HOW INTAKE OF HIGH FRUCTOSE CORN SYRUP RELATES TO REPORTED IBS SYMPTOMS DURING TIMES OF STRESS

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Title

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The Supervisory Committee certifies that this ***disquisition*** complies with North Dakota State University's regulations and meets the accepted standards for the degree of

MASTER OF SCIENCE

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ABSTRACT

The dual purpose was to find whether a relationship exists between high fructose corn syrup (HFCS) intake and irritable bowel syndrome (IBS) symptoms, and if there are differences in intake of HFCS beverages during varying stress periods, measured through Perceived Stress Scale 10 (PSS-10). We recruited twenty-eight university students (89% female, 11% male). Participants average experienced gastrointestinal symptoms did not meet criteria for IBS. There was not a significant correlation found between the amount of HFCS-55 intake and reported IBS symptoms, $r=.040$, $p=.717$. A one-way repeated measures analysis of variance (ANOVA) was conducted to evaluate the null hypothesis that there is no change in participant's HFCS-55 intake when measured during low, moderate, and high stress environments (N=28). The results of the ANOVA did not indicate a significant effect, Wilk's Lambda = .987, $F(2,25) = .164$, $p = .073$. Thus, there is not significant evidence to reject the null hypothesis.

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DEDICATION

This section dedicates the disquisition to a few significant people. The text must be double spaced and aligned center to the page.

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LIST OF ABBREVIATIONS

ANOVA .... Analysis of Variance

ANS... Autonomic Nervous System

BEVQ-15 .... Beverage Questionnaire 15

CH4 .... Methane

CI.. Confidence Interval

CNS.. Central Nervous System

CRF .... Corticotropin-releasing Factor

DII .... Dietary inflammatory index

ENS .... Enteric Nervous System

FODMAP... Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols

G... Gram

GLUT .... Glucose transporter

H2... Hydrogen

HFCS.. High Fructose Corn Syrup

HNES .... Health, Nutrition, and Exercise Sciences

HPA.. Hypothalamic Pituitary Adrenal Axis

IBS .... Irritable Bowel Syndrome

IBS-C .... Irritable Bowel Syndrome- Constipation prominent

IBS-D .... Irritable Bowel Syndrome- Diarrhea prominent

IBS-M .... Irritable Bowel Syndrome- Mixed

IBS-SSS .... Irritable Bowel Syndrome Symptom Severity Scale

M .... Mean

MD .... Mediterranean diet

N..Population

NDSU...North Dakota State University

NHANES ....National Health and Nutrition Examination Survey

ORs ....Odds ratios

PSS-10...Perceived Stress Scale – 10

SD ....Standard Deviation

SLC2 ....Solute Carrier Family 2

SLC2A5 ....Solute Carrier Family 2 Member 5

SSB ....Sugar-sweetened beverage

USDA...United States Department of Agriculture

AND...Academy of Nutrition and Dietetics

CHAPTER 1. INTRODUCTION

Fructose is a monosaccharide naturally present in a variety of foods, including fruits, vegetables, and honey. Young adult males (ages 19–22 years) have been found to have the highest total fructose intakes of 75 g per day (121 to 134 g) (Latulippe & Skoog, 2011). Fructose is also produced as High Fructose Corn Syrup (HFCS), which is commonly found in many food sweeteners and soft drinks. Foods containing HFCS and sucrose represent 64-95% of total fructose intake (Latulippe & Skoog, 2011).

HFCS is the most widely used sweetener in beverages and processed foods worldwide (Duffey & Popkin, 2008). Over the past 50 years, HFCS has seen substantial increases in both production and consumption (Bray, Nielsen, & Popkin, 2004). During the years of 1970-1997, the annual per capita intake of HFCS increased 125% (Latulippe & Skoog, 2011). High-fructose corn syrup is also considered part of the FODMAP family. FODMAP stands for “Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols.” FODMAPs are a group of short-chain carbohydrates that are poorly absorbed in gastrointestinal tract of certain individuals, including those with Irritable Bowel Syndrome (IBS).

HFCS intake is commonly consumed in emotionally and physiologically stressed individuals looking for comfort (Yau & Potenza, 2013). Excess HFCS intake can be problematic for a healthy gastrointestinal system (Latulippe & Skoog, 2011) and therefore, especially problematic for those experiencing Irritable Bowel Syndrome (IBS) symptoms. Controlled IBS symptoms are critically important to the function of gastrointestinal system and proper absorption of nutrients (National Institute of Diabetes and Digestive and Kidney Diseases, 2020).

Therefore, excess intake of HFCS can be a major concern for college students who experience daily IBS symptoms during times of stress, who are at particular risk of increased exacerbation of IBS symptoms.

Stress and its relationship to IBS symptoms has been analyzed mainly in adult populations in relation to the brain and gut disturbances (Qin, Cheng, Tang, & Bian, 2014), HFCS and stress have been commonly linked. However, how HFCS intake relates to IBS symptoms during times of stress has not been extensively investigated. Examining the HFCS intake of college students with reported IBS symptoms during times of stress can help with IBS symptom management and increase quality of life.

Statement of Purpose

The objective of this study was to compare reported IBS symptoms to reported intake of HFCS beverages during times of stress in college students in North Dakota.

Research Questions

1. What is the relationship between intake of HFCS beverages and reported IBS symptoms?
2. What are the differences in intake of HFCS beverages when compared between-groups (i.e., less stressful time and more stressful time)?

Dependent and Independent Variables

The dependent variables of this study were the reported IBS symptoms. The independent variable(s) of this study is the perceived stress level and HFCS-55 beverage intake.

Limitations

First, the study was conducted using a sample of North Dakota State University and Valley City State University college students. There are additional colleges where recruitment was attempted to gain a widespread perspective on HFCS intake, perceived stress and reported IBS symptoms, however, attempts were unsuccessful. A convenience sample of 28 students was used. There are also limited demographic variations in Fargo and Valley City, North Dakota to consider. Additionally, an aspect of unintentially misreporting due to recall bias must be acknowledged with any self-reported survey. With regard to survey data collection, it is recognized that there may be a difference in reporting amongst various survey timelines. With diet recall being over the past 24 hours, reporting IBS symptoms throughout the past month, and perceived stress throughout the past 10 days. We must also acknowledge the fact that their could be an impact on a student's own tolerance to stress with regard to completing all surveys. For example, it could be that only students who were more tolerant to stress were able to handle completing all three surveys.

Delimitations

After a thorough analysis of previous research, as well as a consideration of participant time, participants only had to complete the survey three times. It is recognized there may be a change in stress level throughout each week of college semester, however, it is beyond the scope of this project to do weekly surveys. The surveys utilized are the gold standard and therefore utilized on all participants to measure IBS symptoms, perceived stress levels and HFCS beverage intake.

Assumptions

It was assumed that participants reported their nutrition and supplement use honestly on the food frequency questionnaire. It was also assumed that the participants recorded their perceived stress honestly and accurately. Finally, it was expected that each participant did not incorrectly or inadequately report their IBS symptoms.

Significance of Study

College students may be susceptible to IBS symptoms due to stress from school. Uncontrolled HFCS intake can cause a greater risk of IBS symptoms. Analyzing HFCS intake and IBS symptoms allows students to be aware of their intake and potentially reduce the risk of IBS symptoms. The results of this study were used to determine if there is a correlation between HFCS intake and reported IBS symptoms. Lastly, the results were used to reveal if there is a significant change in HFCS intake between high stress and low stress times throughout the academic semester.

CHAPTER 2. LITERATURE REVIEW

Irritable bowel syndrome (IBS) is the most commonly diagnosed functional gastrointestinal disorder characterized by a group of symptoms that occur together without an identifiable cause (Ikechi, Fischer, DeSipio, & Phadtare, 2017). Symptoms include chronic abdominal pain and changed bowel habits, which may be diarrhea, constipation, or both. Although variation exists, the prevalence of IBS symptoms ranges from 10–15% in population-based studies in North America (American College of Gastroenterology, 2019). In 2012, Lovell and Ford conducted a meta-analysis of studies on the epidemiology of IBS (Lovell & Ford, 2012) and estimated a global prevalence of 11.2% (95% confidence interval [CI], 9.8-12.8%), a rate that has not changed in the last 30 years.

IBS has gained significant interest in healthcare due to its common occurrence, complex pathophysiology, and challenging treatment options. Although true food allergies are uncommon in patients with IBS, exacerbation of IBS symptoms has been frequently observed due to food sensitivities, such as fructose malabsorption (DiNicolantonio & Lucan, 2015; Ikechi, Fischer, DeSipio, & Phadtare, 2017).

Fructose, a natural sugar found in many fruits, has been consumed in significant amounts in Western diets since the 1970's (Talley et al., 1991). High fructose corn syrup (HFCS) is a disaccharide consisting of unequal parts of fructose and glucose. Fructose is sweeter than glucose, therefore, when combined to produce HFCS, the result is a more desired sweetener. An increase in chronic consumption of HFCS, as well as total fructose, over the past 50 years has been linked to various health problems, including obesity, metabolic disorders, and IBS (Ikechi, Fischer, DeSipio, & Phadtare, 2017). Excess HFCS intake is a common problem in stressed individuals looking for comfort (Yau & Potenza, 2013). The purpose of this literature review will be to examine how HFCS intake relates to IBS symptoms during times of stress.

Irritable Bowel Syndrome

Introduction to Irritable Bowel Syndrome

IBS is a common GI disorder impacting between 10-15% of adults in the United States (American College of Gastroenterology, 2019). IBS affects the large intestine with multiple symptoms, which, at times, contradict one another such as cramping, abdominal pain, bloating, gas, and diarrhea or constipation, or both.

Definition

Diagnostic criteria for IBS, commonly referred as Rome III criteria, consists of recurrent abdominal pain or discomfort at least three days/month in the last three months as associated with two or more of the following: improvement with defecation, onset associated with a change in frequency of stool, or onset associated with a change in form of stool (Shih & Kwan, 2007). There are three different types of IBS, namely IBS with constipation, IBS with diarrhea, and IBS with mixed bowel habits.

Each type is defined by National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), (2019) as follows:

IBS with constipation (IBS-C): on days when you have at least one abnormal bowel movement,

- more than a quarter of your stools are hard or lumpy and
- less than a quarter of your stools are loose or watery

IBS with diarrhea (IBS-D): on days when you have at least one abnormal bowel movement,

- more than a quarter of your stools are loose or watery and
- less than a quarter of your stools are hard or lumpy

IBS with mixed bowel habits (IBS-M):on days when you have at least one abnormal bowel movement,

- more than a quarter of your stools are hard or lumpy and
- more than a quarter of your stools are loose or watery (para.6-8).

IBS is not a trivial illness. It affects a person's quality of life and activities of daily living; however, it is important to note that IBS symptoms can be controlled .

Pathophysiology of IBS

There is no one cause of IBS; however, the disease has been linked to many GI abnormalities, including: (1) increased frequency, exaggerated response to dietary intake, prolonged transit time and irregular intestinal contractions, as well as (2) impaired cellular function causing distention and bloating, (3) inflamed mucus and abnormal motor and visceral responses due to a stimulated enteric nervous system, (4) bile acid malabsorption, (5) infection, (6) increased enteroendocrine cells and T lymphocytes following infection, producing increased GI motility and hypersensitivity, (7) antibiotic use, (8) changes in gut microflora, (9) small intestinal bacterial overgrowth; (10) food sensitivities; (11) stress (Lopez-Siles et al., 2018; Mazzawi et al., 2018; Rodiño-Janeiro, Vicario, Alonso-Cotoner, Pascua-García, & Santos, 2018). In brief, IBS genesis has been shown to have many contributing factors, one of which being food sensitivities, including incomplete fructose absorption.

Management of IBS

Many interventions have been advocated in the treatment of IBS, including altering the host's diet, microflora, and fecal bacteria. Additionally, pharmacological therapies such as antidepressants and antispasmodics can be effective, however, research suggests that the majority of patients with IBS use alternative approaches including lifestyle changes, psychotherapy, exercise, and dietary changes either in addition to or instead of medical therapies (Lahner et al., n.d.). Furthermore, over two thirds of patients with IBS relate their symptoms to particular triggering foods (Cozma-Petrut, Loghin, Miere, & Dumitrascu, 2017).

Dietary Interventions: FODMAP

The number of foods thought to exacerbate symptoms of GI disorders, such as IBS, is increasing dramatically. Specifically, current research has identified carbohydrate molecules that seem to worsen symptoms. These substances, including "Fermentable Oligo-, Di-, Mono-saccharides And Polyols" (FODMAP) include short-chain fermentable carbohydrates such as lactose (sugar present in dairy products), galactans (found in lentils, chickpeas, broccoli, beans and soy-based products), and polyalcohols (sugar alcohols including: sorbitol, mannitol, maltitol, xylitol, and isomalt), fructose (sugar present in honey and fruit), fructans (found in wheat products, onions, garlic, artichokes and inulin) ("What Is the Low FODMAP Diet," n.d.). These carbohydrates are poorly absorbed in the small intestine and are quickly fermented by the colonic microbiota (Barrett & Gibson, 2012). FODMAPs exacerbate GI symptoms in IBS by increasing water to the small intestine, which leads to abdominal pain and bloating and gas (BARRETT et al., 2010). Furthermore, IBS symptoms are triggered by luminal distention via FODMAPs gas-producing fermentation process (Major et al., 2017).

Clinical studies have examined the effectiveness of a dietary restriction of FODMAPs on IBS symptoms including a recent meta-analysis identifying 1,725 citations of which 72 were eligible for full review (Dionne et al., 2018). The conducted literature search consisted of the electronic databases MEDLINE (1946- November 2017), EMBASE (1974-November 2017), Cochrane Central Register of Controlled Trials (September 2017), Cochrane Database of Systematic Reviews (2005- November 2017) via OVIDSP for RCTS of exclusion diets in IBS. Included were abstracts and conference proceedings from Digestive Diseases Week (2014 to 2017). There were no language restrictions. Two independent reviewers performed screening of citations and a third reviewer resolved disagreement. The primary outcome was global improvement in IBS symptoms. Secondary outcomes included general quality of life and any occurrence of adverse events. After researchers completed screening, there were seven RCTs comparing a low FODMAP diet with various controls in 397 participants. The dietary interventions included three Low FODMAP vs. Alternative Diet; one Low FODMAP vs. High FODMAP Diet, two Low FODMAP vs. Usual diet, and one Low FODMAP exclusion followed by Low FODMAP challenge vs. placebo, where a low FODMAP diet was implemented and the participants that responded to the diet were then randomized to receive a supplement containing either a FODMAP or a placebo.

Due to the contents of a low FODMAP diet being available on the internet and smart phone applications, there was lack of blinding and therefore bias was likely a confounder in this review. Researchers calculated relative risk (RR) with 95% confidence intervals of symptoms not improving in IBS compared with control. A low FODMAP diet was associated with reduced global symptoms compared with control interventions (RR = 0.69; 95% CI 0.54 to 0.88; I^2 = 25%). The three RCTS that compared low FODMAP diet with control diets had the least diversity between studies, but also the least size of effect. The overall quality of the data was "very low" according to GRADE criteria, a systematic approach to rating the certainty of evidence in systematic reviews. Therefore, the review found very low quality evidence that a low FODMAP diet is effective in reducing IBS symptoms.

Staudacher et al., (2017) studying Low FODMAP diet vs Alternative diet developed a mock diet designed with similar degrees of difficulty and food restrictions as the low FODMAP diet to minimize bias and maximize the validity of the results. Participants (N=104), aged M= 35, range 18-65 participated in a randomized, double blinded study where were provided counseling to follow either a mock diet or low FODMAPs diet for 4 weeks. The diet, paired with a placebo or multi-strain probiotic, resulted in four subgroups (n=27 sham diet/placebo, n=26 sham diet/probiotic, n=24 low FODMAP diet/placebo, and n=27 low FODMAP diet/probiotic). The incidence and severity of gastrointestinal symptoms and overall symptoms were measured through the Gastrointestinal Symptom Rating Scale (GSRS) and IBS Symptom Scoring System (IBS-SSS). Patients' dietary compliance was assessed weekly. All measurable outcomes were repeated at four weeks, with a primary endpoint marked by adequate relief of symptoms.

At the study's conclusion, researchers discovered no significant interaction between the interventions ($p = .52$). In the intention-to-treat analysis, a higher proportion of patients in the low FODMAP diet had adequate symptom relief (57%) than in the sham diet group (38%), although the difference was not statistically significant ($p = .051$). In the per-protocol analysis, a significantly higher proportion of patients on the low FODMAP diet had adequate symptom relief (61%) than in the sham diet group (39%) ($p = .042$). Total mean IBS-Severity Scoring System score was significantly lower for patients on the low FODMAP diet (173 ± 95) than the sham diet (224 ± 89) ($p = .001$). Total mean IBS-SSS score was also significantly lower for patients on the low FODMAP diet (M=173 ± 95) than the mock diet (224 ± 89) ($p = .001$).

There are several limitations that must be acknowledged. First, the low FODMAP counseling was provided without explanation how the diet may improve GI symptoms, which may have impeded diet adherence. Second, it is difficult to quantify the amount of symptom improvement as it requires subjective assessment of whether symptoms are adequately controlled, which is likely to have interpersonal variation. In conclusion, throughout a placebo-controlled study of patients with IBS, a low FODMAP diet was associated with adequate symptom relief and significantly reduced symptom scores compared with placebo, which is clinically important in providing increased quality of life. It is not clear whether changes resulted from collective FODMAP restriction or removal of a single component, such as fructose (Heidi Maria Staudacher et al., 2017).

Although the low FODMAP diet has been studied extensively, only one trial compared a low and high FODMAP diet in a controlled, single blind study. Participants (N=37) were randomized to follow a low (n=19) or high (n=18) FODMAP diet for three weeks. IBS diagnosis was based on Rome III criteria and symptoms were assessed using the IBS-SSS. At the study's conclusion, researchers reported a low FODMAP diet led to a reduction in global IBS symptoms (p=.001) compared with a high FODMAP diet (RR = 0.44; 95% CI = 0.23 to 0.83) (McIntosh et al., 2017). These results support the notion that the low FODMAP diet has efficacy in patients with IBS and support its use as a first-line therapy over a higher FODMAP diet.

In effort to fill gaps in evidence for the efficacy of the diet, a similar study evaluated a low FODMAP diet versus a usual diet on 30 patients with IBS and eight healthy controls. All participants were randomly assigned to groups receiving either 21 days of a low FODMAPs diet or typical Australian diet. The initial three weeks of diet adherence was followed by a washout period of 21 days before transferring to the alternate diet. Daily symptoms were rated using a 0- to 100-mm visual analog scale, which consists of a straight line of 10 cm with endpoints marking one extreme limit such as "no pain" and "pain as bad as it could be". The patient was asked to mark the corresponding pain level between the two points. All of the food was provided with a goal of less than 0.5 g intake of FODMAPs per meal, which facilitated a high degree of adherence to the diets. Subjects with IBS were found to have lower overall GI symptom scores (M=22.8; 95% CI, 16.7-28.8 mm) while following the low FODMAP diet, compared with a usual diet (M=44.9, 95% CI, 36.6-53.1 mm) (p=<.001).

There are limitations of the RCT that must be acknowledged. First, the cross-over study design could cause a potential carry-over effect which may bias the second treatment effects. Additionally, such a controlled diet study design is not representative of reality. In life, diet restriction would have varying degrees of compliance and depend on the patient's degree of understanding, food choices, and motivation for altering dietary habits. Nevertheless, in a controlled, cross-over study, a diet low in FODMAPs did effectively reduce functional GI symptoms (RR = 0.46; 95% CI = 0.25 to 0.84) (Halmos, Power, Shepherd, Gibson, & Muir, 2014; Heidi M. Staudacher et al., 2012).

In summary, the evidence to date indicates that restriction of FODMAPs is an effective dietary intervention for reducing IBS symptoms. More studies are required to assess long-term efficacy of low FODMAP diet following food re-challenge and to determine any adverse outcomes from effects on the gut microbiota. Of the available dietary interventions, a low FODMAP diet currently has the greatest evidence for efficacy in IBS. Based on this, a low FODMAPs diet is now a widely used dietary pattern in managing IBS. The dietary advice consists of the reduction of FODMAPs daily intake from 15–30 g/day to 5–18 g/day. The diet consists of a 4–8-week restriction, followed by a graded FODMAPs reintroduction to determine tolerance.

Food Sensitivities Seen in Patients with IBS

Fructose

Fructose is a natural sugar found in a variety of foods such as (i) fruits, including apples, pears, mango, watermelon and cherries; (ii) vegetables, including asparagus, artichokes and sugar snap peas; (iii) sweeteners, such as fructose, high fructose corn syrup (HFCS) commonly found in soft drinks, processed foods and honey; (iv) concentrated fruit juices, dried fruit, fruit juice. Fructose is found in three main forms in the diet: as a monosaccharide, known as free fructose (such as in fruits and honey); as an ingredient of the disaccharide sucrose; or as fructans, a larger molecule of fructose, usually in oligosaccharide form (present in some vegetables and wheat) (Ikechi et al., 2017).

As mentioned above, the pathophysiology of IBS is not well understood. One causative factor being sensitivities to certain foods. Although true food allergies are uncommon in patients with IBS, exacerbation of IBS symptoms have been frequently observed due to fructose malabsorption (DiNicolantonio & Lucan, 2015; Ikechi et al., 2017). The inability to utilize fructose as an energy source occurs for two reasons: 1) a genetic condition referred to as "hereditary fructose intolerance" occurring from a lack of the liver enzyme aldolase B, or 2) fructose malabsorption, a nongenetic form of incomplete fructose absorption where the capacity to transport fructose across the intestinal epithelial is surpassed (Latulippe & Skoog, 2011).

Fructose intolerance is diagnosed with gastrointestinal symptoms and a positive breath test, most commonly defined as a rise in hydrogen or methane of at least 20 ppm from 1.5 to 3 hours following variable ingestion of carbohydrate containing fructose (Ikechi et al., 2017; Latulippe & Skoog, 2011). This capacity commonly varies, with an estimated 50% of the U.S. population unable to absorb 25 gm of free fructose (Gibson et al, 2007) as seen in clinical trials.

Up to 80% of healthy controls unable to absorb 50 gm of free fructose, or roughly a 48 fluid oz. soft drink, in one setting, with half suffering from GI symptoms such as bloating, diarrhea and belching (Rao, Attaluri, Anderson, & Stumbo, 2007; Rumessen & Gudmand-Hoyer, 1986; Skoog, Bharucha, & Zinsmeister, 2008a). However, some studies have shown as little as 5 gm of fructose may lead to malabsorption (Ikechi et al., 2017). It has been estimated that as much as 33% of patients who suffer with IBS also have fructose malabsorption, which is not surprising considering the delicate mechanism of absorption (DiNicolantonio & Lucan, 2015).

Fructose is absorbed through carrier-mediated facilitated diffusion, an energy-independent process. The transport of fructose across the membranes of eukaryotic cells is mediated by members of the GLUT family of integral membrane proteins that are encoded by specialized SLC2 genes and are members of the major facilitator superfamily. The membrane protein, GLUT-5, has a high specificity for fructose (Corpe & Burant, 1996) and one of its primary functions is to mediate the uptake of dietary fructose across the membrane of the small intestine (Douard & Ferraris, 2008). Fructose is then released into the bloodstream via GLUT2 in the intestinal basolateral membrane. The presence of fructose in the gut regulates SLC2A5 expression in the intestine (Jiang, David, Espina, & Ferraris, 2001), which is also regulated by daily intestinal rhythm independent of fructose availability (Corpe & Burant, 1996). Even though fructose is consumed at high levels in many countries in the form of sucrose and high fructose corn syrup, levels of circulating fructose are generally ~10–100 times lower than that of glucose. This is because most dietary fructose is rapidly metabolized after absorption by the intestine, liver (via GLUT2 uptake) and kidney (also via GLUT2 uptake) (Douard & Ferraris, 2008).

There is a limited space for fructose absorption without overwhelming transporter GLUT-5 capacity. Therefore, the additional unabsorbed fructose leads to water influx into the lumen due to osmotic pressure, which results in rapid propulsion of bowel contents into the colon. Unabsorbed fructose is then fermented by colonic bacteria producing short-chain fatty acids, hydrogen, carbon dioxide and trace gases. This can result in symptoms including abdominal pain, excessive gas, and bloating.

Choi et al.(2008) examined the prevalence of fructose intolerance in patients suffering from IBS and long-term outcome of fructose-restricted diets. Eighty patients who fulfilled the Rome III criteria for IBS and functional abdominal bloating were included in the study. Data from these 80 patients (26 male vs. 54 female); median age 42 y (range=20 to 76) were analyzed**.** Exclusion criteria included patients with abnormal findings on a barium study, computed tomography/ultrasound scan of abdomen, upper or lower gastrointestinal endoscopy, hematologic or biochemical studies or stool tests. Patients were also excluded if they had any coexisting active or inactive gastrointestinal problems.

Patients with a positive fructose breath test received both written and verbal dietary instructions by a dietitian regarding a fructose exclusion or restricted diet. The written instructions consisted of a fructose-restriction diet manual that was developed by the same dietitian. One year later, fructose intolerant patients were invited to participate in a follow-up telephone survey.

The differences in symptom profiles in IBS patients who tested positive or negative to the fructose breath test was compared using the Wilcoxon signed-rank test. The symptom scores reported by patients during the fructose breath test were compared using the student t test. After the fructose-restricted diet, the difference in symptom profiles between the compliant and the noncompliant groups was compared, using the Wilcoxon signed-rank test.

Among the 80 patients with suspected IBS, 31 (33%) patients had a positive breath test (fructose intolerant), and 49 (67%) had a negative breath test (fructose tolerant). Among the 31 fructose intolerant patients, 28 (90%) had elevated breath H_2, 2 (7%) had elevated H_2 and CH_4, and 1 other patient (3%) had elevated CH_4 only. Among those who tested positive (fructose intolerant), 28/31 (91%) patients reported that the breath test reproduced their typical symptom(s) such as bloating, diarrhea, gas, or abdominal pain. Fructose intolerant patients were more likely (p=0.006) to experience symptoms during the breath test when compared with those who were fructose tolerant. All 80 suspected IBS patients had reported more than 1 gastrointestinal symptom. However, loose stools/diarrhea was reported by all patients who were fructose intolerant when compared with 35/49 (71%) patients who were fructose tolerant (p=0.007).

One year later, their symptoms, compliance with, and effects of dietary modification on lifestyle were assessed using a structured telephone interview. Symptoms improved on fructose-restricted diet in compliant patients, while noncompliance was associated with persistent symptoms (Choi, Kraft, Zimmerman, Jackson, & Rao, 2008).

In another double-blinded, randomized, placebo-controlled re-challenge trial, 25 patients were provided foods that were low in free fructose and fructans. These patients had previously shown improvement in their IBS symptoms in response to dietary change. Patients were randomly challenged by graded dose introduction of fructose and fructans, alone or in combination, or glucose taken as drinks with meals for maximum test period of 2 weeks, with at least a 10-day washout period between. For the main outcome measures, symptoms were monitored by daily diary entries and responses to a global symptom question.

It was observed that 70% percent of patients receiving fructose, 77% receiving fructans, and 79% receiving a mixture reported symptoms were not adequately controlled, compared with 14% receiving glucose ($p <$ or $= 0.002$, McNemar test). Similarly, the severity of overall and individual symptoms was significantly and markedly less for glucose than for other substances. Symptoms presented in a dose-dependent manner and mimicked IBS symptoms.

In patients with IBS and fructose malabsorption, dietary restriction of fructose and/or fructans is likely to improve IBS symptoms, indicating the effectiveness is due to restriction of poorly absorbed short-chain carbohydrates (Shepherd, Parker, Muir, & Gibson, 2008).

Fructose is better tolerated in the presence of glucose. This means that food containing a 1:1 ratio of glucose to fructose such as in the disaccharide sucrose, or table sugar is often well tolerated. Glucose can increase fructose absorption, depending on the ratio of glucose relative to fructose. A study with healthy subjects showed that an equal dose of glucose normalizes fructose absorption (Rumessen & Gudmand-Hoyer, 1986).

Glucose increases fructose absorption most likely by passive diffusion, but it is also possible that the facilitation of fructose absorption is due to glucose-mediated delayed gastric emptying. Consistent with this, fruits with high fructose to glucose concentrations, such as blueberries, pears, mangoes, papaya, apples, and watermelon, if consumed in high amount and in isolation, may lead to malabsorption problems, which are exacerbated in patients with IBS (Ikechi et al., 2017). Refined products that are high in fructose relative to glucose (such as HFCS or agave,) may be especially problematic for patients with IBS (DiNicolantonio & Lucan, 2015).

Fructose malabsorption is most strongly influenced by the free fructose content of food, however, consumption of high amounts of total fructose can also result in the symptoms seen in patients with IBS. Studies have shown that breath hydrogen levels were four times higher when

50 g of free fructose was consumed as compared to when 50 g of fructose was consumed in the form of sucrose (Kim, Park, Wolf, & Hertzler, 2011).

High Fructose Corn Syrup

High-fructose corn syrup (HFCS) is derived from corn starch. Starch itself is a chain of glucose molecules joined together. When corn starch is broken down into individual glucose molecules, the end product is corn syrup, which is essentially 100% glucose. To make HFCS, enzymes are added to corn syrup in order to convert some of the glucose to fructose ("High Fructose Corn Syrup Questions and Answers | FDA," n.d.).

High-fructose corn syrup is 'high' in fructose compared to the pure glucose that is in corn syrup. Different formulations of HFCS, such as HFCS-55, HFCS-42, and HCFS-90 contain different amounts of fructose. High Fructose Corn Syrup-55 is made up of 55% fructose and 42% glucose, whereas HFCS-42 is made up of 42% fructose and 55% glucose (Ikechi et al., 2017). In HFCS-90, fructose accounts for 84.3% of the carbohydrate content. The main products that contain HFCS-42 are processed foods, cereals, baked goods, and some beverages. Soft drinks contain HFCS-55, and HFCS-90 is better known as agave syrup. For reference, sucrose, better known as table sugar, is made of up equal parts 50% glucose and 50% fructose.

The introduction of high fructose corn syrups as alternative sweeteners to sucrose in the 1960s resulted in a phenomenal growth in the US food supply, making HFCS one of the most successful food ingredients in history (White, 2008). Arguments for such increases include HFCS's low production cost and its ability to mix well with liquids compared to sucrose. Because it is a syrup, HFCS can be pumped to mixing tanks requiring only dilution before use. Therefore, the product was relied on heavily through the food service industry. HFCS remains the most widely used sweetener in beverages, dairy products, canned, baked, and processed foods worldwide.

High-fructose corn syrup is also considered part of the FODMAP family. FODMAPs are a group of short-chain carbohydrates which are often poorly absorbed in the gastrointestinal tract of susceptible individuals. These different carbohydrates are grouped together based on the length of their carbohydrate chains.

HFCS and Irritable Bowel Syndrome

The elevated chronic consumption of HFCS has been linked to various health problems, including diabetes mellitus, non-alcoholic fatty liver disease, aging, cholesterol, and IBS (Ikechi et al., 2017). IBS symptoms can be triggered by the excess consumption of HFCS (Latulippe & Skoog, 2011). On reaching the distal small intestine and colon, fructose increases the osmotic pressure in the large-intestine lumen and provides a substrate for bacterial fermentation, with consequent gas production, abdominal distension, and abdominal pain (El-Salhy & Gundersen, 2015).

A double blind, randomized, crossover study showed that almost half of the patients with IBS developed one or more symptoms following ingestion of 40 g of fructose (this level of fructose can be obtained by ingesting approximately two 12 oz cans of regular soda) prepared either in water or as HFCS, administered over 2 days in 20 healthy subjects and 30 patients with IBS.

Breath hydrogen excretion was more frequently abnormal ($p < 0.01$) after free fructose (68%) than HFCS (26%) in controls and patients. Fructose intolerance was more prevalent after free fructose than HFCS in healthy subjects (25% vs 0%, $p = 0.002$) and IBS patients (40% vs 7%, $p = 0.062$). Scores for bloating symptoms ($r = 0.35$) were correlated ($p \leq 0.01$) to peak breath hydrogen excretion after free fructose but not HFCS; in the free fructose group, this association did not differ between healthy subjects and patients.

Ventura et al. (2010) conducted an analysis of sugar-sweetened beverages utilizing a third-party laboratory to analyze the fructose content of HFCS in sampled beverages. They found the result was between 47-65% and several major brands seem to be made with HFCS that is 65% fructose. However, researchers have since questioned the methods applied in the study as the International Society of Beverage Technologists conducted a follow up analysis demonstrating that the method applied by Ventura et al. was not sufficiently sensitive to detect maltose and higher sugars typically present in corn sweeteners (Latulippe & Skoog, 2011; Ventura, Davis, & Goran, 2011).

Marriott et al. (2009) reported the most current estimate of fructose intake in the US population using dietary recall data from 1999-2004 NHANES. The total daily fructose intake of all individuals was estimated to be 49 gm at the mean and 87 gm at the 95th percentile. Young adults (ages 19-22 years) males have the highest total fructose intake of 75 gm at the mean and 121-134 gm at the 95th percentile. However, these estimates of fructose intake include a variety of food and beverage sources that also provide glucose and are consumed throughout the day. This is a distinct difference from the way fructose is provided in clinical studies as pure fructose in a liquid bolus, which is important to consider when evaluating the results of free fructose clinical studies.

Clinical trials evaluating fructose malabsorption using a breath test provide noteworthy information about individual fructose absorption capacity and variability. Such studies indicate that fructose is dose-dependent (Ravich, Bayless, & Thomas, 1983), concentration-dependent (Choi, Johlin, Summers, Jackson, & Rao, 2003) and is slowed by concurrent digestion of glucose

(Rumessen & Gudmand-Hoyer, 1986). It has been suggested that fructose malabsorption occurs more frequently in individuals with compromised gut function, such as those with IBS, compared with healthy individuals (Nelis, Vermeeren, & Jansen, n.d.; Symons, Jones, & Kellow, 1992). However, a major limitation must be addressed as fructose was provided simultaneously with varying quantities of sorbitol in the aforementioned studies.

Studies where fructose alone is provided to gut-compromised individuals show a higher incidence of symptoms; however, these studies lack a healthy comparison or a control treatment (Choi et al., 2003). In another study, the incidence of fructose malabsorption by breath testing was not different between patients with or without IBS, although symptom improvement was greater for healthy patients with fructose restriction (Corlew-Roath & Di Palma, 2009). In controlled studies, the differences observed in the incidence of fructose malabsorption or intolerance between patients and healthy subjects are mixed (Shepherd, Parker, Muir, & Gibson, 2008; Skoog, Bharucha, & Zinsmeister, 2008b).

Shepherd et al. (2008) examined whether restriction of fructose is the mechanism for improved IBS symptoms and if relief is specific to free fructose. Twenty six patients with IBS and fructose malabsorption (M=38 yrs., 22–63 years range, 22 female, 4 male) were recruited for the double-blinded, randomized, quadruple arm, placebo-controlled re-challenge. Twenty five patients assigned to dietary change were provided all food, low in free fructose and fructans, for the duration of the study. Patients were randomly challenged by graded dose introduction of fructose, fructans, alone or in combination, or glucose taken as drinks with meals for maximum test period of 2 weeks, with at least 10-day washout period between.

Patients were challenged with 1 of 4 test substances, the drinks were formulated and prepared by an industrial chemist as powders identical in appearance and color and mixed with water. The powders were provided in otherwise empty 500-mL bottles containing 19 g fructans, 50 g fructose, alone or combination, or 20 g glucose. Final doses were low dose g/day (fructan 7, fructose 14, glucose 7), medium dose g/day (fructan 14, fructose 28, glucose 14), and high dose g/day (fructan 19, fructose 50, glucose 20). The amounts for high dose were chosen on the basis of estimated usual daily intake consumed.

Symptoms were monitored by daily diary entries and responses to a global symptom questionnaire. One patient remained asymptomatic across all test arms. Seventy percent of patients receiving fructose, 77% receiving fructans, and 79% receiving a mixture reported symptoms were not adequately controlled, compared with 14% receiving glucose ($p \leq 0.002$, McNemar test). Intensity of overall symptoms increased as the doses of fructose, fructans, and fructose-fructan mix increased ($P < .01$ for all dose comparisons, Wilcoxon matched pairs signed rank test). In contrast, the severity of overall symptoms did not change for increasing doses of glucose ($P > 0.2$). Significant dose-dependent differences were also observed in specific abdominal symptoms for all test drinks ($P < .002$) except glucose.

In patients with IBS and fructose malabsorption, dietary restriction of fructose and/or fructans is likely to be responsible for symptom improvement, suggesting efficacy may be due to restriction of poorly absorbed short-chain carbohydrates in general. Healthy subjects do not have a difficulty tolerating a test drink containing up to 50 gm fructose, whereas 30% subjects with IBS could not tolerate the same dose.

In a systematic review by Kyaw and Mayberry (2011), malabsorption appeared to be more common in patients with functional gut disorders, not patients with IBS, however those with IBS appear to have more frequent symptoms.

The results from clinical trials in which free-living individuals consume fructose in large amounts in the absence of glucose are limited. In most studies, both the amount and form of fructose do not represent free-living diets and fail to mention sucrose, as well as several ingredients in foods that contain glucose and other macronutrients such as fiber, starch, fat, and protein.

Clinical studies of fructose in forms of HFCS and sucrose or in combination with glucose or starch, show that fructose is well absorbed in healthy individuals with compromised gut function. Additionally, positive breath test results are uncommon when pure fructose is provided in a dose of less than 25 gm or simultaneously with other carbohydrates such as starch. It would be odd to consume 25 gm of fructose apart from glucose or other nutrients. For example, one would have to consume more than 50 fluid oz. of cola sweetened with HFCS-55 to ingest 25 gm of fructose in excess of glucose. Furthermore, fructose malabsorption based on large dose of fructose without other food may be overestimated because the breath test does not replicate conditions of fructose consumption in free-living individuals. There exists a clear need for randomized, controlled, double-blind clinical trials that document the frequency of intolerance in the population, if any, to HFCS-55 and other products in which the content of free fructose exceeds that of glucose.

For the individual, symptom ratings are more important to quality of life than breath hydrogen test results. The American Gastroenterological Association, (2010) recommends that individuals with apparent fructose intolerance limit all fruits, honey, and alcohol as well as beverages that contain HFCS. In the fructose intolerance literature, HFCS is often implicated in the descriptive sections as a key ingredient to avoid. However, HFCS-42 contains more glucose than fructose. HFCS-55 has slightly more fructose than glucose and therefore should not be consumed in excess. Foods that should be avoided include ample amounts of fructose and agave nectar, as well as large quantities of apples, pears, apple juice, pear juice, fruit juice concentrates and beverages sweetened with HFCS-55. However, if these items are consumed along with foods that contain other sugars or carbohydrate ingredients, the likelihood of malabsorption may be reduced.

In conclusion, fructose intolerance is more prevalent with fructose alone than with HFCS, in health and in IBS. However, foods containing HFCS and sucrose represent 64-95% of total fructose intake (Latulippe & Skoog, 2011). Current methods for identifying fructose intolerance should be modified to reproduce fructose ingestion more closely in daily life. HFCS-55, in which the content of free fructose exceeds that of glucose, is found in regular soda and soft drinks and does represent fructose intake in daily life. The trials described above emphasize the need to determine the frequency of gastric intolerance to HFCS-55 in daily life, in health and in IBS.

Role of the Nervous System in Gut Health

Composition of the Nervous System

Two-way communication between the central and enteric nervous system has many translators, including the brain and spinal cord (CNS), the autonomic nervous system (ANS) and the hypothalamic pituitary adrenal axis (HPA) (Carabotti, Scirocco, Maselli, & Severi, n.d.). A basic understanding of nervous system functioning is critical in understanding how stress influences the expression of IBS symptoms.

Central Nervous System

The CNS consists of the brain, spinal cord, and the limbic system. The limbic system is comprised of several functionally connected structures, which regulate autonomic and endocrine function, particularly in response to emotional stimuli (“Chapter 9: Limbic System,” n.d.). The

HPA axis is part of the limbic system and coordinates adaptions to any environmental or inflammatory stressors (Carabotti et al., n.d.; Jang et al., 2019). Environmental stress as well as inflammatory cytokines activate this system through secretions of corticotropin-releasing factor (CRF) from the hypothalamus stimulating hormone secretion from the pituitary gland, which releases cortisol from adrenal glands. Cortisol is a major stress hormone affecting the brain and CNS (Carabotti et al., n.d.). In summary, both neural and hormonal lines of communication allow the CNS to influence intestinal activities however, these same cells are under the influence of the gut microbiota.

Autonomic Nervous System

The ANS is comprised of two antagonistic sets of nerves, the sympathetic and parasympathetic nervous systems. The sympathetic nervous system connects the gut to the brain by spinal nerves. When stimulated, these nerves prepare the body for stress by increasing blood flow to the muscles. The nerves of the parasympathetic nervous system are the cranial nerves (Waxenbaum & Varacallo, 2019). When stimulated, these nerves increase digestive secretions. The ANS has two main divisions presenting and receiving communication from the gut to the brain, and brain to the gut.

Enteric Nervous System

The enteric nervous system (ENS) in the intestines contains several classes of neurons through which muscles, mucosal fluid, and blood flow are controlled (Furness, Callaghan, Rivera, & Cho, 2014). The CNS communicates with the enteric nervous system (ENS), muscle layers and gut mucosa through the nervous and immune systems modulating motility, immunity, permeability, and secretion of mucus (Jang et al., 2019). The enteric microbiota has a bidirectional communication with these intestinal targets, modulating gastrointestinal functions and being itself modulated by brain-gut interactions (Carabotti et al., 2015).

Stress

IBS is a stress-sensitive disorder and the treatment of IBS should also focus on managing stress and stress-induced response. For many first year college students, the transition from high school to college brings about emotional or psychological distress (Robotham, 2008). The transfer into a new environment is often accompanied by new relationships, academic and financial demands, as well as a new realm of time management, which may bring additional psychological distress (Khawaja & Dempsey, 2008).

According to American Psychological Association (2020), the psychological distress among college students is increasing. There is ample evidence that when an individual is stressed, there are negative consequences to health (Unusan, 2006). Indirectly, stress has effects on certain behaviors which influence health. One such behavior that is influenced by stress is eating behavior. Zellner et al. (2006), investigated the effect of stress on food choice throughout two studies.

The first consisted of (n=34) female university students with a mean age of 22 years. Subjects were presented with four cardboard disposable bowls containing relatively equal amounts of: plain M&M chocolate candies, Lays potato chips, dry roasted peanuts, and red seedless grapes. Subjects were then given a list of either ten solvable or ten unsolvable five-letter anagrams. The sheet containing the solvable anagrams also contained the answers at the bottom of the page.

Upon arrival, subjects were seated in a small room which contained a table on which were placed the four bowls containing the M&Ms, grapes, potato chips, and peanuts. Subjects were told that the snacks were a “thank you” for their participation and were leftovers. They were told to feel free to help themselves to the food during the experiment. Each subject then received one of the two lists of ten anagrams. Half of the subjects ($n = 17$, no-stress group) were presented with the solvable anagrams and the other half ($n = 17$, stress group) were given the unsolvable anagrams. Subjects had ten minutes to solve the anagrams and were left alone in the room. After 10 min the experimenter returned, took the anagrams from the subjects and asked the subjects to fill out a brief questionnaire containing five questions about their verbal ability and an 11-point rating scale of 0 (low stress) to 10 (high stress), with which they were to rate how much stress they felt from trying to solve the anagrams. The verbal ability questions were not analyzed. After the subjects left, the bowls of foods were again weighed.

The stress group (who got the unsolvable anagrams) reported being significantly more stressed ($M = 5.8$, $SD = 3.0$) than the no-stress group getting the solvable anagrams ($M = 0.7$, $SD = 1.1$), $t(32) = 6.54$, $p < .001$. The no-stress group ate more grapes ($M = 15.6$ g, $SD = 22.3$) than did the stress group ($M = 4.0$ g, $SD = 7.2$), $t(32) = 2.04$, $p < .05$. Furthermore, the stress group ate more M&Ms ($M = 6.9$ g, $SD = 10.4$) than did the no-stress group ($M = 1.2$ g, $SD = 2.4$), $t(32) = 2.20$, $p < .04$. This study demonstrates that stress causes changes in food choice away from healthy low fat foods (grapes) to less healthy high sugar and high fat foods (M&Ms), confirming previous survey research.

The second study, a survey study, consisted of undergraduate student volunteers ($N=169$, 128 females and 41 males). Their mean age was 24 years. The Eating-When-Stressed Questionnaire was administered and asked subjects if they a) overeat or b) under eat when stressed or if c) stress has no effect on their eating. Those who indicated that they overeat when stressed were asked to indicate which food they most frequently overeat when stressed (an open-ended question) and whether they normally avoid eating this food (either yes or no). Additionally, they were asked why they eat the food indicated (an open-ended question). Finally, subjects completed the Restraint Scale which is the most widely used measure for dieting.

Researchers found that more females (46%) than males (17%) report increasing food consumption when stressed ($\chi 2(2) = 10.85$, $p < .01$). Stress over-eaters were significantly more likely to be restrained eaters (71%) than those who reported not over-eating when stressed (35%), ($\chi 2(2) = 20.41$, $p < .05$). The foods that they report overeating when stressed are foods they normally avoid for weight-loss or health reasons. They report eating these foods to feel better (73% women and 71% men) and indicated that when stressed they eat foods that they normally avoid. Sixty-four percent of subjects indicated that when stressed they eat sweet foods, likely containing HFCS (66% women and 43% men). Sixty-seven percent of those who reported eating a sweet food when stressed said that it was a food that they normally avoided (64% and three men). These results are similar to those found in previous self-report studies (Cartwright et al., 2003)

Both studies showed that stress not only increases consumption in certain individuals but also shifts their food choice to sweeter, higher fat foods likely containing HFCS. In contrast, there are studies that have shown there are individuals who tend to consume less when stressed (Cartwright et al., 2003; Steptoe, Lipsey, & Wardle, 1998; Wardle, Steptoe, Oliver, & Lipsey, 2000).

The impact of stress on food selection often leads individuals to increase consumption of ready-to-eat foods and sweets. Wardle et al., (2000) sought to examine the associations between stress and nutritional status in relation to dietary restraint in a community sample of adults. The design included a cross-sectional and a longitudinal study element of 90 staff members of a large department store (58 women and 32 men). Participants were assessed on four occasions over a 6-month period with measures of diet, weight, and perceived stress. For analysis by restraint level, participants were classified on the basis of median split into high- and low-restraint groups. Workload was measured objectively in terms of hours worked in the last 7 days. Subjectively in the terms of the extent to which work interfered with home life. Perceived stress was assessed with the ten-item version of the Perceived Stress Scale. Total scores could range 0-40, which higher scores indicating greater perceived stress.

The highest work-stress session was compared with the lowest work-stress session in the longitudinal analyses, and the moderating effects of restrained eating were examined. As predicted, there were significant work-stress restraint interactions for total energy intake [$F(1,76) = 3.88$, $p < 0.05$], fat intake [$F(1,76) = 3.59$, $p < 0.05$], and saturated fat intake [$F(1,76) = 8.98$, $p < 0.01$]. Sugar intake increased [$F(1,76) = 3.98$, $p = 0.05$] although not statistically significant. Among restrained eaters, a greater stress difference between sessions was associated with a greater energy difference ($r = 0.32$, $p < 0.05$), whereas, among non-restrained eaters, there was no association ($r = -0.01$).

The results indicated that there may be associations between restraint and stress-induced eating. This raises the possibility that restrained eaters are particularly vulnerable to adverse effects of stress on health, through influences on food intake.

There is also data supporting that intake of healthy fruits and vegetables tends to decrease under stress (Unusan, 2006; Zellner et al., 2006). Unusan (2006) recruited randomly selected university students (N=713) aged 17 to 35 years (M=21-24 years) in different regions in Turkey, who completed a survey on the relationship between stress and fruit and vegetable intake. None of the students were food/nutrition majors. Subjects were administered three questionnaires to collect information on benefits and barriers of fruit and vegetable consumption. Additionally, they administered a Brief Symptom Inventory, a widely used scale assessing current psychologic distress in the past 7 days. Along with the Stress Scale, used to measure 13 primary symptom dimensions of stress.

Analyses were performed using Spearman (gender) and Pearson product moment correlations between benefits and barriers of fruit and vegetable consumption. Cronbach α values were determined to assess the interitem reliability of the final scores. Multiple linear regressions with stress scores as the independent variables and benefits and barriers of fruit and vegetable as the dependent variable were calculated. In the multiple regression analyses, effect sizes (F^2) were regarded as large when ≥ 0.35.

Both benefits and barriers to eating more fruits had internal consistency of 0.67 and 0.50 and accounted for 30% of total variance. Both benefits and barriers to eating more vegetables had internal consistency of 0.73 and 0.56, with benefits accounting for 17% and barriers 12% of variance in the study.

Results from the questionnaire indicated that the self-reported mean intake was 3.67 ± 1.81 servings of fruit and vegetables per day. Only 4.0% of the students were consuming 5 or more fruit and vegetable servings per day. Among female and male students, daily fruit servings were positively associated with vegetable servings. There were no differences in fruit ($F = 0.002$, Sig = 0.966) and vegetable ($F = 0.71$, Sig = 0.399) servings between female and male students. These results suggested that most students do not consume the recommended number of fruit and vegetable servings.

A univariate analysis showed that Susceptibility to Stress Scale was negatively and significantly associated with benefits of fruit and vegetable intake, and apart from cognitive, all dimensions of Stress Symptom Scale and Susceptibility to Stress Scale were positively and significantly associated with barriers of fruit and vegetable intake. For students, there were significant linear trends for higher risks of barriers of fruit and vegetable intake and higher stress levels.

There are limitations of the research that should be mentioned, such as a social response bias, as some subjects might be less likely to report stress than others. It is also likely that people most interested in health and nutrition were most likely to volunteer to participate. Nevertheless, the main finding from the study was that increased stress was associated with barriers of fruit and vegetable intake however, more research is needed.

It is of importance to note that the year in college may be an important factor determining stress level. First year college students have an increased risk for having poor mental health during which is commonly related to relocating from home, being younger, taking on adult-like responsibilities as well as academic load for the first time (Pedrelli, Nyer, Yeung, Zulauf, & Wilens, 2015) On the contrary, students with more college experience tend to have decreased stress (Green & Rabiner, 2012). However, it is important to recognize that the occurrence of psychological distress may vary according to the time of the academic year (Cash & Bridge, 2009).

Eating Behaviors

Student Life

The human gut contains over ten thousand species of microorganisms (Eckburg et al., 2005), therefore, to ensure diverse microbial growth, various nutrients and energy sources are required. Limited diversity in dietary intake has been shown to promote intestinal dysbiosis by reducing the availability of essential nutrients for specific microbial growth. (Eckburg et al., 2005). Many college students have been found to eat food items with added fats and sugars while selecting fewer fruits and vegetables than recommended by dietary guidelines (Racette, Deusinger, Strube, Highstein, & Deusinger, 2005). Eating patterns initiated during college may carry on into adulthood, forming life-long habits, placing college age students at risk of many diseases.

Traditional dietary advice is based upon recommendations provided by the U.S. Department of Agriculture (USDA) and the Academy of Nutrition and Dietetics (AND). Dietary advice is considered the first-line therapy for IBS and its principles include healthy eating and lifestyle management. This lifestyle management involves establishing regular eating habits, incorporating smaller portions, optimizing fiber and fluid intake, limiting alcohol and caffeine intake, and decreasing fat, sugar alcohols and carbonated beverage intake. Despite the limited evidence on the association between poor eating patterns and IBS, several studies have reported more irregular meal habits in IBS patients than in healthy controls (Cozma-Petrut et al., 2017). Irregular eating may affect colonic motility, therefore contributing to IBS symptoms (Cozma-Petrut et al., 2017).

Guo et al. highlighted the role of diet and lifestyle habits in Chinese IBS patients (n=78) admitted to the Department of Gastroenterology from January 2011 to December 2012, paired with healthy controls (n=79). Case study patients were selected upon fulfilled diagnostic criteria of Rome III for IBS and were excluded for a history of pharmacologic therapy or previous abdominal surgeries. Following study selection, a health questionnaire was provided to evaluate diet and lifestyle habits to measure sociodemographic variables, health-related conditions, lifestyle habits, dietary habits, and food preferences.

Student t-test and Chi-square tests were used to evaluate differences in sociodemographic variables between patients and controls. Subjects were then divided into two categories by consumption (less than median frequency and equal or more than the median frequency) and Chi-square test was utilized to locate relationships between health-related conditions, lifestyle habits, dietary habits, and food preferences. An ANOVA with multiple regression was used to evaluate variables responsible for IBS. Data were presented as odds ratios (ORs) and 95% confidence intervals (95% CIs).

There were no differences in age, gender, height, weight, and educational level found between the two groups. Perceptions of irregular eating were defined as not eating meals regularly each day and having long periods between each meal. Perceptions of irregular eating were more found to be frequent among IBS patients (65.4%) vs control (36.7%) ($p<0.01$). Subjects with irregular eating habits were 3.257 times more likely to suffer from IBS than those with regular eating habits (95% CI, 1.694 to 6.259; $p<0.01$). There were no significant differences in other dietary habits between groups (time spent eating, eating late-night snacks, having meals with family or outside the home, having meals on time, and picky eating habits).

Using the median as the cutoff for food consumption frequency, there were significant differences between the two groups in the following categories: fruit (not included in the final multivariable logistic model), vegetables ($p= .000$), legumes ($p=.025$) and tea ($p=.008$). However, it cannot be overlooked that these foods may contribute to symptom onset through several unrelated mechanisms such as a food allergy and intolerance or following exposure to food-borne pathogens.

Many subjects with IBS relate their symptoms to their food intake. Most of these subjects modify their diets accordingly. Therefore, individual dietary guidance is a cost-effective option for the management of IBS. In conclusion, the results of this study indicated that lifestyle and dietary factors influence the occurrence of IBS, however, more research is needed.

College students are prone to stress throughout the academic year, stress can have negative impacts on eating habits which includes eating more foods containing higher levels of HFCS (Yau & Potenza, 2013). Excess HFCS intake can be problematic for a healthy gastrointestinal system (Latulippe & Skoog, 2011) and therefore especially problematic for those experiencing IBS symptoms. Controlled IBS symptoms are critically important to the function of the gastrointestinal system and proper absorption of nutrients (NIDDK, 2020). Therefore, excess intake of HFCS can be a major concern for college students who experience IBS symptoms during times of stress, who may be at risk of exacerbation of symptoms and fructose malabsorption.

The efficacy of a fructose restriction in treating symptoms of IBS is demonstrated in several research studies, specifically reduction of bloating, abdominal pain, and normalization of stool consistency. The researchers of these trials reported evidence from well-designed studies; however, there are limitations. The clinical trials by (Choi et al., 2003; Choi, Kraft, Zimmerman, Jackson, & Rao, 2008; Corlew-Roath & Di Palma, 2009; Shepherd et al., 2008) were only representative of free fructose. The trials are not necessarily representative of a US population free-living diet because participants were provided a free fructose bolus instead of a free living diet.

Aside from the limitations, the restriction of HFCS-55 may offer an alternative therapy for IBS symptom treatment. Stress and its relationship to IBS symptoms has been analyzed mainly in adult populations where HFCS and stress have been commonly linked. However, how HFCS intake relates to IBS symptoms during times of stress has not been extensively investigated. Further research is needed in which researcher monitor participant's diet quality, change in gastrointestinal symptoms, and perceived stress in both a high stress and low stress environment. Therefore, the purpose of the current study is to examine HFCS intake of college students with reported IBS symptoms during times of stress.

CHAPTER 3. METHODOLOGY

Purpose

The primary purpose of this study was to compare reported intake of HFCS beverages to reported IBS symptoms in college students in North Dakota. A secondary purpose was to compare the difference in intake of HFCS beverages between-groups of those with low, moderate and high perceived stress. This chapter describes the population of the study, setting of the study, data collection instrumentation, procedures, and the data analysis. The research questions were:

1) What is the relationship between intake of HFCS beverages and reported IBS symptoms?
2) What are the differences in intake of HFCS beverages when compared between-groups experiencing less stress and more stress?

Participants

The target population for this study's sample was university students 18 years and older. Both North Dakota State University (NDSU) and Valley City State University (VCSU) students were recruited through a university email listserv. Students were also recruited through HNES 250: Nutrition Science which is a large general education class. The instructor offered extra credit for research participants. Students were also able to choose from an alternative extra credit project that involved researching and pricing produce from local grocery stores. Inclusion criteria consisted of being a current NDSU student, 18 years of age and older, and the ability to read and write in English. Participants were excluded for pregnancy, a history of an eating disorder, inflammatory bowel disease (Crohn's, Ulcerative Colitis, Diverticulosis), gastrointestinal surgery, or if they followed a diet to lose weight at the time the study was conducted. The North Dakota State University IRB approved the study (HE21040).

Setting

All surveys were conducted online. Surveys could be accessed from computer, iPad, or any smart phone device. There was no physical interaction between researchers and participants.

Study Protocol

At baseline, marking the beginning of the semester, participants completed an online Qualtrics survey comprised of the Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS), Perceived Stress Scale (PSS), a food frequency questionnaire focused on high fructose corn syrup beverage intake, and a 24 hour recall. BEVQ-15 and IBS-SSS with scoring instructionts can be found in Appendices A-C. At roughly 6 and 11 weeks into the semester, participants again completed the exact same surveys.

Equipment and Instruments

Questionnaires

Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS)

The IBS-SSS is a validated tool through a cohort of patients with IBS according to the Rome III criteria, compared with a control group of healthy individuals. The tool is used to examine IBS symptoms and severity. The questionnaire is composed of 12 items investigating 3 domains, and is rated on a Visual Analog Scale (VAS) 100 mm (Francis, Morris, & Whorwell, 1997). The domains include severity (questions 1b, 2b, 3 and 4), bowel habit (questions 5-7), and site of pain (questions 8-9). The response to each of the five severity questions generates a maximum score of 100, leading to possible score of 500. The domains of bowel habits and site of pain are not used for scoring. Higher scores are associated with increased symptom severity and frequency over the past week with a possible range of 0-500. Scores <75 are regarded as “in remission” if in a patient with a previous diagnosis of IBS or as “not IBS”. Scores 75-174 are interpreted as “mild disease”, 175-299 as “moderate disease”, and 300 or greater as “severe” disease. Based on the validation study by Francis et al. (1997), a Minimum Clinically Important Difference (MCID) is equivalent to a change of 50 points or greater on the Severity Score. Thus, a participant who improves by 50 or greater points from before to after treatment could be classified as a treatment responder (Francis et al., 1997). The IBS-SSS and scoring instructions are presented in Appendix B-C.

Beverage Intake Questionnaire (BEVQ)

The Beverage Intake Questionnaire (BEVQ-15) (Hedrick, Comber, Estabrooks, Savla, & Davy, 2010a) is a validated questionnaire developed to estimate daily intake of water, sugar sweetened beverages and total beverages across 15 beverage categories plus one open-ended section for “other” beverages not listed. To score the BEVQ, frequency (“How often”) is converted to the unit of times per day, then multiplied by the amount consumed (“How much each time”) to provide average daily beverage consumption in fluid ounces (FL oz). To quantify total SSB consumption, beverage categories containing added sugars were summed (sweetened juice beverages/drinks, regular soft drinks, sweet tea, sweetened coffee, energy drinks, mixed alcoholic drinks, meal replacement beverages). The BEVQ-15 questionnaire can be found in Appendix A. There is no scoring interpretation of BEVQ-15 results, however there are calculations to find total daily average fl oz and total daily calorie consumption. The BEVQ-15 provides a total count which enables researchers to rapidly assess habitual beverage intake.

Perceived Stress Scale- (PSS)

The Perceived Stress Scale (PSS-14) is a validated tool used to assess the degree to which situations in one’s life are perceived as stressful. The questionnaire has 14 questions, with 7 positive items and 7 negative items rated on a 5-point Likert scale. Five years after the production of PSS-14, it was shortened to 10 items (PSS-10) using factor-analysis based on data from over 285 undergraduate college students (79% female, 21% male) enrolled in one of three public universities. Researchers Roberti, Harrington, & Storch (2006) recruited participants ranging in age from 17-60 (M = 23.8 years, SD= 7.9 years). Of the student sample, 82.1% were Caucasian, 4.2% Hispanic, 4.2% African American, 2.1% Asian, 0.7% Native American, and 6.7% other.

Scores for the PSS are obtained by reversing the scores on the seven positive items and then summing across all 14 items. Scores ranging from 0-13 would be considered low stress, 14-26 would be considered moderate stress, and 27-40 would be considered high perceived stress. The Perceived Stress Scale is important because the perception of what is happening in life is most important. The scores do not reflect a particular diagnosis or course of treatment, they are meant as a tool to help assess one's level of stress.

Software

ESHA: Food Processor

ESHA's Food Processor Nutrition Analysis software is a combination food and ingredient database for more than 129,0000 foods and food items. Food Processor provides accurate and comprehensive nutrition analysis of over 170 nutritional components, including a MyPlate report, diet and exercise tracking and menu planning. The results of the 24 hour dietary recalls were reviewed utilizing ESHA: Food Processor Nutritional Analyzer to complete dietary evaluation.

Procedures/ Research Design

The study protocol was submitted to the Institutional Review Board at North Dakota State University for approval. The IRB approval letter (HE21040) is listed in Appendix D. After

IRB approval, the online questionnaire link was emailed to all students through an NDSU student listserv as well as offered as extra credit to HNES 250: Nutrition Science students. All participants provided informed consent. Email reminders to complete the survey were sent 2 weeks after the initial email invitation. The online questionnaire was sent out three times throughout the academic Fall semester of 2020. The first submission was delivered in September 2020 when the semester was initiating. The survey was not sent during the first week of the semester to allow students time to adjust to campus life during the COVID – 19 pandemic. The second survey distribution occurred during the first week of November following the 2020 presidential general election, and the final questionnaire was sent the week prior to the final week of the semester, the first week of December 2020. The main reasons for choosing an online survey was lower research cost, ease of access to the survey, faster responses, higher response completeness, ease of sending follow ups, and students being comfortable with using the internet. The online questionnaire was sent out three times to study various levels of stress throughout the academic semester with the hypothesis that stress will increase from baseline September questionnaire to beginning of November and again increase from November to December.

Data Analysis

All data analyses were performed using SPSS Statistics 26.0 software package for Windows (IBM, New York, USA). Statistical analysis for research question one was conducted in two ways. The first method analyzed using various correlation coefficients to test for relationships. Significant correlations were to be used to conduct a regression analysis as well to determine the predictive value of the variables. The independent variable being HFCS-55 intake and the dependent variable IBS symptoms. The second research question was explored with repeated measures analysis of variance (ANOVA). The results of the 24 hour dietary recalls were reviewed utilizing ESHA: Food Processor Nutritional Analyzer to complete dietary evaluation.

Conclusion

The primary purpose of this study was to find the relationship between HFCS intake and IBS symptoms in college students. A secondary purpose was to compare the results of HFCS intake during periods of low stress, moderate and high stress environments. With unavoidable stress student life can bring, the results of this study may allow clinicians to incorporate education on decreasing HFCS sweetened beverages to help avoid unwanted gastrointestinal discomfort. Overall, this study was used to determine if college students have varying intakes of HFCS sweetened beverages and IBS symptoms, as well as if those correlated to perceived stress.

CHAPTER 4. MANUSCRIPT[1]

Abstract

BACKGROUND: High Fructose Corn Syrup (HFCS), commonly found in soft drinks, represents 64-95% of a young adult's total fructose intake. Excessive HFCS intake can be problematic for a healthy gastrointestinal system, and especially troublesome for those that experience Irritable Bowel Syndrome (IBS) symptoms. Indeed, diet and stress are linked to IBS, however, how HFCS intake relates to IBS symptoms during times of stress has not been extensively investigated in university students. AIMS: 1) To identify differences in reported IBS symptoms and intake of HFCS soft drink beverages between university students and 2) to identify differences in intake of HFCS soft drink beverages between university students by stress level. METHODS: IBS symptomology was measured with the IBS Symptom Severity Scale, perceived stress by the Perceived Stress Scale, (PSS-10) and beverage intake via Beverage Intake Questionnaire (BEVQ-15). University students (n=28) completed self-report surveys and a 24 hour diet history at three distinct time periods during the fall 2020 semester (September, November, and December). Statistical analysis was conducted using SPSS Statistics 26.0 software package in two ways. First various correlations were run between IBS symptoms and HFCS intake, diet variables, time period and stress level to test for relationships. The second research question was explored with repeated measures analysis of variance (ANOVA). RESULTS: The HFCS-55 average intake was 10.33 gm/day for low stress and 7.77 gm/day for moderate and 6.27 gm/day for high stress. Total HFCS-55 intake during varying stress

[1] The material in this chapter was authored by Brittany Twiss. Brittany Twiss was responsible for the study from its design to writing the article. Brittany Twiss founded the study design and recruited participants through email and video presentation. Brittany Twiss designed the Qualtrics survey; collected the responses and analyzed the data. Brittany Twiss performed sample size calculation and statistical analysis. Brittany Twiss made all recommended revisions.

environments did not indicate a significant effect, Wilk's Lambda = .987, $F(2,25) = .164$, $p = .073$. Participants average experienced gastrointestinal symptoms did not meet criteria for IBS. CONCLUSION: HFCS-55 intake differences were not statistically significant. However, more research with a larger sample size is needed.

Key Words: monosaccharide, corn sugar, glucose-fructose syrup, colon, colitis, school enrollment

Introduction

Fructose is a monosaccharide naturally present in a variety of foods, including fruits, vegetables, and honey. Marriott et al. (2009) reported estimates of fructose intake in the U.S. population using dietary recall data from the 1999–2004 National Health and Nutrition Examination Survey. Young adult males have been found to have the highest total fructose intakes of 75 g per day (Marriott et al., 2009). Fructose is also produced as High Fructose Corn Syrup (HFCS), which is commonly found in many food sweeteners and soft drinks. Depending on the age/sex grouping and level of intake, fructose from foods containing sucrose and HFCS represented 64% to 95% of total fructose intake (Marriott et al., 2009).

HFCS is the most widely used sweetener in beverages and processed foods worldwide (Duffey & Popkin, 2008). Over the past 50 years, HFCS has seen substantial increases in both production and consumption (Bray, Nielsen, & Popkin, 2004). For example, the annual per capita intake of HFCS increased 125% during the years 1970-1997 (Latulippe & Skoog, 2011). HFCS is also considered part of the "Fermentable Oligosaccharides, Disaccharides, Monosaccharides And Polyols" (FODMAP) family, which are a group of short-chain carbohydrates that are poorly absorbed in the gastrointestinal tract of certain individuals, including those with Irritable Bowel Syndrome (IBS).

Intake of HFCS is commonly consumed in emotionally and physiologically stressed individuals looking for comfort (Yau & Potenza, 2013). Excess HFCS intake can be problematic for a healthy gastrointestinal system if it exceeds the normal absorption capacity for this sugar (Latulippe & Skoog, 2011) and may be especially problematic for those experiencing IBS symptoms. Controlled IBS symptoms are critically important to the function of gastrointestinal system and proper absorption of nutrients (National Institute of Diabetes and Digestive and Kidney Diseases, 2020). Therefore, excess intake of HFCS may be a concern for college students that experience daily IBS symptoms during times of stress.

Stress and its relationship to IBS symptoms has been analyzed mainly in adult populations, additionally HFCS intake and stress have been commonly linked. However, how HFCS intake relates to IBS symptoms during times of stress has not been extensively investigated. Examining the HFCS intake of college students with reported IBS symptoms during times of stress can help with IBS symptom management and increase quality of life. Therefore, the purposes of this study were to 1) identify the relationship between intake of HFCS soft drink beverages and reported IBS symptoms in university aged students, and 2) examine differences in intake of HFCS soft drink beverages between university aged students by stress level.

Methods

The study protocol was approved by the Institutional Review Board at North Dakota State University (HE21040). An online questionnaire link was emailed to all students through an NDSU student listserv, and the study was advertised in HNES 250: Nutrition Science as one of two extra credit options. All participants provided written informed consent. An email reminder to complete the survey were sent 2 weeks after the initial email invitation. The online questionnaire was sent out three times throughout the academic Fall semester of 2020. The first link was sent in September 2020 two weeks after the start of the semester to allow students time to adjust during the COVID pandemic. The second link was sent in the first week of November 2020 following the 2020 presidential general election, and the final questionnaire link was sent the last week of the semester in December 2020. The main reasons for choosing an online survey were lower research cost, ease of access to the survey, faster responses, higher response completeness, ease of sending follow ups, and students being comfortable with using the internet. Participants were asked to complete the online questionnaire at three distinct times to study various levels of stress throughout the academic semester. The hypothesis was that stress would increase from the baseline September questionnaire to beginning of November and again increase from November to December.

Survey

The instrument used for this study was an online Qualtrics ("Qualtrics | Group Decision Center | NDSU," n.d.) survey composed of several previously validated measures for stress and HCFS intake, as well as a 24-hour dietary recall. The measures used in the survey included the Irritable Bowel Syndrome Symptom Severity Scale (IBS-SSS), Perceived Stress Scale (PSS), Beverage Intake Questionnaire (BEV-Q) and a 24-hour dietary recall.

The IBS-SSS is a tool used to examine IBS symptoms and severity. The IBS-SSS has been validated through a cohort of patients with IBS according to the Rome III criteria, compared with a control group of healthy individuals. The questionnaire is composed of 12 items investigating 3 domains and is rated on a Visual Analog Scale (VAS) 100 mm (Francis, Morris, & Whorwell, 1997). The domains include severity (questions 1b, 2b, 3 and 4), bowel habit (questions 5-7), and site of pain (questions 8-9). The response to each of the five severity questions generates a maximum score of 100, leading to possible score of 500. Higher scores are associated with increased symptom severity and frequency over the past week with a possible range of 0-500. Scores <75 are regarded as “in remission” if in a patient with a previous diagnosis of IBS or as “not IBS”. Scores 75-174 are interpreted as “mild disease”, 175-299 as “moderate disease”, and 300 or greater as “severe” disease.

The PSS-10 is a tool used to assess the degree to which situations in one’s life are perceived as stressful. The PSS-10 has been validated in multiple populations, including university students (Lee, 2012). The questionnaire has 10 questions, with 5 positive items and 5 negative items rated on a 5-point Likert scale. Scores for the PSS are obtained by reversing the scores on the seven positive items and then summing across all 14 items. Scores ranging from 0-13 would be considered low stress, 14-26 would be considered moderate stress, and 27-40 would be considered high perceived stress. The Perceived Stress Scale is important because the perception of what is happening in life is most important. The scores do not reflect a particular diagnosis or course of treatment, they are meant as a tool to help assess one’s level of stress.

The Beverage Intake Questionnaire (BEVQ-15) (Hedrick, Comber, Estabrooks, Savla, & Davy, 2010) is a questionnaire developed to estimate daily intake of water, sugar sweetened beverages and total beverages across 15 beverage categories plus one open-ended section for “other” beverages not listed. The BEVQ-15 has been validated in healthy adults from a local university community in Virginia (Hedrick, Comber, Estabrooks, Savla, & Davy, 2010b). To score the BEVQ, frequency (“How often”) is converted to the unit of times per day, then multiplied by the amount consumed (“How much each time”) to provide average daily beverage consumption in fluid ounces (FL oz). To quantify total sugar-sweetened beverage (SSB) consumption, beverage categories containing added sugars were summed (sweetened juice beverages/drinks, regular soft drinks, sweet tea, sweetened coffee, energy drinks, mixed alcoholic drinks, meal replacement beverages).

A 24 hour diet recall is a dietary assessment tool in which participants are asked to recall all the food and beverage items consumed in the previous 24 hours. Although a 24-hour dietary recall has been validated in many populations (Foster et al., 2019), there is the potential for human error in the analysis if participants do not accurately report their intake or if that report is not assessed by a qualified professional. To limit this error, researchers cross-examined the HFCS-55 content of the beverage items reported by the 24 hour recall utilizing both ESHA Food Processor Nutrition Analysis and hand calculation. Hand calculation was performed by multiplying the amount of HFCS in sugar sweetened beverages reported in 24 hour diet recall times the amount of beverage consumed. The hand calculation did not include any food items, only reported sugar-sweetened beverage intake.

Software

ESHA: Food Processor

ESHA's Food Processor Nutrition Analysis software is a combination food and ingredient database for more than 129,0000 foods and food items. Food Processor provides accurate and comprehensive nutrition analysis of over 170 nutritional components, including a MyPlate report, diet and exercise tracking and menu planning. The results of the 24 hour dietary recalls were reviewed utilizing ESHA: Food Processor Nutritional Analyzer to complete dietary evaluation.

Statistical Analysis

All data analyses were performed using SPSS Statistics 26.0 software package for Windows (IBM, New York, USA). Statistical analysis for research question one utilized various correlation coefficients to test for relationships. The second research question was explored with paired sample t-test and repeated measures analysis of variance (ANOVA). For any variables that are positively correlated, we planned to conduct a regression analysis to find the variables most predictive of HFCS intake and IBS symptoms. An alpha level of 0.05 was used for all analyses.

Ethical Statement

No surveys were associated with any serious adverse or ethical effects.

Results

There were 166 participant responses to the first survey. Fifty-seven participants (34.3%) returned to complete the second survey, with only 41 (24.6%) completing all three surveys. A final total of 28 participants (16.9%) was used for statistical analysis after excluding another 13 participants for duplicate and erroneous entries.

Differences Between IBS Groups: HFCS Intake and Reported IBS Symptoms

During the study, the average experienced gastrointestinal symptoms did not meet criteria for IBS. Overall, most students reported no IBS symptoms at any of the three time points. There were no severe IBS symptoms reported. With hypothesized connections between reported IBS symptoms and HFCS intake, there was limited data to correlate. There was not a significant correlation found between the amount of HFCS-55 intake and reported IBS symptoms, $r=.040$, $p=.717$.

Table 4.1

Demographics of Study Population

	Female (*n*=25)	Male (*n*=3)
Height (in)	M=65.40 ± 2.51	M=71.33 ± 1.15
Weight (lbs.)	M=146 ± 18.99	M=171.67 ± 22.55
BMI	M=24.07 ± 3.45	M=23.80 ± 3.90
Number of Caucasian	24 (96%)	3 (100%)
Number of Asian American	1 (4%)	0 (0%)
Number of Freshman	11 (44%)	1 (33%)
Number of Sophomores	9 (36%)	1 (33%)
Number of Juniors	2 (8%)	0 (0%)
Number of Seniors	0 (0%)	1 (33%)
Number of Graduate Students	3 (12%)	0 (0%)
Food Allergies/Intolerances	1 (4%)	2 (67%)
Following Special Diet for Allergy/Intolerances	0 (0%)	1 (33%)
Currently Trying to Lose Weight	2 (8%)	1 (33%)
Ability to Buy Enough Food	24 (96%)	3 (100%)
Limited Time Influences Food Choices	22 (88%)	2 (67%)

*****Did not ask specific age of participants

Table 4.2

Frequency of Reported Irritable Bowel Syndrome Symptoms by Survey

	No IBS symptoms	Mild IBS symptoms	Moderate IBS symptoms	Severe IBS symptoms
Survey 1	19	7	2	0
Survey 2	18	7	3	0
Survey 3	15	9	4	0
Total %	62%	27%	11%	0%

Differences in Intake of HFCS Beverages When Compared Between Stress Groups

Average perceived stress of participants was moderate throughout all three surveys (see Table 4.3). The average HFCS intake was more during less stress (10.39 ± 16.15 g) than moderate stress (8.06 ± 18.91 g), and high-stress environment (6.50 ± 18.19 g, $p < .05$). There was not a significant relationship between the amount of HFCS-55 intake and the reported perceived stress level, *r=.112, p=.314.* The results of the ANOVA did not indicate a significant effect, Wilk's Lambda = .987, *F (2,25)* = .164, *p* = .073. There was not a significant increase in intake of HFCS-55 from survey 1, (M = 10.33, SD = 15.85), compared to survey 3, (M = 6.27, SD = 17.89), t(27) = .821, p = .419.

Table 4.3

Percentage of Reported Perceived Stress Levels by Survey

	Low Stress	Moderate Stress	High Stress
Survey 1	32.14%	67.86%	0%
Survey 2	21.43%	75%	3.57%
Survey 3	7.14%	89.29%	3.57%
Total	20.57%	77.38%	2.38%

Table 4.4

Averaged Reported HFC-55 Intake by Stress Level

	HFCS-55 Intake
Low Stress	10.33 g/day
Moderate Stress	7.77 g/day
High Stress	6.27 g/day
Total	8.12 g/day

Dietary Habits

Computer-aided nutritional analysis of the responses to the 24-hour food recall showed there were no significant between-group differences in relation to the mean total calorie, protein, fiber, carbohydrate, total sugar, total added sugar, total fat, total polyunsaturated fat, total trans-fat, total fructose, total glucose, or total sugar alcohol intake with reported IBS symptoms. However, total monounsaturated fat intake was found to be siginificantly negatively correlated with reported IBS symptoms, *r=-.257, p=.023*. An analysis of variance showed that the intake of monounsaturated fat did not have a significant effect on reported IBS symptoms, $F(2, 83) = 2.686$, $p = .074$.

Table 4.5

Correlation between Dietary Intake and Reported IBS Symptoms

	Pearson's r	Significance
Total Energy	.028	.807
Total Protein	.046	.687
Total Carbohydrate	.109	.343
Total Fiber	-.064	.577
Total Sugar	.123	.283
Total Added Sugar	.025	.827
Total Fat	-.100	.384
Total Monounsaturated Fat	-.257	**.023**
Total Polyunsaturated Fat	-.204	.074
Total Trans Fat	-.009	.938
Total Fructose	-.125	.276
Total Glucose	.123	.285
Total Sugar Alcohol	.119	.317
Total Saturated Fat	-.100	.384

Discussion

The elevated chronic consumption of HFCS has been linked to various health problems, including diabetes mellitus, non-alcoholic fatty liver disease, aging, cholesterol, and IBS (Ikechi, Fischer, DeSipio, & Phadtare, 2017). IBS symptoms can be triggered by the excess consumption of HFCS (Latulippe & Skoog, 2011). On reaching the distal small intestine and colon, fructose increases the osmotic pressure in the large-intestine lumen and provides a substrate for bacterial fermentation, with consequent gas production, abdominal distension, and abdominal pain (El-Salhy & Gundersen, 2015).

The factors that influence carbohydrate malabsorption are the dosage of carbohydrate ingested, small bowel transit time, and enzymatic digestive capacity for the carbohydrate used.

To our knowledge, this is the first study that compares the actual real life intake of HFCS in detection of IBS symptoms. We tried to define if increased consumption of HFCS had a similar effect as fructose malabsorption. A one-way repeated measures analysis of variance (ANOVA) was conducted to evaluate the null hypothesis that there is no change in participant's HFCS-55 intake when measured during low, moderate, and high stress environments (N=28). The results of the ANOVA did not indicate a significant effect. Thus, there is not significant evidence to reject the null hypothesis.

Analysis of the responses to the 24 hour dietary recall showed that HFCS-55 intake did not differ significantly between the three times periods. Although a 24-hour dietary recall has been validated in many studies, there is the potential for human error in the analysis if participants do not accurately report their intake or if that report is not assessed by a qualified professional. To limit this error, this study had a dietitian assess the HFCS-55 content of the beverage items covered by the 24 hour recall utilizing ESHA Food Processor. Therefore, the results may be useful as a stepping-stone to obtain the possible correlation between IBS symptoms and HFCS-55 sweetened beverage intake.

A negative correlation was found between monounsaturated fat intake and IBS symptoms. Monounsaturated fatty acids are molecules with one unsaturated carbon bond, or double bond ("Monounsaturated Fat | American Heart Association," n.d.). Common oils that contain monounsaturated fatty acids are olive and canola oil. Given what is understood about anti-inflammatory effects of monounsaturated fatty acids, this is an avenue worth additional exploration.

Low grade inflammation has been shown to contribute to GI motor dysfunction and abdominal symptoms in patients with inflammatory GI disorders, as well as IBS (Salari-

Moghaddam, Keshteli, Esmaillzadeh, & Adibi, n.d.). Individuals with IBS have been shown to have high levels of low-grade systemic inflammation (E et al., 2016). Therefore, factors contributing to systemic inflammation, such as dietary intake, might be involved in the incidence and exacerbation of IBS symptoms. Likewise, dietary factors know to reduce systemic inflammation may be beneficial in addressing symptoms of IBS.

A 2015 review found that commonly consumed monounsatured fat in the form of olive oil resulted in both decreased C-reactive protein (mean difference: 0.64 mg/L, (95% CI 0.96 to 0.31),p< 0.0001,n= 15 trials) and interleukin-6 (mean difference: 0.29 (95% CI 0.7 to 0.02), p< 0.04,n= 7 trials) as compared to controls (Schwingshackl, Christoph, & Hoffmann, 2015). Additionally, flow-mediated dilatation significantly increased in individuals subjected to olive oil interventions (mean difference: 0.76% (95% CI 0.27to 1.24),p< 0.002,n= 8 trials).

In Southern Italy, 1134 subjects (598 M, 536 F; age range 17-83 years) were studied in relation to their dietary habits and the presence of gastrointestinal symptoms. Lack of adherence to a Mediterranean diet (MD), known to be rich in olive oil, was found to possibly trigger functional gastrointestinal symptoms, mainly in younger subjects. An analysis revealed a significantly lower MD adherence score in the 17-24 year and 25-34 year categories for IBS (17-24 years: 0.45 ± 0.20, $P < 0.05$; 24-34 years: 0.44 ± 0.21, $P < 0.001$) (Zito et al., 2016) than in asymptomatic subjects (17-24 years: 0.56 ± 0.21; 25-34 years: 0.69 ± 0.20), showing an inverse relationship between adherence to MD and prevalence of gastrointestinal symptoms. These results provide evidence that olive oil, a commonly consumed monounsaturated fat, might exert beneficial effects on markers of inflammation.

In a cross-sectional study, researchers found that a pro-inflammatory diet was associated with increased odds of IBS (Salari-Moghaddam et al., n.d.). Specifically, a greater dietary inflammatory index (DII) score was significantly associated with higher intakes of energy, saturated fatty acids, trans fatty acids and lower intakes of monounsaturated and polyunsaturated fatty acids. Researchers found that participants in the highest quintile of DII score had greater chance for IBS compared with those in the lowest quintile (OR: 1.36; 95% CI: 1.03–1.80) (Salari-Moghaddam et al., n.d.). Therefore, potential factors, such as dietary intake of saturated and trans fat, that increase systemic inflammation might be involved in the incidence and exacerbation of IBS symptoms.

More recent findings have suggested a positive effect of dietary fat in IBS (Aviello et al., 2016; Feinle-Bisset & Azpiroz, 2013). In particular, polyunsaturated fatty acids and their metabolites have shown beneficial effects on intestinal inflammation (Marion-Letellier et al., 2009). It has been hypothesized that this effect could help relieve IBS symptoms (Feinle-Bisset & Azpiroz, 2013; Lovell et al., 2012; Martínez et al., 2013). Given that low-grade inflammation has been recently revealed as a mechanism involved in IBS (Aviello et al., 2016), the supplementation of polyunsaturated and monounsaturated fatty acids in IBS patients warrants further research.(Cozma-Petrut, Loghin, Miere, & Dumitrascu, 2017).

Majority of students were found to rate their perceived stress as moderate across all survey time periods. High perceived stress for long durations can have negative effects on mental health. Mental health is one of the most significant determinants of life quality and satisfaction, and poor mental health has been found to be a common psychological problem among university undergraduate students in developed countries (Mofatteh, 2021). Recent findings suggest that stress-management programs may be helpful for university students (Buizza, Ciavarra, & Ghilardi, 2020), but further studies are needed to assess a broader range of outcomes, including the correlation of stress-reduction with academic and health conditions.

Limitations

First, the study was conducted using a sample of North Dakota State University and Valley City State University college students. There are additional colleges where recruitment was attempted to gain a widespread perspective on HFCS intake, perceived stress and reported IBS symptoms, however, attempts were unsuccessful. A convenience sample of 28 students was used. There are also limited demographic variations in Fargo and Valley City, North Dakota to consider. Additionally, an aspect of unintentially misreporting due to recall bias must be acknowledged with any self-reported survey. With regard to survey data collection, it is recognized that there may be a difference in reporting amongst various survey timelines. With diet recall being over the past 24 hours, reporting IBS symptoms throughout the past month, and perceived stress throughout the past 10 days. We must also acknowledge the fact that their could be an impact on a student's own tolerance to stress with regard to completing all surveys. For example, it could be that only students who were more tolerant to stress were able to handle completing all three surveys.

The final sample size for this study was based on a relatively small number of participants. Therefore, our findings may need further validation with a larger number of participants. The results from clinical trials in which free-living individuals consume fructose in large amounts in the absence of glucose are limited. In most studies, both the amount and form of fructose do not represent free-living adult diets. While clinical studies of fructose in forms of HFCS have shown fructose to be well absorbed in healthy individuals with compromised gut function (Latulippe & Skoog, 2011), positive breath test results are uncommon when pure fructose is provided in a dose of less than 25 gm or simultaneously with other carbohydrates. It would be odd to consume 25 gm of fructose apart from other nutrients. For example, one would have to consume more than 50 fluid oz. (1.5 liters) of cola sweetened with HFCS-55 in one setting to ingest 25 gm of fructose in excess of glucose. Therefore, fructose malabsorption may be overestimated. For that reason, there exists a clear need for additional randomized, controlled, double-blind clinical trials that document the frequency of intolerance in the adult population, if any, to HFCS-55 in which the content of free fructose exceeds that of glucose.

Conclusion

The primary purpose of this study was to find the relationship between HFCS intake and IBS symptoms. A secondary purpose was -compare the results of HFCS intake during periods of varying stress environments. During the study, the average experienced gastrointestinal symptoms did not meet criteria for IBS. With hypothesized connections between reported IBS symptoms and HFCS intake, there was limited data to correlate. There was not a significant relationship found between the amount of HFCS-55 intake and reported IBS symptoms, $r=.040$, $p=.717$.

Average perceived stress of participants was moderate throughout the entire study of fall 2020 semester. However, total HFCS intake during varying stress environments did not differ at a statistically significant level.

With the unavoidable stress student life can bring, the results of this study may allow clinicians to incorporate education on decreasing stress to help avoid unwanted gastrointestinal discomfort. However, more research with a larger adult population with IBS symptoms is needed.

Statement of Authorship: Brittany Twiss and Dr. Elizabeth Hilliard were responsible for the study from its design to writing the article; Brittany Twiss founded the study design and enlisted patient enrollment; Brittany Twiss designed all of the surveys; collected the responses and analyzed the data; Brittany Twiss performed sample size calculation and statistical analysis; Dr. Elizabeth Hilliard, Dr. Yeong Rhee and Dr. Rick Jansen supervised the study, provided important intellectual contributions, and reviewed the final draft.

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APPENDIX A. UPDATED BEVQ

Beverage Questionnaire (BEVQ-15)

Participant ID: ____________________

Date: ____________________

Instructions:

For the past month, please indicate your intake for each beverage type by marking an "X" in the bubble for "how often" and "how much each time".

1. Indicate how often you drank the following beverages, for example, if you drank 5 glasses of water per week, mark 4-6 times per week.
2. Indicate the approximate amount of beverage you drank each time, for example, if you drank 1 cup of water each time, mark 1 cup under "how much each time". If applicable, indicate the specific type of beverage by marking an "X" in the bubble by the one used (i.e., type of nut milk).
3. When trying to estimate your intake throughout the day, (i.e., water) think about the total amount you drink. For example, 3 times per day and 20 fl oz each time = 60 fl oz per day. **If you consume more 60 fl oz per day select "1 time per day" and write the TOTAL daily amount in the last column.**
4. Do not count beverages used in cooking or other preparations, such as milk in cereal.
5. Count milk/creamer added to tea and coffee in the tea or coffee with creamer beverage category, NOT in the milk categories; this includes non-dairy creamer. Please indicate the type of creamer (flavored, plain or sugar-free) and sweetener used by marking an "X" in the bubble by the one used, if applicable.

Type of Beverage	HOW OFTEN (MARK ONE)							HOW MUCH EACH TIME (MARK ONE)					
	Never or less than 1 time per week (go to next beverage)	1 time per week	2-3 times per week	4-6 times per week	1 time per day	2 times per day	3+ times per day	Less than 6 fl oz (¾ cup)	8 fl oz (1 cup)	12 fl oz (1½ cups)	16 fl oz (2 cups)	20 fl oz (2½ cups)	> 20 fl oz (specify TOTAL daily amount)
Water or unsweetened sparkling water	O	O	O	O	O	O	O	O	O	O	O	O	_____
100% Fruit Juice	O	O	O	O	O	O	O	O	O	O	O	O	_____
Sweetened Juice Beverage/Drink (fruit punch, juice cocktail, Sunny Delight, Capri Sun)	O	O	O	O	O	O	O	O	O	O	O	O	_____
Whole Milk: red cap, Reduced Fat Milk 2%: purple cap, or Chocolate Milk	O	O	O	O	O	O	O	O	O	O	O	O	_____
Low Fat 1%: green cap, Fat Free/Skim Milk: light blue cap, Buttermilk or Soy Milk	O	O	O	O	O	O	O	O	O	O	O	O	_____
Nut Milk (almond, cashew, coconut) O Flavored, Original, or Plain O Unsweetened	O	O	O	O	O	O	O	O	O	O	O	O	_____
Soft Drinks, Regular	O	O	O	O	O	O	O	O	O	O	O	O	_____
Energy & Sports Drinks, Regular (Red Bull, Gatorade, Powerade)	O	O	O	O	O	O	O	O	O	O	O	O	_____
Diet or Artificially Sweetened Soft Drinks, Energy & Sports Drinks (Diet Coke, Crystal Light, artificially sweetened sparkling water, Sugar-Free or Total Zero Red Bull, Powerade Zero)	O	O	O	O	O	O	O	O	O	O	O	O	_____
Sweet Tea (with sugar)	O	O	O	O	O	O	O	O	O	O	O	O	_____
Tea or Coffee, black (no creamer or milk) O Sugar, O Artificial Sweetener, O N/A	O	O	O	O	O	O	O	O	O	O	O	O	_____
Tea or Coffee (w/ milk &/or creamer) O Sugar O Artificial Sweetener O N/A Milk &/or Creamer: O Milk O Half & Half or Cream O N/A Creamer: O Flav. O Plain O Sugar-Free	O	O	O	O	O	O	O	O	O	O	O	O	_____
Wine (red or white)	O	O	O	O	O	O	O	O	O	O	O	O	_____
Hard Liquor (vodka, rum, tequila, etc.)	O	O	O	O	O	O	O	O	O	O	O	O	_____
Beer, Ales, Wine Coolers, Non-alcoholic or Light Beer	O	O	O	O	O	O	O	O	O	O	O	O	_____
Other (list):________________	O	O	O	O	O	O	O	O	O	O	O	O	_____

APPENDIX B. IBSS SEVERITY SCORE

PART 1: SEVERITY SCORE

For office use only

SCORE

1. a) *Do you currently suffer from abdominal (stomach) pain?* **YES** **NO**

Circle appropriate box

b) *If yes, how severe is your abdominal (stomach) pain?*

0 % |———————| **100 %**

no pain — not very severe — quite severe — severe — very severe

☐

c) *Please enter the number of days that you get the pain in every ten days.* *For example if you enter 4 it means that you get pain 4 out of 10 days. If you get pain every day enter 10*

Number of days with pain ☐ x 10 ☐

2. a) *Do you currently suffer from abdominal distension** **YES** **NO**

(bloating, swollen or tight stomach)

(women, please ignore distension related to your periods)*

Circle appropriate box

b) *If yes, how severe is your abdominal distension/tightness*

0 % |———————| **100 %**

no distension — not very severe — quite severe — severe — very severe

☐

3. *How satisfied are you with your bowel movements?*

0 % |———————| **100 %**

very happy — quite happy — unhappy — very unhappy

☐

4. *Please indicate with a cross on the line below how much your Irritable Bowel Syndrome is affecting or interfering with your life in general.*

0 % |———————| **100 %**

not at all — not much — quite a lot — completely

☐

IBS SEVERITY SCORE: ☐

2

APPENDIX C. SURVEY SCORE SHEET

IBS-SSS

IBS Symptom Severity Scale version 2.0

Scaling and Scoring

Version 1.0: May 2015

Mapi Research Trust

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The IBS Symptom Severity Scale is composed of 12 items investigating 3 domains.

Domains and Clusters

Domains	Number of Items	Cluster of Items	Item reversion	Direction of Domains
Severity	5	1b; 2b; 3; 4	No	Higher score = Higher severity
Bowel Habit	3	5-7	NA	Not used for scoring
Site of Pain	2	8-9	NA	Not used for scoring

Scoring of Domains

Item scaling	Visual Analog Scale (VAS) 100 mm
Weighting of items	No
Range of scores	Range of the total score: 0-500
Scoring Procedure	Each of the 5 severity questions generate a maximum score of 100, leading to a total possible score of 500
Interpretation and Analysis of missing data	The recommendations of the Rome Foundation are as follows: 1. All items are equally weighted in computing the Severity Score. Therefore, if no more than two responses to the 5 questions are missing, we recommend substituting the mean of the remaining items for the missing items 2. If more than two of the 5 questions on the Severity Scale are missing, no Severity Score should be computed
Interpretation of multiple answers for one item	The Rome Foundation recommends that the item be treated as "missing" when the subject provides two responses
Interpretation and Analysis of 'non-concerned' answers	If item 1a is ticked "no", the score for item 1b is "zero". If item 2a is ticked "no", the score for item 2b is "zero".
Interpretation of scores	Based on the validation study by Francis et al (Aliment Pharmacol Ther 1997;11:395-402), scores <75 are regarded as "in remission" if they occur in a patient with a previous diagnosis of IBS or as "not IBS" if they occur in an unselected subject. Scores of 75-174 are interpreted as "mild disease", 175-299 as "moderate", and 300 or greater as "severe" disease. Based on the same publication, a Minimum Clinically Important Difference (MCID) is equivalent to a change of 50 points or greater on the Severity Score; thus, a patient who improves by >= 50 points from before to after treatment could be classified as a treatment responder.

Reference(s):

Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. Aliment Pharmacol Ther. 1997 Apr

APPENDIX D. NDSU IRB APPROVAL

NDSU NORTH DAKOTA STATE UNIVERSITY

September 15, 2020

Dr. Elizabeth Hilliard
Health, Nutrition & Exercise Sciences

Re: IRB Determination of Exempt Human Subjects Research:
Protocol #HE21040, "HOW INTAKE OF HIGH FRUCTOSE CORN SYRUP RELATES TO REPORTED IBS SYMPTOMS DURING TIMES OF STRESS"

NDSU Co-investigator(s) and research team: Brittany Twiss
Date of Exempt Determination: 9/15/2020 Expiration Date: 9/14/2023
Study site(s): NDSU Funding Agency: n/a
The above referenced human subjects research project has been determined exempt (category 2(iii)) in accordance with federal regulations (Code of Federal Regulations, Title 45, Part 46, Protection of Human Subjects). This determination is based on the revised protocol received 9/9/2020 and revised consent/survey received 9/15/20.

Please also note the following:
• If you wish to continue the research after the expiration, submit a request for recertification several weeks prior to the expiration.
• The study must be conducted as described in the approved protocol. Changes to this protocol must be approved prior to initiating, unless the changes are necessary to eliminate an immediate hazard to subjects.
• Notify the IRB promptly of any adverse events, complaints, or unanticipated problems involving risks to subjects or others related to this project.
• Report any significant new findings that may affect the risks and benefits to the participants and the IRB.

Research records may be subject to a random or directed audit at any time to verify compliance with IRB standard operating procedures.

Thank you for your cooperation with NDSU IRB procedures. Best wishes for a successful study.
Sincerely,

Kristy Shirley
Kristy Shirley, CIP, Research Compliance Administrator

For more information regarding IRB Office submissions and guidelines, please consult https://www.ndsu.edu/research/for_researchers/research_integrity_and_compliance/institutional_review_board_irb/. This Institution has an approved FederalWide Assurance with the Department of Health and Human Services: FWA00002439.

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