MODERATE CONTINOUS VERSUS HIGH INTERVAL INTENSITY TRAINING ON GUT DYSBIOSIS AND GLUCAGON LIKE PEPTIDE HORMONE IN IRRITABLE BOWEL SYNDROME

BY
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CHAPTER 1
INTRODUCTION

Trillions of microorganisms live inside every human being; The gastrointestinal tract is home to vast microbial communities known as gut microbiota which includes bacteria, fungi, archaea, and viruses. The homeostatic balance of gut microbiota is beneficial to the host as it acts as a gatekeeper to protect epithelial cell integrity from penetration and disease caused by pathogens. Other beneficial effects of gut microbiota include micronutrient production, such as vitamin K and folate **(Singh et al.,2021).**

Colonic bacteria ferment unabsorbed carbohydrates to short-chain fatty acids (SCFAs), which can be subsequently absorbed through the colonic mucosa and used as an additional energy source **(Koh et al., 2016).**

The main products of the bacterial fermentation of carbohydrates and proteins, under anaerobic conditions of the large intestine, are short chain fatty acids (SCFAs). SCFAs such as acetate, propionate, butyrate, are secreted in the gut lumen and their signaling to the multiple gut receptors which are implicated in the control of anorectic gut satiety hormones such as glucagon like peptide GLP-1 **(Koh et al., 2016).**

The imbalance in the microbial equilibrium is termed “dysbiosis”, which has been further defined as a disturbance to gut microbiota homeostasis due to an imbalance in the bacteria itself, changes in their functional composition and metabolic activities. Dysbiosis has been implicated in a wide range of diseases including irritable bowel syndrome (IBS) (**DeGruttola et al.,2016).**

Gut dysbiosis, plays a fundamental role in the pathogenesis of IBS. It was found in IBS patients that gastrointestinal dysbiosis associated with visceral

hypersensitivity, increased gut permeability, mucosal immune activation, chronic inflammation, chronic fatigue, anxiety, and depression **(Wang et al.,2020)**.

Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, with signs and symptoms including cramping, abdominal pain, bloating, gas, and diarrhea or constipation, or both **(Gupta and Maity, 2021).**

Patients with IBS have shown success with dietary interventions; specifically limiting short-chain carbohydrates known as fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP). These carbohydrates have shown to be slowly absorbed and highly fermentable, which contributes to the gastrointestinal symptoms. Restriction of FODMAPs has been shown to improve symptoms in 70% of patients with IBS. Diet modifications and exercise combined showed a significant positive improvement in irritable bowel syndrome. **(Sharaf et al.,2021).**

Exercise is a well-established way to alleviate constipation, distension and also for maintaining proper bowel function and reducing stresses. Physical activity improves colonic transit time, gas transit, and bloating by stimulating gastrointestinal motility and most importantly it is becoming more accepted as a safer and effective treatment for irritable bowel syndrome **(Song et al.,2018).**

Exercise can determine changes in the gut microbial composition playing a positive role in energy homeostasis and regulation. Low intensity exercise can influence the gastrointestinal tract reducing the transient stool time and thus the contact time between the pathogens and the gastrointestinal mucus layer . As a consequence, it seems that exercise has protective effects, reducing the risk of colon cancer and inflammatory bowel disease **(Monda et al.,2017).**

Moderate aerobic exercise affects the intestinal system mainly through gut immune function, gut barrier integrity, as well as gut motility, intestinal pH and gut hormones release; and bile acids metabolism within enterohepatic circulation **(Resende et al., 2021).**

Also High-intensity interval training is a popular, time-efficient mode of exercise to improve metabolic health and aerobic fitness, both of which have been associated with healthier gut bacterial community structure **(Rettedal et al., 2020).**

Statement of the Problem:

Is there a significant difference between the effect of moderate continuous versus high interval intensity training on gut dysbiosis and glucagon like peptide hormone in irritable bowel syndrome?

The Purpose of the Study:

To compare the effect of moderate continuous versus high interval intensity training on gut dysbiosis and glucagon like peptide hormone in irritable bowel syndrome.

Significance of the Study:

Irritable bowel syndrome affects around 11% of the global population with variation by geographic region: the highest in South America (21.0%) and the lowest occurring in South Asia (7.0%). In Egypt, the prevalence was 34% in primary healthcare center attendees. IBS significantly reduces work productivity and health-related quality of life **(Mohamed et al.,2021).**

The quality of life for patients suffering from IBS is greatly affected physically, psychologically, and economically. Several cases reported difficulties in concentration, decreased energy level, and lower self-esteem. In-addition IBS is

inducing occupational hazards as it affects the performance of patients at their jobs **(Elsayed et al.,2021).**

Although half of the cases referred to gastroenterologists is due to IBS, no clear etiology was found; however, some researches revealed that certain factors such as psychological factors, dietary habits, and exercise level were related to IBS onset and course **(Elhosseiny et al.,2019).**

Previous studies have been done separately on the effect of moderate intensity continuous training program and high intensity interval training on irritable bowel syndrome and gut dysbiosis, it is rational to compare between two training programs to know which is more effective to improve gut microbiota balance.

Delimitations:

This study will be delimited to the following aspects:

Subjects will be delimited to patients with irritable bowel syndrome selected from the outpatient of national nutrition institute with the following criteria:

- Sixty six patients with irritable bowel syndrome of both genders.
- Their ages ranged from 20 to 45 years.
- Their Body mass index ranged from 30 to 34.9.
- Patients will be divided into 3 groups
    - **Group A:** Patients will receive moderate intensity continues training exercise program along with following Low fermentable, oligosaccharides, disaccharides, monosaccharides and polysaccharides diet plan (FODMAPs diet).
    - **Group B:** Patient will receive high intensity interval training exercise program along with following FODMAP diet plan.

- **Group C:** Patients will follow FODMAP diet plan only.

- Patients will be excluded if:
  - - Uncontrolled hypertension
  - - Gastrointestinal bleeding
  - - Colorectal cancer or any terminal diseases
  - - Communication disorders

Basic Assumptions:

It will be assumed that:

1) The primary medical assessment will be done to every participating patient who includes:
2) Complete medical history (personal, present and past)
3) All patients will stick to the program and will follow instructions.
4) All other factors which may influence the outcome such as noise and distraction will be controlled.

Hypothesis:

It will be hypothesized that there will be no significant difference between the moderate continuous versus high interval intensity training on gut dysbiosis and glucagon like peptide hormone in irritable bowel syndrome.

CHAPTER II
REVIEW OF LITERATURE

The human gastrointestinal (GI) tract represents one of the largest organ between the host, environmental factors and antigens in the human body. In an average life time, around 60 tonnes of food pass through the human GI tract, along with an abundance of microorganisms from the environment which impose a huge threat on gut integrity. The collection of bacteria, archaea and eukarya colonising the GI tract is termed the 'gut microbiota' and has co-evolved with the host over thousands of years to form an intricate and mutually beneficial relationship **(Thursby and Juge,2017).**

The gut microbiota enjoys a mutualistic relationship with the host, harvesting additional energy and nutrients from the diet and protecting the host from pathogens. The resident bacteria produce a wide range of metabolites and chemicals that influence host function and these include short-chain fatty acids such as butyrate, which is essential for the integrity of the colonic epithelium. However, there is potential for these mechanisms to be disrupted as a result of an altered microbial composition, known as dysbiosis **(Lin and Zhang,2017).**

Human Gut dysbiosis is linked to many pathologic conditions disturbing the energy metabolism; such as obesity and atherosclerosis. The microbiota in the human gut is mostly composed of bacterial phyla: Firmicutes and Bacteroidetes **(Thursby and Juge,2017).**

Firmicutes bacteria are Gram-positive one. It plays a key role in the nutrition and metabolism of the host through SCFA synthesis. Through their metabolic products, Firmicutes bacteria are indirectly connected with other tissues and organs and regulate hunger and satiety. In contrast, Bacteroidetes bacteria are Gram negative and associated with immunomodulation. Increased or decreased

Firmicutes / Bacteroidetes (F/B) ratio are associated with the development of obesity or irritable bowel disease (IBD) **(Stojanov et al.,2020).**

Short-chain fatty acids (SCFAs), the primary metabolite for colonocytes, are produced in the intestinal lumen by commensal anaerobic bacteria via carbohydrate fermentation. they play a role in preserving gut barrier functions, and have immunomodulatory and anti-inflammatory properties also it regulates the synthesis of the hunger-suppressing hormones leptin, peptide YY, and glucagon-like peptide 1. The gut microbiota can also affect appetite and satiety via vagus nerve activation or immune-neuroendocrine mechanisms **(Protincasa et al.,2022).**

Irritable bowel syndrome (IBS) is a common gastrointestinal disorder characterized by chronic abdominal pain and changes in bowel habits without any known organic causes **(Aziz and Simern, 2021).**

Fecal SCFAs abnormalities have been reported in patients with IBS, implying that alterations in SCFAs might be related to IBS. The cause of IBS remains unknown, and no single treatment is found to be universally applicable to all patients with IBS **(Sun et al., 2019).**

Among humans, positive correlations were reported between bacterial diversity, butyrate-producing bacteria and cardiorespiratory fitness (VO2max), and higher turnover of carbohydrates and proteins, and concentrations of short-chain fatty acids in athletes compared to sedentary controls. There is also growing evidence that physical activity status and exercise training may shape the gut microbiome **(Cataldi et al.,2022).**

Physical activity stimulates bacterial community richness by altering SCFAs-producing species, as well as favoring the colonization of health and athletic performance-promoting strains. The ability to promote a bacterial

composition capable of protecting the intestinal mucosa also it was found that the effects on gut microbiome seem to gradually disappear when the physical activity is no longer practiced **(Cataldi et al., 2022).**

Moderate aerobic exercise affects the intestinal system mainly through gut immune function gut barrier integrity through tight junction proteins expression and IgA production hypothalamic–pituitary–adrenal (HPA) axis stimulation which, in turn, affects enteric nervous system and intestinal transit time, as well as gut motility, intestinal pH and gut hormones release and bile acids metabolism within enterohepatic circulation **(Cella et al.,2021).**

High intensity interval training (HIIT) encompasses exercise prescriptions that are tailored to individual needs and can be used in most any exercise setting. This ability to adapt makes HIIT a valuable tool in the exercise programming of patients with a chronic disease. HIIT has a positive effect on the Bacteroidetes/Firmicutes ratio and also increased the alpha diversity in gut microbiota **(Denou et al.,2016).**

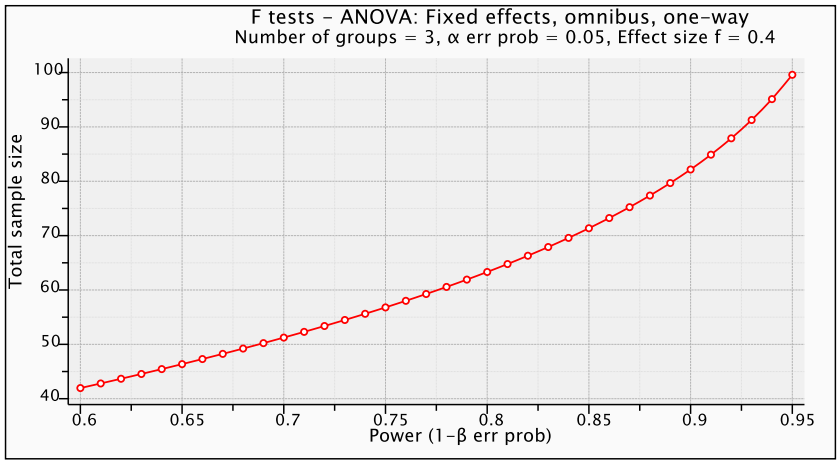
Chapter III
PATIENTS, MATERIALS AND METHODS

The current study is designed to compare between the effect of moderate continuous and high interval intensity training on gut dysbiosis and glucagon like peptide hormone in irritable bowel syndrome.

I. Patients:

This study will be carried out on sixty six irritable bowel syndrome patients of both sexes with an age range between twenty to forty five years. Patients will be recruited and practical work of the study will be carried out in national nutrition institute physiotherapy out clinic. Patient will be randomly assigned to three groups.

To avoid type II error, sample size calculation is performed using G*POWER statistical software (version 3.1.9.2; Franz Faul, Universitat Kiel, Germany). To detect a large effect size of 0.4 with power of 80% and α=0.05, the required sample size required for this study was N=66.



Ethical consideration:

- Approval of faculty ethical committee.
- The study procedure will be explained for all participants.
- Confidentiality will be assured.
- An informed consent will be taken from each subject prior to participation. **(Appendix I)**

Criteria for the patient selection:

Inclusion criteria:

1) Patients will be selected with age range of 20 to 45 years of both genders.
2) Body mass index (BMI) will range from 30 to 34.9 kg\m^2.
3) Having more than one symptom for ROME IV for IBS diagnostic criteria **(Appendix II).**
4) Prediabetic with glycated hemoglobin HbA1c of 5.7 – 6.4.
5) Sedentary subjects with daily steps count less than five thousand steps measured by pedometer **(Prince et al.,2020).**

Exclusion criteria:

Patients with the following criteria will be excluded from the study:

1) Communication disorders
2) Gasterointestinal bleeding
3) Antibiotics or probiotics in the last 2 months
4) Recent surgeries in the last 6 months
5) Colorectal cancer or any terminal diseases
6) Fibromylgia or Multiple sclerosis
7) Palpable abdominal mass
8) Cardiovascular diseases

9) Active smokers
10) Musculoskeletal injuries that interfere with exercise program
11) Upper respiratory infections
12) Uncontrolled hypertension

Patients will be divided into 3 groups:

- **Group (A):** This group will include 22 patients with IBS. These patients will receive 40 minutes of MICT on the treadmill: 5 minutes of warm-up followed by 30 minutes of 65-75% of target heart rate ending with a 5 min cool-down period for 12 weeks along with following low FODMAP diet plan.
- **Group (B)**: This group will include 22 patients with IBS. These patients will receive HIIT sessions consisting of a 30 minutes treadmill session a 5 minutes warm-up followed by 10 bouts of 1 minute at 90% of target heart rate interspersed by 10 bouts of 1 min of active recovery at 50% of target heart rate (totaling 20 min), and a 5 minutes cool-down period for 12 weeks along with following low FODMAP diet plan.
- **Group (C)** This group will include 22 patients with IBS. These patients will follow low FODMAP diet plan for 12 weeks

Materials and Methods

- **Evaluation**

Out comes to be measured:

1) Primary outcomes

a- Short chain fatty acids via gas chromatography

b- Glucagon like peptide 1 via Elisa kit

2) Secondary outcomes

a- Irritable bowel syndrome scoring system

b- Irritable bowel syndrome quality of life questionnaire (IBS QoL)

c- Change in body weight via body mass index (BMI)

Evaluation equipment and tools:

a) Gas chromatography: SCFAs butyrate and acetate

For SCFA analyses, fecal sample will be separated. Applying four analytes, including total SCFAs, acetate, propionate, and butyrate, will be targeted. Final concentrations will be calculated based on internal standards and are expressed as micromoles per gram of wet feces (μmol/g). Techniques and predictive approaches will be used across. gas chromatography will be used to quantify Short Chain Fatty Acids (SCFAs) from fecal samples **(Chen et al.,2021).**

b) Elisa Kit for serum GLP 1 hormone

This kit is an Enzyme-Linked Immunosorbent Assay (ELISA). The plate will be pre-coated with Human GLP-1 antibody **(Kuhre et al.,2015).**

c) Weight and Height measurements

Weight and height will be recorded to calculate body mass index (BMI) according to the following equation: **(Shukohifar et al.,2022)**

BMI= weight/height^2 (Kg/m^2).

d) IBS severity scoring system (Appendix III**)**

This five-item questionnaire will measure IBS symptom severity by addressing abdominal pain (frequency and severity), bloating, dissatisfaction with bowel habits, and interference with daily activities. Each question score ranges from 0 to 100 and a higher score indicates more severe GI symptoms. A total score of 75–175 represents mild IBS, 176–300 moderate IBS and >300 severe IBS **(Zeid et al.,2020).**

e) Irritable bowel syndrome quality of life questionnaire (IBS QoL) (Appendix IV)

The IBS-QoL is a condition-specific instrument will be used to assess the impact of IBS and effects of treatment. It consists of 34 questions which cover eight domains including dysphoria, interference with activity, body image, health worry, food avoidance, social reaction, sexual, and relationships. Each item has a five-point response scale (not at all, slightly, moderately, quite a bit, extremely). The responses are summed and averaged for a total score and transformed to a scale between 0 and 100: higher scores indicating better IBS-specific QoL **(Hou et al.,2015).**

3-Management procedure:

After collecting the consent forms, will be examined by the researcher for the inclusion and exclusion criteria. Each eligible patient (according to the consent form and examination) will participate in the study.

Group A

Patients will receive moderate intensity continuous training (MICT).

The program will be in form of: **(Clark et al.,2020).**

- **Frequency:** Moderate continues training will be scheduled 3 times per week for 12 weeks
- **Intensity:** 65-75% of target heart rate.
- **Duration:** 40 minutes per session. Patients will be instructed to follow low fermentable short chain carbohydrates diet (low FODMAP) intervention for 12 weeks limiting daily fermented carbohydrate and dairy products intake and increase intake of protein, whole grains, fruits and vegetables **(Appendix V)**

- **Group B**

Patients will receive high intensity interval training (HIIT)

The program will be in form of: **(Clark et al.,2020).**

- **Frequency:** High intensity interval training will be scheduled 3 times per week for 12 weeks
- **Intensity:** 90% of target heart rate including 10 bouts of 1 minute interspersed with 10 bouts of 1 minute of active recovery 50% of target heart rate.
- **Duration:** the session will last 30 minutes includes warming up and cooling down periods

Patients will be instructed to follow low fermentable short chain carbohydrates diet (low FODMAP) intervention for 12 weeks limiting daily fermented carbohydrate and dairy products and increase intake of protein, whole grains, fruits and vegetables

Group C

Patients will be instructed to follow low fermentable short chain carbohydrates diet (low FODMAP) intervention for 12 weeks limiting daily fermented carbohydrate and dairy products and increase intake of protein, whole grains, fruits and vegetables **(Vareny et al.,2017)**.

Only the patients who will attend > 80% of the exercise training sessions will be included in this study.

Data Analysis and statistical design

- The collected data was analyzed using the statistical program SPSS ver. 20.0.
- The mean and standard deviation were calculated for all measured variables.
- Pearson correlation coefficient was used to determine the relationship between the measured variables.
- Statistical significance was set at $p < 0.05$.

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Appendix I

Sample consent form

I am …….. freely and voluntarily consent to participate in this research study under the direction of the researcher **Marwa Saeed Mohamed Salama**

A thorough description of the procedures has been explained and I understand that I may withdraw my consent and discontinue participation in this research at any time without prejudice to me.

Date: / / 20

Participant:

Appendix II

ROME IV IBS diagnostic criteria

C1. IRRITABLE BOWEL SYNDROME

*Diagnostic criteria**

Recurrent abdominal pain on average at least 1 day/week in the last 3 months, associated with **two or more** of the following criteria:

1. Related to defecation
2. Associated with a change in frequency of stool
3. Associated with a change in form (appearance) of stool

* Criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

Appendix III

IBS Severity Scoring System

IBS Severity Score

Place an X anywhere on the line between 0 and 100 to indicate as accurately as possible the severity of your symptoms.

How severe is your pain?

0 ——— 100

No pain Not very severe Quite severe Severe Very severe

If currently in pain, how severe is your abdominal pain?

0 ——— 100

No pain Not very severe Quite severe Severe Very severe

If you currently have abdominal distention, how severe is it?

0 ——— 100

No distention Not very severe Quite severe Severe Very severe

How satisfied are you with your bowel habits?

0 ——— 100

Very happy Quite happy Unhappy Very unhappy

How much does your IBS affect or interfere with your life in general?

0 ——— 100

Not at all Not much Quite a lot Completely

NOTE: *Each of the five questions generates a score from 0 to 100 points, with a maximum total score of 500 points. Mild IBS = 75 to 174 points; moderate IBS = 175 to 299 points; and severe IBS = 300 points or more.*

Appendix IV

IBS Quality of Life Questionnaire

Please think about your life over the past month (last 30 days), and look at the statements below. Each statement has five different responses. For each statement, please circle the response that best describes your feelings.

		Not At All	Slightly	Moderately	Quite A Bit	Extremely
Q1	I feel helpless because of my bowel problems.					
Q2	I am embarrassed by the smell caused by my bowel problems					
Q3	I am bothered by how much time I spend on the toilet					
Q4	I feel vulnerable to other illnesses because of my bowel problems					
Q5	I feel fat/bloated because of my bowel problems					
Q6	I feel like I'm losing control of my life because of my bowel problems					
Q7	I feel my life is less enjoyable because of my bowel problems					
Q8	I feel uncomfortable when I talk about my bowel problems					
Q9	I feel depressed about my bowel problems					
Q10	I feel isolated from others because of my bowel problems					
Q11	I have to watch the amount of food I eat because of my bowel problems					
Q12	Because of my bowel problems, sexual activity is difficult for me					
Q13	I feel angry that I have bowel problems					
Q14	I feel like I irritate others because of my bowel problems					
Q15	I worry that my bowel problems will get worse					
Q16	I feel irritable because of my bowel problems					
Q17	I worry that people think I exaggerate my bowel problems					
Q18	I feel I get less done because of my bowel problems					
Q19	I have to avoid stressful situations					

		Not At All	Slightly	Moderately	Quite A Bit	Extremely
	because of my bowel problems					
Q20	My bowel problems reduce my sexual desire					
Q21	My bowel problems limit what I can wear					
Q22	I have to avoid strenuous activity because of my bowel problems					
Q23	I have to watch the kind of food I eat because of my bowel problems					
Q24	Because of my bowel problems, I have difficulty being around people I do not know well					
Q25	I feel sluggish because of my bowel problems					
Q26	I feel unclean because of my bowel problems					
Q27	Long trips are difficult for me because of my bowel problems					
Q28	I feel frustrated that I cannot eat when I want because of my bowel problems					
Q29	It is important to be near a toilet because of my bowel problems					
Q30	My life revolves around my bowel problems					
Q31	I worry about losing control of my bowels					
Q32	I fear that I won't be able to have a bowel movement					
Q33	My bowel problems are affecting my closest relationships					
Q34	I feel that no one understands my bowel problems					

Appendix V

Low FODMAP food List

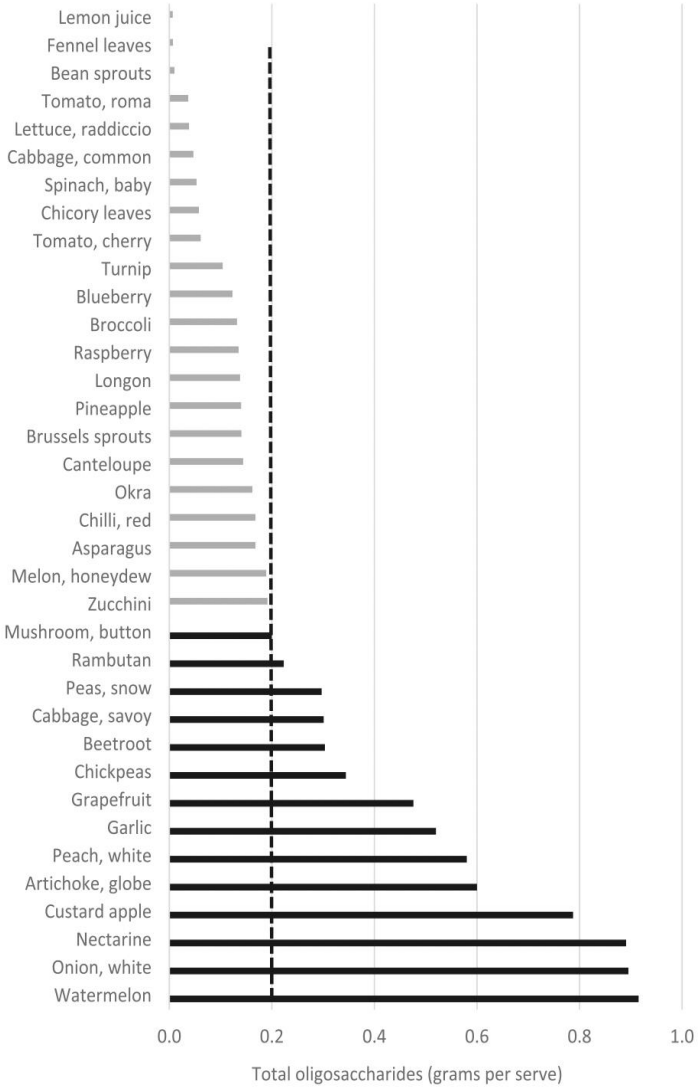
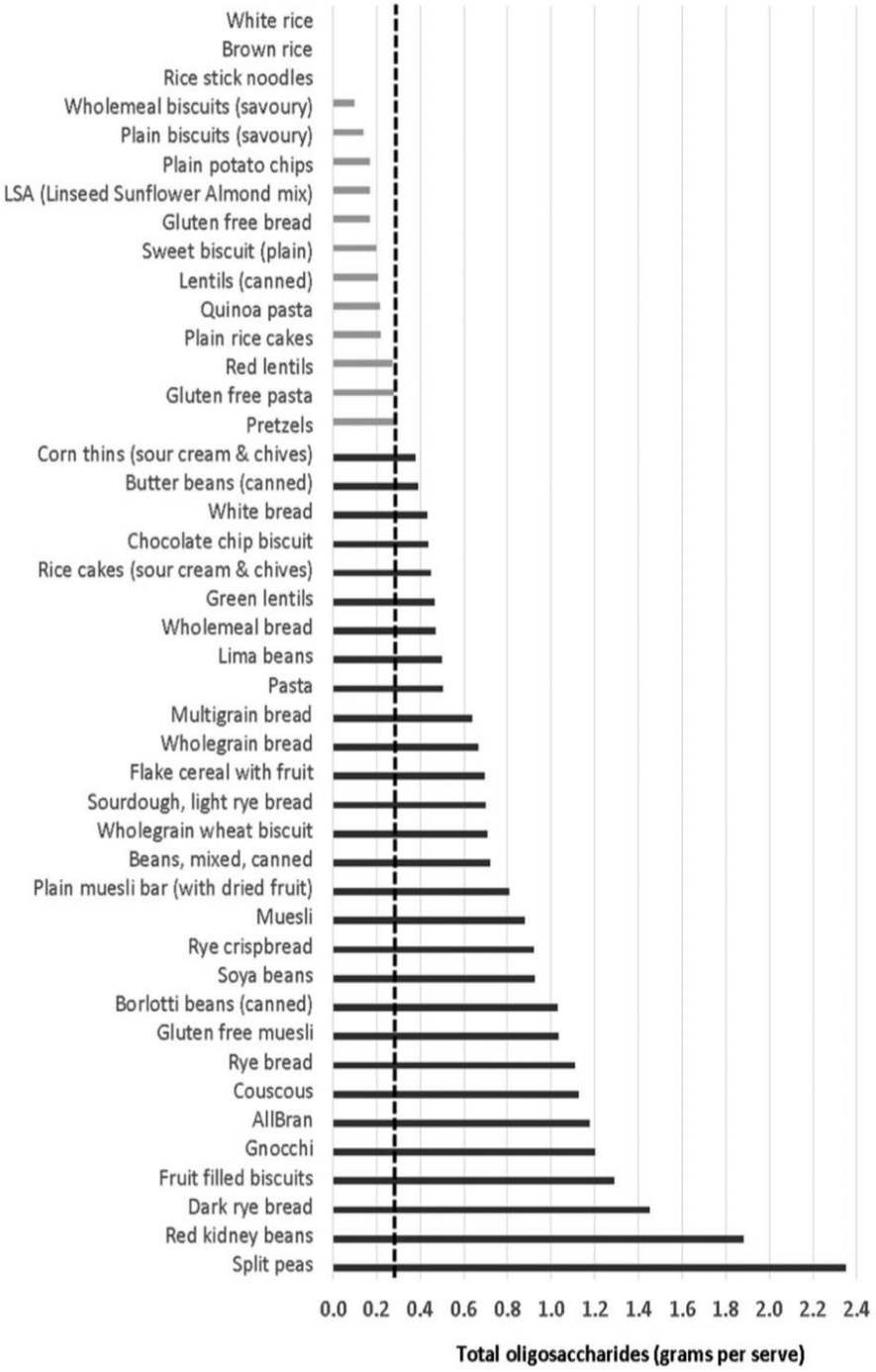


Figure 1 Oligosaccharide content of low-FODMAP (▒) and high-FODMAP (■) fruits and vegetables.[12,13]


White rice
Brown rice
Rice stick noodles
Wholemeal biscuits (savoury)
Plain biscuits (savoury)
Plain potato chips
LSA (Linseed Sunflower Almond mix)
Gluten free bread
Sweet biscuit (plain)
Lentils (canned)
Quinoa pasta
Plain rice cakes
Red lentils
Gluten free pasta
Pretzels
Corn thins (sour cream & chives)
Butter beans (canned)
White bread
Chocolate chip biscuit
Rice cakes (sour cream & chives)
Green lentils
Wholemeal bread
Lima beans
Pasta
Multigrain bread
Wholegrain bread
Flake cereal with fruit
Sourdough, light rye bread
Wholegrain wheat biscuit
Beans, mixed, canned
Plain muesli bar (with dried fruit)
Muesli
Rye crispbread
Soya beans
Borlotti beans (canned)
Gluten free muesli
Rye bread
Couscous
AllBran
Gnocchi
Fruit filled biscuits
Dark rye bread
Red kidney beans
Split peas
0.0 0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4
Total oligosaccharides (grams per serve)