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**PSYCHOLOGICAL FACTORS AND GASTROINTESTINAL
SYMPTOMS DURING RUNNING**

by

Alex Michael Ehlert

B.S. May 2015, University of North Carolina at Greensboro

M.S. May 2017, University of North Carolina at Greensboro

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Approved by:

Patrick Wilson (Director)

Laura Hill (Member)

Gena Gerstner (Member)

Hayley Russell (Member)

ABSTRACT

PSYCHOLOGICAL FACTORS AND GASTROINTESTINAL SYMPTOMS DURING RUNNING

Alex Michael Ehlert
Old Dominion University, 2021
Director: Dr. Patrick B. Wilson

Gastrointestinal (GI) symptoms, such as nausea and gas, are common problems for athletes in endurance sport. There is considerable evidence that psychological factors influence GI function, but little research has evaluated this in the context of exercise-induced GI symptoms. The overall purpose of this dissertation was to explore the role of psychological factors in the incidence and management of GI symptoms during endurance running. Study 1 assessed associations between several psychological factors, GI symptoms, and nutrition intake before and during runs. Study 2 evaluated the effects of daily breathing interventions on GI symptoms, psychological factors, and heart rate variability (HRV) in runners.

Eighty-two runners were recruited for study 1. They tracked information about their running, GI symptoms, and nutrition intake before and during runs for seven days, and completed a survey containing psychological questionnaires. Correlational analyses were used to quantify associations between 1) GI symptoms and psychological factors and 2) psychological factors and nutrition intake. A measure of GI-specific anxiety had statistically significant correlations with GI symptom burden during runs (Spearman's $\rho = 0.32 - 0.38$), which remained significant (although somewhat attenuated) after adjusting for potential confounders. However, GI symptom burden did not have statistically significant correlations with measures of stress, trait anxiety, or body vigilance. There were also no significant negative associations between psychological factors and nutrition intake.

Fifty-six runners with at least mild levels of anxiety and previous experiences with GI symptoms during running were recruited for study 2 and completed baseline measurements to quantify levels of several psychological factors, GI symptom burden, and resting HRV. They were then randomly allocated to slow deep breathing with breath counting (SLOWBC), normal breathing with breath counting (NORMALBC), or control groups. Participants in SLOWBC and NORMALBC were asked to complete daily, 5-minute breathing sessions for four weeks. Additional measurements were completed at the midpoint and during the final week of the intervention. The results generally did not support a treatment effect from either breathing intervention compared to the control group, except for a group x time interaction for anxiety in a per-protocol analysis. Follow-up analyses suggested anxiety tended to decrease over time in the breathing groups, and participants who found the breathing sessions more engaging tended to have larger reductions in anxiety levels. Overall, it seems more intensive breathing- and/or mindfulness-based interventions are required to substantially influence GI symptoms, stress, GI-specific anxiety, mindfulness, and HRV in runners with elevated levels of anxiety and GI symptom burden.

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This dissertation is dedicated to my wife. None of this would have been possible without her love and support each step of the way.

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CHAPTER I

INTRODUCTION

A competitive runner puts substantial effort toward preparing their body and mind for races. They improve their fitness through a demanding training program and carefully develop nutritional strategies to keep their body fueled and healthy. While all this preparation is crucial for optimal performance, it may also be rendered meaningless if the runner has an untimely episode of severe gastrointestinal (GI) distress. This has been the case for many endurance athletes. For example, nausea and vomiting have been reported as a primary reason for athletes to drop out of ultra-endurance races (Hoffman & Fogard, 2011), and even among those who avoid dropping out, up to 44% may suffer worsened performance due to GI symptoms (Stuempfle & Hoffman, 2015). Indeed, marathon legend Bill Rodgers once said that “more marathons are won or lost in the porta-toilets than at the dinner table” (de Oliveira et al., 2014).

The GI system plays a critical role in digesting, absorbing, and transporting nutrients and fluids at rest, during exercise, and in the post-exercise recovery periods (Jeukendrup et al., 2011). This is particularly important for endurance athletes, who must often consume large quantities of exogenous carbohydrates and fluids during exercise to sustain peak performance (Jeukendrup et al., 2011). A well-functioning GI system will allow an endurance athlete to push their body to its optimum level, while a compromised GI system can result in exercise-induced GI disturbances ranging from mild irritations (e.g., mild flatulence, belching) to severe medical complications (GI hemorrhage or ischemic colitis) (Grames & Berry- Cabán, 2012; Papaioannides et al., 1984). As such, endurance athletes must navigate a delicate balance between providing enough exogenous fuel and fluid during competition with the risks of overconsumption, inducing GI symptoms. The ability to maintain this balance can be a primary factor in whether an endurance

athlete places in a race, or even whether they complete the race at all (de Oliveira et al., 2014; Stuempfle & Hoffman, 2015).

Endurance athletes experience GI symptoms at a relatively high prevalence. While rates can be low in recreational athletes in mild environments (e.g., Pfeiffer et al., 2012), large percentages of endurance athletes experience symptoms during training and competition (Peters et al., 1999; ter Steege et al., 2008). Additionally, a study that asked runners to track GI symptoms over a 30-day period found that male and female runners experienced moderate-severe symptoms during 13.8% and 21.7% of runs, respectively (Wilson, 2017). In basic terms, most runners are unlikely to experience major GI problems on any single run, but the risk of having at least one major issue over a several-week period is notably higher.

While all endurance athletes can experience symptoms at a relatively high prevalence, they are particularly common and severe with ultra-endurance exercise. For example, ultra-endurance events performed in hot environments can elicit symptoms in almost all participants (93-96%; Jeukendrup et al., 2000; Stuempfle & Hoffman, 2015), though it's important to keep in mind that some of these cases are mild in severity. Additionally, more bothersome symptoms such as nausea, vomiting, and GI bleeding are commonly reported (Baska et al., 1990; Hoffman & Fogard, 2011; Jeukendrup et al., 2000; Stuempfle & Hoffman, 2015). For example, one study found that over half (60.3%) of participants at the Western States 100-Mile Endurance Run experienced nausea, and that 43.9% thought GI symptoms limited their performance (Stuempfle & Hoffman, 2015). As mentioned previously, GI symptoms such as nausea and vomiting have been cited as common reasons for dropping out of ultra-marathon races (Hoffman & Fogard, 2011; Stuempfle & Hoffman, 2015). Objective markers of GI dysfunction have been noted as well. In one case, mild endotoxemia was observed in 68% of triathletes after a race (Jeukendrup

et al., 2000), while another study reported that 85% of 100-mile run participants exhibited evidence of GI bleeding based on hemocult-positive stool samples (Baska et al., 1990). Notably, runners with hemocult-positive stool samples also reported higher incidence and severity of symptoms such as nausea, bloating, and diarrhea (Baska et al., 1990). These findings are of interest given the growing popularity of ultra-endurance events (Cejka et al., 2014; Knoth et al., 2012).

Taken together, research suggests that GI dysfunction is a relatively common occurrence in endurance sport, that it has the ability to impair performance (O'Brien & Rowlands, 2011; Stuempfle & Hoffman, 2015), and can even be a serious medical concern (Papaioannides et al., 1984). Even in recreational athletes or casual exercisers, a bout of GI symptoms may reduce the enjoyment of training and potentially discourage further participation in endurance sport. As a result, there is significant interest in identifying the pathophysiology of GI dysfunction during exercise, the factors that may place an athlete at a higher risk for GI symptoms, and interventions that prevent or reduce the severity of these symptoms (de Oliveira et al., 2014; van Wijck et al., 2012).

The specific underlying etiology of exercise-induced GI dysfunction has not been fully elucidated, and in reality, the contributing causes are likely to differ depending on the specific symptom(s) being studied (e.g., nausea vs. bloating). In many situations, however, current evidence suggests GI dysfunction and distress result from a complex interaction of several factors including splanchnic hypoperfusion, altered gastric motility, impaired nutrient absorption, and mechanical stress or damage (de Oliveira et al., 2014; van Wijck et al., 2012). At the onset of exercise, blood flow is redistributed towards the active muscles and skin to meet the increased metabolic demands and to aid in thermoregulation (Joyner & Casey, 2015). This can result in

splanchnic hypoperfusion and gut ischemia (van Wijck et al., 2012). In addition to potentially impacting GI motility via changes in oxygen and nutrient supply to intestinal smooth muscle, GI ischemia can compromise the integrity of the intestinal epithelium and ultimately allow intestinal bacterial translocation into the circulation (Costa et al., 2017b; van Wijck et al., 2012). This in turn can cause endotoxemia as well as localized and systemic inflammation, which can further exacerbate damage to the intestinal epithelial cells and affect gastric motility or other GI functions (Grootjans et al., 2010; van Wijck et al., 2012). Additionally, the strong sympathetic drive and release of catecholamines during intense exercise can alter activity at the enteric nervous system of the gut, resulting in delayed gastric emptying, reduced esophageal peristaltic activity and/or sphincter tone, and potentially malabsorption of nutrients (Costa et al., 2017b; de Oliveira et al., 2014; van Wijck et al., 2012). Exercise and increased sympathetic drive can also impact large intestine motility, but results to date are largely mixed, perhaps due to differences in exercise intensity, modality of exercise, and measurement techniques (Cheskin et al., 1992; Rao et al., 1999).

These functional changes may cause or exacerbate GI symptoms during exercise in several ways. Altered upper GI motility could result in greater occurrence of reflux, regurgitation, nausea, and fullness (de Oliveira et al., 2014), particularly with vigorous exercise because of its delaying effect on gastric emptying (Horner et al., 2015). The implications of altered lower GI motility are less clear, but it's been speculated that small and large intestine dysmotility could elicit symptoms through bacterial fermentation of carbohydrates and osmotic shifts of fluids into the intestinal lumen (Costa et al., 2017b). Increases in migrating motor complexes induced by exercise may be partly responsible for the occurrence of loose stools and diarrhea during running (i.e., the "runner's trots") (Gil, Yazaki, & Evans, 1998). Likewise,

mechanical impact and jostling during running may result in damage to the intestinal lining, leading to lower GI symptoms (de Oliveira & Burini, 2009; de Oliveira et al., 2014; Rudzki et al., 1995).

These exercise-induced changes in gut function can be further worsened by factors such as the environment and nutritional intake. For example, exercising in hot and humid environments and while hypohydrated can exacerbate splanchnic hypoperfusion by increasing blood redistribution to the skin for thermoregulation (Kenefick et al., 2007). In a recent controlled experiment, the incidences of upper and lower GI symptoms during 2 hours of running in the heat (35°C) were 90% and 70%, respectively, versus only 40% and 30% when the same intensity of running was carried out in temperate conditions (22°C) (Snipe et al., 2018). In terms of dietary factors, consuming large amounts of fiber, fat, and solid protein can delay gastric emptying, while ingesting highly concentrated carbohydrate beverages also slows gastric emptying and could cause osmotically driven fluid shifts into the gut, increasing the risk of GI symptoms (de Oliveira et al., 2014). Further, dietary supplements such as sodium bicarbonate can elicit GI symptoms during exercise (Kahle et al., 2013). Beyond these factors, younger age, less experience, female gender, and the use of non-steroidal anti-inflammatory drugs (NSAIDs; e.g. Ibuprofen) have been associated with greater GI symptoms during exercise (de Oliveira et al., 2014; Peters et al., 1999; Wilson, 2018), which highlights the complexity of both predicting and preventing GI dysfunction in athletes.

One understudied area of research is that of psychological factors and their effects on GI dysfunction in athletes. There are several notable examples of athletes that have attributed GI symptoms to pre-event stress or anxiety. Soccer superstar Lionel Messi has had several incidences of vomiting before and during big matches which Argentinian manager, Alejandro

Sabella, attributed to anxiety (Associated Press, 2014). Additionally, mixed martial artist Donald “Cowboy” Cerrone reported in an interview that he vomits before every fight (Edgars, 2020). Some sports movies include a scene where athletes or coaches are vomiting due to nerves before monumental games. Given the common belief that pre-competition nerves and anxiety can elicit GI symptoms before or during exercise or sporting events, the relative paucity of research on the topic is somewhat surprising.

There does appear to be a strong biological basis for how acute and chronic psychological stressors could influence GI function. The brain and the GI system have an intricate bi-directional network of communication through several neural, endocrine, and immunological pathways, often referred to as the “brain-gut axis” (Mayer et al., 2015). There is considerable overlap between the pathways of the brain-gut axis and the stress response systems (Boeckxstaens et al., 2016; Vanner et al., 2016). Additionally, studies with animal models and humans suggest that psychological stressors and chronic stress or anxiety can influence GI function through delayed gastric emptying (Bhatia & Tandon, 2005; Enck & Holtmann, 1992; Rolan et al., 1990), alterations in colon motility (Almy et al., 1949; Ford et al., 1995; Holtman & Enck, 1991), compromised epithelial barrier integrity (Hyland et al., 2014; Söderholm et al., 2002), and ultimately increased visceral sensitivity (Larauche et al., 2012).

Indeed, the inter-connectedness of the brain and gut neuroendocrine pathways is now widely recognized as highly relevant in functional GI disorders such as irritable bowel syndrome (IBS) (Halpert & Drossman, 2005; Labanski et al., 2020). For example, chronic stress, anxiety, depressive symptoms, and early life trauma have all been identified as risk factors for IBS (Bennett et al., 1998; Labanski et al., 2020; Lampe et al., 2003; Moloney et al., 2016; Racine et al., 2012). Additionally, perceived stress is associated with symptom severity and exacerbation in

inflammatory bowel diseases (Langhorst et al., 2013; Levenstein et al., 2000). Several studies have also reported correlations between GI symptoms and levels of stress or anxiety in the general population (Haug et al., 2002; Stanghellini, 1999). Considering that endurance athletes are exposed to a combination of stressors related to training, competition, and daily life, it is reasonable to suggest that stress or anxiety may be a significant risk factor for GI symptoms during endurance sport training or competition as well (Wilson, 2020b). To date, there are only a handful of studies that have evaluated psychological factors of GI distress in endurance athletes. Early studies found that GI symptoms were common before competition when athletes were emotionally stressed (Worobetz & Gerrad, 1985), and that 24% of symptomatic triathletes believed anxiety contributed (Sullivan, 1987). More recently, Wilson (2018) found that levels of perceived anxiety and stress were correlated with incidence of meaningful upper and lower GI symptoms (severity of ≥ 3 out of 10) during running over the course of 30 days (Spearman rho = 0.18 – 0.36). Additionally, Wilson et al. (2021) observed that endurance athletes with higher levels of anxiety were more likely to experience certain types of GI symptoms during races, particularly in those with higher anxiety levels on the morning of the race. Finally, Wilson (2020a) found that measures of trait anxiety and sport competition anxiety were significantly correlated with GI discomfort during exercise races (rho = 0.22 – 0.33).

While these initial findings suggest that stress and anxiety may be risk factors for the development of GI symptoms during endurance exercise, much more research is needed. Specifically, more data is needed on how stress and anxiety interact with other risk factors such as nutritional intake (Wilson, 2020b). Endurance athletes are urged to consume exogenous carbohydrates and fluids before and during prolonged exercise (Thomas et al., 2016), but these recommendations are primarily based off laboratory-based studies rather than during competition

when anxiety and stress may be elevated. As a consequence, it is currently unknown whether competition anxiety will interact with nutritional intake to compound the risk of GI symptoms (Wilson, 2020b). Alternatively, athletes who regularly experience symptoms during competition may be forced to alter their nutritional strategies to avoid GI symptoms. Given the lack of data on the interaction between psychological and nutritional risk factors for GI problems, future studies should consider evaluating the interactions between psychological, perceptual, and nutritional measures before and during exercise. One such approach could be to evaluate the associations between athletes' competition anxiety, nutritional intake, and measures of perceived visceral or internal sensations (e.g., visceral sensitivity, body vigilance) to identify if these factors interact to increase the risk of GI distress. Additionally, it would be valuable to evaluate whether athletes with high levels of anxiety, visceral sensitivity, or body vigilance modify their nutrition intake to reduce their risk of GI symptoms.

There is also a need to identify the nature of the relationship between psychological factors and GI problems in athletes. Given that most data are currently observational, and that the brain-gut axis involves bi-directional communication, it is possible that GI symptoms cause increased levels of stress or anxiety rather than vice versa (Labinski et al., 2020; Wilson, 2020b). Indeed, several studies have suggested that a bi-directional association between GI symptoms and stress or anxiety exists in those with bowel disorders as well as the general population (Gracie et al., 2018; Koloski et al., 2012). Experimental studies would offer significant advantages over the current observational literature in determining how these variables are causally related. One specific experimental approach could involve exposing athletes to acute psychological stressors and assessing whether GI symptoms worsen during subsequent exercise. Similarly, the role of stress and anxiety on GI distress in athletes could be clarified through

studies that use stress- or anxiety-reducing interventions. Two of these potential interventions are slow deep breathing (Russo et al., 2017) and mindful breath counting (Gorman & Green, 2016; Shuai et al., 2020). Slow deep breathing has been found to increase heart rate variability (HRV; Tharion et al., 2013) and attenuate GI symptoms in individuals with functional GI disorders (Hjelland et al., 2007). Further, mindful breath counting has recently been demonstrated to reduce negative attentional effects from media multi-tasking (Gorman & Green, 2016) as well as recovery from alcohol-seeking due to stress in students (Shuai et al., 2020). Additionally, mindfulness training has attenuated GI symptoms in IBS patients (Gaylord et al., 2011). Thus, each of these strategies could be potentially effective and feasible interventions for endurance athletes who have elevated levels of stress or anxiety and who are prone to GI symptoms.

Statement of the Problem

GI dysfunction is common in endurance sport, particularly during more extreme events such as ultra-marathons or long-duration triathlons (Costa et al., 2017b; de Oliveira et al., 2014). While severity varies, GI symptoms can impair performance, make training unpleasant, and in more severe cases, have serious health consequences (Papaioannides et al., 1984; Stuempfle & Hoffman, 2015). As such, there is considerable interest in identifying the underlying mechanisms and factors that contribute to GI symptoms, as well as effective interventions to reduce their incidence and severity. The effects of endurance exercise on the GI system are thought to stem partly from the increased sympathetic drive and release of catecholamines into circulation, eliciting a series of changes in circulatory, neuroendocrine, and immunological functions that can affect gut function (Costa et al., 2017b; van Wijck et al., 2012). Additionally, mechanical factors such as the repetitive impact and gut jostling in runners, and the effects of posture in cyclists can

further exacerbate gut function and induce symptoms (de Oliveira et al., 2014; Rudzki et al., 1995; Waterman & Kapur, 2012). Many correlates and predictors of exercise-induced GI symptoms have been identified in observational studies as well. This includes exercise duration, exercise intensity, exercise modality, age, gender, training status or experience, environmental conditions, nutritional intake (e.g., fat, protein, fiber, highly concentrated carbohydrate beverages), and NSAIDs (de Oliveira et al., 2014; Peters et al., 1999; ter Steege et al., 2008). However, one area that is relatively understudied is the role of psychological factors on GI function in endurance sport.

The brain and gut have a complex functional relationship (termed the “brain-gut axis”) and communicate through several neuroendocrine and immunological pathways (Mayer et al., 2015). Several of these pathways overlap with those of stress response systems, suggesting that psychological stressors may result in alterations to gut function and vice versa (Boeckxstaens et al., 2016; Vanner et al., 2016). Indeed, stress, anxiety, and psychiatric conditions are considered risk factors for some functional GI disorders (e.g., IBS, inflammatory bowel disease) (Halpert & Drossman, 2005; Labanski et al., 2020), as well as the general population (Haug et al., 2002; Stanghellini, 1999). Additionally, experimental studies have suggested that acute psychological stressors can cause changes to the GI system including delayed gastric emptying, altered colon motility, and potentially impaired barrier function (Bhatia & Tandon, 2005; Holtman & Enck, 1991; Hyland et al., 2014). These effects could elicit symptoms independently or through increases in visceral sensitivity, as this appears to be an important factor for functional GI disorders (Labanski et al., 2020; Larauche et al., 2012). Given that athletes are exposed to a combination of physical and psychological stressors (Rice et al., 2019), it is reasonable to suggest that stress and anxiety (either acute or chronic) could be risk factors for GI symptoms

during exercise (Wilson, 2020b). Initial studies have supported this hypothesis (Sullivan, 1987; Wilson, 2018; Wilson, 2020a; Wilson et al., 2021), though there are still substantial gaps and limitations that should be addressed moving forward.

Given that many risk factors contribute to GI distress during exercise, it is important to identify how various factors interact. One relevant example could be related to how various psychological (e.g. competition anxiety, body vigilance, etc.) and nutritional (e.g. carbohydrate, fat, protein, fiber, etc.) factors interact and contribute to GI dysfunction. In addition to GI symptoms, it would be useful to evaluate if athletes modify their nutritional strategies based on their levels of anxiety or other factors such as visceral sensitivity and body vigilance.

Additionally, the nature of the association between psychological factors and GI function is not entirely clear. For example, studies in GI disorders and the general population have suggested a bi-directional relationship between psychological factors and GI symptoms (Gracie et al., 2018; Koloski et al., 2012). Experimental studies that induce stress before exercise may help determine the nature of the association. This may be further evaluated with stress- or anxiety-reducing interventions such as mindful breath counting or slow deep breathing (Gorman & Green, 2016; Russo et al., 2017; Shuai et al., 2020). Such studies would also help to identify simple and effective interventions that athletes could use to reduce their risk of GI symptoms.

Statement of Purpose

The purpose of this dissertation is to evaluate the role of psychological factors on the incidence, severity, and management of GI symptoms in trained runners. This will be accomplished through two studies; one survey-based observational study, and one experimental intervention study. The

observational study will involve prospective tracking of training runs, GI symptoms, and nutritional intake before and during runs for one week. Runners will then be asked to complete several psychological questionnaires to evaluate the associations between GI symptoms, nutritional intake, and psychological constructs such as perceived stress, anxiety, GI-specific anxiety, and body vigilance. The experimental study evaluated the effects of daily four-week breathing interventions on HRV, psychological measures (perceived stress, anxiety, GI-specific anxiety, body vigilance, mindfulness), and GI symptoms in runners who had at least mild anxiety and were prone to GI issues. To do so, runners were randomly assigned to one of three groups: 1) slow deep breathing with breath counting (SLOWBC), 2) normal breathing with breath counting (NORMALBC), or 3) a control group. Together, these studies advance our understanding of how psychological factors influence GI distress in trained runners.

Specific Aims

Specific Aim #1: To evaluate whether measures of anxiety, GI-specific anxiety, and body vigilance correlate with GI symptoms during exercise in trained runners.

Hypothesis: GI-specific anxiety, body vigilance, and anxiety have all been suggested to correlate with GI symptoms in IBS and other GI disorders; however, there is limited information available in endurance athletes. It was hypothesized that measures of stress, trait anxiety, GI-specific anxiety, and body vigilance would have positive correlations with GI symptoms during running.

Specific Aim #2: To assess whether levels of perceived stress, anxiety, GI-specific anxiety, and body vigilance are associated with nutrition intake before and during runs.

Hypothesis: Minimal evidence is available in athletic populations, but it has been suggested that individuals who are anxious and who are sensitive to visceral or bodily sensations may modify their nutrition to avoid GI distress. As such, it was hypothesized that athletes who scored high in anxiety, GI-specific anxiety, and body vigilance would consume lower quantities of nutrients and fluids before and during exercise.

Specific Aim #3: To determine whether GI symptoms experienced during runs mediates the relationship between psychological data (anxiety, GI-specific anxiety, body vigilance) and nutrient intake before and during runs.

Hypothesis: Anecdotally, runners report reducing their food and fluid intake when they are experiencing high anxiety and/or hypersensitivity to stressors in their environment. In theory, this would result in lowered nutrition intake (i.e., specific aim 2) in proximity to exercise. However, it's unclear if having GI symptoms during running is on the causal pathway of this proposed relationship. In other words, if anxiety, GI-specific anxiety, or body vigilance correlate with reduced peri-exercise nutrition intake, is it in part due to a higher rate of GI problems? It was hypothesized that GI symptoms would partly mediate the relationships between psychological measures (anxiety, GI-specific anxiety, body vigilance) and nutrient intakes before and during exercise.

Specific Aim #4: To determine the effects of four-week breathing interventions (SLOWBC, NORMALBC) on measures of HRV, perceived stress and anxiety, mindfulness, GI-specific anxiety, body vigilance, and GI symptoms in runners who have elevated levels of anxiety and who are prone to GI problems.

Hypothesis: Some research has suggested that slow deep breathing and mindful breath counting interventions can be effective for increasing HRV, reducing stress, promoting mindfulness, reducing visceral sensitivity, and improving symptom severity in functional GI disorders. Therefore, it was hypothesized that both four weeks of SLOWBC and NORMALBC would increase HRV and mindfulness, reduce measures of stress, anxiety, and body vigilance, and ultimately attenuate GI symptoms in runners who reported elevations in both anxiety and GI problems. However, given that the depth and frequency of breaths can influence cardiopulmonary responses (Russo et al., 2017), it was hypothesized that SLOWBC would have greater effects than NORMALBC on the outcomes.

Study Variables

For Aim #1, the independent variables were measures of perceived stress, trait anxiety, body vigilance, and GI-specific anxiety based on scores from four psychological questionnaires: 1) the perceived stress scale-14 (PSS-14; Cohen et al., 1983), the State-Trait Inventory for Cognitive and Somatic Anxiety-Trait (STICSA-Trait; Ree et al., 2008), the Body Vigilance Scale (BVS; Schmidt et al., 1997), and the Visceral Sensitivity Index (VSI; Labus et al., 2004). The dependent variables were the percentages of runs that they experienced a meaningful GI symptom (defined as subjective severity ≥ 3 out of 10) for upper and lower GI symptoms.

For Aim #2, the independent variables were perceived stress, trait anxiety, GI-specific anxiety, and body vigilance from the psychological questionnaires. The dependent variable were mean intake of total kilocalories, carbohydrates, fat, protein, fiber, caffeine, and fluid before and during runs during one week of training.

For Aim #3, significant associations from Aim #2 were planned to be further analyzed to determine if associations between psychological variables and nutrition intake before or during runs were mediated by GI symptoms. The percentage of runs that runners experienced a meaningful GI symptom was to be inputted as a mediator variable. The lack of significant negative associations resulted in these analyses being dropped from study 1.

For Aim #4, the independent variable was their treatment condition (SLOWBC vs. NORMALBC vs. control). The dependent variables were measures of HRV, psychological measures from questionnaires (perceived stress, anxiety, body vigilance, GI-specific anxiety, mindfulness), and percentage of runs that they experienced a meaningful GI symptom defined as severity ≥ 3 out of 10) for upper and lower GI symptoms over a one-week span. An average GI burden during runs score was also calculated by summing all GI ratings from each run together and averaging the sum scores across all runs.

Limitations

1. Both studies relied on self-report and subjective measures for many outcomes. While this is not the most valid method, it was necessary given the subjective nature of most outcomes (e.g., perceived stress or anxiety, GI-specific anxiety, body vigilance, GI symptoms) and the remote data collection.
2. Due to the remote data collection method for this dissertation, participants completed questionnaires and breathing interventions independently. To minimize problems that arose from this methodology, precise instructions were provided, and regular communication was used to prompt participants when needed. Further, participants were asked to log their breathing

intervention sessions in a provided journal, and weekly correspondence was used to check adherence, and to answer questions.

Delimitations

Participants were trained runners who run at least 15-20 miles per week of total volume. The questionnaires and other measures used are valid and have been used extensively in related literature. Additionally, the nature of questionnaires allows for remote data collection that will advance the field of GI distress in endurance athletes, even during a global pandemic that restricts the ability to conduct human subjects' research.

Chapter II

LITERATURE REVIEW

Introduction

The GI system consists of a series of organs spanning from the oral cavity to the rectum. In addition to several other key functions (e.g., host defense, environmental sensing), it has the vital role of digesting, absorbing, and assimilating nutrients and fluids at rest and during exercise. In endurance athletes, the high metabolic and thermoregulatory demands of training and competition often warrant the consumption of exogenous carbohydrates and fluids to sustain high workloads for long durations of time (Jeukendrup et al., 2011). A well-functioning GI system is a key component of success, while a compromised system can result in issues ranging from mild inconveniences to severe health consequences (Costa et al., 2017b; de Oliveira et al., 2014). As such, competitive endurance athletes must maintain a delicate balance between supplying the body with enough nutrients and fluids to perform optimally, while minimizing the risk of GI dysfunction (de Oliveira et al., 2014). This is particularly true in ultra-endurance events, where nausea and vomiting are relatively common, and are considered primary reasons for worsened performance and dropping out of races (Jeukendrup et al., 2000; Stuempfle & Hoffman, 2015).

A growing number of individuals are participating in endurance sporting events, including extreme variations such as ultra-marathons (Cejka et al., 2014; Knoth et al., 2012). Participating in such activities can have a multitude of health benefits, due to the many beneficial effects of physical activity on health and the GI system specifically (Warburton et al., 2006; Wolin et al., 2009). However, GI symptoms may lessen the enjoyment obtained from

participation in endurance sport, and in some cases result in medical consequences (Grames & Berry- Cabán, 2012; Papaioannides et al., 1984). As a result, there has been a long-standing interest in identifying the effects of exercise on GI function, the factors that affect prevalence and severity of GI symptoms during exercise, and potential interventions to prevent or alleviate symptoms that are common in endurance sport.

To date, most of the research has focused on the pathophysiology of GI dysfunction and the factors that correlate with symptom incidence and severity (Costa et al., 2017b; de Oliveira et al., 2014). Surprisingly, the role of psychological factors such as stress and anxiety has been relatively unexplored, despite a strong psychobiological plausibility (Wilson, 2020b). Stress and anxiety are considered important factors in functional GI disorders such as IBS (Labanski et al., 2020) and have been correlated with GI symptoms in the general population (Haug et al., 2002). Recent studies have suggested that stress and anxiety are associated with GI symptoms during endurance exercise or competition as well (Wilson, 2018; Wilson, 2020a; Wilson et al., 2021). Yet there is still much to be learned about the role of psychological factors on GI discomfort in endurance sport, and whether interventions can be implemented to prevent or alleviate anxiety-induced GI symptoms.

The purpose of this dissertation is to evaluate the role of psychological factors on GI discomfort in runners, which is an understudied area of research. Specifically, two studies (one observational, one experimental) will be used to 1) evaluate the associations between GI symptoms, psychological factors (stress, anxiety, body vigilance, GI-specific anxiety), and nutritional intake before and during running, and 2) assess the effects of SLOWBC and NORMALBC interventions on GI symptoms, as well as measures of HRV, stress, anxiety, GI-specific anxiety, body vigilance, and mindfulness.

This literature review provides a thorough overview of the research on GI discomfort in sport and how it may, in theory, be affected by stress and anxiety. The first section summarizes the effects of exercise on the GI system and its functional capacity. This is followed by a description of the pathophysiology and mechanisms that contribute to GI symptoms during exercise. Factors associated with symptoms are then briefly described, in addition to the current recommendations for endurance athletes who wish to avoid or alleviate GI symptoms during training and competition. The remainder of the literature review focuses on psychological factors and how they influence GI function and symptoms. This includes an overview of the research on the interaction between the central nervous system and GI system, as well as how acute and chronic psychological stressors can affect GI function in both individuals with functional GI disorders, such as IBS, and the general population. A discussion of the available research on the associations between psychological factors and GI symptoms in active or sporting populations is also covered, with specific attention given to the gaps and limitations that should be addressed in future studies.

Effects of Exercise on the GI System

Endurance exercise can cause numerous effects on the GI system and its function. The precise pathophysiology and underlying mechanisms of exercise-induced GI dysfunction require further elucidation, and the mechanisms likely differ between specific GI symptoms (e.g., nausea vs. bloating). However, in many cases GI disturbances during exercise are believed to stem from a complex interaction of circulatory, neuroendocrine, and mechanical mechanisms (Costa et al., 2017b; de Oliveira et al., 2014; ter Steege & Kolkman, 2012), as well as potentially exacerbating factors such as nutritional choices, environmental conditions (heat, altitude, etc.), and the use of

GI-provoking medications (Wilson, 2019). Costa et al. (2017b) recently suggested that two major pathways are responsible for triggering many of the common GI symptoms experienced during exercise: 1) a circulatory-GI pathway stemming from redistribution of blood during exercise, and 2) a neuroendocrine-GI pathway where increased sympathetic drive can alter GI function. These pathways, as well as several mechanical factors, and their effects on GI function are discussed below.

Circulatory-GI Pathway

The gut is perfused by an arterial network consisting of three main routes: the celiac trunk, superior mesenteric artery, and inferior mesenteric artery (Mensink et al., 2001). Each of these main arteries branch into dense vascular plexuses (serosal, submucosal, and mucosal), with the mucosal plexus directing blood into the capillary beds that perfuse the intestinal mucosa. After gas and nutrient exchange with the gut tissues, the blood drains into the superior and inferior mesenteric veins, which merge to form the portal vein. An interesting aspect of the small intestine is the relatively large distance between the arterial blood supply and the epithelial villi (Blikslager, 2008). As such, there is a countercurrent mechanism place that facilitates oxygen diffusion to the epithelium via a steep oxygen gradient (Blikslager et al., 2007; Blikslager, 2008). At the onset of exercise, the sympathetic branch of the autonomic nervous system becomes highly active (Borresen & Lambert, 2008; Joyner & Casey, 2015). Efferent sympathetic fibers are stimulated and catecholamines are released, resulting in a plethora of physiologic effects (e.g. increased heart rate and cardiac output) to accommodate for the increased metabolic demands of the skeletal muscles and heart. The increased cardiac output is accompanied by blood redistribution towards the active musculature to further facilitate nutrient and oxygen

transportation to metabolically active tissues. Some blood is also directed towards the skin to aid in thermoregulation, particularly as body temperature increases or in cases of hypohydration (Kenefick et al., 2007). Ultimately, this results in decreased blood supply to the gut (ter Steege & Kolkman, 2012).

The most pronounced decline in splanchnic blood flow occurs within the first 10 minutes of exercise, which can increase to as much as an 80% decline after an hour of vigorous activity (Rehrer et al., 2001; van Wijck et al., 2011). The magnitude of the hypoperfusion appears to also increase in parallel with exercise intensity (ter Steege & Kolkman, 2012). Several additional factors moderate the magnitude of exercise-induced splanchnic hypoperfusion, including age, training experience, and hydration status. One study matched older and younger athletes by their maximal oxygen consumption (VO_{2max}) and found that older athletes had a less pronounced decline in splanchnic perfusion during exercise (Kenney & Ho, 1995). This could, in part, help explain the lower prevalence of GI symptoms in older individuals reported in some studies (Keefe et al., 1984; Peters et al., 1999; ter Steege et al., 2008), but it could also be related to confounding factors such as total muscle mass or average training intensity. An early study also found that splanchnic hypoperfusion was related to an individual's relative workload, which could indicate that training status moderates the blood distribution to the gut during exercise (Clausen, 1977), though this needs to be confirmed in additional studies. Finally, greater body temperature and dehydration result in greater amounts of blood distributed to the skin for thermoregulation (Kenefick et al., 2007). Regardless of what causes it, splanchnic hypoperfusion during and after exercise can result in gut ischemia (van Wijck et al., 2012a).

The enterocytes of the intestinal epithelium exist in a constant state of mild hypoxia, relying on the countercurrent exchange mechanism for adequate diffusion of oxygen from the

arterial blood to the adjacent villi (Blikslager et al. 2007; Blikslager, 2008). This makes them particularly susceptible to ischemic events. Gut ischemia can increase hypoxia at the tip of the villus, ultimately causing epithelial sloughing and damage (Blikslager et al., 2007; van Wijck et al., 2012a). Gut ischemia appears to affect a variety of intestinal cells, particularly those that form, support, and regulate the epithelial barrier (Costa et al., 2017b; van Wijck et al., 2012a). Damage to intestinal cells can stimulate gene expression of NF- κ B within the epithelium, which then signals the release of pro-inflammatory cytokines (e.g. interleukin-1 β , tumor necrosis factor- α , interferon- γ) (Irving et al., 2014; Kaparakis-Liaskos & Ferrero, 2015). This inflammatory cascade can exacerbate damage and dysfunction to the epithelial barrier (Capaldo & Nusrat, 2009).

A compromised intestinal barrier, which results from physical damage to the enterocytes as well as the proteins that support and regulate barrier tight-junctions, can lead to increased GI permeability (Costa et al., 2017b; Dokladny et al., 2016). When the integrity of the intestinal barrier is compromised, there is substantial translocation of intestinal bacteria into circulation (van Wijck et al., 2012a). This further stimulates NF- κ B expression within the vasculature, facilitating the progression of local and even systemic inflammatory responses (Irving et al., 2014; Kaparakis-Liaskos & Ferrero, 2015; Kulp & Kuehn, 2010). The localized and systemic inflammatory responses can exacerbate damage to the intestinal epithelial barrier, creating a cycle of dysfunction that may ultimately result in endotoxemia, systemic inflammation, and possibly GI symptom provocation (Capaldo & Nusrat, 2009; Costa et al., 2017b; Zuhl et al., 2014), though there is uncertainty as to whether endotoxemia plays an actual causative role in provoking GI symptoms.

Beyond damage to the epithelial barrier, gut ischemia can also affect specialized cells such as Paneth cells that respond to bacterial threats and secrete antimicrobial proteins to prevent and combat bacterial translocation (Ayabe et al., 2000; Vaishnava et al., 2008). Furthermore, the reduced oxygen and nutrient supply to the intestinal smooth muscle could inhibit GI motility (Costa et al., 2017b). Thus, there are clear pathways through which gut ischemia could elicit several detrimental effects on GI function.

While more research is needed, there is evidence that endurance exercise can cause intestinal damage, increase GI permeability, and in some cases, induce endotoxemia (Costa et al., 2017b; de Oliveira et al., 2014). There is no single measure that is considered the gold standard for measuring GI barrier damage and intestinal permeability. Common approaches include measuring blood levels of intestinal fatty acid binding protein (I-FABP) and lipopolysaccharides as well as carrying out sugar probe tests, which evaluate the levels of non-metabolizable sugars in the blood or urine after ingestion. Since I-FABP is primarily an intracellular protein found in intestinal mucosal cells, increasing levels of it in the blood is often used as a marker of intestinal epithelial cell damage. Indeed, prolonged exercise commonly increases the secretion of I-FABP into the blood (Costa et al., 2016; Lis et al., 2015; van Wijck et al., 2011). Although elevations of I-FABP are thought to reflect GI barrier damage, they do not measure GI permeability per se. Instead, the appearance of lipopolysaccharides (i.e., endotoxins) and poorly absorbed sugars (e.g., lactulose) in the blood are better indicators of dysfunction in gut barrier function. Studies using these direct measures have demonstrated that prolonged exercise at high intensities (~70% VO_2max or more) can increase small intestine permeability, which may be exacerbated by high body temperatures and dehydration (Buchman et al., 1999; Lambert et al., 2008; Pals et al., 1997; Yeh et al., 2013). It is less clear whether exercise causes similar effects in gastric or large

intestine permeability, as there are currently limited studies with mixed results (Lambert et al., 2008; Pals et al., 1997; van Wijck et al., 2011). Extreme endurance exercise can increase GI permeability to the point of endotoxemia, characterized by a ≥ 5 pg/mL increase in plasma or serum lipopolysaccharide and an accompanying decrease in endotoxin antibody concentration (Bosenberg et al., 1988; Camus et al., 1997; Camus et al., 1998; Jeukendrup et al., 2000; Stuempfle et al., 2016). However, this is not a universal finding, even in ultra-endurance races, as studies from one ultra-marathon event (Western States 100-mile Endurance Run) did not find evidence of endotoxemia, despite there being a systemic inflammatory response (Nieman et al., 2006; Stuempfle et al., 2016).

It seems likely that exercise duration and intensity, as well as the environmental conditions, all affect the incidence and severity of changes to GI function. The largest observations of intestinal damage and GI permeability have been in studies where participants perform vigorous endurance exercise for long durations (e.g. Lis et al., 2015; van Wijck et al., 2011) and particularly in hot ambient temperatures ($\geq 30^{\circ}$ C) (Lambert et al., 2008; Morrison et al., 2014). Similarly, endotoxemia has primarily been observed after more extreme endurance events, such as ultra-marathons or long-duration triathlons (Gill et al., 2015a; Gill et al., 2015b; Jeukendrup et al., 2000; Stuempfle et al., 2016). Alternatively, current research suggests that endotoxemia is unlikely to occur during more moderate-duration exercise (≤ 2 hours), unless it involves very high-intensity bouts, is performed with substantial heat stress or dehydration (Costa et al., 2017b), or an individual consumes non-steroidal anti-inflammatory drugs (van Wijck et al., 2012b).

Considering that exercise-induced endotoxemia can persist for 1-7 days after cessation of exercise (Gill et al., 2015a; Gill et al., 2015b; Jeukendrup et al., 2000; Stuempfle et al., 2016),

there is a need for more research on its effects during multi-stage endurance events (e.g. Tour de France). It is possible that consecutive days of prolonged endurance exercise could lead to cumulative effects on GI permeability and endotoxemia, and thus increase the risk and severity of GI symptoms or other complications like exertional heat illnesses (Lambert, 2008).

Additionally, while gut ischemia may affect specialized intestinal cells (e.g., Paneth cells), this has not been evaluated in the context of exercise-induced ischemia. Further research is needed to fully elucidate the effects of different exercise protocols on intestinal damage, gut permeability, endotoxemia, and inflammatory responses. There also needs to be further attempts to link changes in gut function (e.g. increased GI permeability, intestinal damage, endotoxemia) with GI symptoms experienced during exercise. Currently, some studies in which endotoxemia or systemic inflammation was observed reported concurrent elevations in the incidence/severity of GI symptoms (e.g. nausea, regurgitation), but there has been some inconsistency in the literature (Brock-Utne et al., 1988; Gill et al., 2015a; Gill et al., 2015b; Jeukendrup et al., 2000; Moore et al., 1995; Stuempfle et al., 2015).

While more data would help clarify the role of circulatory factors on GI function and symptoms, determination of a direct causal relationship will be challenging. Exercise induces an array of physiological and neuroendocrine changes that occur simultaneously and that may contribute to altered GI function and symptoms. Further, it is difficult to experimentally manipulate isolated factors, such as splanchnic hypoperfusion, in a manner that is ethical and sufficient to determine causality. So while current evidence suggests a contributing role of splanchnic hypoperfusion in the development of GI symptoms, the methodological and ethical limitations involved make it challenging to identify causality in humans. There will continue to be reliance on observational and animal model studies for the foreseeable future.

Neuroendocrine-GI Pathway

The enteric nervous system is an intricate neural network that regulates GI function independently from central nervous system input (Furness, 2012). While the enteric nervous system can act independently, it also receives and responds to input from the autonomic nervous system and other neuroendocrine modulators. For example, parasympathetic activity tends to promote GI motility and secretion of acids and hormones (e.g. gastrin), while sympathetic activity primarily inhibits GI functions (Browning & Travagli, 2011). As such, the strong sympathetic drive at the onset of exercise can alter GI function in several ways, including inhibition of gastric motility and impaired nutrient absorption (Costa et al., 2017b). This concept is supported by animal models, where reduced sympathetic activity after spinal injuries was associated with enhancement of gastric emptying and GI motility (Camilleri et al., 1986; Costa et al., 2017b; Song et al., 2014).

Considering the complex interaction of neural, endocrine, and circulatory factors that regulate GI motility and absorption (Browning & Travagli, 2011), more research in this area is clearly needed. However, Costa et al. (2017b) proposed a preliminary pathway through which the neuroendocrine responses to exercise may influence GI motility and absorptive capacity. Specifically, the increased sympathetic drive and release of stress hormones at the onset of exercise could alter enteric nervous system activity. This may in turn inhibit GI motility or transit, leading to delayed gastric emptying, reduced nutrient transporter capacity, and ultimately nutrient malabsorption. This retention of unabsorbed nutrients in the intestinal lumen could further impair gastric motility through neuroendocrine-mediated feedback mechanisms such as the “ileal brake,” which acts to control the rate of nutrient movement through the GI tract to maximize absorption (Layer et al., 1990; Shin et al., 2013). Finally, there is likely a degree of

interaction between circulatory and neuroendocrine pathways, as gut ischemia could impair nutrient absorption by damaging epithelial tissue, while reduced oxygen and nutrient transport can alter GI motility (Costa et al., 2017b).

There are several potential pathways through which altered GI motility and absorption could provoke various GI symptoms during exercise. In the small and large intestines, unabsorbed carbohydrate leads to gas production from bacterial fermentation, osmotic shifts of fluids into the intestinal lumen, and luminal distension (Putkonen et al., 2013; Yao et al., 2016). In the stomach and esophagus, decreased motility could contribute to regurgitation/reflux, fullness, and nausea (de Oliveira et al., 2014). Additionally, exercise could directly induce nausea through activation of the vomiting center in the medulla oblongata via increased catecholamine concentration as part of the sympathetic response to exercise (Becker, 2010; Joyner & Casey, 2015; Wilson, 2019). Taken together, there is a compelling rationale for how exercise could provoke GI symptoms through alterations in the complex network of neuroendocrine pathways that regulate gut function (Browning & Travagli, 2011; Costa et al., 2017b).

Indeed, research has demonstrated that vigorous exercise (e.g. intermittent exercise or steady-state at $\geq 70\%$ max power or $VO_2\text{max}$) impairs gastric motility, delays gastric emptying, and alters oro-caecal transit time (Costa et al., 2017b; de Oliveira et al., 2014). Alternatively, moderate intensities (60-70% $VO_2\text{max}$ or peak power) have had negligible effects in several studies (Leiper et al., 2001; van Nieuwenhoven, 1999; van Nieuwenhoven et al., 2004), while light exercise may stimulate motility (Costa et al., 2017b; Leiper et al., 2001). Most of the alterations in motility have been demonstrated within the stomach and small intestine, and the literature focusing on the colon is largely mixed, likely due to methodological differences in

terms of the exercise protocols and measurement techniques used (Cheskin et al., 1992; Rao et al., 1998).

While the research is currently mixed and inconclusive, nutrient absorption may also be affected during intense exercise. For example, using measurements of urinary excretion of non-metabolizable glucose analogues (e.g. D-xylose, 3-O-Methyl-D glucose), Lang et al. (2006) found that one hour of running at 70% VO_2max reduced passive and active carbohydrate absorption compared to resting conditions and lower exercise intensities (30% and 50% VO_2max). Another study found that resistance exercise increased I-FABP concentrations and reduced protein absorption during the post-exercise recovery period (van Wijck et al., 2013). While this finding needs to be replicated with endurance protocols and absorption of other nutrients or fluids, it supports the idea that intense exercise may influence nutrient absorption. However, it is still not entirely clear to what extent intense exercise alters nutrient or fluid absorption and how this relates to exercise-induced GI symptoms (de Oliveira et al., 2014).

Mechanical Factors

While the circulatory and neuroendocrine effects of exercise are considered primary mechanisms through which GI discomfort is provoked, several other factors may contribute to GI functional changes and exacerbate symptoms. One such factor is the mechanical stress of exercise on the GI system. The repetitive impact of prolonged running has been hypothesized to cause greater damage to the lining of the intestines compared to other exercise modalities (Rudzki et al., 1995). Indeed, the combination of the mechanical impact and gut ischemia are thought to cause GI bleeding that has been observed in some studies with endurance athletes (Costa et al., 2017b; de

Oliveira & Burini, 2009; Moses, 1990). In one study, acceleration output from an actometer positioned at the abdomen was approximately double in magnitude when six subjects ran in comparison to when they cycled at similar relative intensities (Rehrer & Meijer, 1991). Although running is often associated with higher rates of GI symptoms than other exercise modalities, this isn't always true and to some extent depends on the symptom being assessed. For example, the hunched over posture during cycling may contribute to high rates of upper GI symptoms via increased abdominal pressure (Costa et al., 2017b). As another example, an experimental study found that weightlifting elicited more reflux-related symptoms than did running and cycling in experienced athletes (Collings et al., 2003).

Summary of the Effects of Exercise on the GI System

Exercise can affect the GI system in numerous ways, which has been described under a few distinct but interacting pathways (Costa et al., 2017b; de Oliveira et al., 2014). The first is a circulatory-GI pathway, where the redistribution of blood flow to the active muscles and skin can result in splanchnic hypoperfusion and gut ischemia. The ischemia can cause injury to the cells that form, support, and regulate the epithelial barrier, which in turn increases small intestine permeability. The compromised barrier integrity allows for intestinal bacteria translocation into circulation, triggering localized inflammatory responses and the accumulation of endotoxins. Inflammation and endotoxemia can further exacerbate the integrity of the epithelial barrier, creating a vicious cycle that can result in endotoxemia and systemic inflammation. Additionally, the reduced oxygen and nutrient transport to intestinal smooth muscle could inhibit motility.

Costa et al. (2017b) also described a neuroendocrine-GI pathway, where strong sympathetic drive and release of stress hormones affects enteric nervous system activity. This in turn inhibits GI motility and nutrient transit in the GI tract. Delayed gastric emptying and transit may provoke a variety of GI symptoms but could also further affect GI function through reduced nutrient transporter activity, and consequently, carbohydrate absorption. This nutrient malabsorption may also be influenced by epithelial injury and inhibited motility that occurs as part of the circulatory-GI pathway, which may then cycle back to further inhibit GI motility through negative feedback mechanisms (e.g. the “ileal brake”). In addition to the physiological effects of exercise, mechanical impact and gut jostling during running could potentially damage the intestinal lining and worsen certain GI symptoms.

It is important to note that these proposed mechanisms are an attempt to conceptualize pathways that are complex, multi-faceted, and that require further elucidation. Realistically, the effects of exercise on GI function involves a complicated interaction between numerous neuroendocrine, circulatory, mechanical, and immunological factors, as well as choices an athlete makes regarding fueling, hydration, and other factors. Additionally, the underlying mechanisms likely differ by individual symptoms. For example, modified upper GI motility could contribute to symptoms such as reflux, regurgitation, nausea, and fullness (de Oliveira et al., 2014), while intestinal dysmotility has been suggested to contribute to symptoms such as abdominal cramping, gas, and flatulence through bacterial fermentation of nutrients and osmotic shifts of fluids into the lumen (Costa et al., 2017b). Additionally, nausea and vomiting are elicited through activation of the vomiting center within the medulla oblongata, which has many triggers including increased concentrations of circulating catecholamines (Becker, 2010; Joyner

& Casey, 2015; Wilson, 2019). Finally, exercise can induce migrating motor complexes within the GI system that may contribute to loose stools and diarrhea during running (Gil et al., 1998).

Future research should continue to determine the precise effects of various exercise protocols on the GI system, and how these effects contribute to the prevalence and severity of GI symptoms in endurance athletes. Additionally, research should discuss these mechanisms in relation to specific GI symptoms, as they likely have different underlying causes and differential functional effects in terms of GI discomfort (de Oliveira et al., 2014; Jeukendrup et al., 2000).

Prevalence of GI Symptoms in Sport and Exercise

GI symptoms are relatively common in endurance sports (e.g., running, cycling, triathlons), though the prevalence estimates vary substantially between studies depending on the study methodology, athlete population, characteristics of the race or exercise protocol, and other factors such as nutritional intake and environmental conditions (Costa et al., 2017b; de Oliveira et al., 2014). Rates also depend on how GI symptoms are defined, and whether researchers evaluate individual symptoms or categorize them by location. For example, symptoms are often categorized as upper or lower GI symptoms (de Oliveira et al., 2014; ter Steege & Kolkman, 2012). Symptoms such as reflux, regurgitation, heartburn, belching, stomach fullness, vomiting, and nausea are typically categorized as upper GI symptoms, while flatulence, diarrhea, rectal bleeding, abdominal cramps, and urge to defecate are considered lower GI symptoms (Brouns & Beckers, 1993; Moses, 1990; Peters et al., 1999; Simons & Kennedy, 2004; Wilson, 2017). Indeed, the heterogenous approaches in the literature make it difficult to directly compare or

aggregate results across studies. However, it does appear that GI symptoms are a relatively common occurrence, particularly as the duration and intensity of exercise increase.

For example, Pfeiffer et al. (2012) evaluated the prevalence of serious GI symptoms (defined as severity > 4 out of 10) between different endurance athletes during races, including professional cyclists, amateur cyclists, city marathon participants, and triathletes that completed either full-length or half-length Ironman events. They found relatively low incidences of serious GI symptoms in the marathon participants (4%) and both cycling groups (professionals: 7%; amateurs: 4%). However, 14% of the half-Ironman participants, and 31-32% of full-length Ironman participants experienced a severe symptom. Similarly, one study of 707 marathoners found that reports of nausea were much more common during hard training runs than easy ones (12% vs 1.8%; Keeffe et al., 1984). Additionally, prevalences can vary significantly across studies, even in comparable events. For example, only 7% of 227 runners who completed a recreational marathon reported a GI symptom in one study (ter Steege et al., 2008). However, another study found relatively high rates of lower GI symptoms in male (69%) and female (74%) distance runners that completed a marathon (Peters et al., 1999).

One consistent finding is that GI symptoms are common, and at times quite severe, in athletes who complete ultra-endurance running races. For example, during 161-km ultra-marathon events, studies have reported that as few as 60% (Stuempfle et al., 2013) and as many as 96% of participants experience GI symptoms (Stuempfle & Hoffman, 2015). Costa et al. (2016) reported that 73% of athletes who completed a 24-hour continuous run, and 85% that completed a multi-stage ultra-marathon, experienced at least one meaningful GI symptom (defined as ≥ 50 out of 100 on a visual analog scale). Jeukendrup et al. (2000) observed that 93% of athletes who completed a particularly challenging Ironman-length triathlon (hot temperatures,

3600 m of altitude change during the cycle, and running on unpaved roads) experienced some form of GI symptoms. Severe symptoms were also relatively common. For example, 21% of participants experienced nausea that was at least 5 out of 10. Similarly, a study at the Western States 100-mile Endurance Run found that 96% of participants experienced a symptom of some form, and 60.3% experienced nausea, particularly during the hottest portion of the event (Stuempfle & Hoffman, 2015). Notably, nearly half (43.9%) of race finishers believed GI symptoms impacted their performance, while 35.6% of non-finishers stated GI symptoms as a reason for dropping out of the race. Similarly, participants in two different 161-km ultra-marathons reported nausea or vomiting to be the most common reason that non-finishers dropped out of the race (23.0%), while 36.8% of finishers thought those symptoms impaired their performance (Hoffman & Fogard, 2011).

Most studies have reported GI symptoms during an individual race or training session. However recent studies have also prospectively quantified symptoms over time (Wilson, 2017; Wilson, 2018). Wilson (2017) found that over the course of 30 days, male and female runners experienced at least one GI symptom during 84% and 78.3% of training runs, respectively. While less common, moderate-to-severe GI symptoms (≥ 5 on a 0-10 scale) were still fairly prevalent (13.8% and 21.7% of runs for men and women, respectively). Wilson (2018) set the threshold for a significant GI symptom at a severity of at least a 3 out of 10, which was experienced, on average, during 45.6% of runs over a 30-day period across 150 runners. Thus, while meaningful symptoms may not occur during every bout of exercise, a sizable number of athletes will experience at least one meaningful symptom over the course of several weeks of training.

Another consideration is the incidence of GI symptoms after exercise, yet there is currently limited data available. One study found that 11% of recreational runners experienced symptoms after a race, with nausea (5%), shivering (5%), and diarrhea (5%) being the most common (ter Steege et al., 2008). Peters et al. (1999) reported that anywhere from 29-58% of athletes experienced upper GI symptoms and 39-60% experienced lower GI symptoms two hours after exercise, depending on gender and the type of athlete (e.g. distance runners, cyclists, triathletes).

Methodological Considerations

The heterogenous approaches taken across studies has made direct comparison of GI symptom incidence and severity a challenge. While some heterogeneity is to be expected depending on the athlete population or specific event of interest, there are methodological considerations that would improve the ability to interpret and compare findings moving forward. Symptoms are often either compiled together or categorized as upper and lower GI symptoms. Additionally, there are inconsistencies in what constitutes a severe or non-severe symptom. This makes interpretation and comparison across studies difficult. For example, symptoms such as flatulence or fullness may only be a mild inconvenience, while more severe cases of those same symptoms could be detrimental to athlete comfort or performance (de Oliveira et al., 2014). Similarly, certain symptoms like nausea, vomiting, and abdominal cramps are more likely to be an issue whenever they occur. It is important that authors carefully consider how they will classify GI symptoms and their severity in future studies (de Oliveira et al., 2014; Jeukendrup et al., 2000). Many studies have asked participants to retrospectively recall symptoms during runs that occurred months ago (Pfeiffer et al., 2012; ten Haaf et al., 2014; Rehrer et al., 1992). This may

be problematic considering that subjective recall of painful or uncomfortable experiences can change over time (Ariely, 1998; Kahneman et al., 1993; Redelmeier & Kahneman, 1996). Additionally, responses to retrospective questionnaires can be influenced by factors such as the wording, ordering, and format of questions, including how variables are operationally defined (Schwartz & Oyserman, 2001). There should be attempts to collect data within a short timeframe after runs or races, and to use validated questionnaires with standardized terminology and definitions to allow for improved interpretation and comparison between studies in the future.

As mentioned previously, most studies have collected data from single time-points such as during laboratory visits or from individual training sessions and events (de Oliveira et al., 2014). GI symptoms likely vary day-to-day and the severity of a symptom could fluctuate over time. There is also the possibility that damage to the GI system could accumulate over the course of consecutive days of training or competition, such as during an intense training block or during a multi-stage endurance event. If that is the case, single time-point data collections may not accurately reflect GI symptomology during times when risk is the highest (Wilson, 2017). For example, Wilson (2017; 2018) recently evidenced that runners experienced at least one moderate-severe GI symptom (≥ 3 out of 10) on 13.8-45.6% of runs over the course of 30 days. Additionally, endotoxemia induced by prolonged exercise has been shown to persist for 1-7 days after exercise cessation (Gill et al., 2015a; Gill et al., 2015b; Jeukendrup et al., 2000; Stuempfle et al., 2016). Given these findings, it is important that the cumulative effect of multiple exercise bouts and the progression of GI symptoms over time be assessed in future studies.

Correlates and Predictors of GI Symptoms

The effects of exercise on the GI system can vary substantially between studies and within individuals. For example, exercise-induced splanchnic hypoperfusion can range from small changes in blood redistribution to substantial gut ischemia, while GI symptoms can range from mild irritations to serious health complications (Costa et al., 2017b; van Wijck et al., 2012a). As such, research has attempted to identify factors that correlate or predict the prevalence and severity of GI symptoms during endurance exercise. While a thorough discussion of the many factors and their association with GI symptoms is outside the scope of this dissertation, a short summary of previous findings is provided in this section. Readers interested in a more thorough discussion are directed to recent reviews on the topic (e.g. Costa et al., 2017b; de Oliveira et al., 2014; ter Steege & Kolkman, 2012). Several specific factors related to the individual athlete (e.g. genetics, age, gender), exercise modality (running vs. cycling), nutritional factors, and several others are addressed. Each individual factor does not completely explain the heterogeneity in GI symptomology, but an unfavorable combination of factors could increase risk of GI discomfort (ter Steege & Kolkman, 2012; van Wijck et al., 2012a).

A factor that consistently correlates with higher incidence of GI symptoms is a previous history of GI discomfort at rest (Peters et al., 1999; Wilson, 2016) and during exercise (Pfeiffer et al., 2009; Pfeiffer et al., 2012; ter Steege et al., 2008). As a result, authors have suggested that some athletes are either genetically or anatomically predisposed to issues (de Oliveira et al., 2014; Pfeiffer et al., 2009). Indeed, one study found that the degree of intestinal damage during gut ischemia is moderated by the Mannose-binding lectin 2 (MBL2) gene (Matthijsen et al., 2009). Specifically, individuals with the MBL2 null allele appear to experience less epithelial damage in response to gut ischemia and reperfusion, which could theoretically protect them from

GI symptoms during exercise, though this has not yet been directly evaluated. Women also tend to be more prone to GI symptoms than men, though it may depend on exercise modality and the specific symptom (Costa et al., 2017b; Keefe et al., 1984; Koistinen et al., 1991; Peters et al., 1999; ter Steege et al., 2008). Additionally, younger athletes tend to be more prone to GI symptoms than their older counterparts (Keefe et al., 1984; Peters et al., 1999; ter Steege et al., 2008; Wilson, 2018), though others have found no effect of age (Gil et al., 1998; Halvorsen et al., 1990; Koistinen et al., 1991). Along similar lines, more experienced athletes sometimes report less severe GI symptoms (Riddoch & Trinick, 1988; Wilson, 2018), though this association is confounded by age.

As mentioned above, older athletes often report fewer GI problems during exercise, but the underlying mechanisms to explain this are not entirely clear. For example, older adults could be less prone to GI disturbances due to being less sensitive to vascular changes induced by catecholamine release (Lakatta et al., 1987). Indeed, one study found that older athletes had less pronounced splanchnic hypoperfusion than younger athletes matched for $VO_2\max$, though this effect could be a product of differences in muscle mass (Kenney & Ho, 1995). Alternatively, younger athletes could be more likely to push themselves to greater intensities for longer durations, even at the expense of GI symptoms. As referenced previously, it might be partly due to differences in training experience, in that older athletes tend to be more experienced and thus better able to regulate exercise intensity and nutritional intake in a way that minimizes GI symptoms.

With respect to exercise modality, runners tend to experience greater prevalence and severity of symptoms compared to cyclists (Pfeiffer et al., 2012; ter Steege & Kolkman, 2012; van Nieuwenhoven et al., 2004), though in some studies cyclists were at a higher risk of upper GI

symptoms such as reflux or regurgitation (Peters et al., 1999; ter Steege et al., 2008). These differences are likely due to the mechanical factors addressed earlier, as the repetitive jostling, high impact, and induction of migrating motor complexes during running could contribute to greater damage to the intestinal lining and the development of some symptoms (Gil et al., 1998; Rudzki et al., 1995). Theoretically, cyclists may experience upper GI symptoms due to their posture on the bike (Waterman & Kapur, 2012).

The environmental conditions and hydration status of the athlete are also highly relevant to the risk of GI symptoms. The incidence of symptoms and the severity of damage to the GI system is generally greater in hot ambient temperatures ($\geq 30^{\circ}\text{C}$), when athletes have elevated body temperatures ($\geq 39^{\circ}\text{C}$), and when they are hypohydrated (Costa et al., 2016; Costa et al., 2017b). This is likely due to increased blood redistribution to the skin to aid in thermoregulation, resulting in greater splanchnic hypoperfusion (Kenefick et al., 2007; van Wijck et al., 2012a). Additionally, hypohydration could result in elevated secretion of arginine vasopressin during exercise (Hew-Butler, 2010; Montain et al., 1997), a hormone that has been demonstrated to elicit nausea when directly administered to humans (Caras et al., 1997; Kim et al., 1997). While only relevant to some endurance athletes or during specific events, altitude exposure could also result in altitude sickness, with nausea being a primary symptom (Barry & Pollard, 2003).

Endurance sport requires substantial energetic demands to maximize performance and push the body to its physical limits (Jeukendrup et al., 2011). While large intakes of nutrients and fluids may be necessary to sustain high-intensity exercise for prolonged periods, there is also a delicate balance whereas too much consumption may exacerbate GI symptoms and potentially impair performance (de Oliveira et al., 2014). Previous research has found significant correlations between GI symptoms and many nutritional factors. This has included highly

concentrated carbohydrate beverages (Rehrer et al., 1992; van Nieuwenhoven et al., 2005), fiber (Peters et al., 1999; Rehrer et al., 1992), pre-exercise protein, fat, carbohydrate and energy intakes (Peters et al., 1999; Rehrer et al., 1992; Wilson, 2016), and overconsumption of fluid (Rollo et al., 2012). While there are some differences between factors, many of these components are thought to contribute to symptoms through delayed gastric emptying, activation of stretch and mechanoreceptors within the GI tract, and/or osmotic shifts of fluids into the intestines (Gentilcore et al., 2006; Karhunen et al., 2008; Khan et al., 1993; Ma et al., 2009). Given that hypohydration is also a risk factor for symptoms (de Oliveira et al., 2014; Neuffer et al., 1989), consuming the proper quantity of fluids can be a challenge for athletes that have high sweat rates and/or compete and train in hot and humid environments. Athletes should experiment with their fluid consumption strategies in similar conditions as they will be competing and should consider assessing their sweat rates when exercising in similar conditions to estimate fluid needs. While not feasible for all athletes, they should also attempt to acclimate to the environment in which they will be training and competing to reduce the thermoregulatory demands on the body (Périard et al., 2015).

Additionally, aggressive carbohydrate intakes during exercise (e.g. >50-60 g/hour) can increase the risk of symptoms due to saturation of intestinal nutrient transporters, causing the carbohydrates to sit unabsorbed in the gut lumen (Jeukendrup et al., 2010; Wilson, 2015). If athletes are going to consume such large quantities of carbohydrate during exercise, they may limit their risk of symptoms by consuming combinations of glucose and fructose since they are absorbed with different intestinal transporters (O'Brien & Rowlands, 2011; Wilson, 2015; Wilson & Ingraham, 2015). Consuming a combination of carbohydrate types will avoid full

saturation of each transporter (which occurs at ~40-50 g/hour; Jeukendrup et al., 2010) and minimize malabsorption of carbohydrate.

Athletes using aggressive in-race nutritional strategies may also benefit from “training the gut” to tolerate higher quantities of carbohydrate (Costa et al., 2017a; Jeukendrup, 2017). While data in humans is still limited, there are several studies that have suggested supplementing the diet with higher-than-normal carbohydrate doses can increase gastric emptying during subsequent carbohydrate test feeds (Cunningham et al., 1991; Horowitz et al., 1996; Yau et al., 2014). This is thought to occur through nutrient-specific adaptations (Cunningham et al., 1991; Horowitz et al., 1996) and/or attenuated feedback inhibition in response to distension of the lumen (Horowitz et al., 1996). Indeed, animal studies have suggested that digestive enzymes and carbohydrate transporters are responsive to carbohydrate intake and presence in the GI tract (Deren et al., 1967; Dyer et al., 2009; Ferraris et al., 1992), though more research is needed to determine the extent to which these changes occur in humans. Regardless, it is generally recommended that athletes practice with the specific nutritional strategy that they will be using in competition (de Oliveira et al., 2014).

In addition to carbohydrate quantity or type, there is emerging research on the effects of fermentable oligo- di- and monosaccharides and polyols (i.e. FODMAPs) in athletes (Lis, 2019). FODMAPs are short-chain carbohydrates that are not efficiently digested in some individuals, particularly when GI function is impaired such as during vigorous exercise (Lis, 2019). Undigested and absorbed FODMAPs present a similar issue as full saturation of carbohydrate transporters, as the excess will be left sitting in the gut lumen, leading to gas production via fermentation, distention of the lumen, and induction of osmotic fluid shifts into the intestines (Putkonen et al., 2013; Yao et al., 2016). Initial studies have suggested a benefit of a low-

FODMAP diet in some athletes, either chronically, or as a temporary approach prior to competition (Gaskell et al., 2019; Lis et al., 2018; Lis, 2019). The efficacy of this approach likely depends on the individual athlete and whether they experience symptoms from FODMAP-rich food sources.

Several dietary supplements that are commonly used by endurance athletes elicit GI symptoms in some cases, including caffeine and acid-buffering solutions (e.g. sodium bicarbonate and sodium citrate). Caffeine is one of the most studied and commonly used ergogenic aids and has been demonstrated to improve endurance exercise performance at the meta-analytic level (e.g. Shen et al., 2019; Southward et al., 2018). However, it can also have side effects, including nausea, when the dose is relatively high (e.g. 500 mg; Kaplan et al., 1997). This is likely due to elevated catecholamine concentrations, which could exacerbate changes in GI function that occur during exercise (Robertson et al., 1978) or by activating the vomit center within the medulla oblongata (Becker, 2010). Similar findings have been reported with caffeinated pre-workout formulations as well (Vogel et al., 2015). Sodium bicarbonate is another well-studied and effective dietary supplement which acts as an acid-buffer during high-intensity exercise (McNaughton et al., 2008). However, it can also induce moderate-to-severe GI symptoms, which in some cases causes participants to stop exercise (Freis et al., 2017; Kahle et al., 2013). While sodium citrate is thought to be a less risky alternative to sodium bicarbonate, high rates of nausea have been reported in some studies (e.g. Urwin et al., 2016).

A final factor to consider is the use of non-steroidal anti-inflammatory drugs (NSAIDs). Athletes commonly use NSAIDs to reduce or prevent pain or discomfort (Gorski et al., 2011). However, NSAID use has been reported to increase risk of upper GI symptoms and other

complications such as GI bleeding and intestinal damage (Bjarnason & Takeuchi, 2009; Gabriel et al., 1991; Robertson et al., 1987; van Wijck et al., 2012b).

Summary of Factors and Recommendations for Athletes

The research up until this point has identified many factors that are associated with exercise-induced GI symptoms. Exercise that is higher in intensity and longer in duration tends to result in the highest incidence and severity of GI symptoms, particularly when performed in a hot and humid environment. Runners typically experience more symptoms than cyclists, though cyclists sometimes experience high rates of upper GI symptoms specifically. Women tend to be more prone to symptoms compared to men, though this depends on the symptom. Additionally, younger athletes report symptoms more often than their older counterparts. It is not currently clear whether this is due to physiological differences (e.g. differences in blood flow regulation), because younger athletes may push the intensity to the point of increased susceptibility to gut dysfunction, if older athletes are more experienced and better able to manage their workload to minimize risk, or some combination of these explanations. Indeed, fitter and more experienced athletes have generally been shown to be less prone to GI problems.

Several nutritional components have been implicated as risk factors as well. This includes ingesting large amounts of carbohydrate (>50-60 g/hour), highly concentrated carbohydrate drinks, FODMAPs, fiber, fats, protein, and fluid (≥ 1000 mL/h). Several popular dietary supplements including caffeine and sodium bicarbonate may also elicit symptoms in certain cases or when taken in high doses. Finally, NSAIDs and other analgesics can trigger gut dysfunction and provoke GI symptoms during exercise.

Based on these findings, a variety of recommendations have been developed for athletes. From a nutrition perspective, athletes should avoid consuming large quantities of fats, proteins, and fibers in the hour or two leading up to the start of heavy exercise. If they will be consuming large quantities of carbohydrates (≥ 50 -60 g/h) during exercise, then they should consume a combination of glucose and fructose to avoid fully saturating intestinal transporters. Athletes should attempt to replace fluid losses from sweat while avoiding excessive fluid consumption. This balance may require experimenting to determine their individual sweat rates, becoming acclimated to the environment they will train or compete in, and practicing their hydration strategies under similar conditions when feasible. Athletes may also wish to “train their gut” by occasionally supplementing the diet with higher than normal quantities of fluids or nutrients, as this may increase intestinal transporter capacity or improve tolerance of the higher intakes within the GI tract. They should avoid high-dose NSAID ingestion, particularly immediately before, during, and after intense or prolonged exercise. Ultimately, due to the many factors involved and the individual differences in GI discomfort and responses, each athlete should experiment with pre-race and race-day strategies to determine what is effective and what may place them at a higher risk.

Given the wide array of symptoms that athletes experience and the many factors that can contribute to such symptoms, it's perhaps unsurprising that GI discomfort remains a common problem among athletes despite hundreds of studies on the topic to date. Moreover, observational studies consistently find that any single variable typically only correlates modestly with the severity of GI symptoms during endurance competition (e.g., Pfeiffer et al., 2012; Wilson, 2016; Wilson, 2018), which re-enforces the notion that the origins of these problems are complex, multi-faceted, and, to some extent, unresolved.

Psychological Factors: A Missing Piece of the Puzzle

While a substantial amount of research has focused on the pathophysiology of exercise-induced GI discomfort and the factors that contribute to it, surprisingly little has considered psychological factors such as stress or anxiety. Within sport, psychological factors have been recognized as being important not only for performance (Brown & Fletcher, 2017) but also in relation to the risks of illness (Gleeson, 2016) and injury (Ardern et al., 2016; Yadava & Awasthi, 2016). There is also a strong psychobiological basis for how psychological factors can influence GI symptoms in athletes (Wilson, 2020b), while research in both clinical and general populations have suggested that stress and anxiety contribute to the severity of GI symptoms (Haug et al., 2002; Labanski et al., 2020).

The following sections introduce the concept of the brain-gut axis, which is a functional relationship between the central nervous system and the GI system (Mayer et al., 2015). From there, the effects of acute and chronic psychological stressors on GI function are discussed, followed by an overview of proposed mechanisms for how stress and anxiety may influence exercise-induced GI discomfort. These sections are followed by a review of the available literature on psychological factors and GI symptoms in active or athletic populations, with particular focus on some of the many potential future research directions.

Stress and Anxiety Overview

Many different descriptions of stress have been conceptualized over the years. Walter Cannon developed a “fight or flight” response concept based on his early contributions to uncovering the physiology of catecholamine secretion and the stress response systems (McCarty, 2016).

Specifically, he discussed the functional relationship between the sympathetic nervous system and the adrenal medulla, with epinephrine serving as the primary messenger to facilitate a response to emotion or some form of stimuli. Around the same time, Hans Selye developed the “General Adaptation Syndrome” concept, which is considered a primary launching point for increased study and understanding of stress and its effects on human health and physiology (Jackson et al., 2014; Selye, 1936). Selye’s General Adaptation Syndrome describes a triphasic response to generalized stressors. This includes an alarm phase, whereas resources are mobilized for a response, a resistance phase where the organism attempts to cope with the stressor, and then finally a stage of exhaustion if the stressor continues and resources are depleted. While our understanding of stress has evolved substantially since these early descriptions, the work by Cannon and Selye are still considered foundational to how the human body can cope and adapt to various stressors.

Stress is typically defined as either specific or non-specific responses to stimuli that threaten a person’s homeostasis and challenge their coping abilities, while anxiety is referred to as feelings of distress, worry, or manifestations of tension that occur due to the anticipation of future danger or events (American Psychiatric Association, 2013; Chrousos, 2000). Stress and anxiety tend to accompany each other (e.g. Fan et al., 2015; Kurebayashi et al., 2012), but it is important to delineate between the two, which has often not been the case in research on psychological factors and GI function. In a review of the literature, Wilson (2020) recently used the term acute psychological stress to describe transient changes in gut function in response to a stressor, while anxiety was used when measures were anxiety specific. To remain consistent with recent articles in this area, these delineations are used in the remainder of the dissertation.

The Brain-Gut Axis

The enteric system of the gut can act intrinsically, but it also receives and responds to input from the central and autonomic nervous systems (Browning & Travagli, 2011). Indeed, the GI system and brain have an intricate bi-directional connection known as the “brain-gut axis” (Mayer et al., 2015; Molina-Torres et al., 2019). Communication occurs through several neural, endocrine, and immunological pathways (Bercik & Collins, 2014; Mayer et al., 2015). Specifically, the vagus nerve of the autonomic nervous system communicates with the enteric nervous system to help regulate various effector cells within the GI system, including the smooth muscle and secretory cells that regulate functions such as GI motility (Browning & Travagli, 2011). Similarly, sympathetic stimulation can affect the GI system through the release and circulation of catecholamines. Bi-directional communication is allowed through a dense network of visceral afferent nerves that respond to stimuli and relay signals to the central nervous system. Another important connection between the brain and gut is the HPA axis and its neuroendocrine mediators, such as cortisol (Boeckxstaens et al., 2016).

The pathways that connect the brain-gut axis overlap with those of central and peripheral stress systems (Boeckxstaens et al., 2016; Vanner et al., 2016). Stress or anxiety could potentially modulate gut function through several pathways, including increased sympathetic activity and/or dampened vagus nerve stimulation, HPA-axis stimulation, and release of glucocorticoids such as cortisol. One hormone that is especially important in mediating the GI changes with stress is corticotropin-releasing hormone (CRH), which influences GI function through both central and peripheral actions (Boeckxstaens et al., 2016; Taché & Bonanz, 2007). The following sections focus on the research that has evaluated the effects of psychological

stressors on gut function, as well as the association between chronic stress or anxiety and GI symptoms.

Acute Psychological Stressors and GI Function

The role of psychological factors on GI function was reported as early as 1833, when William Beaumont observed an association between gastric secretions, gastric mucosal color, and emotional states such as fear, anger or "...whatever depresses or disturbs the nervous system" in a patient with a permanent fistula in the stomach (Beaumont & Osler, 1996). The role of the vagus nerve on gastric secretion was also implicated as early as 1902, when Pavlov reported that cephalic phase (e.g. central nervous system-mediated) gastric secretion was mediated by vagal activity (Pavlov, 1902). Throughout the 20th century, animal models were evaluated to determine the effects of various psychological stressors, such as cold-restraint, acoustic stress, neonatal maternal separation, and water avoidance, on GI function (Barone et al., 1990; Coutinho et al., 2002; Enck et al., 1989; Gue et al., 1987). While some models' applicability to humans was questioned, the findings from early animal studies were instrumental in identifying the effects of psychological factors on the human GI system, and for sparking the interest in other relevant topics such as the effects of stress on visceral pain and sensitivity (Elsenbruch & Enck, 2017).

Similar studies have since been conducted with human participants using non-invasive psychologic stressors such as the Trier Social Stress Test (Kirschbaum et al., 1993), auditory stressors (Dickhaus et al., 2003), listening to sad music (Coen et al., 2009), performing demanding neurocognitive tasks (Posserud et al., 2004), or viewing emotional images or movies (Fournier et al., 2018; Phillips et al., 2003). Taken together, the available research supplies

evidence that acute psychological stress can affect several aspects of GI function, including GI motility (gastric and colonic) and GI permeability.

GI Motility

Cannon's early work on "fight or flight" responses included several studies on the association between psychological factors and gastric activity (Cannon, 1916; Cannon & de la Paz, 1911). He manipulated the temperament of cats by either restraining them, or placing a barking dog nearby, and evaluated the effects on gastric motility and smooth muscle activity. In one study, gastric motility was reduced in cats that became agitated from being restrained, while those that remained calm had negligible change (Cannon, 1916). Another study found that the presence of a barking dog resulted in relaxation of the intestinal smooth muscle, indicative of altered gastric motility (Cannon & de la Paz, 1911).

Since that time, numerous studies have also found that various acute psychological stressors can inhibit gastric motility in both animal models (Enck & Holtmann, 1992; Taché, 1989) and humans (Roland et al., 1990; Simpson & Stakes, 1987). Inhibition of gastric motility due to psychological stress is relevant to endurance athletes, considering that delayed gastric emptying has been suggested as a cause of GI symptoms both during exercise (Costa et al., 2017b; de Oliveira et al., 2014) and at rest (Khayyam et al., 2010; Sarnelli et al., 2003). Acute psychological stress has also been found to inhibit small intestine motility in some studies with both rodents (Wang & Wu, 2005) and humans (Kellow et al., 1992). Though others have found that the small intestine is less responsive to psychological stressors than other parts of the GI tract (Stam et al., 1995).

Similarly, colonic motility appears to be responsive to psychological stressors. Early studies demonstrated that discussing emotional topics stimulated large intestine motility (Almy et al., 1949), which was replicated in studies that used various other psychological stressors (Bhatia & Tandon, 2005; Ford et al., 1995; Holtmann & Enck, 1991; Rao et al., 1998; Welgan et al., 1988). For example, Rao et al. (1998) found that a dichotomous listening task resulted in increased propagating contractions and colonic motility in 12 healthy subjects. Similar results have been demonstrated in response to mental arithmetic, fear stressors, and mirror tracing tasks in IBS patients (Fukudo & Suzuki, 1987; Welgan et al., 1988). More indirect evidence of alterations comes from animal studies, where exposure to a new environment caused increased defecation frequency in rats (Candland et al., 1967; Hall, 1934) and similar responses in other animals (e.g. Rushen et al., 2001). There are conflicting findings regarding the effects of altered colon motility on GI symptoms. For example, it was originally assumed that hypermotility resulted in diarrhea or loose stools, while hypomotility elicited constipation; however, this has not always been the case (Chey et al., 2001; Parks et al., 1973; Wilson, 2020b). The differences may be due to differences in methodology including where measurements are taken and the specific type of motor activity that was evaluated (Wilson, 2020b).

Epithelial Damage, GI Permeability, and Inflammation

Some non-exercise studies in rats and humans have demonstrated that psychological stressors can damage intestinal epithelial cells, increase GI permeability, and elicit intestinal inflammation (Farhadi et al., 2005; Meddings & Swain, 2000; Saunders et al., 2002; Söderholm et al., 2002; Vanuytsel et al., 2014; Yoshikawa et al., 2017). These effects have been attributed to several potential mechanisms, but a common explanation is that the secretion of CRH and the

subsequent activation of mucosa mast cells triggers an inflammatory cascade and increased uptake of antigens into the mucosa wall (Overman et al., 2012; Taché & Perdue, 2004; Wallon & Söderholm, 2009). Interestingly, Vanuysel et al. (2014) found that psychological stress increased intestinal permeability in response to public speaking but not anticipation of an electrical shock. They also found that the effects on permeability were only evident in participants who had significant increases in cortisol concentrations. As a result, they suggested that the effects of stress on GI permeability were due to coordinated activation of the autonomic nervous system and HPA axis.

Taken together, acute psychological stress appears to alter several aspects of GI function including gastric motility and intestinal permeability. There is also some evidence of altered motility within the small and large intestine, though the results are still somewhat mixed. While there is limited data on how these effects apply to an exercise setting, they do provide a psychobiological mechanism through which acute psychological stress could either elicit or exacerbate GI symptoms during exercise.

Chronic Psychological Stressors and the GI System

Current evidence clearly suggests that acute physiological stress can affect the GI system. However, the role of chronic stress or anxiety is equally as important to identify. While acute stress has relatively transient effects that are meant to prepare the body to respond to a potential threat, chronic stress can result in maladaptive changes to an individual's psychophysiology, with potentially impactful health ramifications (Elsenbruch & Enck, 2017; Schneiderman et al., 2005). This applies to GI health and function as well, as the brain-gut axis is now widely

recognized as an important factor in GI disorders such as IBS and inflammatory bowel diseases (Bonaz & Bernstein, 2013; Halpert & Drossman, 2005; Labanski et al., 2020). Chronic stress, early life trauma, and anxiety have all been identified as risk factors for IBS (Bennett et al., 1998; Labanski et al., 2020; Lampe et al., 2003; Moloney et al., 2016; Racine et al., 2012), while perceived stress is associated with the severity and progression of symptoms in inflammatory bowel diseases (Langhorst et al., 2013). Indeed, functional GI disorders often have a high comorbidity with affective disorders (Tanaka et al., 2011; Van Oudenhove et al., 2016), and depression has been suggested to elicit or promote the onset of IBS (Moloney et al., 2016). This appears to extend beyond GI disorders, as several studies have demonstrated that stress and anxiety are associated with GI symptoms in the general population or otherwise healthy people (Haug et al., 2002; Stanghellini, 1999; Suarez et al., 2002).

While there is observational evidence linking chronic stress and anxiety with GI symptoms or disorders, the specific nature of the association has not yet been completely elucidated. Given that the brain-gut axis has bi-directional communication through various pathways, there is the possibility of reverse causation (e.g. GI dysfunction causes chronic stress and anxiety), or a bi-directional association (Labanski et al., 2020). In fact, GI-specific anxiety (anxiety stemming from GI sensations) has been proposed to be an important factor in IBS symptom severity (Jerndal et al., 2010). Notably, the improved IBS outcomes that result from psychological treatments may be mediated by reductions in GI-specific anxiety or GI-specific cognitions (Windgassen et al., 2017). There is also evidence of a bi-directional association between GI symptoms and stress or anxiety in both GI disorder patients and the general population (Gracie et al., 2018; Koloski et al., 2012).

Several mechanisms have been proposed to explain how chronic stress or anxiety may influence GI symptoms. First, it is possible that chronic stress and anxiety affect GI function in a similar way as acute psychological stress, namely by altering GI motility, increasing GI permeability and damage, and promoting intestinal inflammation (Labanski et al., 2020; Molina-Torres et al., 2019). However, several studies have demonstrated that the effects of acute stress on GI function diminish within a few days of exposure (Ochi et al., 2008; Zheng et al., 2009). Unfortunately, there is little-to-no data available in humans, making it difficult to ascertain whether repeated acute stressors and their effects accumulate. It is also challenging to generalize findings of impaired GI function in patients with IBS or inflammatory bowel diseases to other populations, as it is unclear whether the cause of GI dysfunction was due to stress or another pathophysiological factor. There is, however, strong evidence that chronic stress and anxiety can alter sensitization to GI pain or sensations, resulting in increased GI symptom incidence or severity (Greenwood-Van Meerveld & Johnson, 2018). Ultimately, this may result in visceral hypersensitivity, and as such, increased GI symptomology.

Visceral sensitivity refers to the perception of sensations or stimuli within the gut and visceral organs, such as distension or pressure (Delvaux, 2002). Hypersensitivity to these sensations and stimuli is considered a common feature of functional GI disorders such as IBS (Keszthelyi et al., 2012). This can be characterized by hyperalgesia (enhanced pain response to a stimuli) and allodynia (pain from a stimulus that is not usually perceived as painful) in some IBS patients (Greenwood-Van Meerveld & Johnson, 2018). Notably, visceral sensitivity appears to be responsive to life stress to some degree. For example, animal studies have demonstrated that early life adversity or stress (Chaloner & Greenwood-Van Meerveld, 2013; Hyland et al., 2015; Pohl et al., 2017) and neonatal maternal separation (Coutinho et al., 2002) can alter visceral

sensitivity or perception of visceral sensations. The precise pathways through which visceral hypersensitivity develops is still up for debate, but it is at least partly a result of sensitization of visceral afferent nerves and altered activity in brain regions that process visceral sensations and pain (Laurache et al., 2012).

Physiological Mechanisms: How Psychological Stressors May Influence GI Function

There is a functional relationship between the brain and gut, and both acute and chronic stress and anxiety can influence various aspects of gut function, including altered GI motility, increased GI permeability, and development of visceral hypersensitivity (Labanski et al., 2020).

While the precise mechanisms have not yet been completely elucidated, there is evidence that CRH plays a primary role. CRH contributes to the stress response alongside its associated peptides, urocortin 1, urocortin 2, and urocortin 3 (Takahashi, 2001; Tsigos & Chrousos, 2002). CRH typically has a pulsatile secretion pattern with predictable rises during early morning (Takahasi, 2001), but there is a large surge in secretion during times of stress which is thought to elicit a variety of effects on the GI system (Taché & Bonanz, 2007; Takahasi, 2001).

Additionally, stress may influence GI function through alterations in the sympathomedullary axis, increasing sympathetic activity and release of catecholamines into circulation (Ulrich-Lai & Herman, 2009). These two pathways are briefly described below, including how they contribute to GI discomfort.

The HPA axis and sympathomedullary axis are the two primary pathways through which the body responds to stress (Moloney et al., 2016). The HPA axis is stimulated by acute psychological stress, which initiates a cascade of responses (Smith & Vale, 2006). The first step

is the release of CRH from the hypothalamus, which travels to the anterior pituitary gland and binds to its receptor (CRH₁), triggering the secretion of adrenocorticotrophic hormone (ACTH) into the blood stream. ACTH then binds to the adrenal cortex, causing production and release of cortisol and other glucocorticoids. Cortisol acts on many tissues, but relevant to psychological stress, it stimulates the release of CRH from the amygdala which further facilitates the stress response (Schulkin et al., 1998). The large increase in CRH concentration during acute stress causes numerous metabolic and neurophysiological effects, including altered GI functions such as decreased gastric motility and acid secretion and increased colonic motility and transit (Taché & Bonanz, 2007; Taché et al., 2001). The exact mechanisms through which CRH alters GI function are not entirely clear but could include induction of mucosal mast cells and subsequent epithelial damage and inflammation (Baldwin, 2006), and by altering autonomic nervous system outflow to the GI system by actions at the paraventricular nucleus of the hypothalamus and the dorsal vagal complex nuclei (Taché & Bonanz, 2007). These effects appear to operate independently of the HPA axis cascade, as removal of the pituitary and adrenal glands in rats did not affect CRH's gastric effects (Lenz et al., 1988; Taché & Bonanz, 2007).

The fast-acting sympathomedullary axis is responsible for the “fight or flight” response to acute stressors (Ulrich-Lai & Herman, 2009). It is initiated by activation of preganglionic sympathetic neurons within the intermediolateral cell column of the thoracolumbar spinal cord. Stimulation of the adrenal medulla through pre- and paravertebral ganglia results in the release of catecholamines into circulation and many physiological responses associated with sympathetic drive (e.g. increased heart rate, vasoconstriction of splanchnic vasculature, etc.) (Joyner & Casey, 2015; ter Steege & Kolkman, 2012). Acute or chronic stress and anxiety could exacerbate splanchnic hypoperfusion and gut ischemia during exercise by elevating sympathetic activity

and/or dampening vagal activity. Indeed, some studies have suggested that acute psychological stress or emotional states can reduce GI blood flow (Kuipers et al., 2008; Wolf, 1981), though results have also been somewhat inconsistent (Gelman & Mushlin, 2004; Hayashi et al., 2009). The mixed results could be due to the use of mild stressors in most experimental human studies. Severe stressors (e.g. parachuting) can increase norepinephrine concentrations to levels twice that of mental arithmetic or other mild-moderate stressors (Jern et al., 1991; Morgan et al., 2001). Thus, while there is a strong biological plausibility for how increased sympathetic activity could alter splanchnic blood, more research is needed. Finally, like CRH, increased catecholamine release has been suggested to contribute to intestinal epithelial damage and inflammation through mast cell induction (Baldwin, 2006).

While these mechanisms provide a clear rationale for how acute stress or anxiety could influence GI function, it is also important to discuss the effects of chronic exposures to stressors. Allostasis is a term used to conceptualize the typical stress response, whereas the body reacts by activating the sympathetic nervous system and HPA axis, followed by a period of recovery (Cool & Zappetti, 2019). Specifically, a healthy stress response involves a strong, transient activation of the stress systems and release of neuroendocrine mediators such as catecholamines and cortisol, which then return towards baseline after a period of recovery. Alternatively, allostatic load refers to “wear and tear” that occurs when an individual experiences repeated stressors or chronic exposure to stress with inefficient allostasis and recovery (Cool & Zappetti, 2019; McEwen, 2007). McEwen (2007) described several manners through which allostatic load can develop and eventually cause dysfunction to various body systems. An individual may be exposed to “repeated hits” of acute stressors, where they have inadequate time to optimally recover and adapt in-between. Additionally, some individuals are not only exposed to repeated

stressors but also have an impaired ability to adapt so that each hit causes more dysfunction and less ability to respond and cope. Similarly, some individuals develop a dysfunctional stress response system where the body is unable to produce a robust physiological response to a stressor. Finally, prolonged exposure to a stressor without opportunities for adequate recovery can also contribute to allostatic load. In summary, allostatic load and the resulting dysfunction is primarily due to either 1) inadequate recovery and/or adaptation to stressors, or 2) an inadequate stress response (Cool & Zappetti, 2019; McEwen, 2007).

The precise pathways through which chronic stressors and allostatic load contribute to GI disorders and symptoms is not entirely clear, but functional GI disorders tend to have a high comorbidity with chronic stress, anxiety, and affective disorders (Labanski et al., 2020). Additionally, chronic stress or anxiety is associated with altered GI function and sensitization to visceral stimuli (Greenwood-Van Meerveld & Johnson, 2018; Larauche et al., 2012; Moloney et al., 2016). A series of rodent studies suggested that CRH signaling was heavily involved in altered GI function in response to chronic stress exposure. For example, exposing rodents to water avoidance stress for 7-10 days can increase visceral sensitivity (Bradesi et al., 2005; Hong et al., 2009; Myers et al., 2012). Further, such water avoidance stressors increase CRH expression within the central nucleus of the hypothalamus, and knock down of CRH from this location inhibits stress-induced visceral sensitivity (Johnson et al., 2015). Taken together, these findings suggest that CRH is heavily involved in the development of visceral sensitivity from chronic stress exposure.

Some authors have suggested that cortisol release may also contribute to the effects of psychological stress on alterations to GI function, likely by triggering further release of CRH from the amygdala during periods of stress, amplifying the stress response (Ulrich-Lai &

Herman, 2009). For instance, chronic exposure to various stressors has increased plasma corticosterone (the animal equivalent of cortisol) in animal models (Bradesi et al., 2005; Myers et al., 2012). While the stress was acute in nature, one study in humans found that acute public speaking resulted in increased GI permeability through a mast-cell dependent mechanism; however, this effect was only significant in those with elevated concentrations of cortisol (Vanuytsel et al., 2014). Finally, there is some evidence of altered amygdala activity in IBS patients (Tillisch et al., 2011). Thus, cortisol could facilitate the effects of CRH by stimulating the amygdala and subsequently increasing CRH concentrations. CRH can then affect GI function through numerous central and peripheral effects, but particularly by altering autonomic outflow to the GI tract (Taché & Bonanz, 2007).

Indeed, modulation of vagal tone has been suggested to be a factor in chronic effects of stress or anxiety on GI function (Labanski et al., 2020). For example, Farmer et al. (2013) provided evidence for “pain clusters” that may explain some of the inter-individual differences in visceral and somatic pain responses. Specifically, one cluster was characterized by higher trait anxiety and neuroticism, baseline sympathetic nervous system activity, and HPA axis tone. These participants also exhibited lower pain thresholds and less habituation to visceral and somatic pain. Several additional studies have revealed that modulating vagal tone can reduce pain sensitivity and increase gastroduodenal motility in response to both somatic and visceral pain (Botha et al., 2015; Frøkjaer et al., 2016). This is further supported by studies finding that deep breathing, which dampens sympathetic activity (Jerath et al., 2006), can positively influence GI symptoms during motion-sickness and in those with functional dyspepsia (Hjelland et al., 2007; Jokerst et al., 1999). Finally, recent evidence has suggested that chronic stress could modify the gut microbiota, which is heavily involved in brain-gut axis activities (Grochowska et

al., 2018; Martin et al., 2018). However, much more research is needed to clarify the effect of stress on the gut microbiome and how this influences GI function and symptoms.

In summary, the effects of stress and anxiety on the GI system are complex and reliant on various neural, endocrine, and immunological pathways (Labanski et al., 2020). However, there are a few primary mechanisms through which psychological factors likely influence GI function and symptoms. Acute elevations in stress or anxiety can increase GI permeability and inflammation through activation of the HPA axis and sympathomedullary axis, which in turn stimulate the release of CRH and catecholamines. This can cause an array of effects, including activation of mast cells, which contributes to epithelial damage and changes to GI motility, potentially through input to the enteric nervous system (Browning & Travagli, 2011). The increased sympathetic activity and catecholamine concentrations could also exacerbate splanchnic hypoperfusion and ischemia by altering blood flow away from the splanchnic vasculature, (Joyner & Casey, 2015; ter Steege & Kolkman, 2012), though this requires further study.

The effects of chronic exposure to stress or anxiety are less understood but may be related to the development of visceral hypersensitivity through increased sensitization of visceral afferents and altered activity of brain regions that process pain perception or regulate stress responses (Larauche et al., 2012). These effects have been suggested to stem primarily from increased activity of CRH and the HPA axis, as well as increased sympathetic activity and concomitant dampening of vagal tone (Greenwood-Van Meerveld & Johnson, 2018; Labanski et al., 2020; Moloney et al., 2016).

Little of this aforementioned research has been conducted in sporting contexts, despite the fact that athletes are exposed to a variety of psychological stressors that could affect the GI

system both acutely (e.g. competition anxiety) and chronically through allostatic load. For example, in addition to daily life stressors, athletes must balance rigorous training demands, the stress of competition or injury recovery, and the expectations placed on them by others or themselves (Rice et al., 2019). These sources of stress and anxiety increase their risk of GI symptoms both during exercise and at rest. Thus, the following section reviews the research on the associations between psychological factors and GI symptoms in athletic or physically active populations.

Research in Active or Athletic Populations

Despite the voluminous literature on the gut-brain axis, and research suggesting a role of stress and anxiety in clinical demonstration of GI symptoms, only a few studies have examined the impact of stress and anxiety on GI symptoms in active or athlete populations. An early study by Worobetz and Gerrard (1985) asked 70 endurance athletes to complete a questionnaire about GI symptoms they experience during exercise. Over half (51.4%) reported GI symptoms immediately before competition, when there tends to be competition stress or anxiety. Another study had 110 triathletes complete a survey about GI symptoms during training and competition (Sullivan, 1987). About a quarter (24%) of the athletes who experienced symptoms such as urgent bowel movements, fecal incontinence, and abdominal cramps believed they were more likely when anxious about competition performance. Additionally, while the exact numbers were not clearly reported, the triathletes believed nausea or vomiting and bowel dysfunction to be the GI symptoms most affected by anxiety in terms of incidence and severity. This was followed up by a survey-based study of 109 distance runners, which found that 43% reported “nervous diarrhea” before competition (Sullivan & Wong, 1992). While these early studies identified a

potential relationship between psychological factors and GI symptoms during exercise, they were primarily descriptive designs which included no statistical analysis of associations between the factors or whether psychological factors differed between symptomatic and asymptomatic athletes.

Not much additional research on the topic was conducted until 2013, when Li et al. (2013) assessed the effects of intense combat training on GI symptoms and function. In this study, 39 male soldiers completed a six-week medical response force combat-training course, which included physically and psychologically demanding tasks such as combat simulations and medical evacuations in restrictive gear and hot temperatures. The course was also a stark transition from a period of low stress classroom instruction. They reported GI symptoms and completed several questionnaires, including the Hospital Anxiety and Depression scale and the Perceived Stress Scale (PSS)-10. Blood and urine samples were also collected to assess biomarkers of GI function, stress response (e.g. cortisol and CRH), and inflammation. None of the soldiers reported GI symptoms before training, but 70% reported significant symptoms during training, including abnormal bowel habits (e.g. constipation, diarrhea) and abdominal pain or discomfort. Notably, intestinal permeability, inflammatory markers, stress, anxiety, and depressive symptoms all increased during training as well, and the severity of symptoms was correlated with stress ($r = 0.41$) and depressive symptoms ($r = 0.41$). While this study provides evidence of an association between psychological factors and GI symptoms in healthy, active populations, it is challenging to determine what portion of the changes in GI symptoms and permeability were due to the physical versus psychological aspects of the combat-training.

Three recent studies have evaluated associations between GI symptoms with psychological factors in endurance athletes over the course of 30 days of training (Wilson, 2018)

and during competitive endurance races (Wilson, 2020a; Wilson et al., 2021). Wilson (2018) recruited 150 distance runners to prospectively record the severity of six GI symptoms from each of their runs for a 30-day period on a 0-10 scale. The symptoms were categorized as upper GI (nausea, regurgitation/reflux, stomach fullness) or lower GI (abdominal cramps, flatulence, urge to defecate) symptoms. Considering some GI symptoms are very mild and unlikely to impact performance (Jeukendrup et al., 2000), symptoms were considered meaningful if they were rated as at least a 3 out of 10. At the end of the 30-day period, the runners completed the PSS-14 and the Beck Anxiety Inventory, and the sum scores were correlated with the percentage of runs that included a meaningful upper and lower GI symptom. Perceived stress and anxiety scores had modest, but significant, positive correlations with both upper and lower GI symptoms (Spearman's $\rho = 0.18$ to 0.36), which remained similar after adjusting for potential confounders.

Given that formal competition is associated with additional psychological stressors, Wilson et al. (2021) completed a subsequent study to evaluate whether GI symptoms experienced during endurance racing were associated with stress and anxiety levels. Three electronic surveys were sent to endurance athletes before and after one of their races. The first was sent during the week before the race to obtain information about the athlete (e.g. demographics, anthropometrics) and details about the race. They were also asked to complete valid measures of perceived life stress (PSS-14) and anxiety (Anxiety Sensitivity Index [ASI]-3 and STICSA-Trait) (Cohen et al., 1983; Taylor et al., 2007; Ree et al., 2008). A subset of 125 athletes also completed the state version of the STICSA inventory (STICSA-State) on the morning of their race to evaluate anxiety in the moment. Finally, a questionnaire was sent after their race which asked about GI symptoms. Six different symptoms were evaluated on a 0-10

scale: nausea, reflux/regurgitation, stomach fullness, abdominal cramps, gas/flatulence, and urge to defecate. Logistic regressions were used to evaluate the association between high anxiety and stress (operationally defined as being in the top tertile) and GI discomfort (severity ≥ 3 for a given symptom). There were several statistically significant associations that remained significant after adjusting for age, gender, body mass index, the type and duration of the race, and experience. Specifically, individuals with high PSS-14 scores had increased odds of experiencing nausea (odds ratio [OR] = 2.21; 95% confidence interval; [95CI] = 1.02, 4.78), while high STICSA-Trait scores were associated with nausea (OR = 3.43; 95CI = 1.57, 7.50) and regurgitation/reflux (OR = 3.31; 95CI = 1.26, 8.73). Of the 125 athletes who completed the STICSA-State inventory, high anxiety was associated with increased odds of nausea, regurgitation/reflux, fullness, and cramping (ORs = 2.98-5.57). Interestingly, high ASI-3 scores were not associated with GI discomfort. Similarly, a third study by Wilson (2020a) asked participants to complete a retrospective survey after endurance races and found that scores on the STICSA-Trait and Sport Competition Anxiety Test were significantly correlated with in-race GI discomfort ($\rho = 0.22 - 0.33$; $p < 0.05$). Thus, higher levels of stress or anxiety appear to be associated with in-race GI symptoms in endurance athletes, particularly anxiety during the morning leading up to competitive races.

Gaps and Limitations in the Literature

The current literature strongly supports the idea that stress and anxiety can influence GI function. These effects likely stem from activation of stress systems that overlap with neuroendocrine and immunological pathways of the brain-gut axis (both acutely and chronically), which can elicit damage to epithelial tissues, intestinal inflammation, and sensitization of the visceral afferent

nerves and brain regions that process visceral sensations such as pain and discomfort (Larauche et al., 2012; Moloney et al., 2015). Considering that the vagus nerve mediates many of these responses, increased sympathetic drive and dampened vagal tone from acute or chronic psychological stressors may contribute to the exacerbated stress response and GI symptoms. Altered autonomic outflow in response to stress or anxiety may also influence blood flow redistribution, which could exacerbate splanchnic hypoperfusion that occurs during prolonged or intense endurance exercise (van Wijck et al., 2012a; Wilson, 2020b). While there is surprisingly little data available in athletic populations, initial research seemingly confirms that stress and anxiety are associated with GI symptoms during exercise, particularly when there are high levels of anxiety on the morning of a race (Wilson, 2018; Wilson et al., 2021). However, there is clearly a need for further research on psychological factors and GI discomfort in athletes.

First, considering that many factors contribute to GI symptoms during endurance exercise, it will be important to identify how various factors interact with one another. One specific example that warrants investigation is whether the effects of acute stress or anxiety interact with the stimulatory effects of caffeine supplementation. As mentioned previously, relatively high doses of caffeine can improve physical performance (Grgic et al., 2019) but also increase catecholamine secretion and elicit GI symptoms, such as nausea, during exercise in some individuals (Kaplan et al., 1997; Robertson et al., 1978). Many sport and exercise nutrition studies do not evaluate or report caffeine-induced side effects (e.g. GI symptoms), and those that do are typically performed in laboratory settings rather than competition environments. Thus, little is currently known about whether the combination of stress or anxiety with caffeine results in greater incidence and severity of GI symptoms in endurance athletes. It is possible that

exercise, caffeine, and stress or anxiety could all interact to result in large concentrations of circulating catecholamines and ultimately increase the risk of severe symptoms.

Of particular interest is the role of genetic modifiers of anxiety and caffeine side effects. Caffeine-induced anxiety is moderated by genotype variation for ADORA2A, a gene that encodes for adenosine A_{2A} receptors that caffeine acts upon (Alsene et al., 2003). Specifically, individuals with the T/T genotype variation for ADORA2A consistently demonstrate greater degrees of caffeine-induced anxiety than other individuals (Yang et al., 2010). Interestingly, individuals with this genotype variation are often more prone to anxiety from other stimulants (Hohoff et al., 2005) and panic disorders (Deckert et al., 1998; Hamilton et al., 2004). As such, ADORA2A has been suggested to moderate anxiety on a more general level, not just in response to caffeine (Yang et al., 2010). It would be interesting to evaluate whether T/T carriers for ADORA2A are more prone to GI symptoms during exercise, particularly after ingestion of caffeine. Regardless, it is possible that athletes who are already prone to chronic or acute anxiety (e.g. competition anxiety) could further increase their anxiety levels if they consume caffeine prior to a race, which could subsequently exacerbate GI incidence and severity.

Another area worthy of attention is related to how various psychological (acute and chronic stress or anxiety, GI-specific anxiety), perceptual (visceral sensitivity, body vigilance) and nutritional factors interact and contribute to GI symptoms. For example, a highly anxious runner with visceral hypersensitivity may be particularly prone to GI symptoms when consuming large intakes of energy, carbohydrate, and other nutrients before or during exercise. If so, it is also possible that such athletes modify their nutritional intake to minimize their risk of GI symptoms during training or competition. Thus, not only should studies evaluate whether these

factors interact to contribute to GI discomfort during exercise, but also whether athletes modify their nutritional intake based on psychological or perceptual factors.

There is also a need to explore the nature of the relationship between psychological factors and GI discomfort during exercise. It is possible that some athletes experience anxiety or stress because they are prone to GI symptoms, rather than the anxiety or stress causing the symptoms. Or the association could be bi-directional. Experimental studies that induce mild-to-moderate degrees of stress or anxiety followed by bouts of endurance exercise could help to provide clarification. Stressors that have been used in non-exercise studies, such as the Trier Social Stress Test or mental arithmetic (Holtmann & Enck, 1991; Kirschbaum et al., 1993), could be administered, followed by the evaluation of GI symptoms and function during exercise bouts. Additionally, these lab-based studies should be accompanied by field-based data collection, where athletes are assessed for competition anxiety and measures of GI function or symptomology immediately before and after a race. This would provide an indication of whether competition anxiety influences GI symptoms in a more realistic setting, since it can be difficult to replicate the physical and psychological stressors of competition in controlled laboratory settings (Wilson, 2020b). Another approach would be to evaluate the effects of interventions that can reduce stress or anxiety. Not only would these types of studies help determine the role of psychological stress on GI symptoms during exercise, they would also aid in identifying effective and feasible interventions that athletes could use to reduce their risk of GI discomfort during training or competition. Two examples that may be effective and feasible for athletes include slow deep breathing and mindful breath counting (Gorman & Green, 2016; Russo et al., 2017).

Deep breathing has a variety of effects on cardiopulmonary function, particularly when respiratory rate is decreased to about six breaths per minute with concomitant increases in tidal volume (Russo et al., 2017). Deep breathing can increase ventilation efficiency through enhanced alveolar recruitment and distension, resulting in reduced physiological dead space (Bernardi et al., 1998; Bilo et al., 2012). It also appears to influence cardiovascular hemodynamics, as some data suggests that deep, diaphragmatic breathing enhances venous return and synchronizes blood flow to the beat of the heart (Bordoni & Zanier, 2013; Dick et al., 2014; Hsieh et al., 2003).

Perhaps most relevant to psychological factors and GI symptoms are the effects of slow deep breathing on HRV and autonomic activity. HRV refers to the beat-by-beat variation in heart rate or the duration of time between the R-R intervals in the cardiac cycle (Billman et al., 2011). HRV is a product of both parasympathetic and sympathetic input and is commonly used as an index of sympathovagal balance (Billman et al., 2011; Bootsma et al., 1994). A reduced HRV is reflective of more sympathetic dominance and has been implicated in many disease states and disorders, while a high HRV is often reflective of health and wellbeing (Billman et al., 2011; De Jong & Randall, 2005; Thayer et al., 2010). Both branches of the autonomic nervous system are regulated by the central respiratory centers, and slow deep breathing can dampen sympathetic activity, promote vagal outflow, and ultimately increase HRV (Badra et al., 2001; Bernardi et al., 2001; Chang et al., 2013; Paprika et al., 2014; Tharion et al., 2012). Considering that vagal nerve activity is a primary mediator of pathways within the brain-gut axis and the stress axes that overlap with them, increasing parasympathetic tone via slow deep breathing could be beneficial for highly anxious and GI-prone endurance athletes (Boeckxstaens et al., 2016; Vanner et al., 2016). Indeed, several studies have suggested that slow deep breathing interventions can

attenuate motion-sickness symptoms, such as nausea (Jokerst et al., 1999), and enhance feeding tolerance in those with functional dyspepsia (Hjelland et al., 2007).

Interventions that promote mindfulness may also be useful independently or in conjunction with slow deep breathing may also be useful. Mindfulness is a difficult concept to operationally define, though recent articles have referred to it as openly attending to and being aware of the present moment (Creswell, 2017) or the concept of “bringing back” a wandering mind (Levinson et al., 2014). Regardless, interventions that promote mindfulness have gained popularity in research and practice due to findings of benefits to health, pain, attention, and other outcomes (Brefczynski-Lewis et al., 2007; Hölzel et al., 2011; Ludwig & Kabat-Zinn, 2008; Zeidan et al., 2011). A meta-analysis also found that mindfulness interventions tend to reduce anxiety in individuals with anxiety disorders (Strauss et al., 2014), and one study even reported improved symptom severity in women with IBS (Gaylord et al., 2011). The precise mechanisms are not entirely clear and likely involve a multitude of psychological and neurobiological factors (Creswell, 2017). However, one hypothesis is that mindfulness interventions can buffer stress through enhanced activity of the prefrontal cortex that is responsible for top-down regulation of stress responses, while simultaneously decreasing activity of brain regions involved in the stress axis (e.g. amygdala) (Creswell & Lindsay, 2014; Creswell, 2017). Considering that the amygdala and stress response systems are thought to contribute to stress-induced GI symptoms and dysfunction (Greenwood-Van Meerveld & Johnson, 2018), interventions that promote mindfulness may be effective in alleviating symptoms in athletes with high levels of stress or anxiety. Mindful breath counting in particular may be a viable strategy as it has recently been demonstrated to have positive effects on stress-induced alcohol-seeking behavior (Shuai et al., 2020) and attentional effects associated with media multi-tasking (Gorman & Green, 2016). It

also has the advantage of being simple to perform and brief in duration (Levinson et al., 2014). Thus, if it is demonstrated to reduce GI discomfort in athletes, mindful breath counting could be a feasible intervention for an athlete to incorporate into their daily routine.

Interventions such as slow deep breathing and mindful breath counting could also have benefits to high anxiety athletes besides GI discomfort. For example, interventions that successfully reduce stress or anxiety may also enhance aspects such as sleep and reduce the risk of burnout (Cremades & Wiggins, 2008; Horváth et al., 2016; Uhde et al., 2009). Thus, research should determine not only if these interventions reduce GI discomfort, but also evaluate secondary outcomes that could be beneficial to athletes such as improved sleep quantity and quality or subjective measures of recovery.

Overall Summary of the Literature Review

The GI system is a critical component of health, performance, and recovery for endurance athletes. Compromised GI function can lead to symptoms ranging from mild inconveniences to severe health concerns (de Oliveira et al., 2014; van Wijck et al., 2012a). Considering that an untimely episode of GI discomfort can negatively affect performance or even cause an athlete to drop out of a race (O'Brien et al., 2011; Stuempfle & Hoffman, 2015), a considerable amount of research has sought to identify the underlying pathophysiology of GI dysfunction and the factors that correlate with symptom incidence and severity. The precise pathophysiology of GI symptoms during exercise still requires further elucidation, but current research suggests that a complex interaction of circulatory, neuroendocrine, and immunological factors is involved (Costa et al., 2017b). Specifically, blood flow redistribution during exercise can cause splanchnic

hypoperfusion and subsequent damage to cells that form, support, and regulate the intestinal epithelial barrier (van Wijck et al., 2012a). Increased sympathetic drive and the mechanical stress of exercise can also contribute to altered GI function and potentially provoke symptoms (Costa et al., 2017b; de Oliveira et al., 2014). Additionally, numerous other factors such as hypohydration or heat stress, various nutritional factors (e.g. highly concentrated carbohydrate beverages, fiber, proteins, FODMAPs), dietary supplements, and NSAIDs can all contribute to or exacerbate GI symptoms during exercise (de Oliveira et al., 2014; Wilson, 2019). Other factors may affect the incidence and severity of GI symptoms, including the genetics, age, gender, and training experience of the athlete. Taken together, many individual factors are likely involved in exercise-induced GI discomfort, and an unfavorable combination of factors may expose an athlete to a higher risk of issues.

One potentially impactful area that is relatively understudied is the role of psychological factors on GI discomfort during exercise. The central nervous system and GI system communicate through an intricate bi-directional communication network known as the brain-gut axis (Mayer et al., 2015). Many of the neuroendocrine pathways that form the brain-gut axis also overlap with central and peripheral stress systems, which suggests that stress or anxiety could influence GI function (Boeckxstaens et al., 2016; Vanner et al., 2016). Indeed, chronic stress and anxiety are considered important factors in the development of functional GI disorders such as IBS and inflammatory bowel diseases (Bonaz & Bernstein, 2013; Labanski et al., 2020) and have been correlated with GI symptomology in the general population as well (Haug et al., 2002). Numerous animal and human studies have also demonstrated that acute and chronic stress can influence GI motility, barrier integrity, and visceral sensitivity (Elsenbruch & Enck, 2017; Taché & Bonaz, 2007; Wilson, 2020b). Taken together, there is a strong psychobiological basis for how

acute or chronic psychological factors could influence GI symptoms, most likely through altered autonomic outflow and increased CRH secretion (Wilson, 2020b).

Recent studies have suggested that elevated stress and anxiety is associated with GI symptoms during training and competition in endurance athletes (Wilson, 2018; Wilson, 2020a; Wilson et al., 2021). However, many areas require further exploration. Future studies should seek to evaluate how various factors interact to contribute to symptoms. Experimental studies should be conducted to determine the precise relationship between psychological factors and GI discomfort during exercise. This could be accomplished by inducing small-to-moderate amounts of acute stress prior to exercise to determine if GI symptoms are elicited or aggravated. Another option is implanting stress- or anxiety-reducing interventions such as slow deep breathing and mindful breath counting (Gorman & Green, 2016; Russo et al., 2017). Such studies would not only help identify the role of stress and anxiety on GI symptoms but also help identify effective and feasible interventions that athletes could use to prevent or alleviate GI symptoms during training or competition.

CHAPTER III

METHODS

The overall purpose of this dissertation was to evaluate the role of several psychological factors in the development and management of GI symptoms during running. Trained runners were recruited for two studies. The first was a survey-based study with three primary aims: 1) to evaluate whether measures of chronic stress, anxiety, GI-specific anxiety, and body vigilance correlate with GI symptoms during runs, 2) to assess the associations between these psychological factors and nutrition intake before and during runs, and 3) to analyze whether any resulting associations between these psychological factors and nutrition intake are mediated by GI symptomology. The second study was a randomized controlled trial with the aim of determining the effects of four-week slow deep breathing and mindful breath counting interventions on psychological and perceptual measures, HRV, and GI symptoms in runners who have elevated levels of anxiety and who were prone to GI symptoms.

Study 1 Methods

Participants

A total of 82 trained runners were recruited to track details about their training runs for one week, at the end of which they completed an electronic survey to evaluate several psychological measures. To be eligible for inclusion, runners were required to be at least 18 years of age and currently running ≥ 20 miles per week, with at least one run that was 60 minutes or longer in the past week. This running volume threshold was used to increase the likelihood that recruited participants were accumulating enough volume to be at risk for GI symptoms during runs, and

that they were performing enough training to consider consuming foods and fluids during runs. After initial contact with a prospective participant, they were sent a Qualtrics hyperlink to an online consent form. The consent form provided details about the study's purpose, inclusion and exclusion criteria, the data collection procedures, potential risks and discomforts from participation, time commitments, and measures taken to keep data confidential. Prospective participants were encouraged to ask questions after reading through the consent form. No data was collected until the informed consent process was completed and consent document was signed.

Data Collection Materials and Procedures

The runners were first sent a prospective journal adapted from Wilson (2017). The journal was used to collect information related to each training run for one week. This included the date/time and average rating of perceived exertion (RPE; Borg, 1982) of each run. They were asked to rate the severity of several GI symptoms during runs on a 0-10 scale. The symptoms and their standardized definitions are included below:

- Nausea: A feeling of sickness in the stomach marked by an urge to vomit.
- Regurgitation/Reflux: A sensation of food or fluid returning from the stomach to the esophagus or mouth.
- Stomach Fullness: A sensation of fullness or abdominal pressure in the upper abdomen.
- Bloating: A feeling of distension from a buildup of gas in the gut.
- Abdominal Cramps: Pain or cramping sensation, often experienced in the mid- or lower portion of the abdomen.
- Gas/Flatulence: Gas or flatus expelled through the anus.
- Urge to Defecate: Sensation of needing to pass a bowel movement.

Participants were also be asked to provide information about their nutritional intake before (within 4 hours) and during each run. Detailed instructions prompted the participants to specify the specific brands, flavors, and amounts of foods and fluids. After tracking run information, GI symptoms, and nutrition intake for one week, participants were sent an electronic survey to evaluate several psychological constructs.

The retrospective electronic survey asked about the participants' demographics (age, gender, race/ethnicity), running history (years running, number of miles per week), history of GI conditions, and typical resting GI symptoms. It also contained a series of psychological questionnaires, including the PSS, STICSA-Trait, body vigilance scale (BVS), and visceral sensitivity index (VSI).

The 14-item PSS (Cohen et al., 1983) was designed to evaluate how stressful an individual has perceived life to be over the preceding month. Participants are presented with a series of questions and asked to rate how often they have felt or thought that way in the past month using the following scale: 0 = never, 1 = almost never, 2 = sometimes, 3 = fairly often, and 4 = very often. The positive items are reversed, and then all ratings are summed to obtain a total score ranging from 0 to 56. The original validation study demonstrated adequate coefficient alpha reliability in two samples of college students and one sample of community members of a smoking-cessation program (alpha = 0.84 – 0.86; Cohen et al., 1983). PSS-14 scores were also significantly correlated with outcomes such as life event scores, social anxiety, utilization of health services, and depressive symptomology. Similarly, strong reliability and validity of the PSS has been reported across multiple studies with various populations (e.g., Hewitt et al., 1992; Pbert et al., 1992). Additionally, recent studies have demonstrated that PSS-14 scores are correlated with GI symptoms during running (Wilson, 2018), and that endurance athletes with

high PSS-14 scores were more likely to report nausea during competition (Wilson et al., 2021). As such, the PSS-14 was used as a valid and reliable assessment of perceived stress in the recruited runners.

The 21-item STICSA-Trait (Ree et al., 2008) was used to assess cognitive and somatic aspects of anxiety at the trait level. The STICSA-Trait is considered a valid and reliable questionnaire, with some data suggesting it is a purer measure of anxiety symptomology than other common anxiety measures like the State-Trait Anxiety Inventory (Elwood et al., 2012; Grös et al., 2007). Participants are asked to rate how often each statement generally applies to them on the following scale: 1 = not at all, 2 = a little, 3 = moderately, and 4 = very much so. The ratings are then summed to provide a score ranging from 21 to 84. Wilson et al. (2021) recently found that endurance athletes with high STICSA-State scores had higher odds of reporting nausea and regurgitation/reflux during competition than those with low-to-modest STICSA-State scores. Thus, the STICSA-Trait served as a measure of trait anxiety for this study.

The BVS (Schmidt et al., 1997) is a 4-item questionnaire used to quantify the amount of attentional focus that a person devotes towards internal sensations. Increased body vigilance is a common observation in individuals with high anxiety and panic disorders, and some studies suggest that BVS scores correlate with GI symptoms in IBS patients (e.g., Keough et al., 2011). Further, the BVS has demonstrated high internal consistency (alpha coefficient: 0.82-0.84), and adequate test-retest reliability over a 5-week period across several samples (mean $r = 0.67 - 0.69$; Schmidt et al., 1997). The first two items provide the following two statements: 1) “I am the kind of person who pays close attention to internal sensations”, and 2) “I am very sensitive to changes in my internal bodily sensations.” Participants are asked to rate how much each statement applies to them in the past week using a Likert scales ranging from 0 (“Not at all like

me”) to 10 (“Extremely like me”). The third item asks participants to rate the average amount of time per day spent “scanning” their body for internal sensations on a scale from 0 (“No time”) to 100 (“All the time”). This rating is divided by ten to give an item score ranging from 0-10. The final item asks the participant to rate the amount of focus they give to 15 individual sensations such as heart palpitations, dizziness, and nausea on a scale from 0 (“none”) to 10 (“extreme”). The individual sensation ratings are averaged to provide one item score of 0-10. These scores are then summed across the four items to provide a total score ranging from 0-40. While there is little-to-no data available in athletic populations, it is possible that runners with higher levels of body vigilance are more likely to report GI symptoms during runs.

Finally, the VSI (Labus et al., 2004) is a 15-item questionnaire designed to evaluate GI-specific anxiety, which is thought to contribute to symptomology in functional GI disorders (Jerndal et al., 2010). Specifically, the VSI addresses five dimensions of GI-related behaviors and cognitions: worry, anxiety, avoidance, sensitivity, and vigilance. Participants are presented with a series of statements about how some individuals respond to various symptoms or uncomfortable sensations within their gut and abdomen. They are then asked to rate how much they agree with each statement as it relates to their own responses using the following scale: 1 = strongly agree, 2 = moderately agree, 3 = mildly agree, 4 = mildly disagree, 5 = moderately disagree, and 6 = strongly disagree. The ratings are summed across the 15 statements to calculate a total score ranging from 15-90. Labus et al. (2004) demonstrated that the VSI has strong reliability and correlates with GI symptoms in both IBS and healthy participants (Labus et al., 2004; Labus et al., 2007; Saigo et al., 2014), but there is limited data available in athletic populations. Theoretically, athletes with high VSI scores could be more prone to GI discomfort, either because of anxiety over past experiences or because of higher sensitivity to visceral

sensations. Further, athletes that are more anxious about GI symptoms (i.e., have higher levels of GI-specific anxiety) may be more likely to limit nutrition intake to avoid provoking GI symptoms during their runs. However, there is currently limited data to support or refute these hypotheses. Thus, this study sought to determine if VSI scores were correlated with GI symptoms and nutritional intake in trained runners.

Data Processing

A score was calculated for each psychological questionnaire using the specific scoring instructions for each measure. GI discomfort was quantified as the percentage of runs that a runner reported at least one symptom ≥ 3 out of 10. This was calculated for all symptoms, upper GI symptoms, and lower GI symptoms separately. Nausea, reflux/regurgitation, bloating, and stomach fullness were categorized as upper GI symptoms, while abdominal cramps, gas/flatulence, and urge to defecate were considered lower GI symptoms.

A runner's mean intake of total energy (kcal), carbohydrates (g), protein (g), fat (g), fiber (g), fluid from beverages (mL), and caffeine (mg) before and during runs was calculated separately. These values were estimated from food/product information provided by participants in the running journal. When specific brands or product names were provided by the participant, the websites of the product were searched for nutrition information. For all other food/product information, intake was estimated using Cronometer (<https://cronometer.com/>). Participants were excluded from analyses involving the nutrition variables if they did not provide precise enough information to estimate their intake.

Statistical Analysis

The normality of data for each variable was first assessed with Shapiro-Wilks analysis and inspection of the histograms. Because most variables were non-normally distributed, non-parametric analyses were used throughout this study. Continuous demographic and training information were displayed as medians and interquartile range (IQR). Frequency and percentages were provided for categorical variables (e.g., race/ethnicity, history of GI conditions). This information was reported for the total sample and for men and women separately.

To address specific aim #1, Spearman's rho correlation coefficients were calculated to evaluate the association between psychological scores (PSS-14, STICSA, BVS, VSI) and measures of GI discomfort during runs (% of runs with a symptom ≥ 3 for total GI, upper GI, and lower GI symptoms). Partial correlations were also calculated to evaluate the associations after adjusting for covariates (age, sex, running experience, resting GI symptoms, and mean running RPE).

Specific aim #2 was addressed by calculating the correlations between the psychological measures and mean nutrition intakes (total energy, carbohydrates, fats, proteins, fiber, total fluid, caffeine) before and during runs. Correlations were carried out separately for pre-run and during-run intakes. Because of the highly skewed data distribution and the lack of significant negative associations between psychological data and nutritional intake as hypothesized, the mediation analyses for specific aim #3 were not conducted.

Study 2 Methods

Participants

For this study, 122 runners were screened for eligibility, 68 met the eligibility criteria, and 63 consented to participate. To be eligible for inclusion, participants were required to be at least 18 years of age and running at least 15 miles per week. Further, to maximize the likelihood that the interventions would have meaningful effects on the dependent variables, only participants that had at least mild levels of anxiety and who at least occasionally experienced GI symptoms during runs were eligible. During the initial screening and informational call, participants completed the General Anxiety Disorder-7 (GAD-7) questionnaire (Williams, 2014) and were asked to report how often they had experienced GI symptoms during runs over the previous month on a five-point Likert scale ranging from “never” to “almost always.” The GAD-7 is a seven-item questionnaire that is commonly used to screen individuals for anxiety, which has been validated in both clinical (Ruiz et al., 2011) and general (Lowe & Decker, 2008) populations. Participants are asked to rate how often they have been bothered by seven different problems related to anxiety on a scale from 0 (“Not at all”) to 3 (“Nearly every day”). The ratings are summed, resulting in a sum score ranging from 0-21. A cut-off score of 5 has been recommended as a cut-off for mild anxiety (Williams, 2014). Thus, participants were eligible if they scored ≥ 5 on the GAD-7 and if they reported to occasionally, often, or almost always experience GI symptoms during runs in the previous month.

Additional inclusion criteria included the following: 1) access to the internet and 2) having a Smartphone that runs on an operating system (iOS or Android) that is compatible with an app (Elite HRV) for collecting physiological data for the study. Finally, participants that were

prescribed psychotropic drugs (e.g., SSRIs) needed to be on a stable dose for at least three months prior to enrollment into the study.

Design Overview

A randomized controlled trial was used to evaluate the effects of manipulating breathing rate and using breath counting on several psychological measures, HRV, and GI symptoms in runners who are prone to elevations in anxiety and GI discomfort. Enrolled participants were randomly assigned to one of three conditions: 1) slow deep breathing plus breath counting (SLOWBC), 2) breath counting with breathing at a normal pace and depth (NORMALBC), or 3) control group. The SLOWBC and NORMALBC groups were asked to perform a daily breathing intervention for four weeks using a video imbedded with an adjustable breathing app (eXHALeR v. 2.0.6; <https://xhalr.com/>). The videos were nearly identical except for several key differences. The SLOWBC's video prompted participants to take deep breaths and the breathing app was set to a pace of 6 breaths per minute. The NORMALBC's video prompted them to breathe at a normal depth, and the breathing app was adjusted to a pace of 15 breaths per minute. Both groups were asked to count their breaths over the course of five minutes. The control group did not perform a daily breathing intervention and were asked to not engage in any sort of breathing intervention during their involvement in the study.

Several dependent variables were assessed across multiple time points (pre, mid, post). Electronic questionnaires containing five psychological questionnaires were sent during the pre-intervention period, mid-way through the intervention period, and after the completion of the intervention. These were used to evaluate psychological and perceptual constructs such as perceived stress, anxiety, body vigilance, GI-specific anxiety, and mindfulness throughout the

data collection period. A resting HRV measure was taken before and after the intervention period with a portable HRV monitor to provide an objective physiological measure of the interventions' effects (Billman et al., 2011; Bootsma et al., 1994). HRV measures are particularly relevant given that slow deep breathing can promote vagal stimulation and increase HRV (Chang et al., 2013; Tharion et al., 2012), and this could attenuate GI symptoms due to the large degree of overlap between the pathways of the brain-gut axis and the stress response systems (Boeckxstaens et al., 2016; Vanner et al., 2016). Further, participants were sent a journal to track their run information (date/time, duration, RPE) and GI symptoms during runs for one week before the intervention and during the final week of the intervention period. This information was used to compare GI symptomology before and after the intervention period. More detailed information about the intervention and data collection procedures are provided below. Further, specifics about the data collection procedures are provided in **Table 1** and **Figure 1**.

Table 1. Study 2 Data Collection Overview and Timing

Measures	Proposed Timing of Data Collection
HRV: Ln RMSSD, LF, HF, LF/HF ratio	Pre-Test: Collected during the week before starting the intervention. Post-Test: Collected the day after the intervention is completed.
Psychological surveys: PSS-14, GAD-7, BVS, VSI, FFMQ	Pre-Test: Completed during the week before starting the intervention. Mid-Point: Completed halfway through intervention (end of week 2). Post-Test: Completed during final day of intervention.
GI symptoms during runs	Pre-Test: Tracked for one-week before starting the intervention. Post-Test*: Tracked for one-week during final week of the intervention (Week 4).

Note: * = Analyzed as a post-test measure but collected during final week of the intervention period. HRV, heart rate variability; Ln RMSSD, log transformed root of the mean sum of the squared differences; HF, high frequency; LF, low frequency; PSS-14, perceived stress scale-14; STICSA-Trait, State-Trait Inventory for Cognitive and Somatic Anxiety-Trait; BVS, body vigilance scale; VSI, visceral sensitivity index; FFMQ, five-faceted mindfulness questionnaire

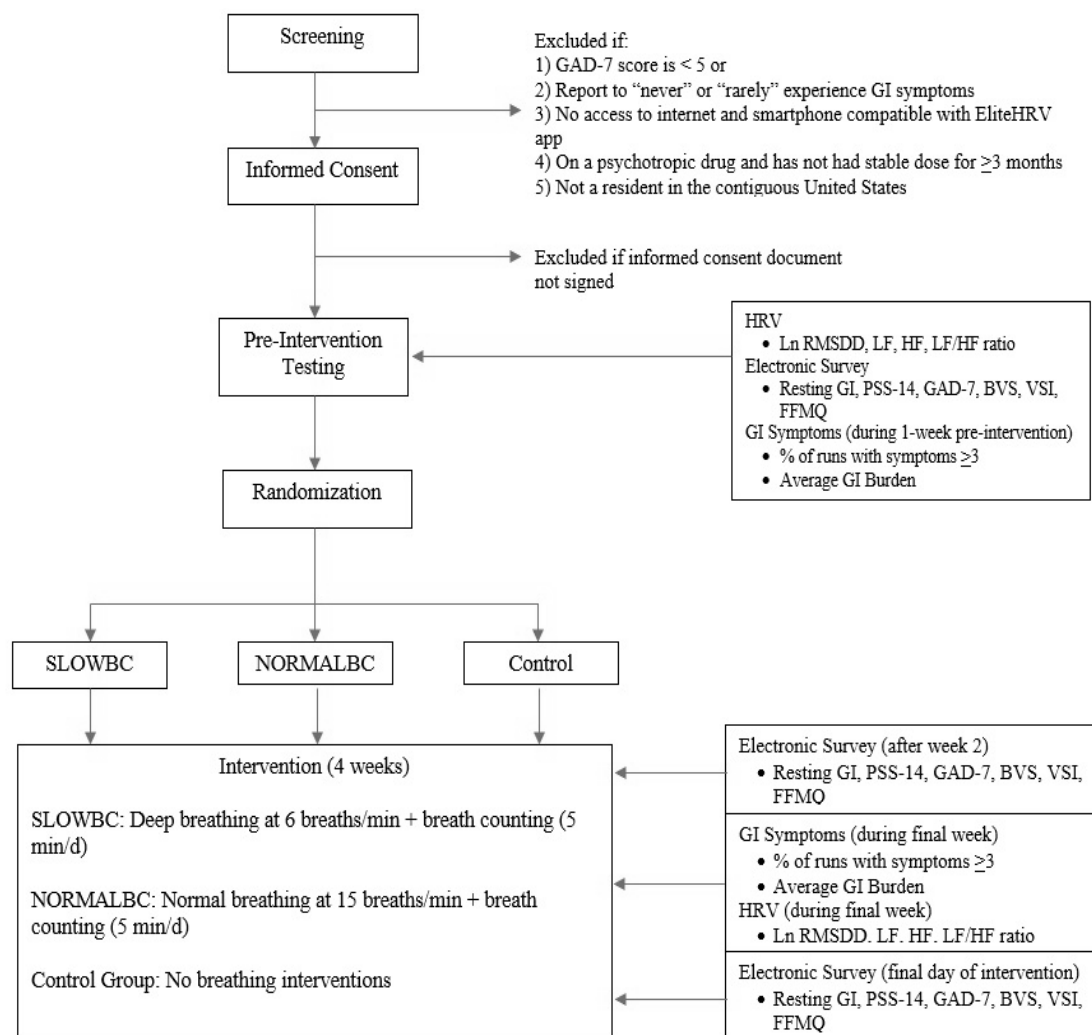


Figure 1. Overview of the data collection procedures for study 2.

Procedures

After screening potential participants based on their self-report anxiety and typical GI symptoms, participants were sent an electronic informed consent document approved by the ODU Institutional Review Board, and the study procedures, risks, etc. were reviewed with them. If they agreed to participate, participants were contacted to begin the pre-intervention data collection procedures.

To provide an objective measure of the intervention's effects, a resting HRV measurement was evaluated using a portable CorSense HRV monitor (EliteHRV, Asheville, NC, USA). The CorSense monitor estimates a variety of HRV measures using pulse detection via a 500 hertz multiwave sensor array. The data was then automatically uploaded to a smartphone application. The participants were asked to send a screenshot of the results page to the investigators through email or text. Time-domain measures evaluate beat-to-beat changes in HRV and can be used as a simple marker of PNS input or stress reactivity (Kim et al., 2018; Kleiger et al., 1992). A common time-domain HRV measure is the root mean square of successive differences (RMSSD), which can be impacted by stress and anxiety (Uusitalo et al., 2011; Vrijkotte et al., 2000). In contrast, frequency-domain measures evaluate the distribution of power across different frequency bands (e.g., high frequency [HF], low frequency [LF]; Kim et al., 2018). Notably, the HF band is a measure of PNS activity, while the LF band is a measure of SNS activity (Kim et al., 2018; Malliani et al., 1991). As such, by assessing each of these and the ratio between them (LF/HF ratio), it is possible to evaluate changes in ANS activity and sympathovagal balance, though the validity of this method is debated. Further, these measures are affected by psychological stress (Delaney & Brodie, 2000; Kaegi et al., 1999) and can be improved with breathing interventions (Pal et al., 2014; Tharion et al., 2013).

Upon enrollment into the study, CorSense monitors were shipped to participants with written instructions on how to measure HRV. They were asked to perform a resting HRV assessment during the baseline week of GI-symptom recording that preceded the intervention, and again immediately after completing the intervention. Participants were asked to download a free app (Elite HRV), which syncs with the CorSense sensors via Bluetooth. While the gold-standard for HRV measurement is electrocardiogram, portable devices can provide a valid

estimate (Dobbs et al., 2019). The Ln RMSSD measure derived using the EliteHRV application software has been found to be similar to when using traditional computer program methods (Perrotta et al., 2017) and was used as the primary HRV measurement. Additionally, HF, LF, and LF/HF ratio were included as frequency-domain measures to evaluate the effects of the interventions. Given the remote nature of the data collection in response to the COVID-19 pandemic, the user-friendly nature of the CorSense HRV monitor, and the relative accuracy of portable devices, this method provided useful objective data to evaluate the effects of the breathing interventions.

During the first week, participants were also sent an electronic survey to complete. The survey asked participants about demographic information (age, gender, height, weight, running experience, history of GI conditions, history of engaging in breathing interventions, etc.) and a series of five psychological questionnaires. Perceived stress, anxiety, body vigilance, and GI-specific anxiety were assessed with the PSS-14, GAD-7, BVS, and VSI, respectively. Additionally, five dimensions of mindfulness were quantified with the 15-item version of the FFMQ (Gu et al., 2016). The psychological measures were sent pre-intervention, at the mid-way point of the intervention period, and during the final day of the intervention. Participants were also provided a journal to track run information (date/time, RPE, and duration for each run) and GI symptoms over the course of one week. This journal was similar to that used for study #1 but with the nutritional intake component removed to reduce participant burden.

After completion of the pre-intervention measures, participants were randomly assigned into one of three groups: 1) SLOWBC, 2) NORMALBC, or 3) control group. The randomization process was done using blocks of 3 and 6. Gender-specific randomization lists were generated using the following website (<https://www.sealedenvelope.com/simple-randomiser/v1/lists>). A

person not involved in the data collection was asked to generate the lists and then fill sequentially labelled envelopes with the results. Once randomized, participants in the SLOWBC and NORMALBC groups were asked to complete a daily 5-minute breathing intervention for four weeks. While a longer duration intervention may maximize the potential benefit of breathing interventions, there is evidence that deep breathing and other mindfulness techniques can confer benefits in as few as four weeks and with sessions as brief as 5-10 minutes each (Chung et al., 2010; Hjelland et al., 2007; Mackenzie et al., 2006). As such, four weeks was used to reduce burden on the participants, increase adherence, and to allow for recruitment of a larger sample size.

The SLOWBC intervention involved five minutes of deep breathing at six breaths per minute each day. Changes in breathing frequency and depth can modify cardiorespiratory responses (Pitzalis et al., 1998; Russo et al., 2017), with deep breathing at about six breaths per minute having greater influence on factors such as baroreflex sensitivity, blood pressure, and HRV than faster breathing rates (Bernardi et al., 2001; Sin et al., 2010; Tharion et al., 2012). Deep breathing routines at six breaths per minute can also increase vagal activity and HRV (Chang et al., 2013; Tharion et al., 2012) and reduce reporting of pain intensity in response to heat stimuli (Jafari et al., 2020). There is also some initial evidence that it can attenuate GI symptoms in some circumstances, such as feeding tolerance in individuals with functional dyspepsia (Hjelland et al., 2007).

However, breath counting at a relatively normal breathing rate could also confer benefits on stress, anxiety, and GI symptoms by promoting mindfulness (Cresswell, 2017; Levinson et al., 2014; Stauss et al., 2014). Indeed, one study found that mindfulness training attenuated GI symptoms in IBS patients (Gaylord et al., 2011), and there is evidence that mindful breath

counting can positively affect outcomes such as stress-induced alcohol-seeking behavior (Shuai et al., 2020). Mindfulness has been suggested to buffer stress by affecting brain regions involved with top-down processing of stress (e.g., prefrontal cortex) while decreasing activity in the amygdala, which contributes to the stress axis (Creswell & Lindsay, 2014; Creswell et al., 2017). As such, the NORMALBC intervention was included to evaluate the effects of mindful breath counting independent of slow deep breathing. This was accomplished by setting the breathing cadence to 15 breaths per minute with a normal depth while asking participants to count their breaths.

Participants in the two breathing groups were sent a reusable link to a video containing imagery from a breathing app (eXHALeR V. 2.0.6; <https://xhalr.com/>) that guided them through their assigned breathing intervention. Upon clicking the link, a recorded voice message prompted the participant to find a comfortable seated or laying position, remove any distractions, and then proceeded to provide instructions for their assigned intervention. Participants in the SLOWBC were instructed to breathe deeply in sync with the video and to count their breaths. The NORMALBC group was asked to sync their breathing with visual cues in the video and count their breaths, but to otherwise breathe at a normal depth. Both groups were prompted to count their breaths until they reached 10, and then restart from 1 and continue as such until the session was complete. After five minutes of regulated breathing, a voice message informed the participant that the breathing session was completed and prompted them to record the time, date, and a rating of their engagement in the task and how pleasant they found the session on a scale from 1-10 in a provided breathing journal.

The breathing app provided a visual cue to help participants sync their breath to a prescribed frequency. A white circle expanded and constricted within a larger circle. The white

circle displayed the word “inhale” as it expanded, “hold” for a brief period at full expansion, and “exhale” as the circle constricted back to the starting position. The timing of each phase was manually adjusted. For SLOWBC, the timing was set to a 4-second inhalation, a 2-second hold, and a 4-second exhalation so that participants breathe at a frequency of 6 breaths per minute. The NORMALBC’s video was set to a 2-second inhale, no hold, and a 2-second exhale so that breathing frequency was approximately normal at 15 breaths per minute. While there is some variability in resting breathing rates between people (Flenady et al., 2017), standardization of the breathing frequency allowed for the two interventions to be as similar as possible except for the breathing frequency and depth. The control group did not perform a breathing intervention and were asked to avoid performing breathing exercises during the intervention period.

Several steps were taken to maximize the standardization of the interventions. First, the participants were asked to schedule a time to perform the interventions within 1-2 hours prior to training runs. On days they did not run, they were asked to perform the intervention at a similar time of day. A journal was provided to them to log information about each intervention session (date/time, number of breaths taken). Finally, weekly email communication, phone calls, or video chats were conducted with each participant to check adherence and answer any questions they had about the intervention.

Statistical Analysis

Normality was first evaluated using the Shapiro-Wilks test with inspection of histograms and Q-Q plots. Both intention-to-treat (ITT) and per-protocol analyses were conducted to deal with imperfect compliance to procedures and missing data (Gupta, 2011; Ranganathan et al., 2016; Schulz et al., 2010). All participants that were randomized to a group were included in ITT

analyses, regardless of their compliance (Gupta, 2011). Missing midpoint and post-intervention data were inputted using “Last Observation Carried Forward” method, where the most recent observation is retained for analysis (Streiner & Geddes, 2001). For the per-protocol analyses, participants in the SLOWBC and NORMALBC groups were excluded if 1) they never completed or sent a treatment journal, 2) there was >42 days between the first and last completed breathing sessions (which equates to >2 additional weeks beyond the prescribed four week treatment), 3) they completed <50% of sessions between the first and last sessions, and 4) post-intervention measurements were completed >10 days after the final breathing session. Control group participants were excluded if there was more than sixty days between pre- and post-intervention measurements, as this equates to three weeks more than the prescribed study timeframe (one week for pre-intervention measurements, four weeks for the intervention and post-intervention data collection).

Independent *t* tests were used to compare measures of intervention compliance and engagement between SLOWBC and NORMALBC groups. Mixed methods ANOVA was used to evaluate normally distributed outcome data, with group allocation as the between-subjects factor and time as the within-subjects factor. Mauchly’s test of sphericity was evaluated, and the Huynh-Feldt correction reported when the assumption of sphericity was violated. Simple main effects were reported in the case of statistically significant time x group interactions. Non-normally distributed data were compared across groups at each timepoint using the Kruskal Wallis test. Bonferroni post hoc tests were used when the ANOVAs or Kruskal Wallis tests detected a statistically significant effect. Partial eta squared (ηp^2) and ranked epsilon squared (ϵ^2) were calculated as measures of effect size for the mixed ANOVAs and Kruskal Wallis tests respectively (Tomczak & Tomczak, 2014). Exploratory a posteriori analyses were conducted to

evaluate whether ratings of engagement in the interventions was associated with changes in primary outcomes across both treatment groups (SLOWBC and NORMALBC).

CHAPTER IV

ASSOCIATIONS BETWEEN PSYCHOLOGICAL FACTORS, NUTRITION INTAKE, AND GASTROINTESTINAL SYMPTOMS IN RUNNERS

Introduction

The causes and implications of gastrointestinal (GI) dysfunction in endurance sport have been a heavily studied topic in recent decades (de Oliveira et al., 2014; Costa et al., 2017b). GI dysfunction can manifest as numerous symptoms affecting both upper (regurgitation/reflux, nausea) and lower (abdominal cramping, gas, loose stools) aspects of the GI system during exercise (de Oliveira et al., 2014). Symptoms are often relatively mild, but many endurance athletes experience moderate-severe symptoms at some point across several weeks of training (Wilson, 2017), particularly if they engage in ultra-marathons or other long duration endurance events (Costa et al., 2017b; Jeukendrup et al., 2000; Stuempfle & Hoffman, 2015). Notably, some symptoms can negatively affect endurance exercise performance and are often reported as a barrier to optimal performance and as reasons for dropping out of a race by endurance athletes (O'Brien et al., 2011; Stuempfle & Hoffman, 2015). At the very least, experiencing GI symptoms may reduce the enjoyment of engaging in recreational or competitive running.

Substantial research has sought to identify causes and risk factors for GI symptoms during exercise, with most focusing on physiological (splanchnic hypoperfusion, altered neuroendocrine activity), mechanical (repetitive stress from running), and nutritional factors (ingestion of highly concentrated beverages, and high intake of fats, proteins, fiber, etc.) (Costa et al., 2017b; de Oliveira et al., 2014; van Wijck et al., 2012). However, despite a strong psychobiological rationale (Wilson, 2020b), and anecdotal reports of stress/anxiety influencing GI function during exercise or sporting events, the potential role of psychological factors has

only been addressed in a few studies (Wilson, 2018; Wilson, 2020a; Wilson et al., 2021). In one study, runners prospectively tracked GI symptoms during training runs for 30 days and completed a retrospective survey (Wilson, 2018). Measures of GI symptoms were significantly associated with levels of perceived stress ($\rho = 0.23 - 0.29$; $p < 0.001$) and anxiety ($\rho = 0.18 - 0.36$; $p \leq 0.02$). More recently, Wilson et al. (2021) asked endurance athletes to complete a series of surveys before and after a race to evaluate the associations between psychological factors and GI symptoms. Those who scored in the top tertile for measures of perceived stress, trait anxiety, and particularly pre-race state anxiety, had higher odds of reporting moderate-severe (≥ 5 out of 10) symptoms such as nausea and regurgitation/reflux during a race. Finally, Wilson (2020a) asked participants to complete a retrospective survey after completing an endurance race. There were significant correlations between ratings of GI symptoms during the race and scores on the STICSA-Trait ($\rho = 0.23 - 0.33$; $p < 0.05$) and Sport Competition Anxiety Test ($\rho = 0.22 - 0.28$; $p < 0.05$). Beyond these few recent studies, there has been limited attempts to evaluate the contribution of psychological factors on GI symptoms during exercise.

The dearth of research is particularly surprising given the large number of studies on how psychological factors influence GI function and health in other contexts. There is a well-established bi-directional communication network between the central nervous system and the GI system which overlaps with central and peripheral stress systems (Boeckxstaens et al., 2016; Mayer et al., 2015; Vanner et al., 2016). Alterations to this “brain-gut axis” are thought to explain why abdominal pain conditions such as irritable bowel syndrome (IBS) are strongly influenced by psychological factors (Labanski et al., 2020; Mayer & Tillisch, 2011). For example, experimental studies have demonstrated that psychological stressors can influence GI function (Bhatia & Tandon, 2005; Elsenbruch & Enck, 2017). Additionally, IBS and other

functional GI disorders are associated with high rates of psychological comorbidity (Lee et al., 2017; Wu, 2012), and numerous psychological factors correlate with IBS symptom severity (Jerndal et al., 2010; McKinnon et al., 2015; Midenfjord et al., 2021). Further, psychological treatments such as cognitive behavioral therapy and hypnotherapy have generally been effective for improving IBS outcomes (Ballou & Keefer, 2017; Kinsinger, 2017).

Given the current paucity of data in exercise contexts, many areas require further exploration. Additional studies should attempt to replicate the findings of recent studies that found significant associations between GI symptoms and levels of perceived stress and anxiety (Wilson, 2018; Wilson, 2020a; Wilson et al., 2021). Additional psychological factors should also be considered. For example, hypervigilance to pain or GI sensations has been observed in IBS patients (Posserud et al., 2009) and measures of body or pain vigilance have previously correlated with GI symptom severity (Keough et al., 2011; McKinnon et al., 2015). Additionally, GI-specific anxiety refers to anxiety and cognitions that are specific to the GI system, which some believe to be highly relevant to GI symptomology (Jerndal et al., 2010; Labus et al., 2004). Measures of GI-specific anxiety have correlated with symptom severity in both IBS and non-IBS samples (Jerndal et al., 2010; Labus et al., 2004; Labus et al., 2007; Saigo et al., 2017), and there is some evidence that the effects of psychological treatments on IBS symptomology are mediated by changes in GI-specific anxiety and/or other GI-specific cognitions (Hesser et al., 2018; Windgassen et al., 2017; Wolitzky-Taylor et al., 2012).

Finally, it is possible that psychological factors interact with well-established risk factors to contribute to GI dysfunction during exercise. Runners often consume exogenous nutrients, fluid, or other substances such as caffeine before and during runs to sustain peak performance. But overconsumption of these substances is a well-established risk factor for GI symptoms (de

Oliveira et al., 2014), and many endurance runners reportedly limit certain foods before exercise to mitigate GI symptoms (Parnell et al., 2020). It is possible that certain psychological factors influence the nutritional choices that runners make before and during runs. For example, runners who have greater levels of GI-specific anxiety or body vigilance may limit nutrition intake in fear of provoking GI symptoms, though this has not yet been evaluated.

This study recruited trained runners to address the gaps in the literature through three specific aims: 1) to evaluate the associations between running-related GI symptoms and several psychological factors (stress, anxiety, GI-specific anxiety, body vigilance), 2) to assess the associations between these psychological factors and nutrition intake before and during runs, and 3) to determine if significant associations (if any) in specific aim #2 were mediated by GI symptoms during runs. It was hypothesized that the psychological factors would have significant positive correlations with GI symptoms, that the psychological factors would be negatively associated with nutrition intake (i.e., higher levels of stress/anxiety are associated with lower nutrition intake before and during runs), and that GI symptoms would mediate such an association.

Methods

Participants and Informed Consent

Runners were recruited for the study by emailing and calling race organizers and contact persons at running clubs/teams. The contact persons were asked to distribute a recruitment flyer that contained information about the study and the contact information for the investigators. To be eligible for inclusion, runners were required to: 1) be at least 18 years of age, 2) run at least 20

miles during a typical week of training, and 3) had run at least one run of at least 60 minutes in duration or longer in the last two weeks. These criteria were selected to increase the likelihood that the participants were engaging in enough training to be at high risk of significant GI symptoms and to consider consuming exogenous nutrients or fluids before/during runs. Interested runners were asked to confirm that they met the inclusion criteria and were then sent an electronic informed consent document. They were encouraged to carefully read through the document and to contact the investigators with questions about the study. No data were collected from the participants until they had this opportunity to seek clarification about the study procedures, risks, etc., and had electronically signed the consent document.

Procedures

This study used an observational design involving a combination of prospective and retrospective measurements. After providing consent, participants were first sent a running journal that was used to prospectively track information about their running for seven days. For each run completed during that period, they were asked to report 1) the time, date, and duration of the run, 2) an overall rating of perceived exertion (RPE) on the 6-20 Borg scale (Borg; 1982), 3) a rating of overall discomfort for seven different GI symptoms during the run, and 4) a list of all foods and beverages consumed in the four hours leading up to each run and during the run separately. The GI symptoms were rated on a 0-10 scale, with descriptors at 0 (“no discomfort”), 5 (“moderate discomfort”) and 10 (“unbearable discomfort”). The following standardized definitions were provided:

- Nausea: A feeling of sickness in the stomach marked by an urge to vomit.

- Regurgitation / Reflux: Sensation of *food* or fluid returning from the stomach to the esophagus or mouth.
- Stomach Fullness: A sensation of fullness or abdominal pressure in the upper abdomen.
- Bloating: A feeling of distension from a buildup of gas in the gut.
- Abdominal Cramps: Pain or cramping sensation, often experienced in the mid- or lower-portion of the abdomen.
- Gas: Gas or flatus expelled through the anus.
- Urge to defecate: Sensation of needing to pass a bowel movement.

Participants were asked to return the journal seven days after their first run. At that time, they were sent a link to an electronic retrospective survey through Qualtrics. The survey first asked participants about their age, sex, race/ethnicity, height, weight, years of running experience, and whether they had a medical disorder that provokes GI symptoms. They were also asked to rate the overall level of discomfort experienced for each of the seven GI symptoms at rest over the past month using the same scale as the running journal. This was followed by a series of questionnaires used to quantify the psychological factors of interest.

The 14-item Perceived Stress Scale (PSS-14) was used to quantify life stress. This scale has been shown to be a reliable and valid means of quantifying life stress (Cohen et al., 1983) and has previously been demonstrated to correlate with GI symptoms during running (Wilson, 2018; Wilson et al., 2021). Participants were presented with a series of thoughts and feelings and were asked to report how often they experienced them with the following scale: 0 (“never”), 1 (“almost never”), 2 (“sometimes”), 3 (“fairly often”), and 4 (“very often”). Scores across the 14 items were summed, with the sum scores ranging from 0-56.

The State-Trait Inventory for Cognitive and Somatic Anxiety-Trait subscale was used to assess perceived anxiety (STICSA-Trait; Ree et al., 2008). The STICSA-Trait consists of 21 items about somatic and cognitive manifestations of anxiety and is considered a valid and reliable measure of anxiety symptomology (Elwood et al., 2012; Grös et al., 2007). Participants are asked to rate how often each statement is generally true for them on a scale ranging from 1 (“almost never”) to 4 (“almost always”). Ratings are summed, providing a score that ranges from 21 to 84.

The 4-item Body Vigilance Scale (BVS) was administered to evaluate the participants’ body vigilance, or the degree to which they consciously attend to internal cues or perceptions (Schmidt et al., 1997). The first two items provided the following statements: 1) “I am the type of person who pays close attention to internal body sensations” and 2) “I am very sensitive to changes in my internal body sensations.” Participants were asked to rate their level of agreement with each statement based on the past week on a scale ranging from 0 (“Not at all like me”) to 10 (“Extremely like me”). Item 3 asked the participant to rate how much time they spend “scanning” their body for sensations such as sweating, heart palpitations, and dizziness. The response options ranged from 0 (“No time”) to 100 (“All of the time”) in increments of 10, with 50 described as “half the time.” This rating was divided by 10 to provide a score ranging from 0-10. Item 4 consisted of a series of 15 specific internal sensations (heart palpitations, chest pain/discomfort, tingling, etc.), and the participant were asked to rate how much attention they pay to each sensation on a scale ranging from 0 (“None”) to 10 (“Extreme”). The ratings across the 15 sensations were averaged to provide a single score ranging from 0-10. The scores were then summed across the four items to provide a BVS sum score ranging from 0-40. The original

validation paper found that the BVS had adequate test-retest reliability and high internal consistency across a five-week sampling period (Schmidt et al., 1997).

The 15-item Visceral Sensitivity Index (VSI) was designed to quantify GI-specific anxiety (Labus et al., 2004). Each item presented the participant with a statement that describes how some people respond to discomfort or symptoms within the GI tract (i.e., pain, diarrhea, sense of urgency, etc.). They were then asked to answer how strongly they agree or disagree with each of the statements on the following Likert scale: “strongly agree”, “moderately agree”, “mildly agree”, “moderately disagree”, “strongly disagree”. The ratings were scored from 0 (“strongly disagree”) to 5 (“strongly agree”), and then summed to provide a total VSI score. The VSI has demonstrated good internal consistency (Cronbach’s $\alpha = .93$), as well as convergent, discriminant, content, and predictive validity (Labus et al., 2004, Labus et al., 2007).

Data Processing

Average run duration and RPE were calculated for each participant. In the case of missing data for an individual run, the mean from the other runs was calculated and inputted. Running-related GI problems were quantified as the percentage of runs that a participant reported at least one symptom ≥ 3 out of 10, which was then converted to a value ranging from 0.0 to 100.0 for analysis. This was done separately for all GI symptoms, upper GI symptoms, and lower GI symptoms. Nausea, reflux/regurgitation, bloating, and stomach fullness were categorized as upper GI symptoms, while abdominal cramps, gas/flatulence, and urge to defecate were categorized as lower GI symptoms. Nutrition intake information provided by the runners was used to estimate their total energy (total Kcal), carbohydrates (g), fiber (g), fat (g), protein (g),

fluid from beverages (mL), and caffeine (mg) both before each run (within 4 hours) and during each run. Intake was estimated using Cronometer (<https://cronometer.com/>) and when applicable, by looking up nutrition intake for specific products on official company websites. These values were then averaged across all runs for each participant. Participants were excluded from analyses involving nutrition or beverage intake if they did not provide specific enough information to allow for accurate estimation of intake. The sum scores for each of the psychological and perceptual variables were calculated using the instructions for each questionnaire.

Statistical Analysis

Data was first checked for normality using the Shapiro-Wilk analysis and inspection of histograms. Because most variables were non-normally distributed, non-parametric analyses were used for the analyses.

First, Spearman's rho correlation coefficients were calculated to evaluate the association between the psychological and perceptual scores (PSS-14, STICSA-Trait, BVS, VSI) and the percentage of runs with a GI symptom ≥ 3 (for all, upper, and lower symptoms separately). Partial correlation coefficients were then calculated after controlling for the following potential confounders: age, sex, years of running experience, a sum score calculated from the seven resting GI symptom ratings, and mean RPE across runs. These control variables were selected because they have previously been demonstrated to be independent predictors of GI symptoms during exercise and as such, are commonly controlled for in other similar studies (Wilson, 2016; Wilson, 2018; Wilson et al., 2021). Second, Spearman's rho correlation coefficients were calculated to quantify the association between the psychological and perceptual scores and the

mean values for the nutrition and beverage intake both before and during runs. Mediation analyses were not conducted due to the lack of significant associations that warranted follow-up analysis based on a priori hypotheses.

Results

A total of 104 runners provided consent, with 22 lost to follow-up or that did not complete the necessary data collection. Of the 82 participants (43 men, 39 women) who completed data collection, 11 provided nutrition intake data that was incomplete or too vague to estimate the outcomes of interest. These participants were excluded from analyses involving the nutrition data but were included for analyses on other outcomes (GI symptoms, psychological factors, etc.). The characteristics of the participants are included in **Table 2**.

The participants reported at least one GI symptom ≥ 3 out of 10 during 50% of their runs. When symptoms were categorized by location (upper or lower GI), the runners reported at least one symptom ≥ 3 out of 10 during 16.7% and 36.7% of their runs for upper and lower GI symptoms, respectively. The sum of resting GI symptoms was significantly correlated with all, upper, and lower GI symptoms during runs ($\rho = 0.35 - 0.42$; $p \leq 0.001$), and mean RPE was associated with upper GI discomfort during runs ($\rho = 0.24$; $p = 0.035$). The remainder of the demographic, anthropometric, and training variables were not significantly correlated with GI symptoms (**Table 3**).

Table 2. Characteristics of the Participants in Study 1

	All Participants (n = 82)	Men (n = 43)	Women (n = 39)
Age (years)	47.0 (19.0)	48.0 (20.0)	46.0 (19.0)
BMI (kg/m ²)†	21.7 (3.4)	22.7 (3.1)	20.5 (3.2)
Running Experience (years)	12.0 (16.0)	12.0 (19.0)	10.0 (15.0)
PSS-14 (0-56)	18.5 (8.0)	18.0 (5.0)	20.0 (10.0)
STICSA-Trait (21-84)	31.0 (8.0)	30.0 (8.0)	32.0 (10.0)
BVS (0-100)	17.0 (10.3)	15.6 (13.4)	17.5 (8.8)
VSI (0-75)	8.0 (11.0)	5.0 (10.0)	8.0 (14.0)
Total GI at Rest (0-70)	8.0 (12.0)	8.0 (10.0)	8.0 (14.0)
Mean RPE† (6-20)	12.7 (1.7)	12.6 (1.4)	12.8 (2.6)
Mean Duration (min)	64.0 (21.2)	62.3 (19.1)	65.0 (24.1)
All GI (% of runs)	50.0 (60.2)	50.0 (50.0)	57.1 (80.0)
Upper GI (% of runs)	16.7 (51.8)	14.3 (42.9)	25.0 (60.0)
Lower GI (% of runs)	36.7 (60.6)	40.0 (60.0)	33.3 (66.7)

Note: All variables displayed as median (IQR). †N=81

Table 3. Correlations of Demographics and Training Data with Running GI Symptoms

	All GI (% of runs)	Upper GI (% of runs)	Lower GI (% of runs)
Age (y)	0.08 (.470)	-0.01 (.935)	0.13 (.240)
BMI (kg/m ²)†	0.06 (.618)	-0.04 (.716)	0.09 (.443)
Running Exp. (y)	0.00 (.990)	0.02 (.889)	-0.01 (.930)
Resting GI Total	0.42 (.000)*	0.40 (.000)*	0.35 (.001)*
Mean Duration (min)	-0.05 (.658)	0.04 (.756)	0.02 (.839)
Mean RPE†	0.15 (.191)	0.24 (.035)*	0.12 (.291)

Note: All correlations are Spearman's rho correlation coefficients. Values in parentheses are p values. * = p < 0.05. †N=81

The associations between the psychological scores and GI symptoms during runs are displayed in **Table 4**. Scores on the VSI were significantly correlated all, upper, and lower GI symptoms during runs ($\rho = 0.32 - 0.38$; $p \leq 0.003$). The associations remained significant after controlling for potential confounders (age, sex, running experience, sum of resting GI symptoms, and mean RPE) (partial $\rho = 0.23 - 0.25$; $p \leq 0.043$). The presence of GI symptoms during runs was not significantly associated with scores from the PSS-14, STICSA-Trait, or BVS.

Table 4. Associations Between Psychological Factors and Running GI Symptoms

	Standard Correlations (Unadjusted)		
	All GI %	Upper GI %	Lower GI %
PSS-14	0.10 (.364)	0.12 (.267)	0.08 (.490)
STICSA-Trait	0.08 (.488)	0.01 (.935)	0.16 (.147)
BVS	0.14 (.196)	0.20 (.076)	-0.05 (.687)
VSI	0.36 (.001)*	0.38 (.000)*	0.32 (.003)*
	Partial Correlation (controlling for age, sex, running experience, resting GI, and mean RPE)		
	All GI %	Upper GI %	Lower GI %
PSS-14	0.04 (.747)	0.06 (.636)	0.04 (.735)
STICSA-Trait	-0.06 (.635)	-0.15 (.193)	0.09 (.437)
BVS	0.07 (.558)	0.10 (.388)	-0.11 (.328)
VSI	0.23 (.043)*	0.23 (.043)*	0.25 (.029)*

Note: N=81 for the partial correlations due to a missing RPE value. Bold font and * are used to indicate statistically significant associations at $P < 0.05$.

Information about the pre- and during-run nutrition intake is shown in **Table 5**. The associations between nutrition intake variables and the psychological scores among the 71 participants with complete dietary data are displayed in **Table 6**. Scores on the PSS-14 were significantly positively associated with pre-run intake of fat ($\rho = 0.31$; $p = 0.009$) and protein intake ($\rho = 0.27$; $p = 0.022$). Scores on the VSI were significantly positively correlated with pre-run intake of energy ($\rho = 0.25$; $p = 0.037$) and fat ($\rho = 0.25$; $p = 0.033$). There were no other significant associations between psychological scores and nutrition intake.

Table 5. Overview of Nutrition Intake Data

	All Participants (n = 71)	Men (n = 32)	Women (n = 39)
Pre-Run Energy (kcal)	220.9 (276.7)	251.2 (299.4)	199.8 (263.5)
Pre-Run CHO (g)	33.2 (35.7)	34.1 (33.9)	30.2 (38.8)
Pre-Run Fiber (g)	3.6 (4.4)	3.6 (4.9)	3.8 (3.9)
Pre-Run Fat (g)	7.4 (15.0)	7.8 (16.4)	6.3 (12.8)
Pre-Run Protein (g)	6.4 (12.3)	7.3 (11.6)	6.2 (12.3)
Pre-Run Fluids (mL)	354.9 (318.5)	334.2 (526.9)	361.6 (263.4)
Pre-Run Caffeine (mg)	41.5 (84.9)	41.3 (70.6)	41.5 (75.7)
During-Run Energy (kcal)	0 (8.6)	0 (0.5)	0 (11.0)
During-Run CHO (g)	0 (2.0)	0 (0.2)	0 (2.8)
During-Run Fiber (g)	0 (0)	0 (0)	0 (0)
During-Run Fat (g)	0 (0)	0 (0)	0 (0)
During-Run Protein (g)	0 (0)	0 (0)	0 (0)
During-Run Fluids (mL)	0 (71.0)	0 (27.1)	0 (78.3)
During-Run Caffeine (mg)	0 (0)	0 (0)	0 (0)

Note: All variables displayed as median (IQR)

Table 6. Associations Between Nutrition Intake and Psychological Factors (n=71)

Pre-Run Nutrition				
	PSS-14	STICSA-Trait	BVS	VSI
Pre-Run Energy	0.23 (.056)	0.10 (.416)	0.02 (.856)	0.25 (.037)*
Pre-Run CHO	0.15 (.226)	0.02 (.844)	-0.04 (.726)	0.19 (.111)
Pre-Run Fiber	0.18 (.134)	0.12 (.335)	0.11 (.359)	0.22 (.064)
Pre-Run Fat	0.31 (.009)*	0.19 (.110)	0.09 (.480)	0.25 (.033)*
Pre-Run Protein	0.27 (.022)*	0.15 (.210)	0.04 (.755)	0.15 (.213)
Pre-Run Fluids	0.13 (.295)	-0.02 (.883)	0.08 (.485)	0.15 (.204)
Pre-Run Caffeine	0.04 (.762)	-0.09 (.444)	-0.02 (.881)	-0.15 (.201)
During Run Nutrition				
	PSS-14	STICSA-Trait	BVS	VSI
During Run Energy	-0.04 (.751)	-0.07 (.591)	0.11 (.349)	0.03 (.833)
During Run CHO	-0.04 (.732)	-0.08 (.507)	0.11 (.366)	0.02 (.873)
During Run Fiber	0.01 (.942)	-0.12 (.321)	0.06 (.649)	0.04 (.742)
During Run Fat	0.03 (.786)	0.06 (.630)	0.06 (.625)	0.15 (.198)
During Run Protein	-0.09 (.466)	0.08 (.507)	0.10 (.389)	0.01 (.943)
During Run Fluids	0.10 (.401)	0.05 (.663)	0.02 (.896)	-0.01 (.932)
During Run Caffeine	-0.09 (.464)	0.11 (.365)	0.02 (.897)	-0.09 (.453)

Note: Bold font and * are used to indicate statistically significant associations at $P < 0.05$.

Discussion

Several recent studies found that measures of perceived stress and anxiety were associated with GI symptoms during endurance exercise (Wilson, 2018; Wilson, 2020a; Wilson et al., 2021).

However, the contribution of psychological factors in the etiology of exercise-induced GI

problems remains relatively unexplored. Many psychological factors have been linked to GI function and symptomology in clinical settings (e.g., hypervigilance, GI-specific anxiety, etc.) but have been understudied in the context of exercise. Further, some endurance athletes limit intake of certain foods before races to reduce their risk of GI symptoms (Parnell et al., 2020), but there has been no attempt to determine if nutritional choices are associated with psychological characteristics of the athlete. As such, the present study sought to determine if GI symptoms were associated with several psychological factors, and whether these psychological factors were associated with peri-run nutrition intake across a week of running.

The present study found no significant associations between running-related GI symptoms and scores on the PSS-14, STICSA-Trait, or BVS, which does not support our hypotheses based on findings from previous research. Wilson (2018) found PSS-14 scores had modest correlations with the occurrence of substantial running-related GI symptoms across a month of training ($\rho = 0.23 - 0.29$). Notably, the runners had similar characteristics to those in the present study in terms of age, running experience, PSS-14 scores, and percentages of runs with GI symptoms that were ≥ 3 out of 10. While the study methodologies and analyses differed, the present findings are also not in-line with Wilson et al. (2021), who found that endurance athletes scoring in the top tertile for PSS-14 and STICSA-Trait were at significantly higher odds for reporting certain GI symptoms of ≥ 5 on a 0-to-10 scale during races. A third investigation by Wilson (2020a) found that scores on the STICSA-Trait and Sport Competition Anxiety Test had significant correlations with GI symptom ratings during endurance races ($\rho = 0.22 - 0.33$; $p < 0.05$). While the methodologies differed across these studies, they each found significant associations between measures of stress/anxiety and GI symptoms during running or endurance exercise, which was not the case in the present study.

There are several potential explanations for the disparate findings between the present study and previous investigations. First, the 7-day training period in the present study may not have been long enough to accurately depict runners' tendencies to experience GI symptoms compared to the 30 days used by Wilson (2018). Though it is difficult to ascertain whether this influenced the results since the percentages of runs with a symptom ≥ 3 were similar between the two studies. Second, it is possible that differences are partially due to how GI problems were defined. Wilson et al. (2021) evaluated GI symptoms individually rather than categorizing them by all, upper, or lower GI problems. Using this methodology, they found that only certain GI symptoms (nausea, reflux/regurgitation) had higher odds of being reported by athletes in the top tertile for PSS-14 and STICSA-Trait.

Perhaps the most likely explanation for the disparate results to date is that Wilson et al. (2021) and Wilson (2020a) evaluated psychological factors and GI symptoms in relation to competition. Theoretically, a competitive setting is when competitive anxiety would be at its highest, athletes are pushing themselves the hardest, and when the associations between psychological factors and GI problems should be most pronounced. Indeed, the largest statistically significant odds ratios in Wilson et al. (2021) were reported for those in the top tertile for state anxiety during the morning of the race (odds ratios = 2.99 – 5.57; $p < 0.05$). The present study suggests that there is minimal association of perceived stress and trait anxiety with GI symptoms during a typical week of training, but results may differ if a study was conducted during the week of a competition, or if a longer timeframe of tracking was employed.

It was also hypothesized that there would be a significant positive association between BVS scores and GI problems. This was the first study to evaluate such an association in exercise contexts, but the BVS and other measures of vigilance have been used in non-exercise contexts.

For example, a study with IBS patients found that BVS scores were associated with GI symptomology (Keough et al., 2011), and hypervigilance to pain or GI symptoms is commonly reported in functional GI disorders (Posserud et al., 2009). However, the present results do not support our hypothesis. Future research could consider evaluating runners' vigilance to painful stimuli specifically, using questionnaires such as the pain vigilance and awareness scale (McCracken, 1997).

There were, however, statistically significant associations between GI-symptom burden and VSI scores, which remained significant after controlling for potential confounders such as age, sex, running experience, resting GI symptoms, and mean running RPE (**Table 4**). Notably, the magnitude of these associations is comparable to those that have been reported for other GI-symptom risk factors such as perceived stress/anxiety, age, and running intensity (Wilson, 2018), as well as pre-race energy, carbohydrate, and caffeine intakes (Wilson, 2016). The VSI was designed to evaluate anxiety that is specific to the GI-system (Labus et al., 2004). While this is, to our knowledge, the first study to evaluate associations between VSI and GI symptoms in an exercise context, this scale has been used extensively in relation to GI symptomology in irritable bowel syndrome (IBS). The findings from these studies may provide some context for the present findings and potential avenues for future research.

Recent evidence has suggested that psychological factors that are specific to the GI system, such as GI-specific anxiety and GI-specific cognitions, may be highly relevant to GI symptomology and outcomes (Hesser et al., 2018; Jerndal et al., 2010; Labus et al., 2007; Windgassen et al., 2017). For example, VSI scores tend to be significantly associated with GI symptomology in individuals with and without IBS (Jerndal et al., 2010; Labus et al., 2007; Saigo et al., 2018), and in some cases, associations between general psychological factors and GI

symptomology have been mediated by VSI scores (Labus et al., 2004; Labus et al., 2007). Further, recent studies have suggested that the effects of psychological treatments on IBS outcomes may be mediated by reductions in VSI scores (Garland et al., 2012; Ljótsson et al., 2013; Windgassen et al., 2017). As such, several authors have suggested that GI-specific constructs such as GI-specific anxiety and maladaptive GI-related cognitions or behaviors should be primary targets for interventions that seek to improve IBS outcomes (Garland et al., 2012; Jerndal et al., 2010; Windgassen et al., 2017). Though it is important to note that others have argued that the primary treatment target should be context-specific, as some patients may respond best to reductions in general psychological comorbidities, while others may need a larger focus on anxiety or maladaptive behaviors/cognitions that are GI-specific (Spiegel et al., 2011). Taken together, there is some evidence that GI-specific anxiety is an important consideration for those with functional GI disorders, though it is currently unknown how well these findings generalize to athletic or physically active populations.

Additional studies should expand on the findings from the present study to determine to what extent GI-specific anxiety or other GI-specific psychological constructs contribute to symptoms in the context of exercise. Studies should include the VSI as a measure of GI-specific anxiety, particularly in competitive settings as done by Wilson et al. (2021) and Wilson (2020a). There are also other factors that may be useful to evaluate, such as the GI-Specific Cognitions Questionnaire, which aims to quantify an individual's GI-specific catastrophic cognitions (Hunt et al., 2014). Further, it may be useful to conduct path analyses with large samples to see how various psychological factors interact and contribute to GI symptoms. For example, a recent study with IBS patients evaluated a comprehensive battery of psychological factors and found evidence of a pathway through which personality factors (higher levels of neuroticism)

contributed to greater amounts of negative appraisal, which in turn led to greater pain catastrophizing and vigilance. The byproduct of these factors was greater levels of GI-specific anxiety, and ultimately worsened symptom ratings (McKinnon et al., 2015). Given the relative paucity of data available in exercise settings currently, such studies may help clarify the role of various psychological factors (if any) on GI symptoms during exercise. Finally, experimental studies could compare the effects of highly GI-specific psychological treatments to those that target general stress or anxiety reduction. The addition of follow-up mediation analyses may help clarify which psychological factors (if any) mediate treatment effects within and across conditions.

A second aim of this study was to evaluate the associations between psychological factors and nutrition intake before and during runs. Surprisingly, there were relatively weak associations between psychological factors and nutrition intake before and during runs (**Table 6**). The few significant associations were positive in direction, which runs in contrast to our hypothesis that those with higher levels of stress or anxiety would consume less food and beverages prior to running to avoid GI symptoms. It is difficult to determine why this result occurred, although it is possible that the few significant positive associations represent confounding by some other unmeasured factor(s). Also, as previously discussed, the associations might differ in a competitive setting. The present study evaluated outcomes during a typical week of running, which may have resulted in lower levels of stress/anxiety and nutrition intake in comparison to competition weeks. Further, it is possible that a 7-day period is not long enough to get an accurate depiction of their typical pre- and during-run fueling strategies, and the remote nature of this study meant that data collection relied on self-report journaling of nutrition intake which could introduce error (Schoeller, 1995). Taken together, future studies should consider

evaluating the associations between psychological factors and nutrition intake immediately before and during a competitive race rather than during a training week and when possible, observe nutrition intake directly or use additional methods to limit self-report error (i.e., have athletes send pictures of their pre-run meals).

There are several limitations to this study. First, the observational design does not allow for evaluation of the causal nature of the observed associations. Indeed, reverse causality or even bi-directional associations are possible. For example, higher scores on the VSI may predispose a runner to report GI symptoms due to a causal relationship between GI-specific anxiety and GI symptomology. However, it is also possible that the GI-specific anxiety/higher VSI scores resulted from runners' previous experiences with GI symptoms. Longitudinal studies are required to parse out the nature of the association between VSI scores and GI symptoms. Second, the use of self-report dietary journals may have resulted in inaccurate nutrition intake estimates. While this is a difficult limitation to circumvent, future studies may consider directly observing food and beverage intake or take steps to improve the accuracy of portion size estimates (e.g., by requiring pictures of food and beverages). Finally, previous studies that have identified psychological correlates have either asked participants to track runs for 30 days (Wilson, 2018) or asked about symptoms during a competitive race (Wilson, 2020a; Wilson et al., 2021). It is possible that the seven days used in this study was not enough to accurately quantify typical GI symptoms and nutrition intake. Further, the associations between psychological factors, nutrition intake, and GI problems could be more prominent during competitive races, when competition anxiety is higher, and runners are more likely to consume larger quantities of foods and beverages to fuel optimal performance. This type of design was not possible for the present study, given the restrictions on races that were imposed due to the COVID-19 pandemic.

CHAPTER V

EFFECTS OF DAILY BREATHING INTERVENTIONS ON GI SYMPTOMS, HEART RATE VARIABILITY AND PSYCHOLOGICAL FACTORS IN RUNNERS

Introduction

The GI system and central nervous system communicate through numerous neuroendocrine and immunological pathways collectively known as the “brain-gut axis” (Mayer et al., 2015). There is considerable overlap between pathways of the brain-gut axis and stress response systems in the body (Boeckxstaens et al., 2016; Vanner et al., 2016), and alterations to such pathways are thought to explain why conditions involving abdominal pain (e.g., IBS) have a strong psychological component (Labanski et al., 2020; Mayer & Tillisch, 2011). For example, experimental models have demonstrated that various acute and chronic psychological stressors have various effects on GI functions such as altered motility (Almy et al., 1949; Holtman & Enck, 1991), delayed gastric emptying (Bhatia & Tandon, 2005; Enck & Holtmann, 1992), damage to the intestinal epithelial barrier (Hyland et al., 2014; Söderholm et al., 2002), and development of visceral hypersensitivity (Larauche et al., 2012). Additionally, psychological factors like stress, anxiety, and depression are risk factors for IBS (Bennett et al., 1998; Labanski et al., 2020; Moloney et al., 2016) and correlate with GI symptomology in the general population (Haug et al., 2002; Stanghellini, 1999). Further, psychological treatments such as cognitive behavioral therapy and hypnotherapy have generally been effective for improving IBS outcomes (Ballou & Keefer, 2017; Kinsinger, 2017). Taken together, current evidence suggests that psychological factors are relevant to GI function and symptomology.

Surprisingly, little research has evaluated the role of psychological factors in the context of exercise-induced GI dysfunction and symptoms. Early descriptive studies found that many

endurance athletes reportedly experience symptoms (including “nervous diarrhea”) before competition (Sullivan & Wong, 1992; Worobetz & Gerrard, 1985) and that some athletes believe GI symptoms are more likely when anxious about competing (Sullivan, 1987). More recently, three studies found that measures of perceived stress and anxiety were associated with GI symptoms during 30-days of running (Wilson, 2018) and during competitive endurance races (Wilson, 2020a; Wilson et al., 2021). These findings appear to demonstrate that psychological factors are associated with exercise-induced GI symptomology, though more research is clearly needed, particularly from experimental designs. For example, some athletes may have higher levels of stress or anxiety because they tend to experience GI symptoms during runs, not because the stress or anxiety caused the symptoms. Or the association could be bi-directional. Randomized trials utilizing psychological treatments may help clarify the causative relationship between psychological factors and exercise-related GI symptoms while also potentially identifying efficacious treatments. Two interventions that could be effective and feasible for endurance athletes are slow deep breathing and mindful breath counting (Gorman & Green, 2016; Russo et al., 2017).

Slow deep breathing at about six breaths per minute has numerous physiological effects, including enhanced HRV by promoting increased vagal outflow and dampened sympathetic activity (Badra et al., 2001; Bernardi et al., 2001; Chang et al., 2013; Paprika et al., 2014; Tharion et al., 2012). This is potentially relevant to GI dysfunction since the vagus nerve is a key mediator of pathways within the brain-gut axis and the stress response systems that overlap with it (Boeckxstaens et al., 2016; Vanner et al., 2016). There is also some evidence that slow deep breathing interventions can impact GI function in some circumstances, such as improving feeding tolerance in functional dyspepsia (Hjelland et al., 2007) and nausea in motion sickness

scenarios (Jokerst et al., 1999). Mindfulness interventions may also be beneficial, due to their positive effects on various health outcomes including anxiety and pain (Strauss et al., 2014; Zeidan et al., 2011). This seems to include benefits to GI function, as one study reported improved IBS symptom severity after a mindfulness intervention (Gaylord et al., 2011). The precise underlying mechanisms are not clear, but mindfulness interventions could buffer stress through effects on brain regions that regulate top-down responses to stress and those involved with stress axes (Creswell & Lindsay, 2014; Creswell, 2017). There is also the possibility that they could promote nonreactivity to gut sensations and reduce GI-specific anxiety or catastrophic thoughts about visceral sensations (Gaylord et al., 2011). There are many different mindfulness interventions, but simple breath counting has the advantage of being simple to perform, time-efficient (Levinson et al., 2014), and has been shown positively affect outcomes such as stress-induced alcohol seeking behavior (Shuai et al., 2020).

Given that recent studies have identified psychological factors as potential risk factors for GI symptoms during exercise (Wilson, 2018; Wilson, 2020a; Wilson et al., 2021), experimental studies that evaluate the effects of stress or anxiety reducing interventions on GI symptoms would be useful. As such, the purpose of this randomized controlled trial was to evaluate the effects of simple daily breathing interventions on GI symptoms, psychological factors (stress, anxiety, GI-specific anxiety, body vigilance, mindfulness), and HRV in endurance runners.

Methods

Participants and Screening

Runners were recruited by contacting race organizers and contact persons at running clubs. The contact persons were sent a recruitment flyer that outlined the study and included the investigators' contact information. A phone or video information call was scheduled with each runner that contacted the investigators. During the call, prospective participants were first screened to ensure they were eligible to participate. To be eligible for inclusion, participants were required to meet the following criteria:

- At least 18 years of age.
- Currently running at least 15 miles during a typical training week.
- Currently residing in the contiguous United States.
- Access to the internet and a smartphone or tablet that was compatible with the iOS or Android versions of the Elite HRV smartphone application.
- If prescribed a psychotropic drug (e.g., SSRIs), the dose had to have been stable for 3+ months prior to enrollment.
- At least sometimes experience GI symptoms during runs. This was assessed by asking them to report how often they had experienced GI symptoms during runs in the past month. The criterium was fulfilled if they answered either “sometimes”, “often” or “always” on a five-point Likert scale.
- Have at least mild anxiety at the time of enrollment. To quantify anxiety levels, participants completed the GAD-7 questionnaire. A score of 5 or higher was used as a cut-off score for mild anxiety based on previous recommendations (Williams, 2014).

Those who met the criteria were sent an electronic informed consent document and provided an overview of the study procedures, risks, etc. They were encouraged to carefully read through the informed consent document and ask questions before indicating their agreement to participate on the consent form.

Design Overview

A parallel-group, unblinded randomized controlled trial was used to evaluate the effects of two breathing interventions on GI symptoms, psychological factors, and HRV. All procedures were completed remotely due to restrictions during the COVID-19 pandemic. After enrollment, participants were provided materials and instructions to complete three pre-intervention measurements: 1) a running journal used to track information about their runs and GI symptoms for seven days, 2) a portable HRV monitor to take a resting HRV measurement, and 3) a pre-intervention survey to collect information about their demographics, training information, and to quantify baseline levels of the psychological factors of interest for this study (stress, anxiety, GI-specific anxiety, body vigilance, mindfulness). Participants were then randomly allocated to one of three groups for four weeks: SLOWBC, NORMALBC, or control (the specifics of each are described later on in the 'Interventions' section). The randomization process was done using blocks of 3 and 6. Gender-specific randomization lists were generated using the following website (<https://www.sealedenvelope.com/simple-randomiser/v1/lists>). A person not involved in the data collection was asked to generate the lists and then fill sequentially labelled envelopes with the results.

Participants were sent a midpoint electronic survey two weeks into their assigned intervention period to assess resting GI symptoms and the psychological factors. At the end of week three, they were sent a second running journal and portable HRV monitor to replicate the pre-intervention measurements. A final electronic survey was sent on the final day of the intervention.

Measurements

Running Journal

The running journal was adapted from study 1 and was used to record the following information about each run participants performed during a 7-day period: 1) the time, date, and duration (in minutes) of the run, 2) an overall 6-20 RPE for the run, and 3) 0-10 ratings for the same seven GI symptoms as used in Study 1. The symptoms and scale were identical to those used for study 1 (**See Chapter III for more information**). Participants were asked to send the journal back seven days after their first completed run. A journal was sent upon enrollment (pre-intervention running journal) and after the third week of the intervention period (post-intervention running journal). The timing of the post-intervention measurement was done to maximize the chances of detecting any transient effects of the breathing sessions by evaluating GI symptoms during the final days of the intervention. The variables assessed from each running journal were the number of runs completed, average run duration (min), average run RPE (6-20), the percentage of runs with at least one symptom ≥ 3 out of 10 across all, upper, and lower GI symptoms independently. Average running GI burden was also calculated by summing GI symptom scores during each run and then averaging the sum scores across runs.

HRV Measurement

A portable CorSense HRV monitor was shipped to participants with instructions to complete a resting measurement. Portable HRV devices are generally considered a valid alternative to gold-standard methods (e.g., electrocardiogram; Dobbs et al., 2019), and user-friendly methods for collecting data remotely were necessary for this study due to the COVID-19 pandemic.

Participants were provided step-by-step instructions for downloading the Elite HRV smartphone application and using the HRV monitor. The participant was told to lay comfortably in the supine position, place the monitor on a fingertip, and initiate a measurement through the smartphone application. After a short sampling period, the monitor collected information for five minutes and results were uploaded to the smartphone application. Participants were asked to take a screenshot of the results page and send it to the investigators through email or text message. A monitor was sent upon enrollment (pre-intervention) and after week 3 of the intervention period (post-intervention). The primary variable assessed and analyzed was Ln (RMSSD) in ms, as this variable has been recently validated using the Elite HRV smartphone application (Perrotta et al., 2017).

Electronic Surveys

Qualtrics-based electronic surveys were sent to each participant upon enrollment (pre-intervention), after week two of the intervention (midpoint), and on the final day of the intervention (post-intervention) through email. The pre-intervention survey first asked participants about demographic information such as age, sex, race/ethnicity, running experience, GI conditions, use of medications to manage GI symptoms during running, history of performing

breathing interventions, employment status, and job stress. Participants were then asked to rate the typical severity of the seven GI symptoms at rest and to complete a series of psychological questionnaires. Perceived stress, anxiety, body vigilance, GI-specific anxiety, and mindfulness were quantified using the PSS-14, GAD-7, BVS, VSI, and FFMQ questionnaires respectively (See Chapter III for more thorough descriptions of each scale). The midpoint and post-intervention surveys excluded the questions about participant demographics but were otherwise identical to the pre-intervention survey. Aside from demographic information (age, sex, running experience, etc.), the variables assessed from each survey were the sum of the resting GI symptom scores and the scores for each of the psychological questionnaires.

Interventions

Individuals in the SLOWBC and NORMALBC groups were asked to complete a guided 5-minute daily breathing sessions for four weeks. The interventions were similar other than the breathing frequency (six breaths/minute for SLOWBC, 15 breaths/minute for NORMALBC) and breathing depth (SLOWBC was asked to take deep breaths, NORMALBC was asked to take normal breaths). They were sent a reusable link to a video embedded with audio instructions and a breathing application (eXHALeR V. 2.0.6; <https://xhalr.com/>) to guide them through the sessions. They were also sent a treatment journal to track their progress. After a short audio message that provided instructions for the intervention, the video displayed a visual aid that participants were asked to sync their breathing to. Each breathing cycle (inhalation, hold, exhalation) was visually shown by a circle that expanded and constricted to simulate the prescribed breathing pattern. The words “inhale”, “hold”, and “exhale” were displayed as the circle constricted, at full expansion, and as the circle constricted respectively (**Figure 2**).

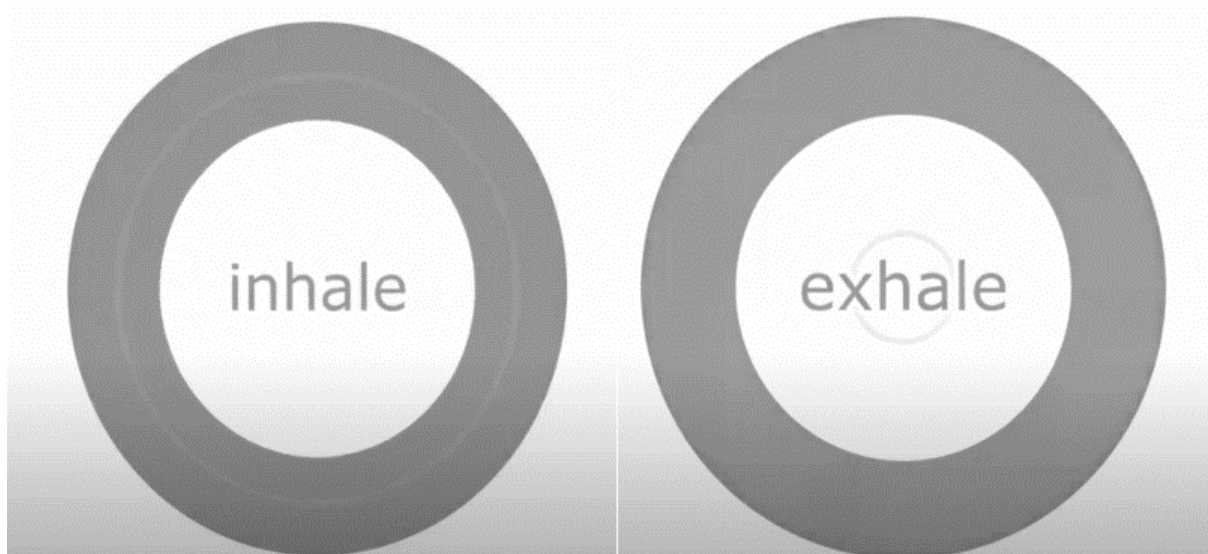


Figure 2. Visual aid used in the SLOWBC and NORMALBC videos.

The SLOWBC video was set to a 4-second inhalation, 2-second hold, and 4-second exhalation so that participants breathed at six breaths per minute. The NORMALBC video was set to 2-second inhalations and exhalations with no hold to equate to 15 breaths per minute. Both groups were asked to count their breaths until they reached 10, restart from 1, and continue that cycle throughout the session. However, the SLOWBC group was prompted to take deep breaths while the NORMALBC group was asked to take regular breaths.

At the end of the five minutes, an audio message prompted participants to record the time/date and 1-10 ratings of how engaged they were in the task and how pleasant they found the session in the treatment journal. Participants were asked to complete each session within two hours of running when possible. On days they did not run, or a pre-run session was not possible,

participants were asked to schedule a time to complete the session and try to be consistent with timing each day. Participants were contacted weekly through phone and email correspondence to check on their compliance to the intervention and answer questions about the intervention. The control group did not perform a daily breathing intervention and were asked to not engage in any sort of breathing intervention during their involvement in the study.

Data Processing

Scores for the psychological factors were calculated according to scoring instructions for each questionnaire. Resting GI symptom burden was quantified by summing resting GI symptom ratings in each survey. The primary method of quantifying GI symptom burden during runs was as the percentage of runs with at least one symptom ≥ 3 out of 10. This was done for all symptoms, upper GI symptoms (nausea, reflux/regurgitation, bloating, stomach fullness), and lower GI symptoms (abdominal cramping, gas, urge to defecate) separately. This methodology tends to result in more normality distributed data and also gives a sense of the burden of notable symptoms over time. Additionally, average running GI-symptom burden was calculated by summing the reported GI symptom scores during each run and averaging across the total number of runs logged. Mean running RPE and duration were calculated for each participant. When data for an individual run was not reported, the mean value across all other runs was inputted.

Due to the remote nature of this study, some participants did not strictly adhere to the prescribed timing of measurements or intervention period. As such, the following information was derived from the treatment journals: 1) the total number of days from the first completed session to the final completed session, 2) the total number of breathing sessions completed

within that timeframe, 3) the percentage of days where a breathing session was completed during that timeframe, and 4) mean ratings of engagement and pleasantness across all breathing sessions completed. Additionally, the dates of each completed measurement and for the first and last breathing session completed were recorded to quantify the degree of compliance to the procedures. The number of days between each of these dates were calculated and reported below (**Table 7**).

Table 7. Overview of Measurement Timing

Number of Days	SLOWBC	NORMALBC	Control
Pre-Running Journal to 1 st Treatment Day	6.4 ± 4.9	6.6 ± 5.2	-
Pre-Survey to 1 st Treatment Day	6.6 ± 5.7	8.2 ± 5.6	-
Pre-HRV to 1 st Treatment Day	7.9 ± 5.2	5.3 ± 6.0	-
1 st Treatment Day to Post-Running Journal	29.7 ± 6.1	28.8 ± 3.4	-
1 st Treatment Day to post-survey	31.1 ± 6.8	30.7 ± 3.5	-
1 st Treatment Day to post-HRV	31.5 ± 7.5	27.1 ± 2.5	-
Last treatment day to post-survey	1.3 ± 3.1	1.9 ± 2.8	-
Last treatment day to post-running journal	-0.2 ± 1.8*	0.0 ± 1.2	-
Last treatment day to post-HRV	1.7 ± 3.9	-0.9 ± 3.8*	-
Pre-running journal to post-running journal	36.1 ± 6.6	35.4 ± 7.1	34.6 ± 9.9
Pre-survey to post Survey	36.9 ± 6.8	39.2 ± 6.6	39.2 ± 9.6
Pre-HRV to Post-HRV	43.5 ± 11.7	34.2 ± 6.4	34.9 ± 4.9

Note: Data from all participants that completed the study. *Negative values indicate that the measurement was completed before the last recorded treatment day. The final date where a run was logged was used as the completion date for the running journals. The first and last treatment days were defined as the first and last day that the participant logged a breathing session on the treatment journal.

Statistical Analysis

Shapiro-Wilk tests with visual inspection of histograms and Q-Q plots were used to evaluate the normality of the data. Imperfect compliance and missing outcomes were handled by conducting both intention-to-treat (ITT) and per-protocol analyses (Gupta, 2011; Ranganathan et al., 2016; Schulz et al., 2010). ITT analyses include all participants that were randomized into groups, regardless of their compliance with the study procedures (Gupta, 2011). This is done to mitigate bias that comes from excluding non-compliant participants, maintain the characteristics of the groups that results from randomization, and reflects the reality of practical implementation of treatments, where compliance is not always perfect (Fergusson et al., 2002; Wertz, 1995). In contrast, per-protocol analyses exclude participants with poor compliance and missing outcomes and allow for a more direct analysis of treatment effects amongst those who completed the study procedures (Ranganathan et al., 2016; Schulz et al., 2010). For the ITT analyses, missing midpoint and post-intervention data was inputted using the “Last Observation Carried Forward” method, where a participant’s most recent observation prior to withdrawal from the study is retained (Streiner & Geddes, 2001). The specific inclusion and exclusion criteria for the per-protocol analysis are listed below:

- Participants in the SLOWBC or NORMALBC groups were excluded if they met one of the following criteria: 1) a breathing treatment journal was never completed or sent to the investigators, 2) poor treatment compliance, defined as completing <50% of sessions between the first and last breathing session; 3) post-intervention measurements were completed >10 days after the final breathing session; 4) poor treatment timing, defined as >42 total days between the first and last breathing sessions. The 42-day cut-off was

selected as this equated to two additional weeks beyond the prescribed four-week intervention.

- Participants in the control group were excluded from analyses for a given outcome if there was ≥ 60 days between the pre- and post-intervention measurements. Sixty days was selected because it equated to more than three weeks longer than the prescribed time between the beginning of the pre-intervention measurements and the end of the intervention period (1 week for baseline measurements, 4 weeks for the intervention).

Data related to the intervention compliance and engagement were compared between SLOWBC and NORMALBC groups with independent t-tests. Normally distributed data were analyzed using mixed methods ANOVA, with group allocation (SLOWBC, NORMALBC, Control) as the between-subjects factor and time (pre-intervention, midpoint, post-intervention) as the within-subject factor. Mauchly's test of sphericity was checked, and in cases of $p < 0.05$, the Huynh-Feldt correction was reported instead. When a significant group x time interaction was detected, simple main effects were reported instead of main effects. Non-normally distributed data was compared across groups with the Kruskal Wallis test at each time point. Bonferroni post hoc tests were used when ANOVAs or Kruskal Wallis tests identified statistically significant effects. Partial eta squared (η^2) and ranked epsilon squared (ϵ^2) were calculated as measures of effect size for the mixed ANOVAs and Kruskal Wallis tests, respectively (Tomczak & Tomczak, 2014).

Results

Participants

A total of 121 runners were screened for eligibility. Sixty-eight were eligible to participate based on the inclusion criteria. Ultimately, 63 runners consented to participate and were enrolled in the study. Of the 63 participants that enrolled in the study, seven did not complete the pre-intervention measurements and were not randomized. The remaining 56 participants were randomly allocated to either the SLOWBC (n=20), NORMALBC (n=18), or control (n=18) groups. An overview of the baseline characteristics of the participants is shown in **Table 8**.

Two participants from the SLOWBC group and three participants from the NORMALBC group were lost to follow-up. The last observed datapoints were inputted for use in ITT analyses. An additional four participants were excluded from the per-protocol analyses due to poor compliance to the treatment (n=2) or because they never sent a completed treatment journal (n=2). The ITT analyses and per-protocol analyses included data from 56 and 47 total participants, respectively. Among the 47 participants available for the per-protocol analyses, there were missing data points for some measurements due to compliance issues, resulting in slightly different sample sizes depending on the outcome being analyzed. The flow of participants through the study is displayed in **Figure 3**.

Table 8. Characteristics of the Participants in Study 2

	SLOWBC (n = 20)	NORMALBC (n = 18)	Control (n = 18)
Age (years)	38.5 (22.0)	30.0 (13.0)	37.0 (14.0)
BMI (kg/m ²)	22.0 (3.6)	21.7 (2.0)	21.6 (3.9)
Job Stress Rating (0-10)	7.0 (3.0)	7.0 (3.0)	6.0 (2.0)
Running Experience (years)	15.5 (17.0)	10.0 (7.0)	10.0 (9.0)
Resting GI burden (0-70)	14.0 ± 7.9	14.4 ± 10.1	17.9 ± 8.8
Pre-Intervention Run RPE (6-20)	11.8 ± 1.7	12.0 ± 1.2	12.6 ± 1.4
Post-Intervention Run RPE (6-20)	11.9 ± 1.9	12.0 ± 1.2	12.2 ± 1.4
Pre-Intervention Run Duration (min)	48.2 ± 16.6	52.7 ± 17.6	75.3 ± 35.0
Post-Intervention Run Duration (min)	47.8 ± 15.3	51.7 ± 18.6	69.0 ± 29.0
% Female	65.0	66.7	72.2
% Male	35.0	33.3	27.8
% Employed	90.0	88.9	83.3
% with Reported GI Condition	25.0	27.8	11.1
% with prior experience with breathing exercises	60.0	44.4	38.9
% that use medications to mitigate GI symptoms during runs	10.0	11.1	5.6

Note: Normally-distributed variables are displayed as means ± standard deviation. Non-normally distributed variables are displayed as medians (Interquartile Range).

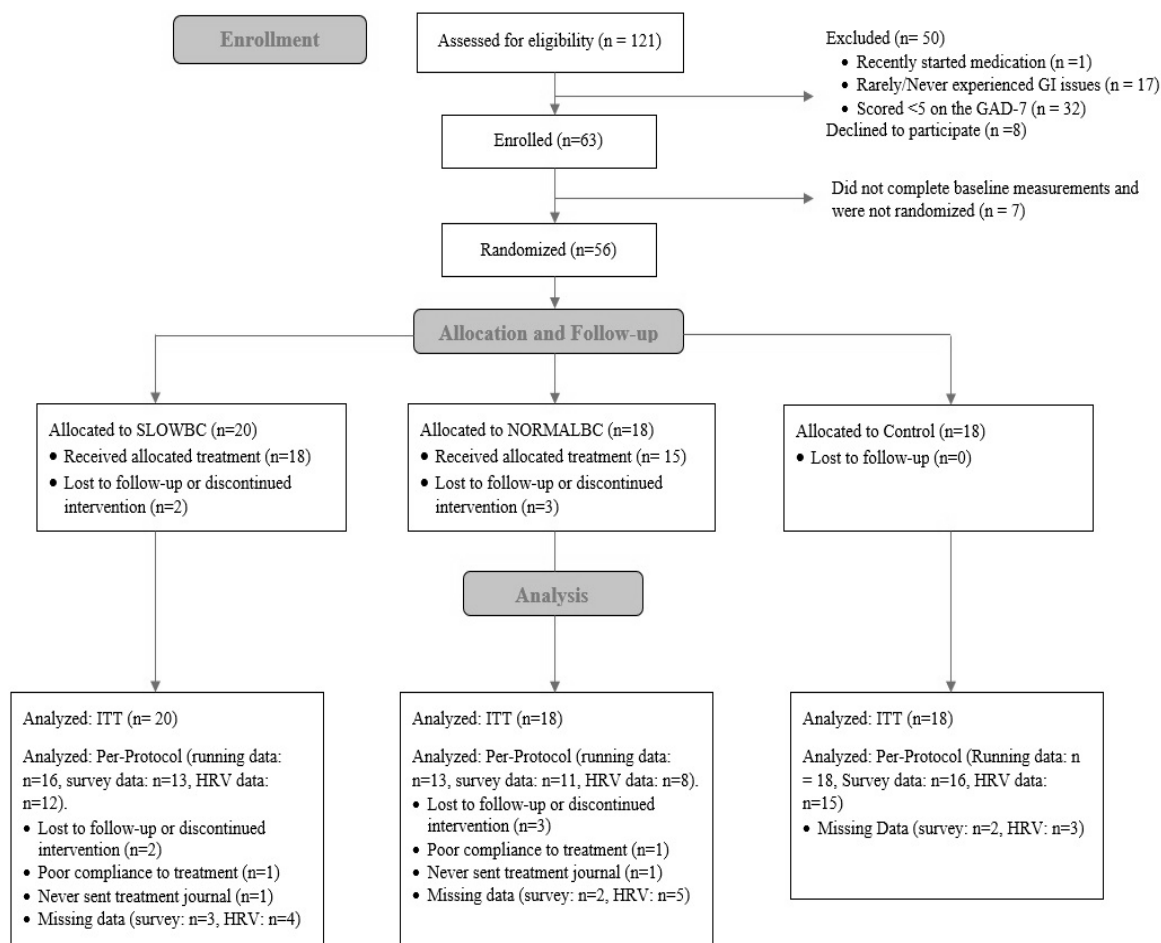


Figure 3. Participant flow through the study.

Intervention Compliance and Comparison

An overview the two interventions is displayed in **Table 9**. Thirty-one participants submitted a treatment journal for either the SLOWBC (n=17) or NORMALBC (n=14) intervention. The SLOWBC participants completed an average of 23.9 ± 4.1 sessions across a timeframe of 30.9 ± 6.0 days, which equated to sessions being completed on $79.4 \pm 16.7\%$ of days. The NORMALBC participants completed an average of 24.4 ± 6.9 sessions across a timeframe of 29.8 ± 3.8 days, which equated to sessions completed on $81.2 \pm 17.4\%$ of days. One participant

from each of these groups was excluded from the per-protocol analyses due to poor compliance. When excluding these participants, compliance values were similar. The SLOWBC group completed 24.2 ± 4.1 sessions across 30.1 ± 4.9 days ($81.7 \pm 14.2\%$ compliance), while the NORMALBC group completed 25.5 ± 6.0 sessions across 30.0 ± 3.9 days ($84.3 \pm 13.4\%$ compliance). There were no significant differences between the two groups in terms of total treatment days, the number of sessions completed, the percentage of treatment days where a session was completed, mean rating of engagement in the task, or mean rating of how pleasant each session was ($p \geq 0.074$ for all outcomes) for data included in either ITT or per-protocol analyses.

Primary Outcomes

Intention-to-Treat Analysis

Table 10 provides a summary of the ITT results for normally distributed variables. There were no statistically significant group effects or time x group interactions for all five psychological factors, resting GI symptoms, or for Ln (RMSSD) ($p \geq 0.093$). However, FFMQ scores tended to increase, and PSS-14 and GAD-7 scores tended to decrease over time as evidenced by modest sized, but statistically significant time effects (**Table 10**).

A summary of results for analyses of non-normally distributed variables is displayed in **Table 11**. There were no statistically significant differences between groups for any of the measures of GI symptoms during runs at any time point ($p \geq 0.468$).

Table 9. Overview and Comparison of the Interventions

Intention-to-Treat Analysis				
	SLOWBC (n = 17)	NORMALBC (n=14)	P value	Cohen's <i>d</i> (95% CI)
Total Treatment Days (d)*	30.9 ± 6.0	29.8 ± 3.8	0.539	0.22 (-0.49, 0.93)
# Sessions Completed (d)	23.9 ± 4.1	24.4 ± 6.9	0.788	-0.10 (-0.81, 0.61)
% of Treatment Days Completed**	79.4 ± 16.7	81.2 ± 17.4	0.771	-0.11 (-0.81, 0.60)
Mean Engagement (1-10)	7.6 ± 1.0	7.2 ± 0.9	0.270	0.41 (-0.31, 1.12)
Mean Pleasantness Rating (1-10)	7.6 ± 1.1	7.0 ± 1.2	0.206	0.47 (-0.26, 1.18)
Per-Protocol Analysis				
	SLOWBC (n = 16)	NORMALBC (n = 13)	P Value	Cohen's <i>d</i> (95% CI)
Total Treatment Days*	30.1 ± 4.9	30.0 ± 3.9	0.971	0.01 (-0.72, 0.75)
# Sessions Completed	24.2 ± 4.1	25.5 ± 6.0	0.503	-0.25 (-0.99, 0.48)
% of Treatment Days Completed	81.7 ± 14.2	84.3 ± 13.4	0.620	-0.19 (-0.92, 0.55)
Mean Engagement (1-10)	7.7 ± 1.0	7.1 ± 0.8	0.074	0.69 (-0.07, 1.44)
Mean Pleasantness Rating (1-10)	7.6 ± 1.1	6.9 ± 1.1	0.080	0.68 (-0.08, 1.43)

Note: *Total treatment days refers to the number of days from the first breathing session completed until the last session completed. This varies from the prescribed four weeks for some participants due to issues with compliance and communication given the remote nature of the study. **Calculated as: (# Sessions Completed/Total Treatment Days)*100. The intention-to-treat analysis comparisons included data from all participants that were allocated and that submitted a treatment journal. The per-protocol analysis comparison included data from participants that met the criteria for the inclusion in the per-protocol analyses as outlined in the methods section. P values and Cohen's *d* values are from independent *t* tests used to compare between groups.

Table 10. Mixed ANOVA Results for Normally Distributed Variables: Intention-to-Treat

Measure	SLOWBC (n=20)	NORMALBC (n=18)	Control (n=18)	Time Effect P value (ηp^2)	Group Effect p value (ηp^2)	Time*Group p value (ηp^2)
Resting GI (0-70)				.087 (.045)	.491 (.026)	.153 (.061)
Pre	13.8 ± 7.9	15.7 ± 10.5	17.4 ± 8.2			
Mid	14.0 ± 9.4	13.9 ± 11.6	15.3 ± 7.0			
Post	14.6 ± 9.9	9.3 ± 7.6	15.1 ± 8.9			
PSS-14 (0-56)				.029* (.065)	.748 (.011)	.538 (.029)
Pre	23.2 ± 8.2	24.6 ± 5.9	24.4 ± 4.9			
Mid	22.5 ± 9.4	23.3 ± 5.2	22.6 ± 4.6			
Post	21.2 ± 8.3	22.8 ± 6.2	23.8 ± 4.8			
GAD-7 (0-21)				.008* (.087)	.740 (.011)	.093 (.072)
Pre	8.2 ± 4.7	9.1 ± 4.7	7.5 ± 3.5			
Mid	6.8 ± 4.7	7.0 ± 4.3	8.1 ± 3.5			
Post	6.0 ± 3.3	7.6 ± 3.7	7.1 ± 3.6			
BVS (0-40)				.776 (.005)	.773 (.010)	.573 (.027)
Pre	19.0 ± 8.5	17.9 ± 8.8	19.2 ± 7.5			
Mid	19.9 ± 7.3	17.7 ± 7.0	19.8 ± 6.3			
Post	19.9 ± 9.1	18.2 ± 7.3	18.1 ± 6.9			
VSI (15-90)*				.674 (.006)	.525 (.024)	.394 (.037)
Pre	22.0 ± 19.7	19.7 ± 17.7	22.4 ± 14.9			
Mid	23.7 ± 22.0	16.1 ± 16.1	21.8 ± 17.2			
Post	20.3 ± 17.6	19.6 ± 18.3	25.8 ± 19.5			
FFMQ (15-75)				.023* (.068)	.367 (.037)	.762 (.017)
Pre	51.5 ± 7.8	49.8 ± 9.2	48.2 ± 7.1			
Mid	52.6 ± 8.1	50.8 ± 7.8	49.5 ± 9.3			
Post	54.0 ± 8.0	50.6 ± 7.2	50.1 ± 6.9			
Ln RMSSD† (ms²)				.738 (.002)	.857 (.007)	.690 (.016)
Pre	4.1 ± 0.6	4.2 ± 0.6	4.1 ± 0.7			
Post	4.1 ± 0.6	4.2 ± 0.7	4.2 ± 0.5			

Note: All descriptive data is presented as means ± standard deviations. Mixed ANOVAs with one between-subject factor (group allocation) and one within-subject factor (time) were used to evaluate the effects of the treatments.

The p values and measures of effect size (ηp^2) are presented for each measure. * signifies that the effect was statistically significant at $p < 0.05$. *VSI results were square root transformed for use in Mixed ANOVA models but are presented here as means ± standard deviations for ease of interpretation. † Due to missing data, sample sizes for Ln RMSSD are as follows: SLOWBC (n=19), NORMALBC (n=15), Control (n=15).

Table 11. Kruskal Wallis Test Results for Non-normally Distributed Data

Intention-to-Treat					
Measure	SLOWBC (n=20)	NORMALBC (n=18)	Control (n=18)	P value	Effect Size (ϵ^2)
All GI %					
Pre	63.3 (62.5)	66.7 (63.8)	60.0 (37.9)	.737	.011
Post	50.0 (73.7)	53.6 (51.3)	50.0 (89.3)	.951	.002
Upper GI %					
Pre	50.0 (64.5)	32.5 (68.8)	33.3 (66.7)	.729	.011
Post	26.8 (76.7)	25.0 (59.5)	45.0 (76.3)	.719	.012
Lower GI %					
Pre	48.6 (72.9)	50.0 (50.0)	40.0 (43.5)	.468	.028
Post	29.2 (57.5)	36.7 (52.7)	33.3 (58.9)	.688	.014
Run GI Burden (0-70)					
Pre	7.0 (6.2)	7.7 (5.9)	6.2 (6.3)	.809	.008
Post	4.0 (9.9)	6.0 (6.1)	6.6 (11.4)	.709	.012
Per-Protocol					
Measure	SLOWBC (n=16)	NORMALBC (n=13)	Control (n=18)	P value	Effect Size (ϵ^2)
All GI %					
Pre	63.3 (62.5)	71.4 (50.0)	60.0 (37.9)	.562	.025
Post	46.4 (70.2)	57.1 (54.2)	50.0 (89.3)	.677	.017
Upper GI %					
Pre	41.7 (67.7)	25.0 (63.7)	33.3 (66.7)	.968	.001
Post	12.5 (60.0)	25.0 (50.0)	45.0 (76.3)	.579	.024
Lower GI %					
Pre	57.1 (69.3)	60.0 (46.4)	40.0 (43.5)	.135	.087
Post	36.7 (57.5)	42.9 (54.2)	33.3 (58.9)	.724	.014
Run GI Burden (0-70)					
Pre	6.2 (6.2)	8.4 (5.7)	6.2 (6.3)	.779	.011
Post	3.7 (11.3)	6.0 (5.9)	6.6 (11.4)	.598	.022

Note: All descriptive data are presented as median (IQR). All p values and effect sizes are based on results from Kruskal H tests comparing groups at the pre-intervention and post-intervention time-points independently. Effect sizes are rank epsilon squared (ϵ^2) statistics that were calculated from Kruskal Wallis H test results.

Per-Protocol Analysis

Table 12 displays the results from per-protocol analyses of normally distributed variables. There was a significant time effect, $F(2,74) = 7.70$, $p < 0.001$, and a significant time x group interaction, $F(4, 74) = 2.53$, $p = 0.047$, for GAD-7 scores. Analyses of simple main effects suggested that GAD-7 scores decreased in the SLOWBC group from pre-intervention to

midpoint (mean difference = 2.5 [95% CI = 0.1, 4.8]; $p = 0.041$) and from pre-intervention to post-intervention (mean difference = 2.9 [95% CI = 0.5, 5.3]; $p = 0.013$). GAD-7 scores in the NORMALBC group significantly decreased from pre-intervention to midpoint (mean difference = 2.6 [95% CI = 0.1, 5.2]; $p = 0.045$) but did not change between other timepoints. Scores did not significantly change between timepoints in the control group. Analysis of FFMQ scores revealed a significant time effect, $F(2,74) = 3.58$, $p = 0.033$, and a significant group effect, $F(2,37) = 4.12$, $p = 0.024$. However, there was not a time x group interaction, $F(4,74) = 0.22$, $p = 0.928$. The remainder of the effects were not statistically significant. Like the ITT analysis, non-parametric analyses did not reveal statistically significant group differences for measures of GI symptoms during runs ($p \geq 0.135$; **Table 11**).

A Posteriori Analyses

To evaluate if compliance or engagement with the interventions affected the results, simple a posteriori analyses were conducted. Data was collapsed across both experimental groups (SLOWBC and NORMALBC) and Pearson's correlation coefficients were calculated between changes in the primary outcomes (post-intervention value – pre-intervention value) and 1) average ratings of engagement with the treatment sessions and 2) average ratings of how pleasant the sessions were. Most associations were not statistically significant ($p > 0.05$), but there was a significant negative association between average ratings of engagement and change in GAD-7 scores from pre-to-post ($n = 31$; $r = -0.43$, $p = 0.012$). There was also a significant negative association between mean rating of engagement and Ln(RMSSD) ($n = 31$; $r = -0.44$; $p = 0.022$).

Table 12. Mixed ANOVA Results for Normally Distributed Variables: Per-Protocol

Measure	SLOWBC (n = 13)	NORMALBC (n = 11)	Control (n = 16)	Time Effect P value (η^2)	Group Effect p value (η^2)	Time*Group p value (η^2)
Resting GI (0-70)				.115 (.057)	.364 (.053)	.075 (.107)
Pre	12.2 ± 7.2	15.3 ± 8.9	16.1 ± 7.2			
Mid	12.5 ± 8.5	14.6 ± 12.0	15.0 ± 7.3			
Post	12.9 ± 9.1	7.0 ± 3.7	15.3 ± 9.4			
PSS-14 (0-56)				.073 (.068)	.252 (.072)	.683 (.030)
Pre	21.0 ± 8.2	24.7 ± 6.6	24.4 ± 5.1			
Mid	20.3 ± 10.7	23.4 ± 6.2	22.5 ± 4.6			
Post	18.5 ± 8.4	23.1 ± 7.4	23.4 ± 4.0			
GAD-7 (0-21)				.001* (.172)	.357 (.054)	.047* (.120)
Pre	8.4 ± 4.8	10.3 ± 4.0	7.4 ± 3.6			
Mid	5.9 ± 4.6	7.6 ± 4.7	8.1 ± 3.5			
Post	5.5 ± 3.3	8.1 ± 4.2	6.7 ± 3.0			
BVS (0-40)				.396 (.025)	.939 (.003)	.767 (.024)
Pre	17.1 ± 8.8	18.3 ± 9.4	18.8 ± 6.8			
Mid	18.5 ± 6.5	17.9 ± 6.4	19.5 ± 5.3			
Post	17.7 ± 8.2	17.6 ± 7.9	17.4 ± 6.2			
VSI (15-90)*				.457 (.021)	.428 (.045)	.208 (.075)
Pre	16.3 ± 12.0	18.5 ± 13.7	21.6 ± 12.8			
Mid	20.8 ± 19.1	14.4 ± 13.4	20.4 ± 14.4			
Post	18.8 ± 18.0	12.5 ± 11.6	23.8 ± 18.3			
FFMQ (15-75)				.033* (.088)	.024* (.182)	.928 (.012)
Pre	54.2 ± 4.3	46.3 ± 8.5	48.1 ± 6.7			
Mid	54.8 ± 7.0	48.3 ± 7.3	49.8 ± 9.3			
Post	55.7 ± 6.2	48.1 ± 6.9	50.3 ± 6.7			
Ln (RMSSD)† (ms²)				.892 (.001)	.746 (.018)	.289 (.075)
Pre	4.2 ± 0.6	4.3 ± 0.6	4.1 ± 0.7			
Post	4.0 ± 0.6	4.3 ± 0.8	4.2 ± 0.5			

Note: All descriptive data is presented as means ± standard deviations. Mixed ANOVAs with one between-subject factor (group allocation) and one within-subject factor (time) were used to evaluate the effects of the treatments. The p values and measures of effect size (η^2) are presented for each measure. * signifies that the effect was statistically significant at $p < 0.05$. *VSI results were square root transformed for use in Mixed ANOVA models but are presented here as means ± standard deviations for ease of interpretation. † Due to missing data, sample sizes for Ln(RMSSD) are as follows: SLOWBC (n=12), NORMALBC (n=8), Control (n=15).

Discussion

The purpose of this randomized controlled trial was to evaluate the effects of simple breathing interventions on GI symptoms, psychological factors, and HRV in runners. The SLOWBC and NORMALBC groups were assigned to complete five minutes of daily breathing

sessions over the course of four weeks. The only evidence of a significant treatment effect was a time x group interaction for GAD-7 scores in the per-protocol analysis. Specifically, GAD-7 scores tended to decrease over time in the SLOWBC and NORMALBC groups, but not the control group. However, scores significantly declined from pre-intervention to post-intervention in SLOWBC only, which suggests that this intervention had more persistent effects than NORMALBC. However, there were no other statistically significant effects of either treatment on the remaining outcomes. The generally null findings are somewhat surprising considering the recently reported associations between psychological factors and GI symptoms during exercise (Wilson, 2018; Wilson, 2020a; Wilson et al., 2021), the beneficial effects of psychological treatments on GI symptomology in other contexts (Ballou & Keefer, 2017; Kinsinger, 2017), and the previously reported effects from other simple breathing interventions (Chung et al., 2010; Hjelland et al., 2007; Russo et al., 2017).

There are several potential explanations for the null findings. First, the interventions may not have been intensive enough to produce meaningful changes in the outcomes. The short duration (five minutes daily) and simplicity of the interventions were chosen because the remote nature of the study required simple-to-perform interventions. Further, we were interested in evaluating interventions that (if efficacious) would be simple and feasible for athletes to add to their busy schedules. Previous studies have reported significant benefits from other simple and short-duration interventions across similar timeframes (Chung et al., 2010; Hjelland et al., 2007; Mackenzie et al., 2006). However, these previous studies had additional aspects that may have facilitated larger effects. For example, Chung et al. (2010) also used a home-based breathing intervention over the course of four weeks, but participants were first given a 30-minute training session on proper breathing technique before the intervention. They also completed the breathing

three times each day compared to once daily in the present study. Like the interventions used in the present study, Hjelland et al. (2007) used a breathing intervention that was five minutes per day for four weeks. But the intervention had an additional vagal biofeedback component that could have enhanced the effects. Thus, it is possible that SLOWBC and NORMALBC did not provide a strong enough stimulus to induce noticeable changes. Or the five minutes of breathing per day could have caused short-lasting benefits on the psychological factors that did not persist long enough to be detected in the post-intervention measurements.

Another possibility is that the effectiveness of the interventions and statistical power may have been influenced by suboptimal compliance. Participants completed, on average, about 80% of the breathing sessions, but this ranged from 40.7% to 100%. Given that the interventions were just five minutes/day for four weeks, it is possible that greater compliance was needed to elicit a detectable treatment effect. Additionally, several participants were excluded from the per-protocol analysis due to poor compliance (completing <50% of sessions) or because they were lost to follow-up, which likely affected statistical power. While these participants were retained in the ITT analysis, ITT analyses tend to be more conservative than per-protocol analyses since they assume no change in outcomes for those that withdraw prematurely and retain data from those with poor compliance to the treatment (Gupta, 2011).

In addition to compliance, the general nature of the interventions may have become repetitive over time or affected how engaged participants felt during the sessions. A posteriori analyses were conducted to evaluate whether engagement levels in the interventions could have influenced the null findings. Higher average ratings of engagement in the interventions were associated with larger reductions in GAD-7 scores ($r = -0.43$; $p = 0.012$). Notably, SLOWBC tended to have higher mean ratings of engagement, though it did not reach statistical significance

(Cohen's $d = 0.69$; $p = 0.074$; **Table 9**). The association between GAD-7 change scores and ratings of engagement, and the group differences in engagement, may partially explain why GAD-7 significantly declined from pre-intervention to post-intervention for SLOWBC, but not NORMALBC in the per-protocol analysis. Regardless, levels of engagement should be considered in future studies, though it is still not clear whether this explains the null findings since engagement ratings were not significantly associated with change scores for the outcomes besides GAD-7.

As seen in **Table 7**, there was also variability in terms of compliance to study procedures in terms of timing of measurements. It is inevitable that compliance will vary in a remote study of this nature, but it could theoretically influence the results. For example, any transient effects of the breathing interventions may not be detected in participants that have a multiple-day delay between the final treatment session and completion of post-intervention measurements.

Finally, the relatively small sample size combined with outcomes that had relatively large amounts of variance could have affected the ability to statistically detect group differences. For example, several of the measurements of GI symptoms during running had measures of variance that were larger than the measures of central tendency (See **Table 11**). Given the large variance in some outcomes, it is possible that detecting statistically significant changes would have required a relatively large treatment effect and/or more statistical power.

There are several limitations to this study. First, all aspects of the study were done remotely, which may have influenced the accuracy of the measurements, compliance to study procedures, and potentially the effectiveness of the interventions. This decision was made due to the restrictions placed on human subjects' research at the time of study design and throughout data collection due to the COVID-19 pandemic. To maximize the likelihood of success,

participants were regularly contacted throughout the study through video calls, phone calls, and email. Detailed instructions were provided for each measurement, and participants were encouraged to contact the investigators if they had any difficulty with the procedures. Regardless, it is possible that the remote nature of the study affected the results, particularly since the investigators could not directly observe compliance to the measurement or intervention procedures. Second, because of the remote nature of the study and to reduce burden on the participants, there was no effort to account for some potential confounding factors such as nutrition intake. Well-controlled studies in a laboratory setting may be useful to identify the effects of psychological treatments on GI dysfunction during exercise, or at least to identify interventions that are most likely to elicit positive results in future remote studies such as this one. Finally, the sample of participants included in the analyses was relatively small after accounting for those that withdrew or declined to participate. The decision was made to require participants to report at least occasional GI discomfort during runs, and to score at least a 5 on the GAD-7. This was done to maximize the likelihood of the intervention having a benefit, but it may have also limited sample size. Further, recruitment was restricted to the contiguous United States so that HRV monitors could be efficiently shipped to participants at the beginning and end of the study.

In summary, the present findings suggest that five minutes of breathing exercises per day for four weeks did not clearly influence psychological factors, GI symptoms (at rest or during running), or HRV. Results of per-protocol and exploratory *a posteriori* analyses suggest that runners who comply with breathing interventions and find them engaging may experience some modest reductions in GAD-7 with little change in other outcomes. Future studies should evaluate

the effects of more intensive psychological treatments in well-controlled studies to determine whether reductions in stress or anxiety positively influences GI symptoms during exercise.

CHAPTER VI

SUMMARY AND CONCLUSIONS

GI disturbances and symptoms are a common problem for many endurance athletes, particularly those that compete in events such ultra-marathons and long-duration triathlons (de Oliveira et al., 2014; Jeukendrup et al., 2000; Stuempfle & Hoffman, 2015). Considerable research has attempted to identify the underlying pathophysiology of exercise-induced GI symptoms, which appears to be due to a complex interaction of circulatory, neuroendocrine, and mechanical factors (Costa et al., 2017b; de Oliveira et al., 2014; van Wijck et al., 2012). Further, there are numerous well-established risk factors for experiencing symptoms during exercise such as younger age, less training experience, higher intensity and longer duration exercise, hot and humid environments, consumption of various nutritional components (protein, fats, fibers), and use of certain dietary supplements (caffeine, sodium bicarbonate) and NSAIDs (de Oliveira et al., 2014; Peters et al., 1999; Pfeiffer et al., 2012; Snipe et al., 2018; Wilson, 2018). The role of psychological factors in causing GI symptoms during exercise remains underexplored, despite a strong psychobiological plausibility (Wilson, 2020b) and considerable research on the how psychological factors influence GI function in other contexts (Haug et al., 2002; Labanski et al., 2020; Mayer & Tillisch, 2011). Recent studies found that measures of stress and anxiety were associated with GI symptoms during 30 days of running (Wilson, 2018) and during endurance races (Wilson, 2020a; Wilson et al., 2021), but much more research is needed.

The overall purpose of this dissertation was to evaluate the role of psychological factors in the context of GI symptoms during running. This was addressed via two studies. Study 1 was an observational survey-based study that sought to evaluate: 1) the associations between several psychological factors (stress, anxiety, GI-specific anxiety, body vigilance) and GI symptoms across seven days of running, 2) the associations between the psychological factors and nutrition

intake before and during runs and 3) if any resulting associations between psychological factors and nutrition intake were mediated by reported GI symptoms. It was hypothesized that running-related GI symptoms would be positively associated with scores on the psychological questionnaires, that scores on the psychological questionnaires would be negatively associated with the nutrition intake variables (i.e., higher levels of stress/anxiety would be associated with lower intake before and during runs), and that the associations between the psychological scores and nutrition intake would be mediated by the measures of GI symptoms. Study 2 was a randomized controlled trial that evaluated the effects of two simple daily breathing interventions (SLOWBC and NORMALBC) on measures of GI symptoms (resting and during runs), psychological factors, and HRV. It was hypothesized that both the SLOWBC and NORMALBC would mitigate GI symptoms and measures of stress and anxiety and increase mindfulness and HRV compared to the control group, with SLOWBC having larger effects than NORMALBC.

For study 1, 82 runners (43 males, 39 females; age = 47.0 ± 19.0 years; running experience = 12.0 ± 16.0 years) tracked information about their runs (duration, RPE, GI symptoms, nutrition intake before and during) for seven days and completed an electronic survey that contained questions about demographic information and four psychological questionnaires (PSS-14, STICSA-Trait, BVS, VSI). All participants were at least 18 years of age, currently running at least 20 miles per week, and had completed at least one run that was ≥ 60 minutes in duration during the two weeks leading up to enrollment. Surprisingly, measures of GI symptoms during runs were not significantly associated with scores on the PSS-14, STICSA-Trait, or BVS. Further, there were not significant negative associations between psychological scores and nutrition intake as hypothesized. This lack of negative associations meant that mediation analyses were not performed to evaluate specific aim #3. However, scores on the VSI were

significantly associated with the measures of GI discomfort ($\rho = 0.32 - 0.38$; $p \leq 0.003$), and the associations remained significant after controlling for potential confounders (partial $\rho = 0.23 - 0.25$; $p \leq 0.043$).

The VSI questionnaire was designed to evaluate GI-specific anxiety, or fears and anxiety related to sensations within the GI system specifically (Labus et al., 2004). GI-specific anxiety and other GI-specific psychological constructs are thought to be important factors in the severity of functional GI conditions such as IBS (Jerndal et al., 2017; Labus et al., 2004; Labus et al., 2007), and there is some evidence that the benefits of psychotherapies on IBS outcomes are mediated by reductions in VSI scores (Windgassen et al., 2017). VSI scores have also been shown to correlate with GI symptom scores in healthy controls or non-IBS comparison samples (Labus et al., 2007; Saigo et al., 2014). Thus, the finding of VSI scores being significantly associated with GI symptoms in exercise contexts is interesting and requires further research. Notably, studies should continue to evaluate whether GI-specific anxiety or other GI-specific psychological constructs are associated with symptomology in exercise settings. Further, experimental studies could attempt to target reductions in GI-specific anxiety and determine if that reduces GI symptomology during exercise.

For study 2, 63 runners with at least mild anxiety and occasional GI symptoms during runs were enrolled, with 56 being randomized into one of the three groups (18 males, 36 females; age = 37.4 ± 12.4 years; running experience = 15.4 ± 10.4 years). Each participant was sent materials and instructions for three pre-intervention measurements: 1) a running journal to track information about their runs and GI symptoms for seven days, 2) a portable HRV monitor to take a resting HRV measurement, and 3) an electronic survey that asked about demographic information, resting GI symptoms, and contained five psychological questionnaires (PSS-14,

GAD-7, BVS, VSI, FFMQ). After these measurements were completed, participants were randomly allocated into one of the three groups. The SLOWBC and NORMALBC groups were sent materials and instructions for video-guided 5-minute breathing interventions, which they were asked to complete daily for four weeks. The interventions were similar except that the SLOWBC group was asked to breathe deeply at six breaths/minute while the NORMALBC group was asked to breathe normally at 15 breaths/minute. Both groups were asked to engage in breath counting. The control group was asked to not engage in breathing exercises during their time in the study. A second running journal and HRV monitor were sent to participants three weeks into the intervention to complete post-intervention measurements during the final week. Additional electronic surveys were sent after week two (midpoint) and on the last day of the intervention (post-intervention).

Overall, there was no significant effects of either intervention on the primary outcomes compared to the control group except for a time x group interaction for GAD-7 scores in the per-protocol analysis (**Table 12**). Simple main effects analyses suggested that GAD-7 scores decreased from pre-intervention to midpoint in SLOWBC and NORMALBC groups, and from pre-intervention to post-intervention in the SLOWBC group. There were no significant changes over time in the control group. These findings suggest that the treatments may have had a modest effect on anxiety, but that it was more persistent in the SLOWBC group. The persistent effect may be related to higher mean ratings of engagement in the treatment. For example, exploratory a posteriori analyses suggested that higher ratings of engagement in the treatment sessions was associated with greater reductions in GAD-7 scores ($r = -0.43$; $p = 0.012$) and the SLOWBC participants tended to report higher mean ratings of engagement in a per-protocol analysis, though it did not reach statistical significance (Cohen's $d = 0.69$; $p = 0.074$; **Table 9**).

However, the remainder of the analyses did not suggest significant treatment effects for any of the other outcomes. There are several potential explanations for the null findings. It is possible that the interventions were not intensive enough to meaningfully affect the outcomes during the midpoint and post-intervention periods. While other similar interventions have elicited significant results, they have also tended to include additional components such as pre-intervention training sessions and sessions multiple times per day (Chung et al., 2010), or the addition of vagal biofeedback to the five minutes of breathing (Hjelland et al., 2007). Additional factors that could have affected the results are poor compliance to study procedures, a relatively small sample size, and large amounts of variance in some of the primary outcomes.

Across the two studies, the findings did not support most of the a priori hypotheses. In study 1, VSI score was the only measure of psychological factors that significantly correlated with GI discomfort during seven days of running. The hypothesis of a negative association between psychological scores and nutrition intake was also not supported. It is important to note that these measurements were taken during a typical training week. Future studies should evaluate these factors during the week of a competitive race when it is expected that anxiety levels and nutrition intake would be higher. For example, Wilson et al. (2021) found that individuals in the top tertile for state anxiety on the morning of a race had significantly higher odds of experiencing GI symptoms such as nausea and regurgitation/reflux during the race. However, the finding of a significant association between VSI scores and GI symptoms is interesting and will hopefully spur additional research on the role of GI-specific anxiety or other GI-specific psychological constructs in the context of exercise. The hypothesis that the SLOWBC and NORMALBC interventions would positively influence the primary outcomes in study 2 was also mostly not supported. As mentioned previously, this could be attributed to

several explanations. Regardless, the results suggest that if a runner wishes to reduce exercise-related GI symptoms, then five minutes of daily breathing exercises is not a sufficient intervention to achieve substantial improvements. Future research should evaluate more intensive psychological treatments in well-controlled settings. If highly effective interventions are identified in well-controlled settings, then follow-up studies should consider evaluating their efficacy in less controlled settings.

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VITA**ALEX EHLERT**

Department of Human Movement Sciences

2016 Recreation Center, Norfolk, VA 23529

Education

- Ph.D. Old Dominion University, Norfolk, VA
Human Movement Sciences, 2018-Present
GPA: 4.0/4.0
Concentration: Applied Kinesiology
- M.S. University of North Carolina at Greensboro, Greensboro, NC
Kinesiology, 2017
GPA: 4.0/4.0
Concentration: Exercise Physiology
Thesis: Evaluation of the reliability of a goalkeeper-specific adaptation to the Yo-Yo Intermittent Recovery Test Level 1
- B.S. University of North Carolina at Greensboro, Greensboro, NC
Kinesiology, 2015
GPA: 3.78/4.0
Concentration: Sports Medicine

Academic Positions

- Fall 2021- Assistant Professor: Department of Exercise Science
North Carolina Wesleyan College
- 2018-2020 Teaching Assistant: Human Movement Sciences Department
Old Dominion University
- 2017-2018 Adjunct Instructor: Department of Human Performance & Leisure Studies
North Carolina Agricultural & Technical State University
- 2016-2017 Teaching Assistant: Department of Kinesiology
University of North Carolina at Greensboro
- 2015-2016 Graduate Assistant: Health and Human Sciences Academic Advising
University of North Carolina at Greensboro