# Does an increased intake of dietary proteins lead to improvements in perceptions of appetite in people with obesity during a period of calorie restriction?

*A systematic review*

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Självständigt arbete i klinisk nutrition 15 hp
Dietistprogrammet 180/240 hp
Handledare: Therese Karlsson
Examinator: Sofia Klingberg
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## Sammanfattning

Titel: Leder ett högre proteinintag till förbättrade aptitrelaterade känslor hos obesa personer under en period av kalorirestriktion?

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***Bakgrund*:** Övervikt och fetma är en växande pandemi på global skala. Protein har länge ansetts ge positiv effekt på mättnad och aptit, vilket, om använt, skulle kunna leda till en mer effektiv viktminskningsbehandling hos överviktiga och obesa.

***Syfte*:** Syftet med denna systematiska översikt är att undersöka huruvida det finns evidens för om en ökad mängd protein (från tillskott och ordinarie livsmedel) kan ge förbättrade aptitrelaterade känslor jämfört med ett lägre intag vid kaloriunderskott hos personer som lider av övervikt och fetma.

***Sökväg:*** Den systematiska litteratursökningen skedde i två databaser: PubMed och Scopus. Sökord var MeSH termer skapade från orden: Protein, Hunger, Appetite, Satiation, Caloric Restriction, Hypocaloric, Energy restriction, RCT, Control.

***Urvalskriterier*:** Inklusionskriterier: Vuxna personer på ett kaloriunderskott, BMI>25, humanstudier, randomized controlled trials (RCTs), studien måste ha åtminstone två specificerade nivåer av proteinintag, språk; endast engelska, utfallsmått: visual analogue scale (VAS).
Exklusionskriterier: Patienter som genomgått bariatrisk kirurgi, studier som inkluderar personer med kronisk/pågående sjukdom som allvarligt påverkar mättnad eller aptitreglering.

***Datainsamling och analys*:** Datainsamling skedde i flera steg. Vi filtrerade efter titel, abstract, och metod, tio artiklar lästes i fulltext innan vi valde ut de granskade artiklarna. Vi genomförde bedömingar av risk för bias och tillförlitlighet av de sammanvägda resultaten enligt GRADE.

***Resultat:*** Ingen tillförlitlig evidens för hypotesen att ett ökat proteinintag skulle leda till förbättrade aptitrelaterade känslor hos obesa observerades.

***Slutsats:*** Det finns låg tillförlitlighet (++) för att stödja hypotesen att ett ökat intag av dietärt protein skulle leda till förbättrade aptitrelaterade känslor hos överviktiga/obesa.

***Nyckelord:*** Systematisk översiktsartikel, Protein, Fetma, Mättnad, Aptit

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## Abstract

Title: Does an increased intake of dietary proteins lead to improvements in perceptions of appetite in people with obesity during a period of calorie restriction?

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***Background***: Overweight and obesity is a growing pandemic on a global scale. Protein is largely believed to induce positive effects on perceptions of appetite, which, if applied, could lead to a more efficient weight loss treatment in people with obesity/overweight.

***Objective:*** The objective of this systemativ review is to determine whether there is evidence to support an increased intake of dietary protein, in the form of either supplements or regular food, to induce positive effects on perceptions of appetite during a caloric restriction, compared to a lower protein intake, for individuals suffering from overweight/obesity.

***Search strategy:*** The systematic literature search was conducted on two databases: PubMed and Scopus. The search terms used were MeSH terms based on the words: Protein, Hunger, Appetite, Satiation, Caloric Restriction, Hypocaloric, Energy restriction, RCT, Control.

***Selection criteria:*** We used the following inclusion/exclusion criteria: Inclusion: Studies containing adults in a caloric deficit, BMI>25, human studies, RCT, study must include at least two predefined intake levels of protein, language: English, outcome measure: VAS. Exclusion: Studies on individuals who have previously undergone bariatric surgery, studies including persons with a chronic disease and/or sickness that severely affect satiety or appetite.

***Data collection and analysis:*** Data collection was conducted in several steps. We filtered based on title, abstract, and method, before choosing the articles for examination. Ten articles were read in full. We assessed risk of bias and certainty of the results according to GRADE.

***Main results:*** No certain evidence was found to support the hypothesis that increased protein intake would lead to improved perceptions of appetite in people with obesity/overweight.

***Conclusions:*** There is low certainty (++) to support the hypothesis that increased dietary protein would improve perceptions of appetite in people with obesity/overweight.

***Keywords***
Systematic review, Protein, Obesity, Satiation, Appetite

# List of abbreviations with explanations

| | |
|---|---|
| **RCT** | Randomized controlled trial. A type of study design. |
| **BMI** | Body mass index. Bodyweight divided by height squared ($kg/m^2$). |
| **KG** | Kilograms. Measurement of weight. |
| **Kcal** | Kilocalories. Measurement of energy. |
| **NCD** | Non-communicable disease. Disease that cannot pass from one person to another. |
| **VAS** | Visual analogue scale. Method used to measure subjective perceptions and attitudes. |
| **LDL** | Low density lipoprotein. A protein body uses to transfer lipids in the blood. |
| **HDL** | High density lipoprotein. A protein body uses to transfer lipids in the blood. |
| **VLCD/VLED** | Very-low-calorie diet or very-low-energy diet. Diets with ≤800 kcal per day with the purpose of inducing fast weight loss. |
| **TEF** | Thermic effect of food. Energy expended for digesting and metabolising food. |
| **T2DM** | Type 2 diabetes mellitus. Metabolic disorder that is often a result from obesity and lack of physical activity. |

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# 1. Introduction

## 1.1 Obesity

The prevalence of obesity has skyrocketed worldwide in the last 50 years and is continuing to rise in recent years (1). Obesity is per definition caused by a prolonged calorie surplus, which eventually leads to a high accumulation of adipose tissue. As of 2016, 39% of the world population was classified as overweight, and 13% as having obesity (2). A future rise is expected, and it is believed that the global obesity prevalence will reach almost 20% by 2025 (3). Causes of obesity are linked to increased availability of high-energy foods rich in sugar and fat, a decrease in physical activity, and an increasingly sedentary lifestyle brought on by, for example, working in an office environment. Through this increased energy intake and the lowered energy spent through physical activity, weight gain becomes likely, and if left unchecked can lead to obesity and all the comorbidities that it brings. Certain diseases, chronic illnesses, and the drugs used to treat these, can also induce rapid weight gain.

Obesity is classified by using body mass index (BMI), which describes the ratio of weight to height. It is calculated by dividing weight with height squared (kilogram/$m^2$). It is a useful tool in epidemiologic research and allows us to observe weight trends on a population scale, and it is primarily with this tool that we can establish whether a person may need obesity treatment. BMI is only inappropriate on people with extremely atypical body compositions, such as professional bodybuilders. See table 1 below for exact classifications.

**Table 1. Classification of weight status with BMI (4)**

| | |
|---|---|
| BMI <18.5 | Underweight |
| BMI 18.5-24.9 | Normal weight |
| BMI 25-29.9 | Overweight |
| BMI 30-34.9 | Obesity class 1 |
| BMI 35-39.9 | Obesity class 2 |
| BMI ≥40 | Obesity class 3 |

## 1.2 Consequences of obesity

Obesity is accompanied by many problems for individuals and society, such as an increased risk of many noncommunicable diseases (NCDs). NCDs are diseases that are not directly infectious between people and are the cause of approximately 70% of all deaths worldwide (5). The most common NCDs associated with obesity are cardiovascular diseases, cancers and type 2 diabetes mellitus (T2DM).

Obesity is also correlated with increased causal risk factors for NCDs. These risk factors are elevated blood pressure, decreased insulin sensitivity, chronic inflammation, unfavourable blood lipids such as high levels of low-density-lipoprotein (LDL) cholesterol, triglycerides and low levels of high-density-lipoprotein (HDL) cholesterol (6).

Obesity is also closely linked to depression. A 2020 meta-analysis (7) examined the prevalence of depression in children and adolescents of normal weight and compared these to equal groups of children with obesity/overweight and adolescents. The analysis concluded that the group with obesity had a significantly higher risk to either develop or to already have developed medically diagnosed depression. This signifies the importance of mental health alongside obesity treatment.

The economic burden of obesity is massive (6). These costs come in both direct and indirect form. Direct form includes the cost of treatment, preventive services, diagnostics, drugs for treatment, etc. Indirect costs can be marketed as loss of income and productivity through sickness, inability to work, disability, and premature death, among others. The American Centers for Disease Control and Prevention estimates that costs of obesity as of 2008 were an

estimated $147 billion(8)(8). This number is sure to have increased due to the continued surge of global obesity.

## 1.3 Treatment of obesity

Weight loss occurs when the individual eats less energy than their energy need for weight maintenance, as the individual must be in a negative energy balance. Very simple in theory, however it is a struggle for many in practice. When calories are tightly controlled, the distribution between macronutrients (particularly between carbohydrates and fats) does not appear to make a practical difference when it comes to actual weight lost (9). It is believed, however, that the type of food consumed affects the number of calories consumed in free living people eating ad libitum.

There are many guidelines and reviews on the treatment for overweight and obesity. They share the same principles. Primarily a reduction of energy and an improvement in diet quality. Physical activity is also recommended mainly for its health benefits, better weight management and improved body composition. The different guidelines all agree that health benefits can be observed from a relatively modest weight loss of 5-10%. The Swedish Agency for Health Technology Assessment (SBU) published a systematic review 2013 titled "Dietary treatment for obesity" (10). In the review it is concluded that no specific diet is superior for long term weight loss (six months or more). An American obesity expert panel recommends a daily intake consisting of 1500 kcal (kilo-calories) for men or 1200 kcal for women, or a daily deficit of 500-750 kcal (11). The NICE guidelines on obesity recommend behavioural interventions such as self-monitoring, stimulus control and goal setting (12). The European guidelines for obesity management (13) recommend high intake of vegetables, legumes, whole grains and increased intake of fish. A reduced intake of foods with added sugar and/or added fats is recommended. Moreover, they advocate for food with lower energy density and smaller portion sizes. Snacking between meals should be avoided, breakfast should not be skipped and eating at night should be avoided, and they recommend trying to control episodes of binge eating. Lastly, they discuss and confirm the efficiency of pharmacological treatment such as Orlistat, bariatric surgery such as gastric bypass and diets such as very low-calorie diets (VLCD) for weight loss.

## 1.4 Appetite and the challenges faced in obesity treatment

Appetite control is often one of many issues experienced during prolonged hypocaloric periods. To promote weight loss, the individual needs to consume less energy from food than their body requires to maintain itself. Existing below the maintenance level, or being in a negative energy balance, is widely believed to induce increased feelings of hunger, which in turn can lead to another meal being consumed, hindering the weight loss process as the individual overeats (14).

It is important to understand what hunger is. Hunger is a physical absence of fullness experienced hours after the latest meal and does not indicate a negative energy balance. It merely means that the stomach has been emptied and that the food is now in the intestinal tract.

There are two primary hormones in the regulation of hunger and appetite, namely, ghrelin and leptin. Ghrelin causes appetite, while leptin supressess it. Ghrelin is produced in the stomach walls as the blood glucose levels fall, this is to induce appetite, increasing stomach motility and production of gastric acid. The main issue, however, is that several hormonal

balances are disturbed or shifted in individuals with obesity, including that of ghrelin (15). Counterintuitively, obese individuals have been shown to have lower, but constant, levels of plasma ghrelin, that do not spike in the early morning or before meals, and that does not recede after meals as it does in individuals of normal weight. This might indicate that obese individuals will not feel satiated to the same degree as those of normal weight (16). The production of ghrelin is inhibited by distention of the stomach, which may be achieved more slowly in individuals with obesity as studies have shown that the stomach stretches from prolonged periods of high food intake (17).

Satiety is the opposite of hunger and is induced by an intake of food. However, it is important to note that not all foods have an equal effect on satiety. Food high in fat and sugar, such as soda, snacks, fried foods, chocolate, etc, rate lower on the satiety index, and these types of food items are often more commonly consumed amongst people with obesity (18). Food items such as these result in greater feelings of reward, while traditionally healthier foods, such as beans, lentils, vegetables, oats, etc., do not. This will naturally drive a person to crave the more appealing food choices (19). This results in a challenge for those that wish to undergo obesity treatment, where their own hormonal system works against them.

In this systematic review, the phrase perceptions of appetite is used as an umbrella term for all feelings related to the absence or abundance of food. The most common feelings investigated in appetite-related research are hunger, satiety, fullness, desire to eat and prospective consumption (likeliness to eat in the future). A common tool for measurements of perceptions of appetite is to use a visual analogue scale (VAS), which will be described next.

## 1.5 Measurements of appetite

The VAS is a horizontal line that goes from 0mm to a 100mm. Respondents are asked to specify their agreement to a statement on the line, such as “I feel satiated”. If they put 100mm it would mean that they fully agree on what the statement says. In this example it would mean that they feel extremely satiated and if they would have put 0mm it would have meant that they do not feel satiated at all. VAS was originally developed as a measurement of pain but has since then been adapted and used for measurements of appetite responses (20). It is a validated and commonly used tool for measuring perceptions of appetite in research (21, 22). Positive results in perceptions of appetite would mean increased ratings of satiety and fullness and reduced ratings of hunger, desire to eat, amount desired to eat and prospective consumption.

## 1.6 Protein and weight loss

Higher protein is sometimes recommended in weight loss programs. Three main benefits of higher protein that are often put forth are increased muscle retention, elevated thermic effect of food (TEF) and higher ratings of satiety (23, 24).

Retaining as much muscle as possible should always be the goal during long-term weight loss, and many experts today agree that a higher intake of protein aids in this regard (25). Weight loss on a diet with a higher intake of protein appears to bring all the regular benefits of weight loss in individuals with obesity, i.e., improved cardiovascular health, lowered blood pressure, decrease in visceral fat, improved blood lipid levels, and more. These improvements are not necessarily brought on by the protein levels, however. Studies show that increased protein intake increases muscle retention when looking at amounts lost, as muscle will always be lost alongside fat(26).

## 1.7 Protein and appetite

Protein is the macronutrient that is often said to suppress appetite the most out of the three main macronutrients, whereas fat is the least satiating (27). This can, in part, be explained by the cost of absorption of the different macronutrients, also called TEF as mentioned before. Carbohydrates, fat, and protein, all have different chemical compositions that are absorbed at different speeds (28). Carbohydrates lacking in fibre, as well as fats are more easily digested and absorbed than protein, as protein is made up of thousands of connected amino acids that must be picked apart before absorption. This is the basis of the idea that protein has a greater effect on satiety, as it needs more time and room to be processed compared to simple sugars and fat (28).

Recently, a meta-analysis was published investigating the effect of protein consumption on appetite (29). It was concluded that meals higher in protein reduce hunger and increase fullness compared to isocaloric control meals lower in protein. They did not, however, see an effect on protein intake and appetite on long-term trials (i.e., trials going on for three days or longer).

The meta-analysis mentioned above (29) included studies of people of all different types of weights and included diets of all types of caloric intakes. Moreover, they only included trials with healthy participants. This review intends to investigate the effect of protein intake on appetite in a more clinical setting, during weight loss for patients with obesity/overweight with possible comorbidities (e.g. T2DM) that are trying to lose weight. By answering this question, additional information could be added to the question whether an increased intake of protein for patients with obesity/overweight in their hypocaloric diet could be beneficial. This question is especially relevant in a clinical setting for the treatment of obesity.

## 1.8 Problem formulation

Hunger and satiety is often a problem that hinder weight loss for people with obesity/overweight during weight loss treatment. By shifting focus towards a diet higher in dietary protein, we may be able to increase the efficacy of treatment by reducing the symptoms of hunger and lack of satiety that individuals with obesity/overweight will experience during a prolonged hypocaloric period.

## 1.9 Aim

The aim of this systematic review is to investigate if there is evidence for a positive effect of increased intake of protein on perceptions of appetite in individuals with obesity/overweight during weight loss.

## 1.10 Question at hand

Does an increased intake of dietary proteins lead to improvements in perceptions of appetite in people with obesity/overweight during a period of calorie restriction?

# 2 Method

## 2.1 Outcome measure

The chosen outcome measure for this article is perceptions of appetite measured by a VAS in millimetres. Specific appetite-related perceptions and feelings investigated in this systematic

review are fullness, satiety, hunger, desire to eat, amount desired to eat and prospective consumption.

## 2.2 Inclusion- and exclusion criteria

The following criteria were used to decide on inclusion or exclusion of articles:

**Inclusion:** The participants must be >18 years old, must be in a caloric deficit or in a period of weight loss, must have a BMI>25. The study must be conducted on humans, must contain a minimum of two predetermined levels of protein intake that are iso-caloric (same amount of energy between diets), must be a RCT, must be in English. Outcome measure: VAS.

**Exclusion:** The study must not have been conducted on people who have undergone bariatric surgery, must not contain people with sickness or disease that severely alter appetite. Studies that presented and did statistical analysis of VAS as area under the curve (AUC) were excluded.

## 2.3 Data collection

We conducted a primary literature search on the medicinal database Pubmed and the multidisciplinary database Scopus. Prior to the search we constructed search terms for both search engines. Using Swedish MeSH (30) by the Karolinska Institute we identified the proper synonyms for the relevant terms. The search terms used were variations of Protein, Hunger, Appetite, Satiation, Caloric Restriction, Hypocaloric, Energy restriction, RCT, Control. Full details are included in Table 1. Due to the comprehensive nature of our search terms, and the quantity of articles found, we decided not to perform any further searches.

**Table 2. Literature search**

| *Search* | *Database* | *Date* | *Terms* | *Boundaries* | *Hits* | *Chosen hits (*)* | *Reference # for chosen articles* |
|---|---|---|---|---|---|---|---|
| *1* | *PubMed* | *2020-02-04* | *("amino acids, peptides, and proteins"[MeSH Terms] OR ("Amino Acids"[Title/Abstract] OR "Peptides"[Title/Abstract] OR "protein*"[Title/Abstract])) AND ("Satiation"[Title/Abstract] OR "Hunger"[Title/Abstract] OR "Appetite"[Title/Abstract] OR "Satiety"[Title/Abstract] OR "Satiation"[MeSH Terms] OR ("Hunger"[MeSH Terms] OR ("Appetite"[MeSH Terms] OR ("Satiation"[MeSH Terms])) AND ("random*"[Title/Abstract] OR "control*"[Title/Abstract] OR "RCT"[Title/Abstract])* | | *190* | *19* | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | | *AND ("Caloric Restriction"[Title/Abstract] OR "Calorie Restriction"[Title/Abstract] OR "Energy Restriction"[Title/Abstract] OR "Low Calorie"[Title/Abstract] OR "Hypocaloric"[Title/Abstract] OR "hypo caloric"[Title/Abstract] OR "hypo caloric"[Title/Abstract])* | | | | |
| *2* | *Scopus* | *2020-02-11* | *"Amino Acids" OR Peptides OR Proteins AND satiation* OR satiety OR satiated OR satiate OR satiating OR appetite* OR hunger OR appetite* OR appetitive OR appetitively OR appetitiveness AND "Caloric Restriction" OR "Calorie Restriction" OR "Energy Restriction" OR "Low Calorie" OR "Hypocaloric" OR "hypo caloric" AND Random OR Control OR RCT* | | *224* | *14 (7*)* | |
| **Total # of studies** | | | | | *414* | *33(7*)* | |
| **# of chosen studies for examination** | | | | | *10* | ***2*** | ***34, 35*** |

** =Duplicate articles*

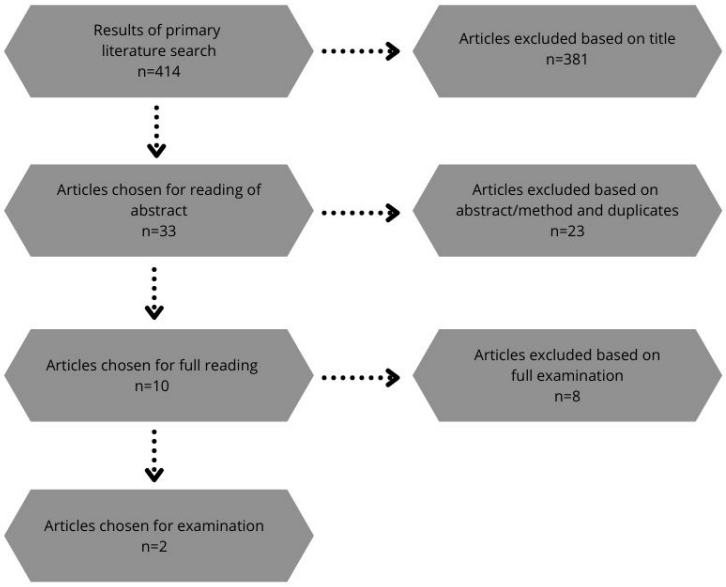
## 2.4 Data analysis

Both authors took part in the literature search and in the exclusion/inclusion of articles in the first, second, and third stages. During all stages, both authors individually read through all material, and then together decided on which articles to include/exclude for final examination.

All articles were found on Pubmed and Scopus (n=414) and were filtered through in several stages. During the first stage articles were excluded based on title alone. The remaining articles (n=33) were put through the reference program Endnote20 to check for duplicates.

After duplicates were removed, the remaining articles were excluded by abstract and method (n=26). At the final stage, the remaining articles (n=10) were examined in full by the authors of this article. See figure 1 below for a schematic view of the process. A search of other articles' reference lists to find relevant studies for this systematic review (backward snowballing) was not conducted.

**Figure 1. Schematic overview of the literature search.**




## 2.5 Evaluation of risk of bias

An evaluation of the risk of bias was conducted separately by both authors using the SBU's "Bedömning av randomiserade studier" review template (31) on the two articles selected. The evaluations were then compared and discussed between both authors. The template is based on Cochrane's Risk of Bias tool 2 (32). It contains questions on five domains of risk of bias that are assessed separately; bias from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result (32). The author only had the outcome measure of perceptions of appetite in VAS in mind while assessing each question. After answering the questions in each domain, a grade is given based on the perceived risk of bias for each domain (either low, moderate, or high risk of bias). The risk of bias from conflict of interest is also assessed. Lastly, the results from all five domains and conflict of interest are combined to evaluate the overall risk of systematic bias, graded as either low, moderate, or high risk of bias.

## 2.6 GRADE

The two studies chosen for further analysis were assessed to determine the certainty of evidence for the outcome measure for this review; perceptions of appetite (measured with VAS). The analysis was first conducted by the authors separately and then a second time together. The document "Underlag för sammanvägd bedömning av (33)nligt GRADE" that is based on the GRADE handbook OBJOBJOBJ(33)OBJ was used. This is used to rate the certainty of evidence for one outcome within one or several studies. In this document, five factors can be

investigated: limitations in study design or execution (risk of bias), inconsistency of results, imprecision, indirectness of evidence and publication bias. Total certainty of evidence for the outcome perception of appetite measured with VAS can be divided into four grades: high (++++), moderate (+++), low (++) or very low (+). RCTs start with (++++), but with each of the five factors mentioned above there is a possibility of deduction.

# 3 Results

## 3.1 Luscombe-Marsh et al., 2005 (34). "Carbohydrate-restricted diets high in either monounsaturated fat or protein are equally effective at promoting fat loss and improving blood lipids".

Luscombe-Marsh et al., is a parallel RCT that compared a low-fat, high protein (LF-HP) diet with a high fat, standard protein (HF-SP) diet. In the LF-HP diet the participants were prescribed to eat 30% of energy from fats (30E%), 40E% from protein and 30E% from carbohydrates. In the HF-SP diet the participants were prescribed 50E% from fats, 20E% of protein and 30E% from carbohydrates. The first 12 weeks the participants were prescribed a 30% energy deficit per day (eating approximately 1400-1500 kcal per day). The following four weeks was a maintenance period where they ate to maintain their weight loss while eating the same macronutrient composition they had been prescribed. Participants received set menus and were given food consisting of 60E% of their daily need to increase compliance and to achieve the macronutrient composition desired. The two diets had similar dietary fibre content.

Participants were asked to weigh and record their dietary intake. From these food diaries they concluded that the participants in LF-HP diet ended up eating 34E% from protein, 29 E% from fat and 35E% from carbohydrates. Participants in the HF-SP diet ended up eating 18E% from protein, 45E% from fat and 35E% from carbohydrates.

73 men and women with obesity/overweight (26 men and 47 women) were recruited. Subjects that were included were aged between 20 and 65 years old, had BMI between 27 and 40 kg/m$^2$. They excluded participants that had diabetes mellitus. The majority of study participants were sedentary, and they were asked to maintain the same levels of physical activity as before the trial. The mean age of the participants included was 50 years and the mean BMI was 34 kg/m$^2$.

At baseline and at week 16, participants received test meals that were supposed to represent the diets as a whole. The LF-HP test meal consisted of 630 kcal, 37E% of protein, 30E% of fat and 32E% from carbohydrates. The HF-SP test meal consisted of 618 kcal, 18E% protein, 49E% fat and 32E% carbohydrates. Just before the meal (baseline) and at 30, 60, 120 and 180 minutes after the test meal perceptions of appetite were measured with VAS. Perceptions of appetite measured were hunger, fullness, satiety, desire to eat and amount desired to eat. Data is presented as change from baseline at each of the timepoints mentioned above (30, 60, 120 and 180 minutes after test meal).

The overall risk of systematic bias was deemed to be high. Bias from the randomization process was deemed moderate/high. Detailed information on how the randomization was conducted was missing and it is uncertain if a concealed allocation sequence was used. Bias due to deviations from intended interventions was deemed moderate because it is not clear if

the authors knew or somehow tried to conceal for the participants which person got which diet. It is also plausible that the participants were aware of which dietary intervention they were assigned, as it is impossible to hide when it involves regular meals. Bias due to missing outcome data was deemed high because of the high dropout rate (22%) and due to the fact that no sensitivity analysis was made. Bias in measurement of the outcome was deemed high since it is unknown who collected and analysed the outcome measure for perception of appetite (with VAS) and the fact that VAS is a subjective outcome measure. Bias in selection of the reported result was deemed to be moderate/high because there was no study protocol published. The authors reported no conflict of interest.

## 3.2 Struik et al., 2020, Australia (35). "Very Low and Higher Carbohydrate Diets Promote Differential Appetite Responses in Adults with Type 2 Diabetes: A Randomized Trial"

Struik et al., is an RCT, aimed at investigating appetite response in energy-restricted very low carbohydrate (VLC) diets compared with a higher carbohydrate diet (HC) in adults with obesity and T2DM. The study included 84 participants with a mean BMI of 34.5 kg/m$^2$ and all participants were randomly assigned to one of the diets. Both groups were assigned progressive multicomponent exercise regimes, lasting 60 minutes, 3 days per week, and supervised by a professional tutor.

The diets were made up of the following compositions: VLC: 14E% Carbohydrate, 28E% protein, and 58E% fat (<10E% saturated fat). HC: 53E% Carbohydrate, 17E% protein, 30E% fat (<10E% saturated fat). The diets were designed with a 500-1000kcal/day deficit, to promote weight loss, and both diets were equal in number of calories. The following data was gathered through 100mm VAS at baseline (0wk), 4 weeks, and 16 weeks; hunger, fullness, prospective consumption, and desire to eat. Participants were provided with information on how to fill the questionnaires. The data was gathered for all seven days of the weeks (three weeks; 0, 4 and 16) and the data of each week were then used to calculate averages. Participants were asked to estimate their perceived appetite with VAS just before and after meals and at 60 and 120 minutes after their three main meals. This means a total of four ratings per meal and 12 ratings per day and 84 ratings over the seven-day period. The authors calculated a "daily fasting rating" (mean VAS score before meals on all seven days) and a "daily overall rating" (mean of all the 12 VAS scores per day on all seven days).

This study is a secondary analysis of Tay et al. (36) that was conducted at the CSIRO clinical research unit in Australia, lasting from 2012 through 2014. The participants were instructed to follow the diet for the entire two years. For the first twelve weeks of the trial, participants were provided approximately 30% of the total food needed for their prescribed diet. These foods were considered key foods for their assigned diet and were delivered to their homes. For the remainder of the study the participants were provided with 50AUD every two months to pay for parts of the prescribed diets. The participants prepared their own meals in accordance to the diet.

The study was deemed to have a low risk of systemic bias. The risk for selection bias was deemed to be low due to the randomized group allocation being made in an appropriate manner making both groups as equal as possible. Risk for treatment bias was deemed as low-moderate caused by the risk of wrongful intervention as the study participants were in charge of their own treatment during the majority of the study. Risk of bias through dropout and

missing data was deemed to be low as a sufficiently large number of participants completed the study. Risk of bias through outcome was deemed to be low as all participants were included in the results. Risk of reporting bias was deemed to be low as the study followed a pre-published protocol, the study measured its data through several set collection points, and the reported data was analysed through several venues. The authors reported no conflicts of interests.

**Table 3. An overview of the two articles included.**

| **Article** | **Luscombe-Marsh et al. (34)** | **Struik et al. (35)** |
|---|---|---|
| *Study design* | Parallel randomized clinical trial | Parallel randomized controlled trial |
| *Study population* | n=73 (26 men and 47 women)<br><br>Mean age: 50 years<br><br>Mean BMI: 34 kg/m$^2$<br><br>Comorbidities: none | n=84 (44 men and 40 women)<br><br>Mean age: 59 years<br><br>Mean BMI: 34.5 kg/m$^2$<br><br>Comorbidities: T2DM |
| *Intervention* | LF-HP (*intervention*) diet vs. HF-SP (*control*) diet<br><br>Macronutrient distribution *intervention*: 34E% protein, 29E% fat, 35E% carbohydrate<br><br>Macronutrient distribution *control*: 18E% protein, 45E% fat, 35E% carbohydrate<br><br>Calorie deficit: ~30E%<br><br>Difference in caloric intake between intervention/control: isocaloric<br><br>Duration: 16 weeks<br><br>Exercise regime: mostly sedentary | VLC (*intervention*) diet vs. HC (*control*) diet<br><br>Macronutrient distribution *intervention*: 28E% protein, 58E% fat, 14E% carbohydrate<br><br>Macronutrient distribution *control*: 17E% protein, 30E% fat, 53E% carbohydrate<br><br>Calorie deficit: ~30E%<br><br>Difference in caloric intake between intervention/control: isocaloric<br><br>Duration: 16 weeks<br><br>Exercise regime: 60 minutes three times per week |
| *Outcome measure* | Perception of appetite with VAS (hunger, fullness, prospective consumption, desire to eat) | Perception of appetite with VAS (hunger, fullness, satiety, desire to eat, amount desired to eat) |
| *Time of measurement of outcome measure* | Immediately before meal and 30, 60, 120 and 180 minutes after meal (total of five measurements) | Immediately before and after meal, 60 and 120 minutes after meal (total of four measurements) |
| *Risk of bias* | High | Low |

## 3.3 Results for the outcome measure perceptions of appetite (VAS)

In Luscombe-Marsh et al. amount desired to eat was lower in the LF-HP (higher protein) group compared to the HF-SP (lower protein) group (P = 0.02). This difference was observed on both test meals on week 0 and week 16. Desire to eat was lower in the LF-HP group week 0 but there was no difference week 16. Hunger was decreased for both groups between week 0 and week 16. However, there was no difference reported between groups on hunger. Both groups reported similar levels of satiety on week 0 and week 16 and no difference between groups was reported. Results on fullness was not reported. In conclusion, no conclusive main effect of diet on perceptions of appetite could be observed. However, amount desired to eat was decreased on the LF-HP (higher protein) diet.

Struik et al. found an increased fullness rating in the HC group (lower protein) compared to the VLC (higher protein) group overall (P = 0.004), specifically on week four (P = 0.001) and week 16 (P = 0.019) on the "daily overall rating". The HC group had lower ratings of prospective consumption overall on the "daily overall rating" compared to the VLC group (P = 0.03), especially on week four (P = 0.008). No difference between groups was found on ratings of hunger and desire to eat on the "daily overall rating". No difference between groups was found on the "daily fasting rating". In conclusion, there was no difference in perceptions of appetite on hunger and desire to eat. However, the HC group (lower protein) did have increased fullness and decreased ratings of prospective consumption.

**Table 4. Difference between intervention and control week 16 in VAS (mm) between studies**

| Perception of appetite | Luscombe-Marsh et al. | Results favor | Struik et al. | Results favour |
|---|---|---|---|---|
| Hunger | 0mm | Neither | 1mm | Higher protein (P = 0.21) |
| Desire to eat | 0mm | Neither | 1mm | Lower protein (P = 0.22) |
| Amount desired to eat | 6mm | Higher protein (P = 0.02) | No data | No data |
| Fullness | No data | No data | 6mm | Lower protein (P = 0.019) |
| Prospective consumption | No data | No data | 2mm | Lower protein (P = 0.289) |

## 3.4 Certainty of the evidence according to GRADE

**Table 5. Certainty of the evidence according to GRADE.**

| | Outcome measure – perception of appetite with VAS |
|---|---|
| Number of studies | 2 |
| Risk of bias | (-1) |
| Inconsistency of results | (-1) |
| Indirectness of evidence | (?) |
| Imprecision | (?) |
| Publication bias | (0) |
| Overall/total quality of the evidence | low (++) |

### 3.4.1 Risk of bias
There appears to be a risk of bias, as Luscombe-Marsh et al. had a severe lack of information regarding the randomization process among other things described under risk of bias. Struik et al. conducted an acceptable randomization process, including block-randomization as well as computer-generated assignment for the study participants. However, the lack of such measures in Luscombe-Marsh et Al. warrants a lowering of GRADE, as these are the only two articles included in this review.

### 3.4.2 Inconsistency of results
There is inconsistency of the results as the results reported are not heterogeneous despite both studies using similar methods. In Luscombe-Marsh et al. it is suggested that protein may have a positive effect on perceptions of appetite, while the opposite results are observed in Struik et al. The inconsistent results warrant a lowering of GRADE.

### 3.4.3 Imprecision
There are some problems with imprecision, but not enough to warrant a downgrade. Null results were observed for many appetite-related perceptions investigated. That is, many times no difference between groups could be observed. In Luscombe-Marsh et al., no confidence interval is presented for this outcome measure. Moreover, imprecision is more sensitive to flaws when there are few studies analysed, as in this systematic review.

### 3.4.4 Indirectness of evidence
There are problems with the indirectness of evidence but not enough to warrant a downgrade. This is due to some differences in the populations and the interventions themselves between the two studies, which makes it difficult to draw strong conclusions. For example, in Luscombe-Marsh et al., the participants were not in a caloric deficit for the entirety of the study, while in Struik et al., they were in a caloric deficit throughout the study. Differences such as this makes it difficult to judge whether the results are transferable to clinical use, even if the methods are sound.

### 3.4.5 Publication bias
The studies were conducted without outside influence, where the authors of both studies report no financial ties, no dependency, and report that no input over study-design was granted to the sponsors. It is important to note that author Luscombe-Marsh was also involved in Struik et al., but shared responsibilities with another author. The time gap between the two studies, and difference in results leads us to believe the risk of publication bias here is low.

In conclusion, there is low (++) evidence that higher protein intake improves perceptions of appetite for patients with obesity/overweight that are in a caloric deficit.

## 4 Discussion
This systematic review sought to explore the efficacy of an increased protein intake in obesity treatment. The studies presented in this systematic review presented results that were deemed inconclusive in improving perceptions of appetite during a caloric deficit.

## 4.1 Method

### 4.1.1 VAS

The fact that VAS was used in this systematic review to measure appetite-related perceptions can be seen both as a strength and a weakness. A positive aspect of VAS is that it is a validated and commonly used method for appetite research. Moreover, it is a measurement of feelings of appetite that participants are perceiving instead of implying what participants should be feeling. Some peptides, polypeptides and hormones, for example, are well correlated with feelings of appetite for most people (37, 38), but it appears as if that correlation is not always true. For instance, people with obesity are many times leptin resistant (39). They do have elevated levels of a "satiety hormone" but do in fact not feel more satiated.

There are also negative aspects with VAS. VAS is subjective, which makes it harder to compare than more objective measurements like appetite hormones. Moreover, different studies sometimes investigate different feelings when researching perception of appetite with VAS. Most common feelings participants are asked about are hunger, satiety and fullness. Some studies also ask about desire to eat, amount desired to eat, prospective consumption etc. Lastly, there appears to be no standardized time to collect measurements. VAS can be collected every 15 minutes after a meal, or every two hours, or participants can be instructed to report perceived appetite with one VAS measurement for an entire day or week.

Similarly to the metaanalysis by Kohanmoo et al. (29), this systematic review did not include studies that expressed data as AUC instead of actual values (VAS in mm) before and after a meal. Including studies that express data as AUC would have made it impossible to compare data between studies fairly.

### 4.1.2 Hormones affecting appetite

As a result of limitations of time, a separate analysis on peptides, polypeptides and hormones affecting appetite-related perceptions was not made. This can be seen as a weakness with this review. However, as previously mentioned, there are also problems with looking at these hormones and presuming that they always correlate with perceptions of appetite.

### 4.1.3 Data collection and data analysis

Data collection was made using two databases: PubMed and Scopus. A weakness with this systematic review is that more databases were not included, which could mean that relevant studies were missed. Scopus and PubMed are two of the biggest databases that exist, however. Furthermore, PubMed is the foremost database for health, medicine, and biological research, which encompasses the disciplines for this review. Moreover, the fact that backward snowballing was not made could be viewed as a weakness as it is a valid method for finding relevant studies (40). The method for data collection was monitored and deemed appropriate by three university librarians with experience in using these databases.

The data analysis was conducted using a standardized testing template from SBU and the template was filled by cross referencing to the instructional manual provided by SBU, titled "GRADE Handbook" (33). By utilizing a predefined ruleset for defining certainty of evidence, we can ensure the highest chance of unbiased judgements. Couple this with both authors having graded each article separately and then together, a low chance of author bias can be ensured. One potential risk for this type of grading, however, is the difference in

personality between authors. If one author is more driven or “aggressive” then it is possible that this author’s opinion will be overrepresented in the final analysis. In this analysis, however, both authors came to the same conclusion, which makes this a non-issue.

## 4.3 Results

### 4.3.1 Main results

This systematic review finds no conclusive positive results on perceptions of appetite from an increased protein intake on people with obesity during a period of weight loss. Luscombe-Marsh et al. has a calculated power of 80%, while Struik et al. notes that despite the quality of their method, there is a possibility that the power is not great enough to detect the very small differences in outcome, but they offer no percentage or number.

The only positive results are found in Luscombe-Marsh et al. where amount desired to eat is lower in the higher protein group. In contrast, in Struik et al. the results show negative effects from a higher protein intake, where fullness is lower and prospective consumption is higher in the higher protein group. Overall protein intake does not appear to have a significant effect on perceptions of appetite. Many appetite-related perceptions and feelings are similar between intervention and control groups as no difference is observed in feelings of hunger, satiety, and desire to eat.

These results go against some literature but go along with other literature. Rigamonti et al. (41) observes that a higher protein shake lowers hunger and increases satiety for up to 120 minutes compared to a lower protein shake. In contrast, in Heden et al. (42) there is no significant difference on hunger and fullness between high and low protein drink groups. Similarly, Li et al. (43) concludes that the amount of protein has minimal effect on perceptions of appetite. In contrast, Gwin et al. (23) finds positive results on perceptions of appetite from a higher protein diet.

The results of this systematic review go hand in hand with the meta-analysis (29) published in 2020 investigating the correlation between higher protein intake and appetite. This metanalyses distinguishes between short-term (one to two days) and long-term (three days or longer) trials. They observe positive results on higher protein intake on perceptions of appetite in the acute short-term trials, but no positive results during long-term trials. This systematic review only includes studies that are classified as long-term trials, and similarly does not find an effect on higher protein long term. It is possible that protein only has an acute positive effect on perceptions of appetite. Another possibility is that compliance to the intervention diets decline in long term trials. In the latter case, it is possible that participants do not eat higher protein which could explain why no differences between groups are observed.

### 4.3.2 Differences between included studies

There are some differences between the two included studies in this systematic review that may explain opposing results. In Struik et al. the participants have T2DM whereas in Luscombe-Marsh et al. they do not. There is evidence that people with T2DM have higher cravings for food compared with people without (44). However, the same relative differences in perceptions of appetite between groups should be observed within studies if protein has an effect.

Moreover, in Struik et al. participants are prescribed exercise three times per week whereas in Luscombe-Marsh et al. participants are mostly sedentary. There is evidence that exercise has positive effects on perceptions of appetite (45). There are claims, however, that strenuous exercise increases hunger and therefore could lead to an increased energy intake and positive energy balance. This claim does not appear to be in line with the evidence. An RCT from 2015 finds no differences in hunger or satiety between sedentary and physically active groups even though they consumed the same amounts of calories (46). Moreover, this RCT observes that exercise actually induces lower desire to eat. Lastly, it should be mentioned that an individual's appetite response to exercise and physical activity seem to vary between individuals (47).

In Luscombe-Marsh et al. they are not in a calorie deficit on all 16 weeks and perceptions of appetite was not the primary outcome measure. The last four of the 16 weeks participants were in weight maintenance. They did lose significant amounts of weight during the first 12 weeks, and their caloric intake to maintain weight was lower after 12 weeks of weight loss compared to baseline. Nevertheless, it makes comparisons between the studies harder to make. Furthermore, perceptions of appetite was not the primary outcome measure. Some data, for example fullness, is not presented at all. Risk of bias is deemed to be high, but the study is still included in the final analysis because of the lack of studies.

In Struik et al. the main focus of the study is to observe how lower or higher carbohydrate intake affects perceptions of appetite. However, in the introduction of the study positive effects on appetite from the higher protein intake that often follows a very low carbohydrate is put forth. The very low carbohydrate (higher protein) group only eats 14E% carbohydrate. The body produces more ketones when that low amount of carbohydrates is consumed. Ketones are linked to positive results on perceptions of appetite (48). Thus, it is possible that the ketones induce improvements in appetite instead of extra protein or some other factor. Interestingly, the very low carbohydrate group reports negative results on perceptions of appetite. The increased protein intake and the extra ketones do not appear to have a positive effect on appetite in this study.

There are some other differences between the two studies. Fat intake varies greatly in the intervention and control groups between studies. As previously mentioned, fat is the macronutrient that generally induces the least satiety per calorie (27). Therefore, it is feasible that the differences in fat intake between studies could confound the results. It should be mentioned that there is no detailed information on exactly what specific foods participants ate between studies. Some foods appear to be more satiating than others (they have different satiety indexes) which could affect the results. Different satiety indexes on specific foods are discussed in 4.4.1 below. Lastly, the VAS data is collected in different settings. In Struik et al. data is collected in a home setting, whereas in Luscombe-Marsh et al. it is collected in a clinical setting.

### 4.3.3 Similarities between included studies

There are also many similarities between the studies that can be seen as a strength with this systematic review. The two studies have similar amounts of participants. Participants between studies have similar BMI and age. Moreover, intervention and control groups have similar distribution of protein and the calorie deficit is the same. Lastly, the two studies also have the same duration (16 weeks) and data is collected at similar timepoints before and after meals.

### 4.3.4 Comparing perceptions of appetite with VAS between studies

There is an overall problem with comparing perceptions of appetite with VAS between different studies. Participants could be asked to rate appetite-related perceptions at different times after a meal. Sometimes an average score over several meals is analysed, and other times scores after only one meal is analysed. That one meal could be any of the main meals typically consumed over a day. Participants could also be asked to report a rating over a whole day or week (instead of after a specific time before and after a meal). Moreover, different terms for perceptions or feeling about appetite are used between studies. One study could use the term "fullness" whereas another could use "satiety", or both can be used. Even though two terms are synonyms they could have different meanings for different people. Furthermore, results with VAS in mm are presented differently between studies. Sometimes VAS is presented as AUC. Other times a "cravings score" or something similar is presented in results instead of VAS in mm. As a result of the points mentioned above it is hard to compare studies and come to strong conclusions. Appetite researchers should strive to come up with, and consistently use, standardize methods to conduct, collect, analyse and present appetite-related perceptions with VAS.

### 4.3.5 Compliance

All dietary interventions come with risk of poor compliance amongst the participants. In the analysed studies, compliance is only presented in Luscombe-Marsh et al., in which compliance was also measured in the form of measuring urea to creatine ratio in urine which can be used as an indication for protein intake. Luscombe-Marsh et al. reports no differences in compliance between the study groups, which might indicate an even progression in the analysed outcome measures through the course of the study. As Struik et al. does not report compliance, we are limited in our analysis. In both studies participants are supplied with parts of the food needed in their daily intake to increase compliance, however.

## 4.4 Overarching discussion

It is possible that appetite is too complex to see an effect on only one factor such as protein intake. In this section we seek to explore other aspects of appetite that are important to note during obesity treatment, on top of what this systematic review has already explored.

### 4.4.1 Other aspects of appetite

An article published in 1995 dubbed "A satiety index of common foods" (49) put together a comprehensive list of 38 common food items, and compared equal amounts of food counted in calories to each other in terms of satiety. According to this study, the foods content of fibre, protein, and water, were closely correlated to satiety, while fat content correlated negatively.
This correlates with the typical dietary choices in patients with obesity, which contain more saturated fats and sugars, and less fibre and, to a lesser degree, protein, than the diet of average normal weight individuals.

There are several other aspects that must be regarded when it comes to the foods effect on appetite and induction of satiety. Oro-sensory exposure duration is one major component. A study from 2017 concluded that the texture and number of chews required to swallow was the primary factor in promoting feelings of satiety, regardless of sweetness. This may play part in proteins proposed effect as satiety inducing, as protein, generally, comes in tougher or chewier textures (50).

Palatability plays a major role, with studies having found that palatable food induces lower feelings of satiety, while unpalatable foods induce higher levels of satiety, but lower overall feelings of satisfaction (51). However, it is unreasonable to expect a person to eat unpalatable food in order to induce weight loss.

Being brought up in an obesogenic environment has long been considered one of the major deciding factors in adulthood obesity. Obesogenic environment is defined as an environment that promotes excessive weight gain. Availability of healthy food, areas fit for exercise, safety, and access to education, are only some of the factors at play. A child born to parents with obesity, especially mothers with obesity, are at greater odds of developing childhood obesity (52). This does not mean that mothers are more prone to cause obesity in children but is likely caused by mothers being more often responsible for child rearing responsibilities.

### 4.4.2 Psychological aspects

There are many psychological aspects at play in the human animal when it comes to food. Cravings, hunger, feelings of reward, etc. This section will explore several relevant aspects in regards to obesity and the treatment of it.

The terms “homeostatic eating” and “hedonic eating” are of central importance in the treatment of obesity. Homeostatic eating describes eating for the purpose of fulfilling a physiological need for energy and nutrients, while hedonic eating is the act of eating for the pleasure that can be derived from food, and especially from typically unhealthy foods high in saturated fats and refined sugar (53).

Hedonic hunger naturally is a large obstacle for many undergoing weight loss. Evidence suggests that obesity is closely correlated with a higher amount of experienced hedonic hunger. Incidentally, patients undergoing weight loss treatment who, at baseline, report higher feelings of hedonic hunger, tend to lose more weight during the treatment than patients who experience less hedonic hunger (54). A possible explanation for this is that patients who rank higher on hedonic hunger have more room for improvements. It is important to note that hedonic eating is not a description of a typical diet, but rather of a subjective behaviour that varies from person to person.

Another side of eating behaviour is the term “disinhibitory eating” in which an individual who has self-imposed dietary restrictions. For example, number of calories per day. If the person then breaks this self-imposed limit, they may succumb to this disinhibitory eating in which they will then eat until their satiety limits are reached. This cycle undermines the efforts of weight loss and may lead to fluctuations in overall intake of food, but not in overall weight (53). This type of behaviour must be discouraged and treated for feasible long-term weight loss.

### 4.4.3 Clinical relevance

Obesity is as previously mentioned a growing global problem. The prevalence of obesity is higher in western countries such as Sweden. According to self-reported data, between 15% and 16% of the Swedish population has obesity as of the year 2020. According to more objective data, that number is higher as it was almost at 17% 2017 (55). Moreover, the increased prevalence of obesity has increased drastically the last 30 years and is continuing to

rise. Therefore, it is important to find effective ways to improve obesity treatment in a clinical setting to stop or slow the rise of obesity.

While protein's effect on appetite is not entirely clear, there are other reasons why higher protein could be recommended in a clinical setting for the treatment of obesity/overweight. It is well established that protein aids in muscle retention during weight loss in all individuals, not only people with obesity/overweight (25). Furthermore, a higher protein intake seems to be perfectly safe in otherwise healthy individuals (56, 57). Lastly, there is evidence that higher protein improves perceptions of appetite in the acute setting according to short-term trials. Based on this data, it is the belief of the authors of this review that an increased protein intake could still be a valid recommendation to people with obesity/overweight undergoing weight loss.

It is important to note what downsides such recommendations could have, however. A very high protein intake could push out fibre and water rich foods that might have positive effects on perceptions of appetite from an individual's diet. Some patients might find a higher protein diet harder to eat which could decrease a patients compliance to a prescribed diet which could have negative effects on weight loss. Furthermore, a diet higher in protein is generally more expensive, although cheap protein sources do exist.

The advice to patients with obesity/overweight to increase their protein intake could be valid advice for more successful weight loss. However, practitioners must have a cost-benefit mindset with each specific patient and give individualized advice based on each patient's preferences and situation. However, it is important to note that this advice does not represent the findings of the examined articles discussed within this review.

### 4.4.4 Human rights and equality perspectives

The right to good health, or "the right to the highest attainable standard of health" is a part of the universal human rights (58). It implies that states should offer citizens high quality health services that are non-discriminatory and available for everyone. However, when looking at global rates of obesity, inequalities exist. People with lower socioeconomic status tend to have a higher rate of obesity compared to those with higher socioeconomic status (59). The same trend is seen in Sweden, where those with lower income and lower education living in rural areas have a higher prevalence of obesity (55). Thus, obesity treatment and prevention of people in lower socioeconomic groups should be a focus to promote human rights and to decrease social inequalities.

## 5 Conclusion

In conclusion, there is low certainty (++) that higher protein intake improves perceptions of appetite for people with obesity/overweight patients in a caloric deficit.

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