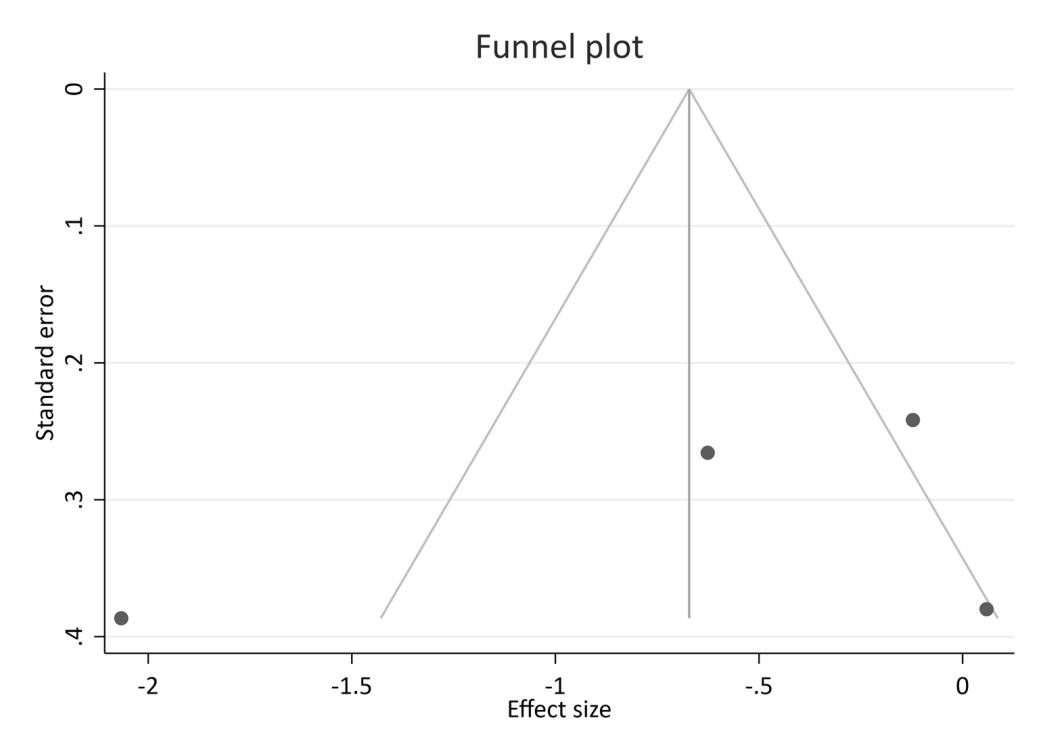

Figure 10: Funnel plot for active GLP-1 (AUC).

Total PYY (AUC)

Table 10: Summary of contributing articles for total PYY (AUC)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m^2)	n	% female	Age (years)	BMI (kg/m^2)
Brownley, 2010 [120]	Crossover	20	50.0	34.9 (9.0)	34.7 (2.8)	20	50.0	27.9 (7.0)	22.9 (1.4)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Meyer-Gerspach, 2014 [15]	Cross-sectional	20	NR	29.8 (1.9)	39.3 (1.9)	20	NR	24.1 (0.6)	21.8 (0.4)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

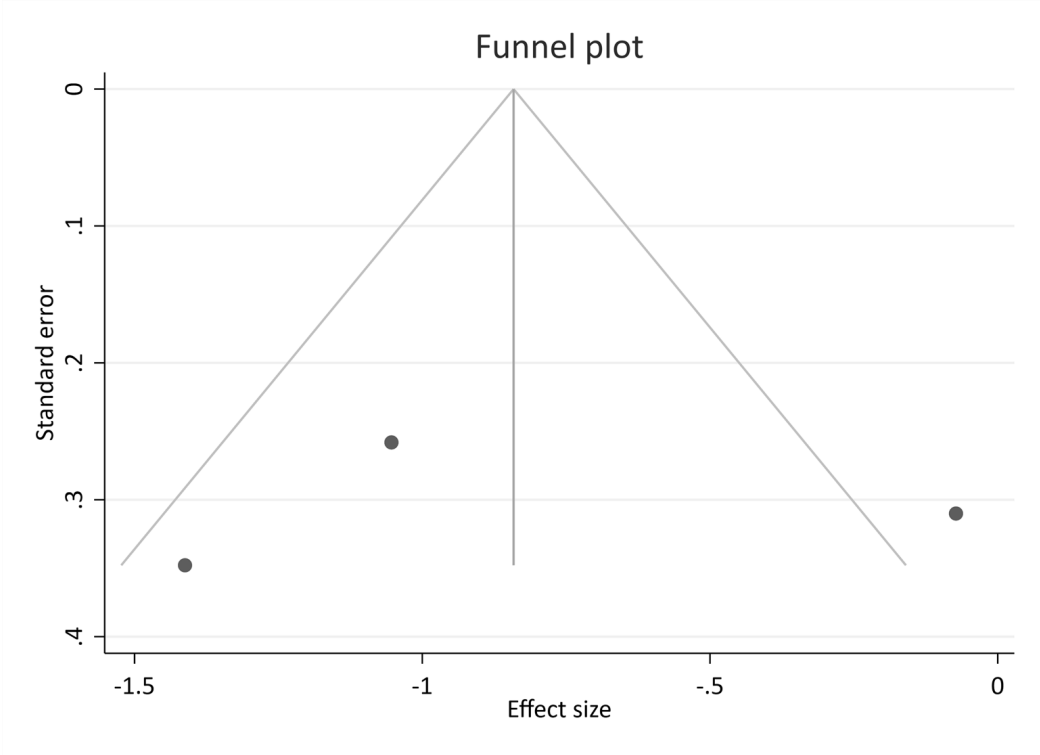

Figure 11: Funnel plot for total PYY (AUC).

Fasting appetite feelings

Hunger (fasting)

Table 11: Summary of contributing articles for hunger (fasting)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m^2)	n	% female	Age (years)	BMI (kg/m^2)
Andarini, 2017 [47]	Cross-sectional	16	0.0	21.4 (1.9)	33.6 (4.8)	16	0.0	20.6 (1.1)	21.3 (1.1)
Barkeling, 1995 [132]	Cross-sectional	38	50.0	43.5 (12.0)	39.4 (6.5)	38	50.0	40.0 (10.9)	22.3 (1.9)
Damgaard, 2013 [107]	Crossover	13	0.0	32.3 (7.7)	30.6 (3.5)	8	0.0	27.1 (6.1)	22.1 (2.3)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Dirksen, 2019 [104]	Crossover	10	0.0	42.1 (9.8)	57.6 (17.2)	10	0.0	43.1 (8.9)	24.1 (3.8)
El Helou, 2019 [58]	Crossover	15	0.0	21.7 (3.5)	35.1 (3.9)	15	0.0	20.1 (1.5)	22.0 (1.9)
Heden, 2013 [97]	Crossover	14	57.0	25.1 (5.0)	34.8 (4.4)	14	43.0	26.0 (6.0)	22.9 (1.7)
Iceta, 2019 [31]	Cross-sectional	55	100.0	38.0 (11.1)	41.5 (5.9)	29	100.0	37.0 (10.8)	21.5 (2.2)
Korner, 2005 [90]	Cross-sectional	12	100.0	NR	34.1 (1.8)	8	100.0	NR	21.6 (0.7)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

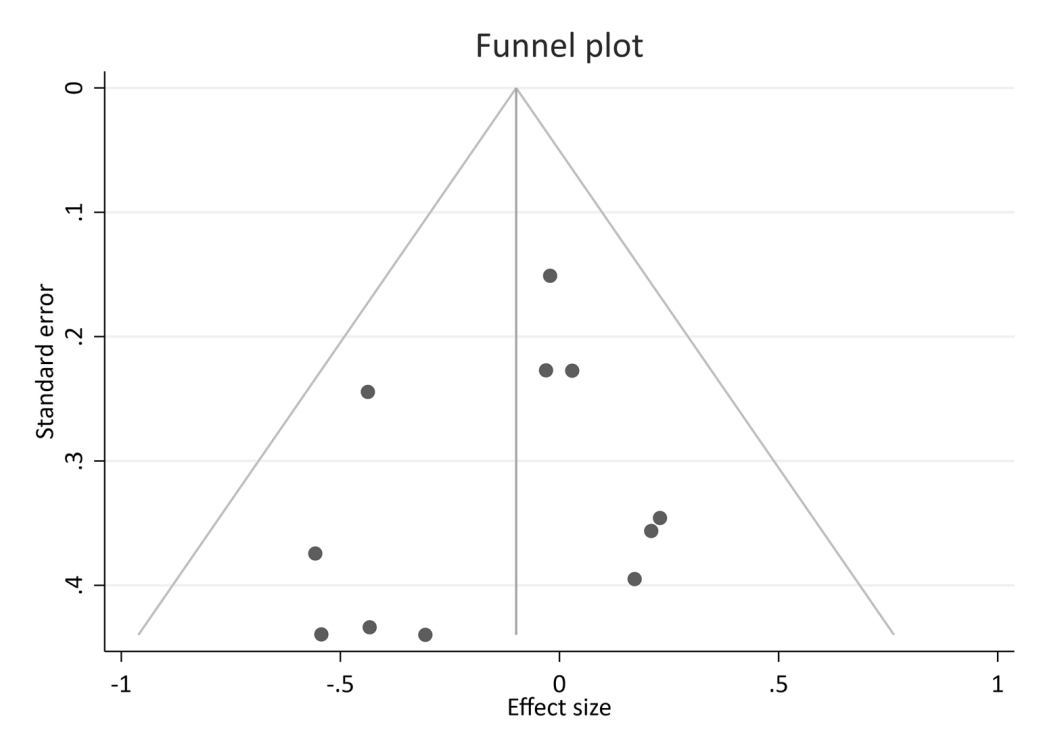

Figure 12: Funnel plot for hunger (fasting).

Fullness (fasting)

Table 12: Summary of contributing articles for fullness (fasting)

Author (year)	Study design	Obesity group n	Obesity group % female	Obesity group Age (years)	Obesity group BMI (kg/m²)	Control group n	Control group % female	Control group Age (years)	Control group BMI (kg/m²)
Barkeling, 1995 [132]	Cross-sectional	38	50.0	43.5 (12.0)	39.4 (6.5)	38	50.0	40.0 (10.9)	22.3 (1.9)
Damgaard, 2013 [107]	Crossover	13	0.0	32.3 (7.7)	30.6 (3.5)	8	0.0	27.1 (6.1)	22.1 (2.3)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Dirksen, 2019 [104]	Crossover	10	0.0	42.1 (9.8)	57.6 (17.2)	10	0.0	43.1 (8.9)	24.1 (3.8)
El Helou, 2019 [58]	Crossover	15	0.0	21.7 (3.5)	35.1 (3.9)	15	0.0	20.1 (1.5)	22.0 (1.9)
Heden, 2013 [97]	Crossover	14	57.0	25.1 (5.0)	34.8 (4.4)	14	43.0	26.0 (6.0)	22.9 (1.7)
Korner, 2005 [90]	Cross-sectional	12	100.0	NR	34.1 (1.8)	8	100.0	NR	21.6 (0.7)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

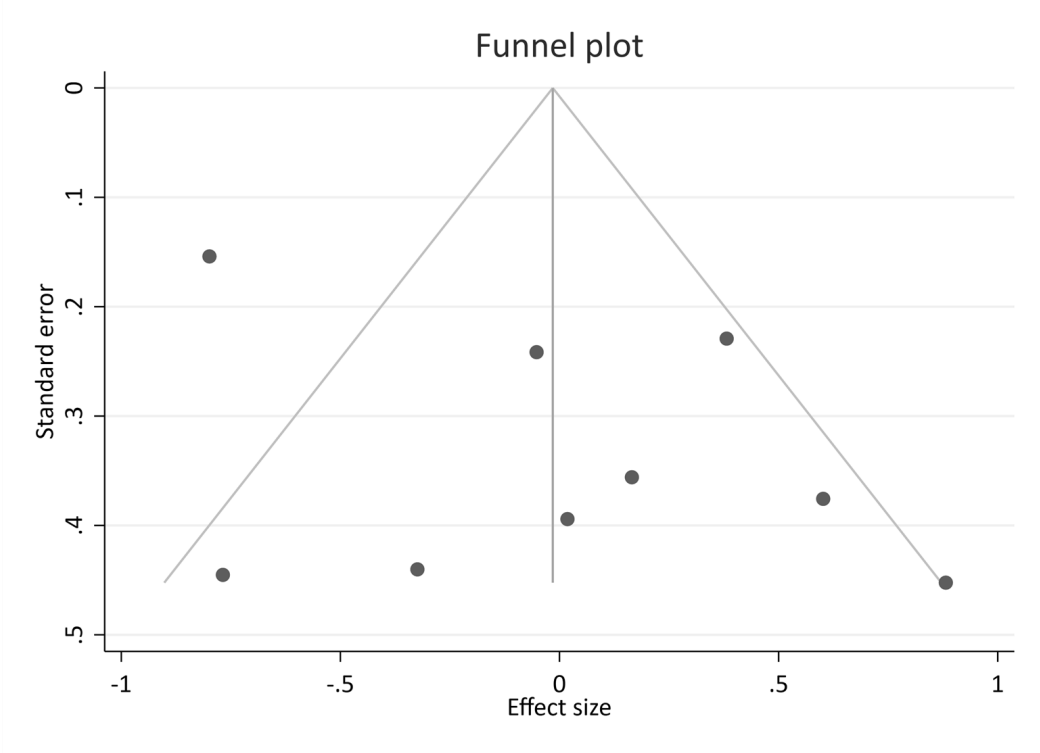

Figure 13: Funnel plot for fullness (fasting).

Desire to eat (DTE) (fasting)

Table 13: Summary of contributing articles for DTE (fasting)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m^2)	n	% female	Age (years)	BMI (kg/m^2)
Andarini, 2017 [47]	Cross-sectional	16	0.0	21.4 (1.9)	33.6 (4.8)	16	0.0	20.6 (1.1)	21.3 (1.1)
Barkeling, 1995 [132]	Cross-sectional	38	50.0	43.5 (12.0)	39.4 (6.5)	38	50.0	40.0 (10.9)	22.3 (1.9)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

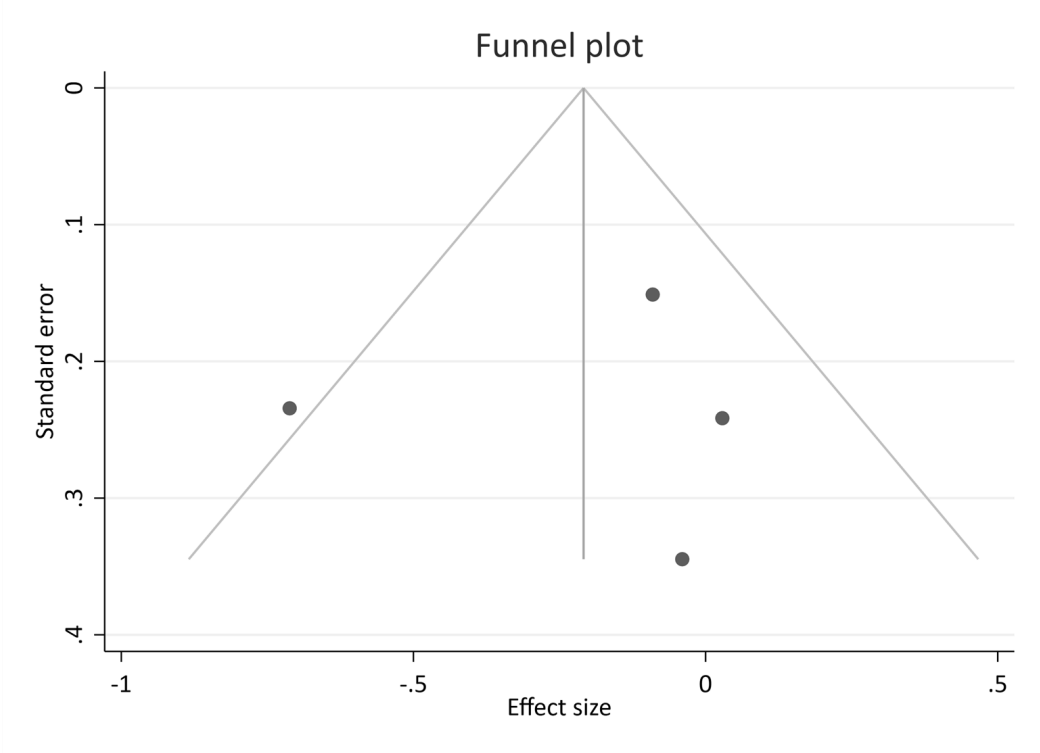

Figure 14: Funnel plot for DTE (fasting).

Prospective food consumption (PFC) (fasting)

Table 14: Summary of contributing articles for PFC (fasting)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m²)	n	% female	Age (years)	BMI (kg/m²)
Barkeling, 1995 [132]	Cross-sectional	38	50.0	43.5 (12.0)	39.4 (6.5)	38	50.0	40.0 (10.9)	22.3 (1.9)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
El Helou, 2019 [58]	Crossover	15	0.0	21.7 (3.5)	35.1 (3.9)	15	0.0	20.1 (1.5)	22.0 (1.9)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

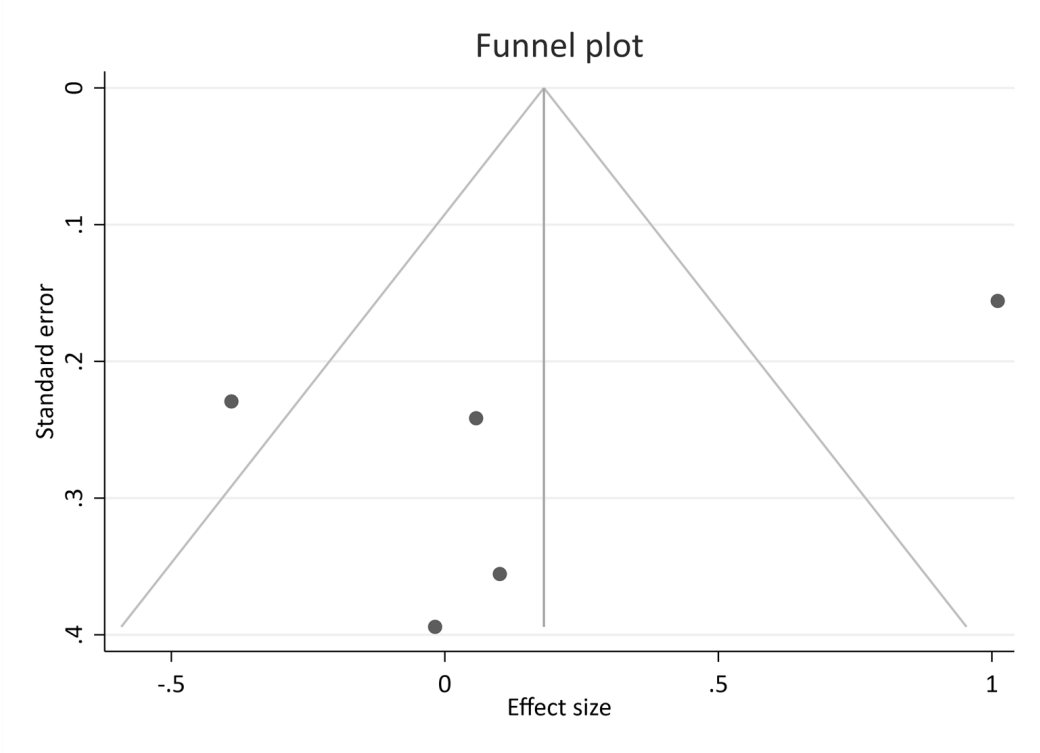

Figure 15: Funnel plot for PFC (fasting).

Postprandial appetite ratings

Hunger (AUC)

Table 15: Summary of contributing articles for hunger (AUC)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m^2)	n	% female	Age (years)	BMI (kg/m^2)
Andarini, 2017 [47]	Cross-sectional	16	0.0	21.4 (1.9)	33.6 (4.8)	16	0.0	20.6 (1.1)	21.3 (1.1)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Frecka, 2008 [88]	Cross-sectional	5	40.0	32.0 (9.6)	32.2 (1.6)	7	57.0	24.3 (4.2)	23.3 (1.6)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

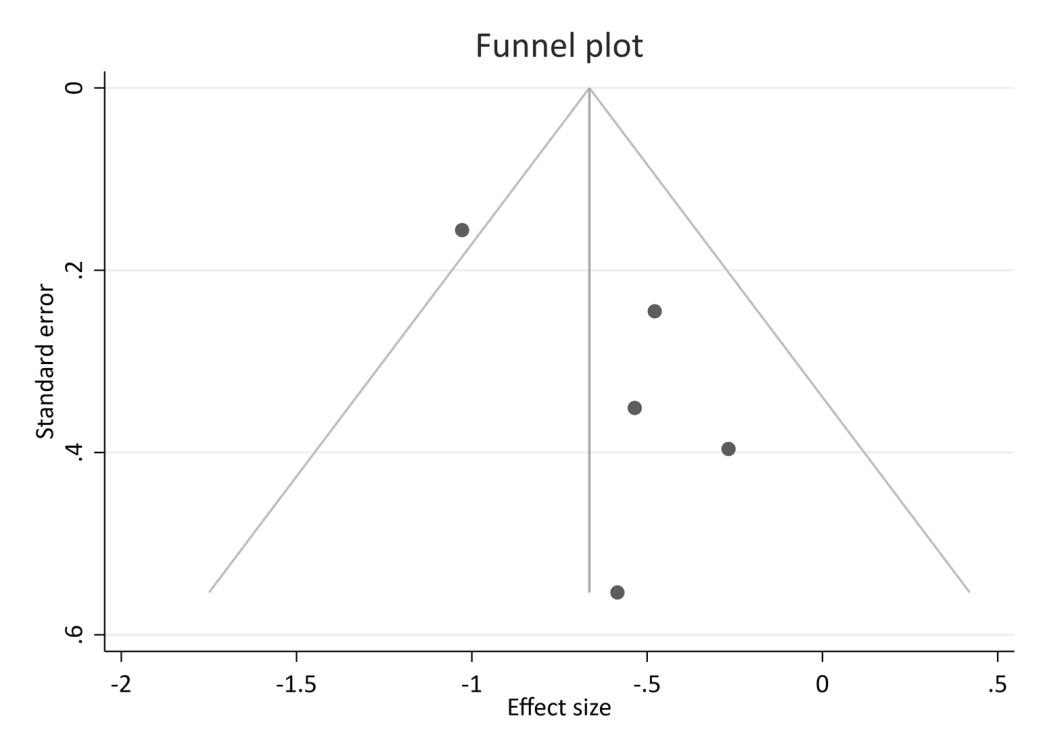

Figure 16: Funnel plot for hunger (AUC).

Fullness (AUC)

Table 16: Summary of contributing articles for fullness (AUC)

Author (year)	Study design	Obesity group n	Obesity group % female	Obesity group Age (years)	Obesity group BMI (kg/m^2)	Control group n	Control group % female	Control group Age (years)	Control group BMI (kg/m^2)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Frecka, 2008 [88]	Cross-sectional	5	40.0	32.0 (9.6)	32.2 (1.6)	7	57.0	24.3 (4.2)	23.3 (1.6)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

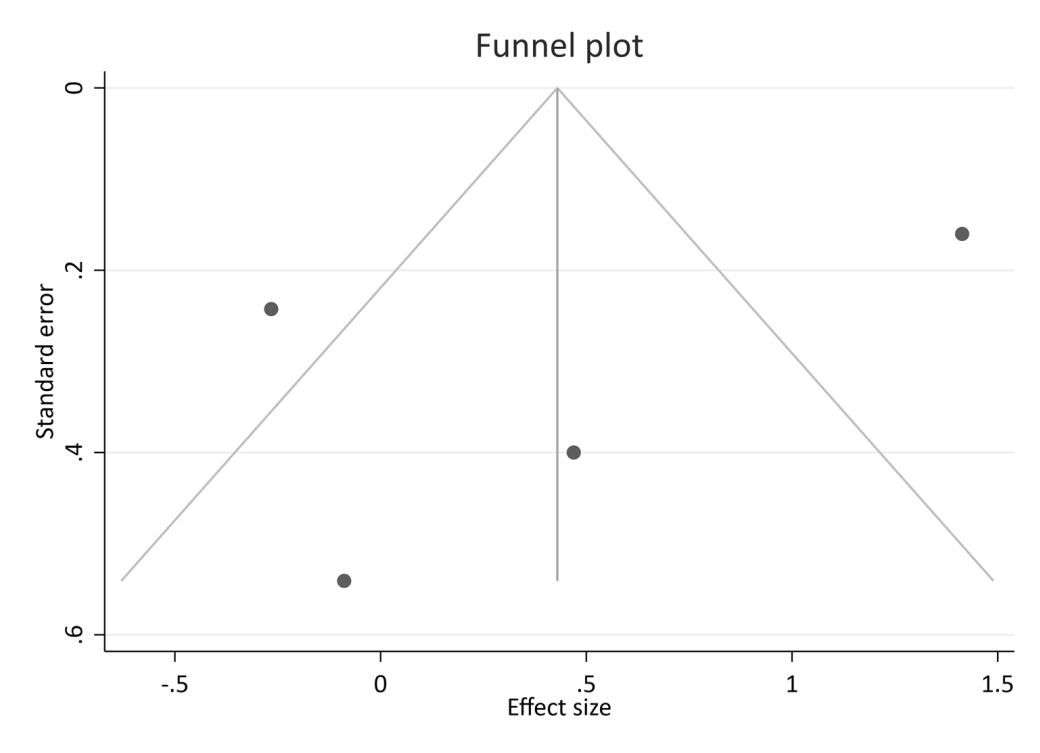

Figure 17: Funnel plot for fullness (AUC).

Desire to eat (DTE) (AUC)

Table 17: Summary of contributing articles for DTE (AUC)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m^2)	n	% female	Age (years)	BMI (kg/m^2)
Andarini, 2017 [47]	Cross-sectional	16	0.0	21.4 (1.9)	33.6 (4.8)	16	0.0	20.6 (1.1)	21.3 (1.1)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Frecka, 2008 [88]	Cross-sectional	5	40.0	32.0 (9.6)	32.2 (1.6)	7	57.0	24.3 (4.2)	23.3 (1.6)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

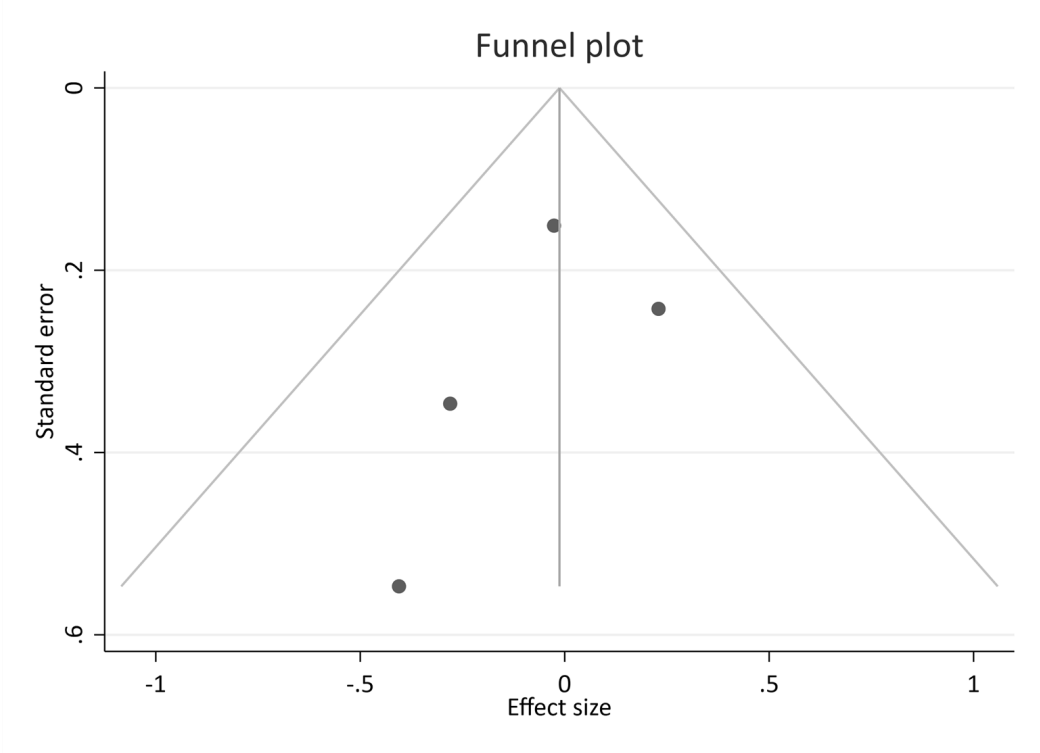

Figure 18: Funnel plot for DTE (AUC).

Prospective food consumption (PFC) (AUC)

Table 18: Summary of contributing articles for PFC (AUC)

Author (year)	Study design	Obesity group				Control group			
		n	% female	Age (years)	BMI (kg/m^2)	n	% female	Age (years)	BMI (kg/m^2)
DeBenedictis, 2020 [16]	Cross-sectional	34	50.0	38.9 (2.0)	34.0 (0.4)	33	49.0	45.0 (1.5)	24.8 (0.4)
Frecka, 2008 [88]	Cross-sectional	5	40.0	32.0 (9.6)	32.2 (1.6)	7	57.0	24.3 (4.2)	23.3 (1.6)
Painchaud Guerard, 2016 [135]	Parallel RCT	51	55.0	44.2 (16.2)	33.1 (3.6)	302	53.0	36.7 (14.7)	24.2 (2.9)
Smith, 2021 [103]	Crossover	12	0.0	34.8 (7.4)	33.7 (2.4)	12	0.0	35.8 (10.6)	23.7 (1.8)

BMI: Body mass index; NR: not reported; Values for age and BMI are presented as mean (SD)

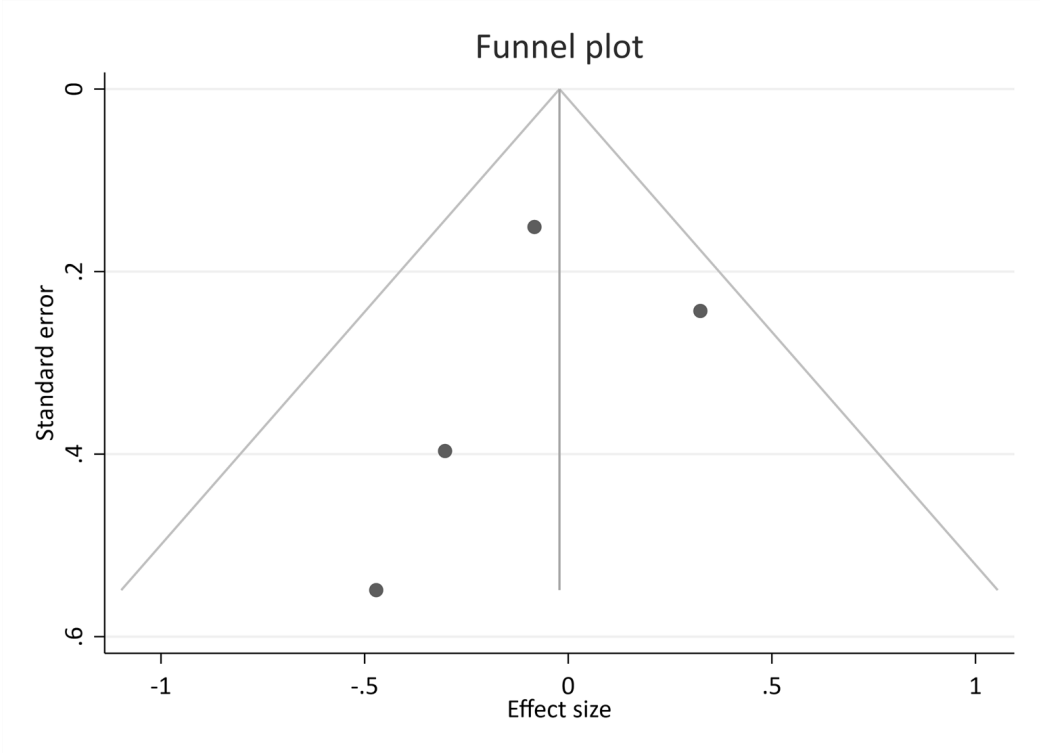

Figure 19: Funnel plot for PFC (AUC).

Supplementary table 19 – Risk of bias assessment

	Non-randomized trials							Randomized control trials					
Author (Year)	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to deviations from intended interventions	5. Bias due to missing data	6. Bias in measurement of the outcome	7. Bias in selection of the reported result	1. Bias arising from the randomization process;	2. Bias due to deviations from intended interventions;	3. Bias due to missing outcome data;	4. Bias in measurement of the outcome	5. Bias in selection of the reported result	6. Overall
Acosta (2015)	low	moderate	low	moderate	moderate	low	low						
Adam (2005)								low	low	NA	moderate	low	moderate
Andarini (2017)	low	low	low	low	NA	moderate/high	low						
Arafat (2013)								low	low	NA	low	low	low
Barkeling (1995)	low	moderate	low	low	NA	moderate	low						
Batterham (2003)								low	low	NA	low	low	low
Bogdanov (2019)	low	low	low	moderate	moderate	moderate	low						
Bowen (2006)								low	low	NA	low	low	low

Brownley (2010)	**moderate**	**moderate**	**low**	**low**	**moderate**	**low**	**low**							
Brownley (2012)	**low**	**moderate**	**low**	**moderate**	**NA**	**low**	**low**							
Cahill (2011)	**low**	**low**	**low**	**low**	**NA**	**moderate**	**low**							
Cahill (2014)	**low**	**low**	**low**	**low**	**moderate**	**moderate**	**low**							
Calanna (2013)	**moderate**	**low**	**low**	**low**	**NA**	**moderate**	**low**							
Carlson (2009)	**low**	**moderate**	**low**	**moderate**	**NA**	**low**	**low**							
Carr (2010)	**low**	**moderate**	**low**	**low**	**NA**	**low**	**low**							
Carroll (2007)	**moderate**	**low**	**low**	**moderate**	**NA**	**low**	**low**							
Cassar (2015)								**low**	**low**	**NA**	**low**	**low**	**low**	
Chearskul (2012)	**low**	**low**	**low**	**low**	**NA**	**low**	**low**							
Chia (2017)								**low**	**low**	**NA**	**moderate**	**low**	**moderate**	
Clamp (2015)	**low**	**low**	**low**	**low**	**NA**	**low**	**low**							
Cremonini (2006)								**low**	**low**	**moderate**	**low**	**low**	**moderate**	
Daghestani (2009)	**moderate**	**moderate**	**low**	**low**	**NA**	**moderate**	**low**							
Damgaard (2013)								**low**	**low**	**NA**	**low**	**low**	**low**	
Dardzinska (2014)	**low**	**low**	**low**	**low**	**NA**	**moderate**	**low**							
DeBenedictis (2020)	**low**	**moderate**	**low**	**low**	**NA**	**moderate**	**low**							
Dirksen (2019)								**low**	**moderate**	**NA**	**low**	**low**	**moderate**	

Douglas (2017)								**low**	**low**	**NA**	**modertae**	**low**	**moderate**
Druce (2005)								**moderate**	**low**	**NA**	**low**	**low**	**moderate**
El Helou (2019)								**low**	**low**	**NA**	**moderate**	**low**	**moderate**
Elahi (2016)	**moderate**	**low**	**low**	**low**	**NA**	**modertae**	**low**						
English (2002)	**moderate**	**low**	**low**	**low**	**NA**	**low**	**low**						
Erdmann (2005)	**low**	**low**	**low**	**low**	**NA**	**low**	**low**						
Espelund (2005)	**low**	**moderate**	**low**	**low**	**NA**	**low**	**low**						
Frecka (2008)	**low**	**low**	**low**	**low**	**NA**	**low**	**low**						
French (1993)								**low**	**low**	**NA**	**low**	**low**	**low**
Greenfield (2009)								**low**	**low**	**NA**	**low**	**low**	**low**
Guo (2007)	**low**	**low**	**low**	**low**	**NA**	**low**	**low**						
Haltia (2010)								**moderate**	**moderate**	**NA**	**low**	**low**	**moderate**
Heden (2013)								**low**	**low**	**NA**	**moderate**	**low**	**moderate**
Heden (2013)								**low**	**low**	**NA**	**modertae**	**loe**	**moderate**
Heni (2015)	**low**	**moderate**	**low**	**low**	**NA**	**moderate**	**low**						
Homaee (2011)	**low**	**moderate**	**low**	**low**	**NA**	**moderate**	**low**						
Iceta (2019)	**low**	**moderate**	**low**	**low**	**low**	**moderate**	**low**						
Karcz-Socha et al. 2011	**low**	**low**	**low**	**low**	**NA**	**low**	**low**						

Kheirouri et al. 2017								low	moderate	NA	moderate	low	moderate
Kiessl et al. 2017								low	moderate	NA	moderate	low	moderate
Kocak et al. 2011	low	moderate	low	low	NA	moderate	low						
Kolodziejski et al. 2018	low	moderate	low	low	NA	low	low						
Korek et al. 2013	low	low	low	low	NA	low	low						
Korner et al. 2005	low	moderate	low	low	low	low	low						
Krzyzanowska-Swinirska (2007)	low	moderate	low	low	NA	low	low						
Lambert et al. 2011								low	moderate	NA	high	low	moderate
Leonetti et al.2003	low	low	low	low	NA	low	low						
Lieverse et al. 1993								low	low	NA	low	low	low
Lieverse et al. 1998								low	low	NA	low	low	low
Lopez-Aguilar et al. 2018	low	moderate	low	low	NA	moderate	low						
Marzullo et al. 2004	moderate	low	low	low	NA	low	low						
Marzullo et al. 2006	low	low	low	low	low	low	low						
Mersebach et al. 2003	low	low	low	low	NA	low	low						
Meyer-Gerspach et al. 2014	low	moderate	low	low	moderate	moderate	low						
Milewicz et al. 2000	low	moderate	low	low	NA	low	low						
Nguyen et al. 2018	low	moderate	low	low	NA	low	low						

Outeiriño-Blanco et al. 2011	**low**	**moderate**	**low**	**low**	**NA**	**low**	**low**						
Ozkan et al. 2009								**low**	**low**	**NA**	**low**	**low**	**low**
Painchaud Guerard et al. 2016								**low**	**moderate**	**moderate**	**low**	**low**	**moderate**
Papandreou et al. 2017	**low**	**low**	**low**	**low**	**NA**	**moderate**	**low**						
Pavlatos et al. 2005								**low**	**low**	**NA**	**low**	**low**	**low**
Pfluger et al. 2007								**low**	**low**	**NA**	**moderate**	**low**	**moderate**
Smith et al. (2021)								**low**	**low**	**NA**	**moderate**	**low**	**moderate**
Verdich et al. (2001)	**low**	**low**	**low**	**moderate**	**NA**	**low**	**low**						

NA= not assessed/applicable

Supplementary table 20. Study characteristics

Study	Participants CO/OB	Test meal composition	Postprandial period	Hormone measure	Basal hormone concentrations CO vs OB	Postprandial hormone response CO vs OB (AUC)	Self-reported appetite ratings CO vs OB (VAS)
Acosta (2015) # (14)	BMI (kg/m^2): 27.6 ± 0.1 / 35.5 ± 3.9 Age: 37.3 ± 12.0 / 37.8 ± 12.1 N (F%): 105 (61%) / 201 (72%)			Total ghrelin [a *]	No difference P=0.063		
Adam (2005) (94)	BMI: 22.9 ± 1.5 / 30.4 ± 2.7 Age: 31.6 ± 12.8 / 44.4 ± 9.8 N (F%): 30 (50%) / 28 (68%)	454 kcal Protein (28.5%) CHO (48.8%) Fat (22.6%) Fiber (NA)	120 minutes 0, 30, 60, 90, 120	Active GLP-1[b *]	No difference P>0.05	CO > OB P=0.03	No differences in fullness or DTE for both fasting and postprandial (P>0.05)
Andarini (2017) (47)	BMI: 21.3 ± 1.1 / 33.6 ± 4.8 Age: 20.6 ± 1.1 / 21.4 ± 1.9 N (F%): 16 (0%) / 16 (0%)	570 kcal Protein (3.2%) CHO (14.8%) Fat (4.6%) Fiber (5.9 g)	120 minutes 0, 30, 60, 120	Active ghrelin [c*]	CO < OB P<0.01	CO < OB P<0.01	No differences in hunger or DTE for both fasting and postprandial (P>0.05)*
Arafat (2013) (26)	BMI: 21.7 ± 2.2 / 34.4 ± 5.6 Age: 25.1 ± 2.2 / 28.4 ± 8.6 N (F%): 13 (54%) / 11 (55%)			Active ghrelin [a*] Total ghrelin [a*]	CO > OB P<0.01, for both		
Barkeling (1995) # (132)	BMI: 22.3 ± 1.9 / 39.4 ± 6.5 Age: 40.0 ± 10.9 / 43.5 ± 12.0 N (F%): 38 (50%) / 38 (50%)						Fasting hunger, DTE, and PFC: CO>OB (P<0.0001) * Fasting fullness: CO<OB (P<0.0001) *
Batterham (2003) (49)	BMI: 20.5 ± 0.3 / 33.0 ± 3.1 Age: 27.3 ± 1.4 / 29.0 ± 8.3 N (F%): 12 (50%) / 12 (50%)			PYY 3-36 [d *] Total ghrelin [e*]	PYY CO > OB P<0.001 Ghrelin CO > OB P<0.001		
Bogdanov (2019) (51)	BMI: 21.8 ± 2.6 / 41.2 ± 2.1 Age: 37.0 ± 7.1 / 38.7 ± 9.4 N (F%): 15 (87%) / 15 (80%)			Total ghrelin [f*]	CO > OB P<0.001		
Bowen (2006) (52)	BMI: 23.3 ± 1.0 / 30.1 ± 3.4 Age: 50.5 ± 12.0 / 56.8 ± 7.5			Total ghrelin [g*] Active GLP-1 [h*]	Ghrelin CO > OB P<0.001		

	N (F%): 25 (0%) / 47 (0%)			CCK [i*]	GLP-1 CO < OB P<0.001 CCK no difference P>0.05	
Brownley (2010) # (120)	BMI: 22.9 ± 1.4 / 34.7 ± 2.8 Age: 27.9 ± 7.0 / 34.9 ± 8.9 N (F%): 20 (50%) / 20 (50%)	625 kcal Protein (14.7%) CHO (55.0%) Fat (30.2%) Fiber (NA)	180 minutes 0, 30, 60, 120, 180	Total PYY [a*]		
Brownley (2012) # (53)	BMI: 22.9 ± 1.4 / 34.7 ± 2.8 Age: 27.9 ± 7.0 / 34.9 ± 8.9 N (F%): 20 (50%) / 20 (50%)	625 kcal Protein (14.7%) CHO (55.0%) Fat (30.2%) Fiber (NA)	180 minutes -20, 30, 60, 90, 105, 120, 135, 150, 180	Total ghrelin [a*]	CO>OB P<0.001	CO> OB P<0.05
Cahill (2011) # (124)	BMI: 23.1 ± 2.3 / 29.1 ± 4.9 Age: 23.1 ± 3.5 / 23.2 ± 2.6 N (F%): 41 (0%) / 28 (0%)			Total PYY [f*]	No difference P>0.05	
Cahill (2014) # (122)	BMI: 24.4 ± 3.1 / 30.6 ± 4.8 Age: 42.2 ± 13.2 / 43.8 ± 12.1 N (F%): 1315 (76%) / 779 (74%)			Total PYY [f*]	No difference P>0.05	
Calanna (2013) (95)	BMI: 22.1 ± 2.0 / 34.6 ± 3.9 Age: 38.3 ± 9.8 / 42.8 ± 13.1 N (F%): 24 (83%) / 43 (67%)			Active GLP-1 [f*]	No difference P>0.05	
Carlson (2009) (54)	BMI: 23.1 ± 1.3 / 44.5 ± 7.1 Age: 32.2 ± 8.6 / 35.6 ± 9.7 N (F%): 10 (100%) / 13 (100%)			Total ghrelin [a*]	CO > OB P=0.001	
Carr (2010) (105)	BMI: 22.3 ± 0.3 / 33.8 ± 0.6 Age: 22.0 ± 1.8 / 25.6 ± 4.0 N (F%): 12 (0%) / 13 (0%)	560 kcal Macronutrient content of meal not specified.	300 minutes 0, 30, 45, 60, 90, 120, 150, 180, 240, 300	Total GLP-1 [j*]	No difference P>0.05	CO > OB P=0.022
Carroll (2007) # (40)	BMI: 22.6 ± 1.3 / 36.8 ± 4.8 Age: 39.2 ± 10.3 / 47.2 ± 10.9	379 kcal (528 ml) Protein (25.4 %)	60 minutes	Active ghrelin [a*] Active GLP-1 [a*]	No differences in ghrelin or GLP-1.	No differences in ghrelin or GLP-1.

	N (F%): 19 (47%) / 20 (55%)	CHO (42.3 %) Fat (7.6 %) Fiber (15.0g)	0, 10, 20, 30, 40, 50, 60		P>0.05	P>0.05	
Cassar (2015) (55)	BMI: 22.0 ± 2.0 / 31.0 ± 3.0 Age: 28.0 ± 6.0 / 35.0 ± 5.0 N (F%): 22 (100%) / 18 (100%)			Total ghrelin [k] Total GLP-1 [k]	Ghrelin CO > OB P<0.05. No difference in GLP-1 P>0.05		
Chearskul (2012) (41)	BMI: 20.7 ± 2.2 / 29.4 ± 3.6 Age: 30.1 ± 5.8 / 33.6 ± 6.3 N (F%): 53 (100%) / 33 (100%)			Active ghrelin [a*]	No difference P>0.05		
Chia (2017) (106)	BMI: 23.6 ± 1.3 / 35.6 ± 4.0 Age: 68.5 ± 13.0 / 68.5 ± 13.0 N (F%): 20 (50%) / 20 (50%)			Total GLP-1 [l*]	No difference P>0.05		
Clamp (2015) (84)	BMI: 22.3 ± 1.6 / 33.2 ± 3.0 Age: 25.0 ± 5.0 / 30.0 ± 6.0 N (F%): 10 (0%) / 10 (0%)			Total ghrelin [g*] Total PYY [a*]	No differences in ghrelin and PYY P>0.05		
Cremonini (2006) (85)	BMI: 22.0 ± 2.0 / 36.0 ± 4.0 Age: 34.0 ± 12.0 / 35.0 ± 8.0 N (F%): 13 (100%) / 25 (80%)			Total ghrelin [a*]	No difference P=0.068		
Daghestani (2009) # (57)	BMI: 22.3 ± 3.3 / 35.9 ± 6.2 Age: 23.5 ± 4.5 / 26.5 ± 6.4 N (F%): 77 (100%) / 45 (100%)	527 kcal Protein 21.5% CHO 54.4% Fat 24.1% Fiber (NA)		Total ghrelin [m*]	CO > OB P<0.001		
Damgaard (2013) # (107)	BMI: 22.1 ± 2.3 / 30.6 ± 3.5 Age: 27.1 ± 6.1 / 32.3 ± 7.7 N (F%): 8 (0%) / 13 (0%)		240 minutes Blood collection: 0, 7.5, 15, 22.5, 30, 37.5, 45, 52.5, 60, 90, 120, 150, 180, 210, 240 VAS: 0, 30, 60, 90, 120, 150, 180, 210, 240	Total GLP-1 [d] CCK [d] PYY 3-36 [n*]	No difference in GLP-1 or CCK P>0.05 No difference in PYY P= 0.15*		No differences in fasting hunger or postprandial hunger or fullness P>0.05 *

Dardzinska (2014) (27)	BMI: 23.0 ± 3.5 / 43.8 ± 6.8 Age: 37.2 ± 9.4 / 35.4 ± 9.1 N (F%): 12 (92%) / 12 (71%)	300 kcal (200 ml) Protein 16.0% CHO 49.0% Fat 35.0% Fiber (NA)	120 minutes Intervals not given	Active ghrelin [o*]	CO > OB P<0.00001	Ghrelin CO > OB P<0.05	
DeBenedictis (2020) (16)	BMI: 24.8 ± 0.4 / 34.0 ± 0.4 Age: 38.9 ± 2.0 / 45.0 ± 1.5 N (F%): 33 (49%) / 34 (50%)	600 kcal Protein (17%) CHO (48%) Fat (35%)	150 minutes Intervals not given	Active ghrelin [ø*] Total GLP-1 [r*] Total PYY [ø*] CCK [r*]		Ghrelin, GLP-1, PYY and CCK CO > OB P<0.001, for all	No differences in fasting or postprandial hunger, fullness, DTE or PFC * P > 0.05
Dirksen (2019) # (104)	BMI: 24.1 ± 3.8 / 57.6 ± 17.2 Age: 43.1 ± 8.9 / 42.1 ± 9.8 N (F%): 10 (0%) / 10 (0%)			Total GLP-1 [d*] PYY 3-36 [n*] CCK [d*]	GLP-1: CO > OB P<0.05 No differences in PYY or CCK P>0.05		No differences in fasting hunger or fullness P>0.05, for both*
Douglas (2017) (42)	BMI: 22.4 ± 1.5 / 29.2 ± 2.9 Age: 37.5 ± 15.2 / 45.0 ± 12.4 N (F%): 22 (44%) / 25 (50%)	610 kcal Protein 10.0 % CHO 72.0 % Fat 18.0 % Fiber (NA)		Active ghrelin [p*] Total GLP-1 [f*] Total PYY [f*]	No differences in ghrelin, GLP-1, or in PYY P>0.05, for all		No differences in hunger, fullness, or PFC (both in fasting and postprandially) P>0.05, for all
Druce (2005) (86)	BMI: 20.5 ± 0.6 / 31.9 ± 3.5 Age: 24.7 ± 4.6 / 33.4 ± 6.9 N (F%): 12 (50%) / 12 (50%)			Total Ghrelin [d*]	No difference. P>0.05		
El Helou (2019) (58)	BMI: 22.0 ± 1.9 / 35.1 ± 3.9 Age: 20.1 ± 1.5 / 21.7 ± 3.5 N (F%): 15 (0%) / 15 (0%)		240 minutes 0, 15, 30, 60, 120, 180, 240	Total ghrelin [q*] Total GLP-1 [f*]	Ghrelin: CO > OB P=0.050 GLP-1: No difference P>0.05		No differences in fasting hunger, fullness, or PFC P>0.05
Elahi (2016) (96)	BMI: 22.3 ± 1.4 / 37.2 ± 5.2 Age: 29.0 ± 6.4 / 42.0 ± 6.9 N (F%): 12 (50%) / 12 (50%)			Total GLP-1 [b*] Active GLP-1 [b]	total GLP-1 not compared No difference in active GLP-1		
English (2002) (28)	BMI: 22.5 ± 1.9 / 42.8 ± 6.4 Age: 32.0 ± 8.3 / 42.8 ± 7.0 N (F%): 13 (60%) / 10 (30%)	632 kcal Protein 12.2% CHO 56.8%	180 minutes 0, 15, 30, 60, 120, 180	Total ghrelin [d*]	CO > OB P=0.002		

		Fat 31.0% Fiber (NA)					
Erdmann (2005) (59)	BMI: 22.0 ± 2.2 / 33.8 ± 5.7 Age: 30.0 ± 10.5 / 45.0 ± 13.6 N (F%): 56 (80%) / 128 (36%)	260 kcal Protein 6.0% CHO 62.0% Fat 32.0% Fiber (NA)	180 minutes -15, 0, 15, 30, 60, 90, 120, 150, 180	Total ghrelin [g*]	CO > OB P<0.01		
Espelund (2005) (87)	BMI: 23.4 ± 2.5 / 29.5 ± 4.0 Age: 33.7 ± 14.0 / 39.7 ± 12.4 N (F%): 17 (47%) / 16 (56%)			Total ghrelin [r*]	No difference P>0.05		
Frecka (2008) (88)	BMI: 23.3 ± 1.6 / 32.2 ± 1.6 Age: 24.3 ± 4.2 / 32.0 ± 9.6 N (F%): 7 (57%) / 5 (40%)	501 ± 218 kcal Protein (11.1%) CHO (47.2%) Fat (29.7%)	330 minutes Intervals not given	Total ghrelin [a*]	No difference P>0.05	No difference P>0.05	No differences in fasting hunger, fullness, DTE, or PFC P>0.05, for all
French (1993) (18)	BMI: (20-25) / (<30) Age: (22-44) / (21-48) N (F%): 7 (57%) / 8 (63%)	317 kcal Macronutrient content of meal not specified	180 minutes 0, 10, 20, 30, 60, 90, 120, 150, 180	CCK [d*]	CO < OB P<0.01	CO < OB P<0.05	No differences in fasting hunger, fullness or DTE, P>0.05, for all. Postprandial hunger CO > OB P<0.05. No differences in postprandial fullness or DTE P>0.05, for both
Greenfield (2009) (108)	BMI: 21.9 ± 2.2 / 34.5 ± 4.4 Age: 30.0 ± 5.8 / 39.0 ± 9.8 N (F%): 7 (57%) / 8 (63%)			Total GLP-1 [d*]	No difference P>0.05		
Guo (2007) (60)	BMI: 21.6 ± 1.7 / 30.1 ± 1.9 Age: 54.4 ± 5.4 / 59.4 ± 7.3 N (F%): 16 (50%) / 14 (50%)	500 - 600 kcal Macronutrient content of meal not specified	Blood collection at 0 minutes	Total ghrelin [g*]	CO > OB P<0.01		
Haltia (2010) (89)	BMI: 21.7 ± 1.3 / 33.0 ± 4.5 Age: 26.0 ± 5.0 / 27.0 ± 6.0 N (F%): 12 (50%) / 13 (38%)			Total ghrelin [a*] PYY 3-36 [a*] Total GLP-1 [b*]	No differences in ghrelin, PYY or GLP-1 P>0.05, for all		

Heden (2013) (97)	BMI: 23.0 ± 1.8 / 34.6 ± 3.6 Age: 26.0 ± 7.2 / 25.4 ± 3.6 N (F%): 13 (46%) / 13 (54%)	600 kcal Protein (15%) CHO (45%) Fat (40%)	240 minutes 0, 5, 10, 15, 20, 30, 40, 50, 60, 75, 90, 120, 150, 180, 210, 240	Active GLP-1 [s*]		No difference P>0.05	
Heden (2013) (29)	BMI: 22.9 ± 1.7 / 34.8 ± 4.4 Age: 26.0 ± 6.0 / 25.1 ± 5.0 N (F%): 14 (43%) / 14 (57%)	600 kcal Protein (15%) CHO (45%) Fat (40%)	Blood collection at 0 minutes	Active ghrelin [s*]	No difference P=0.06		No differences in fasting hunger and fullness P>0.05, for both
Heni (2015) (109)	BMI: 21.2 ± 3.8 / 30.5 ± 6.2 Age: 23.0 ± 6.9 / 25.0 ± 6.9 N (F%): 12 (50%) / 12 (50%)			Total GLP-1 [t*]	No difference P>0.05		
Homaee (2011) (30)	BMI: 18.5 ± 2.2 / 31.0 ± 3.6 Age: 26.9 ± 5.6 / 27.5 ± 5.8 N (F%): 19 (0%) / 19 (0%)			Active ghrelin [u*]	CO > OB P=0.008		
Iceta (2019) (31)	BMI: 21.5 ± 2.2 / 41.5 ± 5.9 Age: 37.0 ± 10.8 / 38.0 ± 11.1 N (F%): 29 (100%) / 55 (100%)			Active ghrelin [o*]	CO > OB P<0.001		No differences in fasting hunger P>0.05
Karcz-Socha (2011) # (45)	BMI: 23.4 ± 1.5 / 35.7 ± 2.9 Age: 51.2 ± 6.5 / 51.5 ± 6.5 N (F%): 46 (52%) / 96 (50%)			Active ghrelin [a*] Total ghrelin [a*] PYY 3-36 [a*]	No difference in acylated ghrelin. Total ghrelin CO > OB P<0.001 PYY CO > OB P<0.001		
Kheirouri (2017) (62)	BMI: 23.1 ± 0.8 / 31.4 ± 0.7 Age: 35.2 ± 7.9 / 37.2 ± 7.5 N (F%): 40 (100%) / 37 (100%)			Total ghrelin [v*]	CO > OB P = 0.03		
Kiessl (2017) (63)	BMI: 21.7 ± 2.0 / 31.5 ± 1.8 Age: 18-30 / 18-30 N (F%): 42 (100%) / 43 (100%)	500 g pudding, eat as much as wanted. per100 g 158 kcal	60 minutes 0, 30, 60	Total ghrelin [f*]	CO > OB P<0.001	CO > OB P<0.001	
Kocak (2011) (64)	BMI: 25.2 ± 1.7 / 34.1 ± 4.0 Age: 58.6 ± 10.3 / 53.0 ± 8.5 N (F%): 19 (100%) / 22 (100%)			Total ghrelin [w*]	CO > OB P<0.001		

Kolodziejski (2018) (43)	BMI: 22.3 ± 0.5 / 39.8 ± 1.0 Age: 42.9 ± 5.3 / 42.2 ± 3.3 N (F%): 15 (100%) / 15 (100%)			Active ghrelin [n*] Total ghrelin [n*] Total GLP-1 [m]	Acylated ghrelin: CO < OB P<0.01 No difference for total ghrelin or GLP-1 P>0.05	
Korek (2013) (32)	BMI: 21.1 ± 1.85 / 34.7 ± 4.92 Age: 19-35 / 20-35 N (F%): 17 (89%) / 19 (90%)	260 kcal Protein (8%) CHO (43%) Fat (49%)	Blood collection at 0 and 120 minutes after breakfast	Active ghrelin [a*] Total ghrelin [n*]	CO > OB P<0.05	
Korner (2005) (90)	BMI: 21.6 ± 0.7 / 34.1 ± 1.8 Age: 30.6 ± 3.6 / 44.3 ± 4.3 N (F%): 8 (100%) / 12 (100%)	320 kcal Protein (35%) CHO (50%) Fat (15%)		Total ghrelin [g*] PYY 3-36 [g*]	No difference Ghrelin, P = 0.1 PYY, P>0.05	No differences in fasting hunger or fullness P>0.05
Krzyzanowska-Swinirska (2007) (46)	BMI: 21.3 ± 1.7 / 34.4 ± 4.1 Age: 28.8 ± 4.8 / 32.5 ± 6.5 N (F%): 32 (100%) / 30 (100%)			Active ghrelin [a*]	No difference	
Lambert (2011) # (91)	BMI: 21.3 ± 0.6 / 29.3 ± 0.6 Age: 21.5 ± 0.5 / 20.8 ± 0.6 N (F%): 11 (0%) / 11 (0%)			Total ghrelin [x*]	No difference	
Leonetti (2003) (65)	BMI: 23.0 ± 2.5 / 35.9 ± 3.6 Age: 40.2 ± 10.6 / 41.2 ± 11.6 N (F%): 10 (50%) / 8 (70%)			Total ghrelin [g*]	CO > OB P<0.01	
Lieverse (1993) (126)	BMI: 22.3 ± 2.1/ 40.7 ± 6.6 Age: 41.2 ± 11.6 / 40.2 ± 10.6 N (F%): 7 (100%) / 7 (100%)			CCK [d*]	No difference	
Lieverse (1998) (125)	BMI: 39 ± 2.0 / 22 ± 0.3 Age: 43 ± 3 / 42 ± 3 N (F%): 7 (100%) / 7 (100%)			CCK [d*]	CO > OB P<0.05	

Lopez-Aguilar (2018) (33)	BMI: 22.7 ± 1.5 / 35.4 ± 5.2 Age: 26.4 ± 5.6 / 29.2 ± 6.3 N (F%): 80 (67%) / 50 (52%)			Active ghrelin [v*]	CO > OB P=0.009	
Marzullo (2004) (35)	BMI: 22.4 ± 0.6 / 41.3 ± 1.1 Age: 31.7 ± 1.3 / 32.4 ± 1.6 N (F%): 20 (50%) / 20 (50%)			Active ghrelin [a*] Total ghrelin [g]	CO > OB P<0.05	
Marzullo (2006) (17)	BMI: 21.8 ± 1.4 / 43 ± 0.9 Age: 33.5 ± 2.4 / 31.8 ± 2.5 N (F%): 6 (50%) / 10 (50%)	500 kcal Liquid meal Proteins (17%) CHO (53%) Fat (30%)	120 minutes 0, 20, 40, 60, 80, 100, 120	Total ghrelin [g*]		CO > OB P<0.01
Mersebach (2003) (98)	BMI: 21.5 ± 1.3 / 36.1 ± 2.4 Age: 37.9 ± 5.9 / 39.3 ± 3.5 N (F%): 10 (70%) / 16 (75%)			Active GLP-1 [d*]	No difference	
Meyer-Gerspach (2014) (15)	BMI: 21.8 ± 0.4 / 39.3 ± 1.9 Age: 24.1 ± 0.6 / 29.8 ± 1.9 N (F%): 20 (NA%) / 20 (NA%)	750 kcal (500ml) Liquid meal Protein (17%) CHO (54%) Fat (29%)	180 minutes −1, 30, 60, 120, 180	Total ghrelin [a*] Active GLP-1 [f*] Total PYY [a*]	Ghrelin: CO > OB P = 0.027	Ghrelin: CO > OB P = 0.001 GLP-1: CO > OB P<0.001 PYY: CO > OB P<0.001
Milewicz (2000) # (127)	BMI: 21.2 ± 0.4 / 34.6 ± 1.4 Age: NA / NA N (F%): 16 (NA%) / 25 (NA%)			CCK [v*]	No difference	
Nguyen (2018) (110)	BMI: 23.9 ± 0.7 / 48.6 ± 1.8 Age: 38.6 ± 8.4 / 50.2 ± 2.5 N (F%): 10 (59%) / 22 (50%)	302 kcal 50 g minced beef 150 ml dextrose solution 75 g glucose loading	240 minutes −2, 15, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240	Total GLP-1 [d*]	No difference	
Outeiriño-Blanco (2011) (67)	BMI: 22.3 ± 0.7 / 38.8 ± 1.2 Age: 34.4 ± 3.6 / 39.8 ± 2.9 N (F%): 13 (100%) / 23 (100%)	75 g glucose loading	150 minutes 0, 30, 60, 90, 120, 150	Total ghrelin [a*] PYY 1-36[a*]	Ghrelin: CO > OB P= 0.01 PYY: no difference	Ghrelin: CO > OB P= 0.026 PYY: no difference

Ozkan (2009) (68)	BMI: 24.8 ± 3.1 / 37 ± 3.6 Age: 36.1 ± 9.8 / 37.4 ± 12.4 N (F%): 10 (60%) / 21 (71%)			Total ghrelin [z*]	CO > OB P= 0.001		
Painchaud Guerard (2016) # (135)	BMI: 24.2 ± 2.9 / 33.15 ± 3.6 Age: 36.7 ± 14.7 / 44.2 ±16.2 N (F%): 302 (53%) / 51 (55%)	Ad libitum oatmeal raisin snack	60 minutes -10, 0, 20, 40, 60				No differences in fasting or postprandial hunger, fullness, DTE or PFC *
Papandreou (2017) (69)	BMI: 20.6 ± 3 / 31.3 ± 2.1 Age: 21 ± 0.8 / 21 ± 2.07 N (F%): 13 (NA%) / 7 (NA%)			Total ghrelin [w*]	CO > OB P= 0.002		
Pavlatos (2005) (70)	BMI: 22.9 ± 2.1 / 37.2 ± 8.4 Age: 38.7 ± 14.1 / 39.5 ± 14.5 N (F%): 9 (100%) / 9 (100%)			Total ghrelin [a*]	CO > OB P= 0.001		
Pfluger (2007) # (117)	BMI: 22.1 ± 0.2 / 35.1 ± 4.8 Age: 41.5 ± 2.2 / 47.7 ± 2.9 N (F%): 66 (70%) / 79 (73%)			Total PYY [æ*]	No difference		
Pfluger (2007) # (117)	BMI: 22.0 ± 0.5 / 31.1 ± 0.5 Age: 51.6 ± 1.9 / 52.0 ± 2.0 N (F%): 17 (100%) / 15 (100%)			PYY 3-36 [a*]	No difference		
Smith (2021) # (103)	BMI: 23.7 ± 1.8 / 33.7 ± 2.4 Age: 35.8 ± 10.6 / 34.8 ± 7.4 N (F%): 12 (0%) / 12 (0%)	387 kcal Protein (15%) CHO (58%) Fat (27%)	240 minutes	Active GLP-1 [å*] Total GLP-1 [å*]	No difference in active GLP-1 Total GLP-1: CO<OB P <0.05		No differences in postprandial hunger, fullness, or PFC*
Verdich (2001) (113)	BMI: 23.1 ± 1.4 / 38.1 ± 3.1 Age: 24.2 ± 9.6 / 35.0 ± 10.9 N (F%): 12 (0%) / 19 (0%)	597 kcal Protein (20%) CHO (50%) Fat (30%)	180 minutes 0, 20, 40, 60, 80, 100, 120, 140, 160, 180	Total GLP-1[d*]		CO > OB P<0.01	

AUC: area under the curve. BMI: body mass index. CCK: cholecystokinin. CHO: carbohydrate. CO: control. DTE: desire to eat. GLP-1: glucagon-like peptide 1. NA: not assessed/compared. OB: obesity. PFC: prospective food consumption. PYY: peptide YY. VAS: visual analogue scale. Superscript letters denote hormone analyses method used: [a]RIA (Linco Research, Inc., St. Charles, MO). [b]ELISA (Linco, St. Charles, MO, USA). [c]ELISA (Elabscience, Biotechnology, Beijing). [d]RIA manufacturer not specified. [e] Hormone assay not specified. [f]ELISA (Millipore Corporation Pharmaceuticals, Billerica, MA). [g]RIA (Phoenix Pharmaceuticals, Belmont, CA). [h]Fluorescence immunoassay (Linco). [i]RIA (Euria-Diagnostica, Malmo, Sweden). [j]Amino terminal-specific assay (Linco Research). [k]Bio-Plex Pro Diabetes assay (CAT#171-A7001M; Biorad Laboratories, Hercules, CA, USA). [l]ELISA (Alpco Diagnostics, Salem, NH). [m]ELISA (Phoenix Pharma-ceuticals, INc (Belmont, CA)). [n]RIA (Millipore, Billerica, MA, USA). [o]Human Acylated Ghrelin EIA Kit (Biovendor, Czech Republic). [p]ELISA (SPI BIO, Montigny le Bretonneux, France). [q]ELISA (EMD Millipore Corp., St. Charles, Missouri). [r]«inhouse » RIA. [s]MILLIPLEX magnetic bead-based quantitative multiplex immunoassay with the MAGPIX instrumentation (Millipore, Billerica, MA). [t]ELISA (Millipore, Watford, UK). [u]ELISA (Acylated ghrelin Human ELISA, BioVendor, Germany. [v]ELISA, inspecified. [w]Immunochemilunometric assay, (IDS, SMBH, Germany). [x]ELISA (Phoenix Pharmaceuticals, Inc, Burlingame, CA). [y]RIA (Peninsula Lab., Belniont, CA). [z]RIA (Phoenix, Europe, Kalsruhe, Germany). [æ]ELISA (Diagnostic Systems Laboratories, Webster, TX). [ø]Human Metabolic Hormone Magnetic Bead Panel (LINCOplex Kit, Millipore, St Louis, MO). [å]ELISA (Merck Millipore). Stars * denote that data was included in meta-analysis. # denotes that group characteristics was merged for the purpose of this analysis.

Appendix II

Supplementarty file: Differences in gastrointestinal hormones and appetite ratings among obesity classes.

Authors: Marthe Isaksen Aukan [1], Siren Nymo [1,2,3], Karoline Haagensli Ollestad [1], Guro Akersveen Boyesen [1], Julia Nicole DeBenedictis [1], Jens Frederik Rehfeld [4], Silvia Coutinho [1] and Catia Martins [1,3].

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Table 1. Mean basal and postprandial concentrations of gastrointestinal hormones (without adjusting for age, sex and total physical activity level).

	Controls	OB	OB I	OB II	OB III
Basal ghrelin (pmol/l)	70.2 ± 4.5 [abcd]	29.6 ± 3.1 [a (<0.001)]	32.4 ± 5.2 [b (<0.001)]	30.7 ± 4.5 [c (<0.001)]	21.5 ± 7.2 [d (<0.001)]
Ghrelin tAUC (pmol/l *min)	7596.6 ± 481.0 [abcd]	3027.9 ± 327.1 [a (<0.001)]	3341.6 ± 553.2 [b (<0.001)]	3046.3 ± 481.0 [c (<0.001)]	2372.9 ± 770.0 [d (<0.001)]
Ghrelin iAUC (pmol/l *min)	-2934.0 ± 328.8 [abcd]	-1441.4 ± 224.1 [a (<0.001)]	-1518.5 ± 378.2 [b (0.033)]	-1615.0 ± 328.8 [c (0.032)]	-846.8 ± 526.4 [d (0.006)]
Basal GLP-1 (pmol/l)	1.3 ± 0.9	2.6 ± 0.6	2.3 ± 0.9	2.5 ± 0.9	3.3 ± 1.4
GLP-1 tAUC (pmol/l *min)	1007.9 ± 120.8 [a]	655.0 ± 81.9 [a (0.017)]	687.9 ± 138.9	623.9 ± 120.8	676.7 ± 193.4
GLP-1 iAUC (pmol/l *min)	816.7 ± 57.9 [abcd]	268.7 ± 39.6 [a (<0.001)]	341.5 ± 66.7 [b (<0.001)]	246.7 ± 57.9 [c (<0.001)]	184.3 ± 92.8 [d (<0.001)]
Basal PYY (pmol/l)	26.1 ± 3.4 [ac]	11.8 ± 2.4 [a (0.001)]	13.9 ± 4.1	10.9 ± 3.6 [c (<0.017)]	9.9 ± 5.6
PYY tAUC (pmol/l *min)	5135.6 ± 466.5 [abcd]	2206.9 ± 336.3 [a (<0.001)]	2732.3 ± 567.2 [b (0.009)]	1978 ± 505.1 [c (<0.001)]	1786.5 ± 754.4 [d (0.002)]
PYY iAUC (pmol/l *min)	1228.1 ± 175.4 [acd]	425.8 ± 126.2 [a (<0.001)]	601.7 ± 213.2	341.5 ± 189.9 [c (0.005)]	302.6 ± 283.6 [d (0.040)]
Basal CCK (pmol/L)	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.9 ± 0.1	1.2 ± 0.2
CCK tAUC (pmol/L*min)	428.1 ± 24.5	391.9 ± 17.3	403.7 ± 29.2	393.6 ± 25.4	364.5 ± 40.7
CCK iAUC (pmol/L*min)	292.4 ± 19.0 [ad]	237.2 ± 13.6 [a (0.020)]	253.2 ± 22.7	247.5 ± 19.7	179.8 ± 31.6 [d (0.017)]
Basal insulin (pmol/l)	2826.9 ± 497.4 [abcd]	6581.7 ± 366.6 [a (<0.001)]	5767.6 ± 602.4 [b (0.002) f]	6202 ± 515.3 [c (<0.001) g]	9080 ± 824.8 [d (<0.001) f (0.009) g (0.022)]
Insulin tAUC (pmol/l *min)	1761430.3 ± 272438.2 [abcd]	3794870.2 ± 207411.0 [a (<0.001)]	3321542.6 ± 329939.1 [b (0.002) f]	3414972.6 ± 282229.5 [c (<0.001) g]	5655847.1 ± 451787.7 [dfg (<0.001)]
Insulin iAUC (pmol/l *min)	1337531.5 ± 231763.4 [abcd]	2771771.0 ± 175484.5 [a (<0.001)]	2456408.3 ± 280679.4 [b (0.016) f]	2408587.1 ± 2400902.8 [c (0.01) g]	4293757.8 ± 384336.0 [dfg (<0.001)]

Data presented as estimated marginal means ± SEM. Conversion from metric to SI units has been made in table 2 and figure 1 and is as follows: ghrelin pg/mL × 0.3 = pmol/L, GLP-1 pg/mL x 0.33 = pmol/L, PYY pg/mL × 0.25 = pmol/L, and insulin pg/mL x 6 = pmol/L. CCK: cholecystokinin. GLP-1: glucagon-like peptide-1. iAUC: incremental area under the curve. OB: obese. PYY: peptide YY. tAUC: total area under the curve. Mean values with equal superscript letter denote significant differences between groups (P<0.05).

Table 2. Mean fasting and postprandial subjective appetite ratings (without adjusting for age, sex and total physical activity level).

	Controls	OB	OB I	OB II	OB III
Fasting hunger (mm)	45.3 ± 3.2 [a]	37.6 ± 2.2 [a] **(0.049)**	38.4 ± 3.6	37.9 ± 3.3	35.4 ± 4.9
Hunger tAUC (mm*min)	3193.6 ± 360.4	343 ± 25.9	3775.1 ± 408.6	3644.7 ± 364.4	3354.4 ± 554.6
Hunger iAUC (mm*min)	-3279.8 ± 453.4	-2425.9 ± 307.8	-2001.6 ± 514.1	-2965.1 ± 458.5	-1958.8 ± 697.7
Fasting fullness (mm)	23.9 ± 2.8	22.4 ± 1.9	17.9 ± 3.2	26.7 ± 2.8	20.5 ± 4.3
Fullness tAUC (mm*min)	8496.3 ± 383.1	8925.1 ± 260.5	8404.3 ± 434.4	9393.8 ± 387.4	8798.8 ± 589.5
Fullness iAUC (mm*min)	4903.1 ± 496.5	5567.7 ± 334.3	5708.6 ± 562.9	5386.4 ± 502.1	5727.8 ± 764.1
Fasting DTE (mm)	46.5 ± 2.9	46.7 ± 1.9	46.1 ± 3.3	45.3 ± 2.9	40.6 ± 4.5
DTE tAUC (mm*min)	3394.5 ± 391.0	4006.1 ± 266.9	4635.6 ± 443.4	3440.3 ± 395.4	4154.9 ± 601.7
DTE iAUC (mm*min)	-3582.2 ± 390.6 [a]	-2699.3 ± 267.8 [a] **(0.067)**	-2281.1 ± 442.9	-3363.2 ± 395.0	-1932.4 ± 601.1
Fasting PFC (mm)	59.9 ± 3.1	57.6 ± 2.2	62.1 ± 3.6	52.0 ± 3.2	62.3 ± 4.8
PFC tAUC (mm*min)	5329.4 ± 510.9 [a]	6447.7 ± 350.1 [a] **(0.077)**	7035.5 ± 579.4	5475.9 ± 516.7	7615.4 ± 786.4
PFC iAUC (mm*min)	-3657.3 ± 424.4 [ad]	2184.4 ± 286.2 [a] **(0.005)**	-2273.4 ± 481.3	-2311.8 ± 429.2	-1725.5 ± 653.2 [d] **(0.086)**

Data presented as estimated marginal means ± SEM. DTE: desire to eat. iAUC: incremental area under the curve. OB: obese. PFC: prospective food consumption. tAUC: total area under the curve. Mean values with equal superscript letter denote differences between groups (P<0.05).

Appendix III

FORESPØRSEL OM DELTAKELSE I FORSKNINGSPROSJEKTET

Effekt av diett /kost-indusert vekttap vs fedmekirurgi på appetitt

BAKGRUNN OG HENSIKT

Dette er en forespørsel om du vil delta i en studie hvor vi ønsker å sammenligne hvilken effekt diett-indusert vekttap og vekttap etter fedmekirurgi (Sleeve Gastrectomy (SG) eller Roux-en Y Gastric Bypass (RYGB)) har på appetitt.

Pasienter godkjent for kirurgi og pasienter i forløp på fedmepoliklinikken ved St.Olavs Hospital og Namsos sykehus vil bli rekruttert til en av tre følgende grupper: Diett, SG, RYGB. Oppslag for rekruttering til diett gruppen vil også bli lagt ut på NTNU og St.Olavs intranett, samt Friskliv og Mestring i Trondheim Kommune. Alle deltagere i studien går gjennom en 10 ukers veldig-lav-kalori diett uavhengig om de skal til kirurgi eller ikke og dato for kirurgi vil ikke bli berørt.

Problemsstillinger for studien er:

- Hvordan påvirkes lysten på mat og spiseatferd av tilsvarende (likt) vekttap oppnådd ved diett eller fedmekirurgi?
- Hvordan påvirkes appetittregulerende hormoner av tilsvarende vekttap oppnådd ved diett eller fedmekirurgi?
- Hvordan påvirkes tarmens bakterieflora av tilsvarende vekttap oppnådd ved diett eller kirurgi?
- Kan forandringer i sultfølelse, appetittregulerende hormoner, tarmens bakterieflora eller hjernens funksjon som skjer ved vekttap ha noe å si for vekttap etter 1 år?

NTNU, Norges teknisk-naturvitenskapelige universitet er ansvarlig for studien.

HVA INNEBÆRER PROSJEKTET?

Pasienter som skal til kirurgi følger det vanlige løpet i klinikken, inkludert veldig-lav energi diett 2 uker før kirurgi og de 8 første ukene etter (dietten er en del av klinisk praksis ved begge sykehusene). Kontrollgruppen (diettgruppen) får en 10-ukers veldig-lav energi diett. En slik diett kan gi noen bivirkninger (beskrevet senere).

Alle gruppene innkalles til 3 testdager. Undersøkelsene på testdagene er de samme uansett hvilken gruppe deltageren kommer i, og disse innebærer blodprøver før og etter et måltid, urinprøver, måling av energibehov, kroppssammensetning, avføringsprøver, samt ulike former for spørreskjema. Disse variablene skal testes ved baseline (før oppstart), etter vekttap (uke 11) og etter 1 år. Testdagene tar totalt ca. 4 timer på hvert tidspunkt. Deltagerne følges for øvrig opp i tråd med standard pasientforløp ved sykehuset vedkommende er i forløp.

MULIGE FORDELER OG ULEMPER

Pasienter som skal til fedmekirurgi vil få hjelp, og ukentlig oppfølging, til den pre- og post-operative lavkalori kuren. Pasienter som deltar i kontrollgruppen får hjelp til å komme i gang med vekttap og

ukentlig oppfølging gjennom hele diett-intervensjonen. Deltakelse kan også gjøre at du blir bedre kjent med appetitt-mekanismene i kroppen din. Deltageren vil også få informasjon om sin kroppssammensetning og energibehov. Studien anses ikke som risikabel, men undersøkelsene innebærer noen blodprøver.

Lavkalorikuren kan ha flere bivirkninger. Omfanget av disse varierer fra person til person og kan være enten helt fraværende eller temmelig plagsomme. Bivirkningene er forbigående. Rapporterte bivirkninger er:

- slapphet
- svimmelhet
- forstoppelse
- hårtap
- tørr hud
- neglene kan bli sprøere
- kvalme
- diaré
- forstyrret menstruasjonssyklus
- økt kuldefornemmelse

Fedmekirurgi er assosiert med sjeldne, men noen ganger alvorlig komplikasjoner. Du kan bare delta i dette prosjektet hvis du har fått godkjenning til det fra lege. Det betyr at det er flere fordeler ved vekttap, enn ulemper med mulige komplikasjoner ved å delta i denne studien.

FRIVILLIG DELTAKELSE OG MULIGHET FOR Å TREKKE SITT SAMTYKKE

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, undertegner du samtykkeerklæringen på siste side. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling. Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte studiekoordinator Catia Martins, telefon 72825358 eller Siren Nymo, telefon 74098014.

HVA SKJER MED OPPLYSNINGENE OM DEG?

Prøvene tatt av deg og informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer, eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger og prøver gjennom en navneliste. Noen helseopplysninger vil også lagres i din pasientjournal, og disse vil være knyttet til ditt personnummer.

Det er kun autorisert personell knyttet til prosjektet, som har adgang til navnelisten og som kan finne tilbake til deg. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Ulike opplysninger vil registreres om deg som del av dette prosjektet. Prøvesvar og innledende screeningnotat vil legges i din pasientjournal og er derfor personidentifiserbart. Opplysninger på bakgrunn av testene du gjennomgår og intervjuet vil lagres på NTNU server og vil være avidentifiserte så lenge studien pågår (det vil si at et unikt ID-nummer erstatter navnet ditt). Kodenøkkelen som knytter navn til nummer makuleres 5 år etter at studien er slutt, slik at data da anonymiseres. Alle som jobber med data fra studien har taushetsplikt.

NTNU ved administrerende direktør er databehandlingsansvarlig

HVA SKJER MED PRØVER SOM BLIR TATT AV DEG?

Blodprøvene for analyser av appetitthormoner som blir tatt vil bli lagret i en forskningsbiobank ved Institutt for Klinisk og Molekylær Medisin (NTNU). Hvis du sier ja til å delta i studien, gir du også samtykke til at det biologiske materialet og analyseresultater inngår i biobanken. Prosjektleder Catia Martins er ansvarshavende for forskningsbiobanken. Det biologiske materialet kan bare brukes etter godkjenning fra Regional komité for medisinsk og helsefaglig forskningsetikk (REK). Biobanken opphører ved prosjektslutt

Noen plasmaprøver skal sendes til Universitet i København for å analysere CCK og GLP-1 konsentrasjon. Disse prøvene destrueres ved prosjektslutt.

FORSIKRING

Du er dekket gjennom Norsk pasientskadeerstatning jfr. Pasientskadelovens § 1.

ØKONOMI

Det er ingen økonomisk kompensasjon for å delta i studien. Du får dekket 10 uker med VLED produkter i intervensjonsperioden.

GODKJENNING

Regional komité for medisinsk og helsefaglig forskningsetikk har vurdert prosjektet, og har gitt forhåndsgodkjenning REK **2019/252**. Studien er registrert i Clinicalrials.gov (ref: NCT04051190)

Etter ny personopplysningslov har behandlingsansvarlig NTNU og prosjektleder Catia Martins et selvstendig ansvar for å sikre at behandlingen av dine opplysninger har et lovlig grunnlag. Dette prosjektet har rettslig grunnlag i EUs personvernforordning artikkel 6 nr. 1a og artikkel 9 nr. 2a og ditt samtykke.

Du har rett til å klage på behandlingen av dine opplysninger til Datatilsynet.

KONTAKTOPPLYSNINGER

Dersom du har spørsmål til prosjektet kan du ta kontakt med Catia Martins, telefon 72825358 prosjektleder, Siren Nymo, bi-veileder, telefon 99514188, siren.nymo@ntnu.no; eller Marthe Aukan, PhD kandidat, telefon 92804568, mail: marthe.i.aukan@ntnu.no

Personvernombud ved institusjonen er Thomas Helgesen (thomas.helgesen@ntnu.no).

JEG SAMTYKKER TIL Å DELTA I PROSJEKTET OG TIL AT MINE PERSONOPPLYSNINGER OG MITT BIOLOGISKE MATERIALE BRUKES SLIK DET ER BESKREVET

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver
Sted og dato	Signatur
	Rolle i prosjektet

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