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Association between Food Intake and Gastrointestinal Symptoms in Patients with Obesity

--Manuscript Draft--

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Abstract:	Background and Aims: Hunger, satiation, postprandial satiety, and hedonic eating constitute key food intake parameters. We aim to study whether these symptoms are associated with gastrointestinal symptoms (GIS) in patients with obesity. Methods: This is a cross-sectional study of patients with obesity. Patients completed the following validated biomarkers and questionnaires: Hunger was measured via visual analog scale (100mm) following a standard meal, satiation via ad-libitum meal (calories to fullness; kcal), postprandial satiety via gastric emptying scintigraphy (T 1/2 ;mins) and hedonic eating via the Hospital Anxiety and Depression Scale questionnaire. Participants completed the abridged Bowel-Disease-Questionnaire to evaluate their GIS. We calculated the odds ratios adjusted for sex, weight, and age between food intake parameters <25 th or >75 th percentile observed in a prior cohort of 450-participants with obesity and GIS. Results: A total of 274 participants (41±10 [SD] years, 75%females, body-mass index 39±8kg/m 2) were included in the analysis. Increased hunger was associated with a lower prevalence of lumpy stools (OR=0.18, p=0.02). Satiation was associated with abdominal pain/discomfort [relieved by defecation (OR=2.4, p=0.02) or associated with change in stool consistency (OR=2.92, p<0.01)], loose/watery stools (OR=2.09, p=0.02) and bloating (OR=2.49, p<0.01).

	Abnormal postprandial satiety was associated with bloating (OR=2.26, p<0.01) and loose/watery stools (OR=1.84, p=0.04). Hedonic eating was associated with abdominal pain/discomfort with stool frequency change (OR=2.4, p=0.02), >3 bowel movements/day (OR=1.93, p=0.048), bloating (OR=2.49, p=0.01), abdominal pain after meals >1/month (OR=4.24, p<0.01), and nausea >1/week (OR=4.51, p<0.01). Conclusion: Alterations in hunger, satiation, postprandial satiety, and hedonic eating are associated with GIS in patients with obesity.
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Cover Letter

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July 1st, 2022

Samantha Curtin
Editorial Staff
Gastro Hep Advances

Dear Dr. Samantha Curtin,

On behalf of my co-authors, I wish to submit the enclosed manuscript entitled **"Association between Food Intake and Gastrointestinal Symptoms in Patients with Obesity"** for consideration of publication in Gastro Hep Advances in the "**Alimentary Tract**" group.

Food intake regulation is a complex essential process that is closely associated weight gain. Several functional gastrointestinal symptoms appear to be more prevalent in patient with obesity. Although food intake parameters including hunger, satiation, postprandial satiety, and hedonic eating control weight change, little is known about their relationship with chronic gastrointestinal symptoms. Exploring this association can help better understand the higher prevalence of such symptoms in this increasing group of patients. By targeting food intake regulators, new fields of research for the treatment of functional symptoms may also become more reachable.

In our original article, we conducted a cross-sectional study at Mayo Clinic Hospital to study the association between food intake and functional gastrointestinal symptoms in patients with obesity. Functional gastrointestinal symptoms have always been a challenge for physicians. We aim to contribute to this field by providing a new perspective to tackle such an important and demanding topic. Hence, and based on previous publications in your journal, we believe that our manuscript align with Clinical Gastroenterology and Hepatology's scientific aims.

This manuscript has not been published elsewhere and is not under consideration by another journal. There are no previous submissions or reports that may be regarded as redundant publication of this work. All authors have approved the manuscript and agree with its submission to this journal. We are not using any copyrighted information, patient photographs, identifiers, or other protected health information in this paper. No text, text boxes, figures, or tables in this article have been previously published or owned by another party.
Please do not hesitate to contact me if you have any questions.

Sincerely,

Andres Acosta, M.D, Ph.D.
Assistant Professor of Medicine
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Detailed Response to reviewers:

Editor and Reviewer comments:

1. The study would be strengthened with a comparison to a non-obese group of participants which would have confirmed that these associations are unique to obesity.

Response: In this manuscript, we are showing that these gastrointestinal symptoms are associated with a subset of patients with obesity. Although previous publications associate these symptoms with obesity which we have cited in the manuscript, we are showing an association of these symptoms with specific phenotypes/characteristics in patients with obesity: Altered satiation, postprandial satiety, and hedonic eating. Hence, the aim is to compare these two groups of normal vs altered food intake parameters in patients with obesity.

2. Page 10. Postprandial satiety and GI symptoms. Was postprandial satiety associated with rapid GE as stated in the paper? The data is not clearly shown. This seems assumed in the discussion.

Response: We have made it clearer in the methods section that postprandial satiety is associated with rapid GE in a previous publication by Gonzalez-Inzudegui et al.:

"Postprandial satiety was studied via measuring the gastric emptying (GE $T_{1/2}$) by scintigraphy for a total of 240 mins after radiolabeled solid (320-kcal, 30% fat) standard breakfast. Postprandial satiety has been previously associated with rapid GE by Gonzalez-Izundegui et al.[6]"

Reviewer #1: CGH-D-22-01104

Introduction:
The introduction is very well written. The authors highlight that alterations in hunger, satiation, postprandial satiety and hedonic eating contribute to food intake symptoms. These symptoms led to the development of a phenotype-guided method which differentiates the causes of obesity based on the pathogenesis: satiation, postprandial satiety, hedonic eating, and resting energy expenditure. The authors further state that such classification contributes to a better understanding and treatment of obesity. Then the authors further summarize the link between obesity and GI symptoms.

However, there were a few points that needed further clarification.
1. The current introduction is lacking the link between ingestive states (hunger, satiation, postprandial satiety, and hedonic eating) and GI symptoms. This needs to be explored further in order to better conceptualize the aims and associated hypotheses of the study. Otherwise, it appears as a purely correlational (association) study.

Response: In the introduction, we try to establish through reporting previous studies that

1. Obesity has been associated with alteration in alteration of ingestive states: "differentiates the causes of obesity based on the pathogenesis: satiation, postprandial satiety, hedonic

eating, and resting energy expenditure.[8] Such classification contributes to a better understanding[6, 9] and treatment of obesity.[8]"

2. Obesity is associated with functional gastrointestinal symptoms: "Although several studies measure the correlation between obesity and functional GI symptoms,[25-29] none explain their association with food intake symptoms. Moreover, these studies are limited by inconsistent conclusions,[30, 31] selection bias[31], young-age participants,[28] small sample size,[32] and using diverse tools to measure same objective parameters (i.e., GE)[30]".
3. Following this, we state that, to the best of our knowledge, there are no studies that simultaneously study the relationship between alterations in food intake parameters and chronic functional gastrointestinal symptoms: "In addition, none of the studies in the literature simultaneously examined food intake symptoms and their relationship with common GI symptoms in obesity"

Hence, our study aims to study if an association between alterations of food intake parameters and gastrointestinal symptoms is present.

2. The comparison in non -obese participants also requires some level of discussion. Is there any literature on non-obese subjects? Are these phenomenon specific to obesity and altered ingestive behaviors.

Response: Alterations in food intake parameters have been so far only studied in patients with overweight and obesity. We have made this clearer in the manuscript: "These symptoms led to the development of a phenotype-guided method which differentiates the causes of obesity based on the pathogenesis: satiation, postprandial satiety, hedonic eating, and resting energy expenditure.[8] Importantly, these alterations have been only studied in patients with obesity or overweight."

3. Relatedly not all obese subjects have hedonic eating. This aspect requires further elaboration and discussion.

Response: We agree with the reviewer that not all patients with obesity have hedonic eating behavior. We show in the results section that only 51 patients in our cohort belong to the hedonic eating group.

In addition, in the result section we state that anxiety has been linked to a subset of patients with obesity: "Anxiety has been previously linked to increased food intake is a subset of patient with obesity,[38]"

4. The current introduction and discussion also seems heavily focused on the author's own prior publications. Therefore, summary of other studies in the field using these variables would be helpful, especially in longitudinal studies (if any).

Response: This manuscript is based on the novel topic of obesity phenotypes (satiation, postprandial satiety, and hedonic eating) which are not widely studied in the literature. Hence, there is a need to cite the publications that we used. No further studies have studied obesity phenotypes and food intake parameters simultaneously yet.

5. The aims are stated, but with no clear hypotheses (related to a point stated above).

Response: Based on the explanation that we have provided in the previous responses, we adjusted our introduction to better state the hypothesis "We hypothesized that food intake symptoms (e.g., altered hunger, satiation, postprandial satiety, and hedonic eating) are associated with diverse functional GI symptoms in obesity."

Materials and Methods/Results:

1. Critical is regarding the study is that it is cross sectional in nature and mechanistic interpretation is currently not feasible. As such it is purely exploratory and correlational in nature.

Response: We agree with the reviewer. Hence, we are only stating correlations that need to be further studied.

2. This Reviewer is concerned about the use of the HADs measure as a measure for hedonic eating. There are other well established and validated measures for hedonic eating, this is rarely used in such a way. Sure there are correlates of anxiety and depression symptoms with hedonic eating but not always. This is another big concern. This Reviewer questions the interpretation associated with the data on hedonic eating using the HADs.

Response: We agree with the reviewer that anxiety and depression are not always correlated with emotional eating. Hence, we added to our manuscript the association established between the HADS questionnaire and other validated measures of hedonic eating as the three-factor eating questionnaire: "Hedonic eating was evaluated using the Hospital Anxiety and Depression Scale (HADS) questionnaire.[33] A correlation between HADS anxiety score and the three-factor eating questionnaire (emotional eating factor; r=0.36) has been recently established. In addition, higher HADS anxiety scores were associated with emotional and uncontrolled eating ($p<0.001$ for both), and lower levels of cognitive restraint ($p=0.04$)[34]."

3. I am also confused how the sample went from 450 participants to 274? This is not clear and needs to be elaborated on as it is a substantial reduction in N.

Response: We mentioned the 450 participants from an independent previous study to explain our choice of the cutoffs only. We made an adjustment to our methods section to avoid this confusion. The participants in this study are 274 patients with obesity. Hence, we edited this section: "Using standard quantile regression approach to identify normal range[36] and based on the fact that these variables are different in obesity when compared to healthy controls[37], the abnormal traits in the key components of food intake were determined based on quartiles – 25th or 75th percentile as observed from our previous study[33]. Thus, the cutoffs were: increased hunger was defined as VAS-hunger: > 80 mm for females and

> 87 mm for males; abnormal satiation was defined as *ad libitum* meal test > 970 Kcal for females and > 1359 Kcal for males; accelerated GE, which is a biomarker of abnormal postprandial satiety, was defined as <25th percentile of GE $T_{1/2}$: < 106 mins for females and < 87 mins for males; and hedonic eating was defined with a score >7 for HADS-Anxiety for both sexes (Table 1)."

4. This study was predominantly females, some attention/statement regarding sex differences in obesity and especially hedonic eating is warranted, as obesity and hedonic eating have clear sex differences. Maybe rerun the analyses without the males. I feel that using sex as a covariate does not appropriately account for sex differences in analyses. There have been a few meta-analyses and reviews out there that have highlighted this issue. Same comment applies to race/ethnic differences. What is the breakdown by race/ethnicity as this is a critical issue related to obesity and ingestive behaviors.

Response: We totally agree with the reviewer that hedonic eating is more common females. We added this to our discussion section to make it clearer for the readers: "In addition, previous studies show an increased susceptibility of hedonic eating in female patients which account for 75% of our cohort.[64]"

We have also stated that this limits the generalizability of the study considering that our cohort is mainly composed of White Americans and female patients: "This study also included mostly white Americans and female patients which limits the generalizability of our results to other populations."

5. I am not clear on why alcohol use disorder was used as an exclusion criteria. I can understand the overlap between hedonic eating and other addition disorders, but this would apply to all addition disorders. Were binge eating excluded, or other eating disorders?

Response: This manuscript is based on baseline characteristic of patients participating in a weight loss trial. The mentioned exclusion criteria were part of that trial.

We aimed to include healthy individuals with no known gastrointestinal or any eating disorders including binge eating disorder. This is edited to be clearer: "We performed a cross-sectional study analyzing baseline characteristics of adult participants between 18 and 65 years old with obesity (Body-mass Index [BMI] > 30 kg/m^2) with no evidence of any chronic gastrointestinal diseases, use of medications that may alter gastrointestinal motility, appetite or absorption, active psychiatric symptoms, eating disorders (e.g., bulimia, binge eating disorder), or alcohol use disorder."

6. The analyses were appropriate for the study. The use of quartiles to account for a lack of health/non obese comparison made sense and was adequately justified. However, is there published data on these cut off values used. Was the data normalized.

Response: Yes, there is data of the cutoff quartiles used and we cited the study that has adapted these cutoffs: "Using standard quantile regression approach to identify normal range[36] and based on the fact that these variables are different in obesity when compared to healthy controls[37], the abnormal traits in the key components of food intake were determined based on quartiles – 25th or 75th percentile as

observed from our previous study[33]. Thus, the cutoffs were: increased hunger was defined as VAS-hunger: > 80 mm for females and > 87 mm for males; abnormal satiation was defined as *ad libitum* meal test > 970 Kcal for females and > 1359 Kcal for males; accelerated GE, which is a biomarker of abnormal postprandial satiety, was defined as <25th percentile of GE $T_{1/2}$: < 106 mins for females and < 87 mins for males; and hedonic eating was defined with a score >7 for HADS-Anxiety for both sexes (Table 1)."

Discussion and Conclusion

1. Overall, this is a well written paper and very interesting but this section needs further development.
2. There is a stretch regarding the interpretation of the results that are purely associational. Overall, there are too many overstatements of the results in the discussion. This Reviewer is not sure how the association between obesity, alterations in food intake, and GI symptoms lead to treatments. I would have liked to see some discussion on how this expands the literature and how these variables are mechanistically linked.

Response:

In our discussion, we state that the correlation of GI symptoms with altered food intake parameters of potential clinical importance. We understand that this might be an overstretch; thus, we do not draw any conclusion. Based on the observed correlation, we believe that it would be justifiable to study this with further depth. As stated in the discussion section, a GLP-1 agonist can be of benefit for fast gastric emptying (altered postprandial satiety) and watery diarrhea at the same time. Hence, it might be a good option to treat both conditions and obesity at the same time (i.e., liraglutide and semaglutide). We have adjusted the wording of the following paragraph in order not to confuse the reader with any conclusion that can be falsely drawn:

"The correlation with GI symptoms is of potential clinical importance. First, it might provide the rationale to propose treatments to address both the obesity phenotype as well as postprandial symptoms. For example, it would be advantageous to treat abnormal postprandial satiety (associated with accelerated GE) and watery diarrhea with an agent that delays gastrointestinal motility and GE such as a GLP-1 agonist.[40, 41] A second rationale is that both abnormal food intake and GI symptoms are highly prevalent and may co-exist in the same person; thus, abnormal satiation is present in 32% of patients with obesity[8] and bloating is reported in 31% of the general population.[42]"

3. The biggest issue was the lack of integration with ingestive behaviors/alterations in food intake and the lack of appropriate measure for hedonic eating. Do the authors believe that the alterations in food intake cause the GI symptoms of vice versa. I realize that this is difficult to answer without some level of longitudinal or intervention present.

Response: Since this is a correlational study, it is not feasible to draw any conclusion. We state this as a part of the limitations. We have made more clarifications for the use of the HADS score in the methods section as stated in our response to a previous question. Hence, we hope to study these interesting finding with future randomized controlled trials.

4. The rationale of the study is missing. And related to the above comment regarding an absence of hypotheses, seems extremely exploratory and not grounded in some theory

Response: The rational of this study is to determine if any association is present between altered food intake parameters and chronic gastrointestinal symptoms. As stated in a previous response, we have edited our introduction to better indicate our hypothesis and aim:

"In addition, none of the studies in the literature simultaneously examined food intake symptoms and their relationship with common GI symptoms in obesity. We hypothesized that food intake symptoms (e.g., altered hunger, satiation, postprandial satiety, and hedonic eating) are associated with diverse functional GI symptoms in obesity."

Since both factors (altered food intake parameters and GI symptoms) are more prevalent in patients with obesity, we intended to study if any correlation is present. The strength of this study is due to the fact that there is scarcity of these data in the literature. Hence, we hope that this established association can provide a base for realizing that there is indeed an association present. We have tried to show a potential clinical illustration of this association which can be of great significance if proven in future trials:

"The correlation with GI symptoms is of potential clinical importance. First, it might provide the rationale to propose treatments to address both the obesity phenotype as well as postprandial symptoms. For example, it would be advantageous to treat abnormal postprandial satiety (associated with accelerated GE) and watery diarrhea with an agent that delays gastrointestinal motility and GE such as a GLP-1 agonist.[40, 41] A second rationale is that both abnormal food intake and GI symptoms are highly prevalent and may co-exist in the same person; thus, abnormal satiation is present in 32% of patients with obesity[8] and bloating is reported in 31% of the general population.[42]"

Title: Association between Food Intake and Gastrointestinal Symptoms in Patients with Obesity

Short Title: Food Intake and Gastrointestinal Symptoms

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Abbreviations: aBDQ: Abridged Bowel Disease Questionnaire, BMI: Body-Mass Index, CI: Confidence Intervals, CTF: Calories to Fullness, GE: Gastric Emptying, GI: Gastrointestinal, HADS: Hospital Anxiety and Depression Scale, IBS: irritable bowel syndrome, OR: Odds Ratios, VAS: Visual Analog Scale.

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Data Transparency Statement: Deidentified individual participant data can be shared upon request

- Data on participants' tests and questionnaire results; Bowel Disease Questionnaire

- Data can be sent to journal if needed
- No limited timeframe

Authors Contribution: Wissam Ghusn: Writing- Original draft preparation, Writing- Reviewing and Editing Software, Methodology; **Lizeth Cifuentes, Alejandro Campos, Daniel Sacoto, Alan De La Rosa, and Fauzi Feris:** Writing- Reviewing and Editing; **Gerardo Calderon, Daniel Gonzalez-Izundegui**, and **Jessica Stutzman**: Investigación and Resources; **Maria Daniela Hurtado** and **Michael Camilleri**: Supervision; **Andres Acosta**: Funding acquisition and Supervision

Abstract:

Background and Aims: Hunger, satiation, postprandial satiety, and hedonic eating constitute key food intake parameters. We aim to study whether these symptoms are associated with gastrointestinal symptoms (GIS) in patients with obesity.

Methods: This is a cross-sectional study of patients with obesity. Patients completed the following validated biomarkers and questionnaires: Hunger was measured via visual analog scale (100mm) following a standard meal, satiation via *ad-libitum* meal (calories to fullness;kcal), postprandial satiety via gastric emptying scintigraphy ($T_{1/2}$;mins) and hedonic eating via the Hospital Anxiety and Depression Scale questionnaire. Participants completed the abridged Bowel-Disease-Questionnaire to evaluate their GIS. We calculated the odds ratios adjusted for sex, weight, and age between food intake parameters $<25^{th}$ or $>75^{th}$ percentile observed in a prior cohort of 450-participants with obesity and GIS.

Results: A total of 274 participants (41±10 [SD] years, 75%females, body-mass index 39±8kg/m^2) were included in the analysis. Increased hunger was associated with a lower prevalence of lumpy stools (OR=0.18, p=0.02). Satiation was associated with abdominal pain/discomfort [relieved by defecation (OR=2.4, p=0.02) or associated with change in stool consistency (OR=2.92, p<0.01)], loose/watery stools (OR=2.09, p=0.02) and bloating (OR=2.49, p<0.01). Abnormal postprandial satiety was associated with bloating (OR=2.26, p<0.01) and loose/watery stools (OR=1.84, p=0.04). Hedonic eating was associated with abdominal pain/discomfort with stool frequency change (OR=2.4, p=0.02), >3 bowel movements/day (OR=1.93, p=0.048), bloating (OR=2.49, p=0.01), abdominal pain after meals >1/month (OR=4.24, p<0.01), and nausea >1/week (OR=4.51, p<0.01).

Conclusion: Alterations in hunger, satiation, postprandial satiety, and hedonic eating are associated with GIS in patients with obesity.

Keywords: Obesity; Hunger; Satiation; Postprandial Satiety, Gastric Emptying; Hedonic Eating

Introduction:

Obesity is a chronic multifactorial disease that results from increased energy intake and/or decreased energy expenditure. Energy balance is governed by food intake and energy expenditure. An imbalance between these two key factors can lead to weight gain. Food intake is regulated by homeostatic and hedonic factors; homeostatic factors can be further divided into three stages: hunger, satiation, and postprandial satiety.[1] Hunger is an internal motivational state elicited by a lack of nutrients in the body, which drives eating and food-seeking behavior.[2] Satiation is the process that brings an eating episode to an end[3], whereas postprandial satiety is the constellation of sensations that inhibits eating in the postprandial period[4, 5] and it is reflected objectively by gastric emptying (GE) time.[6] In addition, hedonic eating is the desire to eat solely to elicit pleasurable feelings regardless of the individual's nutritional status.[7] Alterations in hunger, satiation, postprandial satiety and hedonic eating contribute to food intake symptoms. These symptoms led to the development of a phenotype-guided method which differentiates the causes of obesity based on the pathogenesis: satiation, postprandial satiety, hedonic eating, and resting energy expenditure.[8] Importantly, these alterations have been only studied in patients with obesity or overweight. Such classification contributes to a better understanding[6, 9] and treatment of obesity.[8]

Obesity affects almost every system in the body, raising the risk of a variety of illnesses.[10] It can either be the primary cause, as seen in nonalcoholic fatty liver disease,[11, 12] or a substantial risk factor for numerous gastrointestinal (GI) and hepatic diseases such as reflux esophagitis caused by gastroesophageal reflux disease.[12-14] Low-grade chronic inflammation, fluctuations in GI hormones, and adipose tissue redistribution in the abdominal cavity contribute to GI morbidity in obesity.[12] Moreover, several studies show that food intake results in a significant colonic response change (e.g., fat composition).[15-17] Obesity was also shown to be associated with chronic symptoms including dyspepsia, upper abdominal pain, diarrhea, heartburn, vomiting and retching.[18] Furthermore, weight loss can play a possible role in improvement of common GI symptoms in patients with obesity, such as gastroesophageal reflux disease[19], abdominal distention, diarrhea and constipation.[20]

Previously, satiation and satiety tests have been used to explore the prevalence of dyspepsia in the community.[21, 22] Postprandial fullness and early satiation are typical dyspeptic

symptoms that have been investigated [23, 24] using physiological GI tests such as GE of solids and liquids, gastric volumes, and liquid nutrient meal. However, little is known about the association between altered hunger, satiation, postprandial satiety, and hedonic eating with functional GI symptoms in patients with obesity. Although several studies measure the correlation between obesity and functional GI symptoms,[25-29] none explain their association with food intake symptoms. Moreover, these studies are limited by inconsistent conclusions,[30, 31] selection bias[31], young-age participants,[28] small sample size,[32] and using diverse tools to measure same objective parameters (i.e., GE)[30]. In addition, none of the studies in the literature simultaneously examined food intake symptoms and their relationship with common GI symptoms in obesity. We hypothesized that food intake symptoms (e.g., altered hunger, satiation, postprandial satiety, and hedonic eating) are associated with diverse functional GI symptoms in obesity.

Methods:

Study design and participants

We performed a cross-sectional study analyzing baseline characteristics of adult participants between 18 and 65 years old with obesity (Body-mass Index [BMI] > 30 kg/m^2) with no evidence of any chronic gastrointestinal diseases, use of medications that may alter gastrointestinal motility, appetite or absorption, active psychiatric symptoms, eating disorders (e.g., bulimia, binge eating disorder), or alcohol use disorder. This study was approved by the institutional human research review committee at Mayo Clinic. The participants were recruited from the community using standard advertisement and here we report the baseline characteristic of participants enrolled in the ClinicalTrials.gov NCT03374956 trial. In this study, all the physiological studies (i.e., GE and *ad libitum* meal) and questionnaires were completed to assess baseline characteristics of our patients prior to starting the clinical trial. All authors had access to the study data and reviewed and approved the final manuscript.

Measurements:

All tests were performed at the Mayo Clinic Clinical Research and Trial Unit after an 8-hour fasting period (Figure 1 and 2):

A. Hunger was evaluated using 100mm visual analog scale (VAS) after 240 mins of a 320-kcal standard breakfast meal.[6]

B. Satiation was assessed by measuring calories to fullness (CTF) during an *ad libitum* meal.[33]

C. Postprandial satiety was studied via measuring the gastric emptying (GE $T_{1/2}$) by scintigraphy for a total of 240 mins after radiolabeled solid (320-kcal, 30% fat) standard breakfast. Postprandial satiety has been previously associated with rapid GE by Gonzalez-Izundegui et al.[6]

D. Hedonic eating was evaluated using the Hospital Anxiety and Depression Scale (HADS) questionnaire.[33] A correlation between HADS anxiety score and the three-factor eating questionnaire (emotional eating factor; r=0.36) has been recently established. In addition, higher HADS anxiety scores were associated with emotional and uncontrolled eating ($p<0.001$ for both), and lower levels of cognitive restraint ($p=0.04$)[34].

Participants completed the abridged Bowel Disease Questionnaire (aBDQ), a 16-item form that has been used to evaluate various functional GI symptoms (supplementary material)[35].

Statistical analysis:

Using standard quantile regression approach to identify normal range[36] and based on the fact that these variables are different in obesity when compared to healthy controls[37], the abnormal traits in the key components of food intake were determined based on quartiles – 25th or 75th percentile ~~– of each variable measured in 450 participants with obesity,~~ as observed from our previous study[33]. Thus, the cutoffs were: increased hunger was defined as VAS-hunger: > 80 mm for females and > 87 mm for males; abnormal satiation was defined as *ad libitum* meal test > 970 Kcal for females and > 1359 Kcal for males; accelerated GE, which is a biomarker of abnormal postprandial satiety, was defined as <25th percentile of GE $T_{1/2}$: < 106 mins for females and < 87 mins for males; and hedonic eating was defined with a score >7 for HADS-Anxiety for both sexes (Table 1). We used a multivariate logistic regression model to calculate the odds ratios (OR) and 95% confidence intervals (CIs) associating hunger, satiation, postprandial

satiety, and hedonic eating with the aBDQ results while adjusting for sex, weight, and age. Statistical significance was set at 2-sided $p< 0.05$. We used JMP®, Version 14.3.0 (SAS Institute Inc., Cary, NC, 1989-2019) to perform the statistical analysis. Data are summarized as mean (standard deviation).

Results:

Participants Demographics:

A total of 274 participants with obesity were recruited for this study. Our participants were predominantly females (75%), mean age 40.7 (10.3) years and BMI 39.2 (7.5) kg/m^2. The distribution of our participants among the hunger, satiation, postprandial satiety, and hedonic eating groups is shown in Table 2.

Association between food intake and GI symptoms

Increased hunger was associated with a lower prevalence of lumpy stools (OR 0.18, 95% CI 0.04-0.76; p= 0.02) (Figure 2A).

Abnormal satiation was associated with a higher frequency for ≥3 months of continuous or recurrent symptoms of abdominal pain or discomfort that is relieved by defecation (OR 2.4, 95% CI 1.15-5.01; p= 0.02), or associated with change in stool consistency (OR 2.92, 95% CI 1.34-6.34 p< 0.01), bloating (OR 2.49, 95% CI 1.33-4.66; p< 0.01), bloating after meals (OR 2.09, 95% CI 1.14-3.83; p= 0.02), and loose/watery stools (OR 2.09, 95% CI 1.14-3.84; p= 0.02) (Figure 2B).

Abnormal postprandial satiety was associated with a higher prevalence of bloating (OR 2.26, 95% CI 1.23-4.2; p< 0.01), bloating after meals (OR 1.83, 95% CI 1.02-3.29; p= 0.04), and loose/watery stools (OR 1.84, 95%CI 1.02-3.34; p= 0.04) (Figure 2C).

Hedonic eating was associated with a higher frequency for ≥3 months of continuous or recurrent symptoms of abdominal pain or discomfort associated with a change in stool frequency (OR 2.4, 95% CI 1.15-5.01; p= 0.02), > 3 bowel movements per day (OR 1.93 95% CI 1.005-3.692; p= 0.048), bloating (OR 2.49 95% CI 1.24-5; p= 0.01), upper abdominal pain after meals more than once a month (OR 4.24 95% CI 1.82-9.85; p< 0.01), bloating after meals (OR 2.1 95%CI 1.1-4.04; p= 0.03), and nausea regularly more than once a week (OR 4.51 95% CI 1.79-11.37; p< 0.01) (Figure 2D).

Discussion:

Our present study shows an association between symptoms associated with food intake and chronic functional GI symptoms in patients with obesity. These GI symptoms which are prevalent in obesity,[26] seem to be linked to specific alterations in parameters of food intake. In fact, these symptoms associated with food intake are found to be coexisting with a wide range of upper (bloating, abdominal pain, nausea) and lower (diarrhea) GI symptoms.

Functional GI symptoms and obesity are highly prevalent in adults.[25, 26] Several studies show a high prevalence of various symptoms (i.e. bloating and diarrhea) in patients with obesity.[38] Here, we showed the association of each component of food intake with GI symptoms. These components were labeled as increased or decreased based on the data in an independent cohort of 450 adults with obesity, from which we proposed a pathophysiological and behavioral phenotype-based classification of obesity.[39] The correlation with GI symptoms is of potential clinical importance. First, it might provide~~s~~ the rationale to propose treatments to address both the obesity phenotype as well as postprandial symptoms. For example, it would be advantageous to treat abnormal postprandial satiety (associated with accelerated GE) and watery diarrhea with an agent that delays gastrointestinal motility and GE such as a GLP-1 agonist.[40, 41]

A second rationale is that both abnormal food intake and GI symptoms are highly prevalent and may co-exist in the same person; thus, abnormal satiation is present in 32% of patients with obesity[8] and bloating is reported in 31% of the general population.[42]

Hunger and lumpy stools: The association between increased hunger and lower prevalence of lumpy stools may be explained by diverse mechanisms. Hunger is one of the driving factors of food intake[43] and perhaps craving for high fat intake, which can stimulate a colonic motor response,[44] increased colonic phasic contractile activity[45] and therefore, avoidance of constipation,[46] or the associated lumpy stools (type 1 or 2 on the Bristol Stool Form Scale.[47]). Increased hunger may also reflect a higher level of ghrelin in the body.[48] Ghrelin and its analogs (e.g. relamorelin) regulate GI motility by accelerating gastric and intestinal motility,[49, 50] and may play a potential role in treating constipation by stimulating gastrointestinal motility[51] and significantly changing stool consistency as previously shown in a placebo-controlled trial of relamorelin.[52]

Satiation and GI symptoms: Abnormal satiation in this study is reflected in increased intake of calories at an ad libitum meal; the sensation of bloating in patients with abnormal satiation is poorly understood but it is conceivable that it reflects increased visceral afferent activation as occurs with dyspeptic symptoms, [53] and may result in changes in eating habits [54]

Continuous or recurrent abdominal pain or discomfort for at least 6 months associated with a change in stool frequency, change in stool form, and related to defecation are the three Rome IV criteria for irritable bowel syndrome (IBS) classification. Any patient with ≥2 of these bowel function symptoms is sufficient for IBS diagnosis.[55] Our study showed that participants with abnormally higher satiation level (that is increased kcal intake) are more likely to have abdominal pain associated with change in stool frequency and/or relieved by defecation.

However, other studies show that patients with IBS have a similar satiation level compared to healthy individuals.[56] Similarly, ingesting certain types of food in high quantities can promote osmotic diarrhea which can partially explain the high prevalence of diarrhea in patients with obesity. Patients with obesity and abnormal satiation are more likely to ingest a greater quantity of food [29] containing poorly absorbed sugars (i.e., fructose corn syrup) that can contribute to diarrhea.

Postprandial Satiety and GI symptoms: Patients with rapid GE may present with dyspepsia symptoms (e.g., bloating),[14, 57] possibly as a result of rapid transit of hyperosmolar food into the duodenum, as occurs in dumping syndrome,[58] which is associated with bloating especially after meals.[59]

In a study on patients with chronic diarrhea, Charles et al, showed a higher prevalence of rapid GE which may be a possible mechanism of diarrhea in patients with functional bowel disorders.[60] Similarly, in our study, patients with accelerated GE were more likely to report watery, loose stools.

Hedonic eating and GI symptoms: Anxiety has been previously linked to increased food intake is a subset of patient with obesity,[39] and it has been associated with bloating[61], functional abdominal pain[62], and nausea[63]. In addition, previous studies show an increased susceptibility of hedonic eating in female patients which account for 75% of our cohort.[64]

Strength and limitations:

The strengths of our study include the adequate sample size of participants who completed simultaneously during the same day the required tests and questionnaires, exclusion of patients with any GI disease and eating disorder, and the nature of the cross-sectional study which limits the attrition bias.

This study also has several potential limitations. Considering the nature of our study, no casual inference can be made for any of the results. In fact, we cannot study the temporal relation between the food intake and the chronic GI symptoms. For example, it cannot be concluded whether higher levels of anxiety were due to GI symptoms in obesity or vice versa. In addition, our participants were required to fill in questionnaires which makes the study more susceptible to recall bias. This study also included mostly white Americans and female patients which limits the generalizability of our results to other populations.

Conclusion:

In patients with obesity, homeostatic (hunger, satiation, and postprandial satiety) and hedonic components of food intake are associated with various chronic GI symptoms. These symptoms are known to be observed with a significantly higher prevalence in patients with obesity.[30] Our study further shows an association between food intake and functional GI symptoms. This linkage requires more study to better understand, treat and prevent the occurrence of such GI symptoms in obesity.

References:

1. Cifuentes L, Acosta A. Homeostatic regulation of food intake. Clinics and Research in Hepatology and Gastroenterology 2021:101794.
2. Lin S, Senapati B, Tsao C-H. Neural basis of hunger-driven behaviour in Drosophila. Open biology 2019;9:180259.
3. Bellisle F, Drewnowski A, Anderson GH, et al. Sweetness, satiation, and satiety. The Journal of nutrition 2012;142:1149S-1154S.
4. Blundell JE. Perspective on the Central Control of Appetite. Obesity 2006;14:160S-163S.
5. Cifuentes L, Acosta A. Homeostatic regulation of food intake. Clin Res Hepatol Gastroenterol 2021;46:101794.
6. Gonzalez-Izundegui D, Campos A, Calderon G, et al. Association of gastric emptying with postprandial appetite and satiety sensations in obesity. Obesity 2021;29:1497-1507.
7. Monteleone P, Piscitelli F, Scognamiglio P, et al. Hedonic Eating Is Associated with Increased Peripheral Levels of Ghrelin and the Endocannabinoid 2-Arachidonoyl-Glycerol in Healthy Humans: A Pilot Study. The Journal of Clinical Endocrinology & Metabolism 2012;97:E917-E924.
8. Acosta A, Camilleri M, Dayyeh BA, et al. Selection of antiobesity medications based on phenotypes enhances weight loss: A pragmatic trial in an obesity clinic. 2021.
9. Pajot G, Camilleri M, Calderon G, et al. Association between gastrointestinal phenotypes and weight gain in younger adults: a prospective 4-year cohort study. International Journal of Obesity 2020;44:2472-2478.
10. Apovian CM. Obesity: definition, comorbidities, causes, and burden. Am J Manag Care 2016;22:s176-85.
11. Polyzos SA, Kountouras J, Mantzoros CS. Obesity and nonalcoholic fatty liver disease: From pathophysiology to therapeutics. Metabolism 2019;92:82-97.
12. Camilleri M, Malhi H, Acosta A. Gastrointestinal Complications of Obesity. Gastroenterology 2017;152:1656-1670.
13. Anand G, Katz PO. Gastroesophageal reflux disease and obesity. Gastroenterol Clin North Am 2010;39:39-46.
14. Delgado-Aros S, Camilleri M, Cremonini F, et al. Contributions of gastric volumes and gastric emptying to meal size and postmeal symptoms in functional dyspepsia. Gastroenterology 2004;127:1685-1694.
15. Steed KP, Bohemen EK, Lamont GM, et al. Proximal colonic response and gastrointestinal transit after high and low fat meals. Dig Dis Sci 1993;38:1793-800.
16. Deiteren A, Camilleri M, Burton D, et al. Effect of meal ingestion on ileocolonic and colonic transit in health and irritable bowel syndrome. Dig Dis Sci 2010;55:384-91.
17. Ragnarsson G, Bodemar G. Pain is temporally related to eating but not to defaecation in the irritable bowel syndrome (IBS). Patients' description of diarrhea, constipation and symptom variation during a prospective 6-week study. Eur J Gastroenterol Hepatol 1998;10:415-21.
18. Eslick G. Gastrointestinal symptoms and obesity: a meta-analysis. Obesity reviews 2012;13:469-479.
19. Singh M, Lee J, Gupta N, et al. Weight loss can lead to resolution of gastroesophageal reflux disease symptoms: a prospective intervention trial. Obesity 2013;21:284-290.
20. Foster A, Laws HL, Gonzalez QH, et al. Gastrointestinal symptomatic outcome after laparoscopic Roux-en-Y gastric bypass. J Gastrointest Surg 2003;7:750-3.
21. Castillo EJ, Camilleri M, Locke GR, et al. A community-based, controlled study of the epidemiology and pathophysiology of dyspepsia. Clinical Gastroenterology and Hepatology 2004;2:985-996.

22. Jones KL, Doran SM, Hveem K, et al. Relation between postprandial satiation and antral area in normal subjects. The American Journal of Clinical Nutrition 1997;66:127-132.
23. Fischler B, Tack J, De Gucht V, et al. Heterogeneity of symptom pattern, psychosocial factors, and pathophysiological mechanisms in severe functional dyspepsia. Gastroenterology 2003;124:903-10.
24. Parkman HP, Hallinan EK, Hasler WL, et al. Early satiety and postprandial fullness in gastroparesis correlate with gastroparesis severity, gastric emptying, and water load testing. Neurogastroenterology and motility : the official journal of the European Gastrointestinal Motility Society 2017;29:10.1111/nmo.12981.
25. Delgado-Aros S, Locke III GR, Camilleri M, et al. Obesity is associated with increased risk of gastrointestinal symptoms: a population-based study. Official journal of the American College of Gastroenterology| ACG 2004;99:1801-1806.
26. Eslick GD. Gastrointestinal symptoms and obesity: a meta-analysis. Obes Rev 2012;13:469-79.
27. Talley NJ, Quan C, Jones MP, et al. Association of upper and lower gastrointestinal tract symptoms with body mass index in an Australian cohort. Neurogastroenterol Motil 2004;16:413-9.
28. Talley NJ, Howell S, Poulton R. Obesity and chronic gastrointestinal tract symptoms in young adults: a birth cohort study. Am J Gastroenterol 2004;99:1807-14.
29. Aro P, Ronkainen J, Talley NJ, et al. Body mass index and chronic unexplained gastrointestinal symptoms: an adult endoscopic population based study. Gut 2005;54:1377-83.
30. Ho W, Spiegel BMR. The relationship between obesity and functional gastrointestinal disorders: causation, association, or neither? Gastroenterology & hepatology 2008;4:572-578.
31. van Oijen MG, Josemanders DF, Laheij RJ, et al. Gastrointestinal disorders and symptoms: does body mass index matter? Neth J Med 2006;64:45-9.
32. Bluemel S, Menne D, Milos G, et al. Relationship of body weight with gastrointestinal motor and sensory function: studies in anorexia nervosa and obesity. BMC Gastroenterology 2017;17:4.
33. Acosta A, Camilleri M, Abu Dayyeh B, et al. Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic. Obesity (Silver Spring, Md.) 2021;29:662-671.
34. Cifuentes L, Campos A, Silgado MLR, et al. Association between anxiety and eating behaviors in patients with obesity. Obesity Pillars 2022;3:100021.
35. Brandler J, Miller LJ, Wang XJ, et al. Secretin effects on gastric functions, hormones and symptoms in functional dyspepsia and health: randomized crossover trial. Am J Physiol Gastrointest Liver Physiol 2020;318:G635-g645.
36. Koenker R. Quantile regression. Cambridge ; New York: Cambridge University Press, 2005.
37. Acosta A, Camilleri M, Shin A, et al. Quantitative gastrointestinal and psychological traits associated with obesity and response to weight-loss therapy. Gastroenterology 2015;148:537-546 e4.
38. Alkhowaiter S, Alotaibi RM, Alwehaibi KK, et al. The Effect of Body Mass Index on the Prevalence of Gastrointestinal Symptoms Among a Saudi Population. Cureus 2021;13.
39. Acosta A, Camilleri M, Abu Dayyeh B, et al. Selection of Antiobesity Medications Based on Phenotypes Enhances Weight Loss: A Pragmatic Trial in an Obesity Clinic. Obesity 2021;29:662-671.
40. Acosta A, Camilleri M, Burton D, et al. Exenatide in obesity with accelerated gastric emptying: a randomized, pharmacodynamics study. Physiological reports 2015;3.
41. Halawi H, Khemani D, Eckert D, et al. Effects of liraglutide on weight, satiation, and gastric functions in obesity: a randomised, placebo-controlled pilot trial. The lancet. Gastroenterology & hepatology 2017;2:890-899.

42. Lacy BE, Cangemi D, Vazquez-Roque M. Management of Chronic Abdominal Distension and Bloating. Clin Gastroenterol Hepatol 2021;19:219-231 e1.
43. Davis J. Hunger, ghrelin and the gut. Brain Res 2018;1693:154-158.
44. Bouchoucha M, Odinot JM, Devroede G, et al. Simple clinical assessment of colonic response to food. International Journal of Colorectal Disease 1998;13:217-222.
45. Ford MJ, Camilleri M, Wiste JA, et al. Differences in colonic tone and phasic response to a meal in the transverse and sigmoid human colon. Gut 1995;37:264-269.
46. Sarna SK. Integrated Systems Physiology: From Molecule to Function to Disease. Colonic Motility: From Bench Side to Bedside. San Rafael (CA): Morgan & Claypool Life Sciences

47. Chumpitazi BP, Self MM, Czyzewski DI, et al. Bristol Stool Form Scale reliability and agreement decreases when determining Rome III stool form designations. Neurogastroenterology & Motility 2016;28:443-448.
48. Müller TD, Nogueiras R, Andermann ML, et al. Ghrelin. Mol Metab 2015;4:437-60.
49. El-Salhy M, Lillebø E, Reinemo A, et al. Ghrelin in patients with irritable bowel syndrome. Int J Mol Med 2009;23:703-707.
50. Tack J, Depoortere I, Bisschops R, et al. Influence of ghrelin on interdigestive gastrointestinal motility in humans. Gut 2006;55:327-333.
51. Gürkan OE, Dalgıç B, Bideci A. Relation between ghrelin level and treatment response in functional constipation. Turk J Gastroenterol 2013;24:515-20.
52. Acosta A, Kolar G, Iturrino J, et al. Sa2051 A Phase II, Randomized, Double-Blind, Placebo-Controlled, Multiple-Dose, Parallel-Group Study to Evaluate the Efficacy, Safety, and Pharmacodynamics of RM-131 in Patients With Chronic Constipation. Gastroenterology 2014;146:S-364.
53. Giurcan R, Voiosu TA. Functional dyspepsia: a pragmatic approach. Rom J Intern Med 2010;48:9-15.
54. Levine ME. Sickness and satiety: physiological mechanisms underlying perceptions of nausea and stomach fullness. Current gastroenterology reports 2005;7:280-288.
55. Patel N, Shackelford KS. Irritable Syndrome Syndrome. 2018.
56. Camilleri M, McKinzie S, Busciglio I, et al. Prospective study of motor, sensory, psychologic, and autonomic functions in patients with irritable bowel syndrome. Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association 2008;6:772-781.
57. Bharucha AE, Manduca A, Lake DS, et al. Gastric motor disturbances in patients with idiopathic rapid gastric emptying. Neurogastroenterol Motil 2011;23:617-e252.
58. Hui C, Dhakal A, Bauza GJ. Dumping syndrome. StatPearls [Internet] 2020.
59. Scarpellini E, Arts J, Karamanolis G, et al. International consensus on the diagnosis and management of dumping syndrome. Nature reviews. Endocrinology 2020;16:448-466.
60. Charles F, Phillips SF, Camilleri M, et al. Rapid gastric emptying in patients with functional diarrhea. Mayo Clin Proc 1997;72:323-8.
61. Seo AY, Kim N, Oh DH. Abdominal bloating: pathophysiology and treatment. Journal of neurogastroenterology and motility 2013;19:433-453.
62. Walter SA, Jones MP, Talley NJ, et al. Abdominal pain is associated with anxiety and depression scores in a sample of the general adult population with no signs of organic gastrointestinal disease. Neurogastroenterol Motil 2013;25:741-e576.
63. Haug TT, Mykletun A, Dahl AA. The prevalence of nausea in the community: psychological, social and somatic factors. Gen Hosp Psychiatry 2002;24:81-6.

64. Buczek L, Migliaccio J, Petrovich GD. Hedonic Eating: Sex Differences and Characterization of Orexin Activation and Signaling. Neuroscience 2020;436:34-45.

Tables and Figures:

Table 1:

Cohort distribution of participants adjusted by sex upon the food intake tests.

Food Intake Tests	**Abnormal Value**		Cut-off
	Female	Male	
Hunger (VAS, mm)	>80	>87	75%
Satiation (*Ad Libitum* meal, Kcal)	>970	>1359	75%
Postprandial Satiety (Gastric Emptying T½, min)	<106	<87	25%
Hedonic Eating Behavior (HADS, score)	>7	>7	
Abbreviations: HADS, hospital anxiety and depression scale; VAS, visual analogue scale.			

Table 2:

Demographic distribution of the hunger, satiation, postprandial satiety, and hedonic eating groups of participants.

Demographics	**Hunger**			**Satiation**			**Postprandial Satiety**			**Hedonic Eating**		
	Normal	Abnormal	P-value	Normal	Abnormal	P-value	Normal	Abnormal	P-value	Normal	Abnormal	P-value
Participants, n	215	51		205	68		205	69		222	51	
Age, y	41±10	40±10	0.76	41±10	40±10	0.24	41±10	41±11	0.65	41±10	39±11	0.1
Sex, Female (%)	155 (72)	45 (88)	**0.02**	154 (75)	51 (75)	1	154 (75)	52 (75)	1	167 (75)	38 (75)	1
Weight, kg	114±26	108±21	0.09	110±25	119±25	**0.02**	112±24	113±27	0.72	113±26	113±20	0.94
BMI, kg/m^2	40±7.6	38.5±7.3	0.70	41±8.3	38.7±7.2	0.05	39±7.4	40±8	0.70	39±7.8	39±6.5	0.8

Figure 1: The flowchart of the testing day.

Figure 2: The food intake parameters and their assessment methods.

Figure 3: The odds ratio of gastrointestinal symptoms based in the bowel disease questionnaire in patients with obesity and abnormal hunger (A), satiation (B), postprandial satiety (C), or hedonic eating (D).

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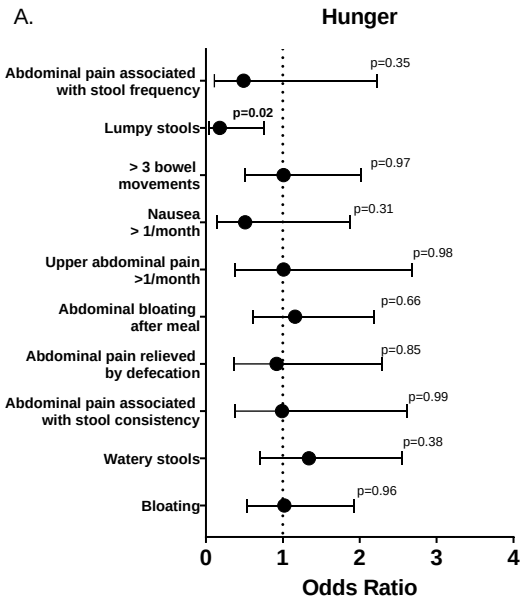
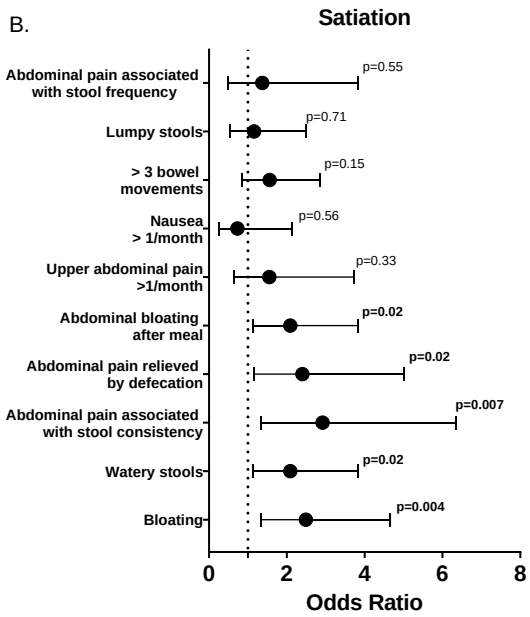
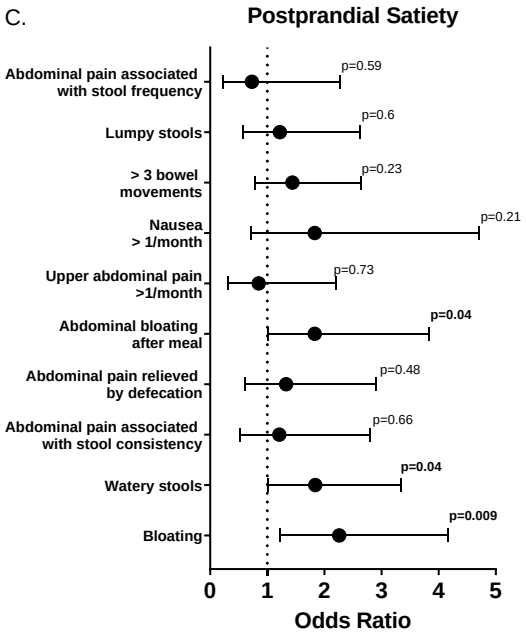
Table 2:

Demographic distribution of the hunger, satiation, postprandial satiety, and hedonic eating groups of participants.

Figure 3







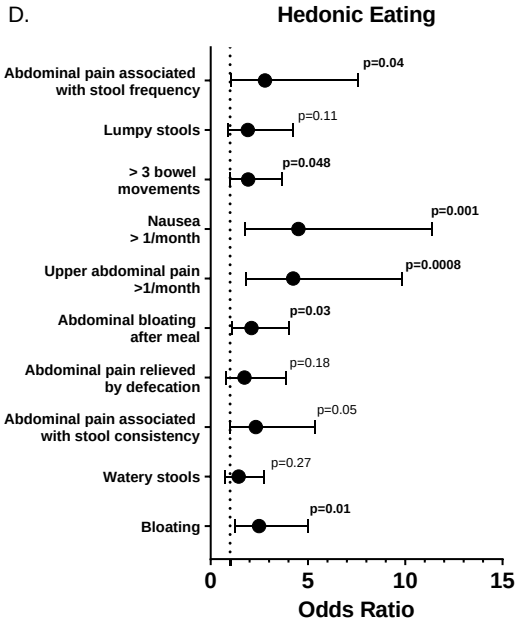


Figure 2

Visual Analog Scale → **Hunger**: Desire to eat

Ad Libitum meal → **Satiation**: Knowing when the meal is over

Gastric Emptying → **Postprandial Satiety**: Eating inhibition in the postprandial period

Hospital Anxiety and Depression Scale → **Hedonic Eating**: Eating in response to emotions

Figure 1

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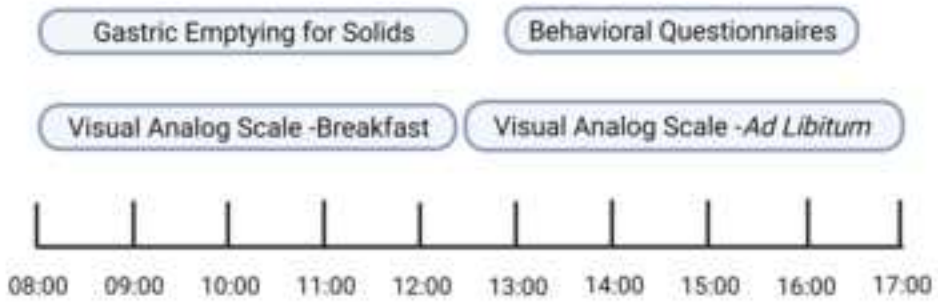

Abridged Bowel Disease Questionnaire