UNIVERSITI TEKNOLOGI MARA

EFFECT OF INTEGRATED VISCERAL AND SPINAL MANIPULATION ON ABDOMINAL PAIN, SEVERITY OF DYSPEPSIA, PSYCHOLOGICAL STATUS, SLEEP DISORDER, AND QUALITY OF LIFE AMONG ADULT PATIENTS WITH FUNCTIONAL DYSPEPSIA: A SINGLE BLIND RANDOMIZED CONTROLLED TRIAL

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PhD

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CONFIRMATION BY PANEL OF EXAMINERS

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ABSTRACT

Functional Dyspepsia (FD) is a highly prevalent functional gastrointestinal disorder associated with significant physical symptoms, psychological distress, and impaired quality of life. Current treatments often fail to address the underlying neuro-visceral pathophysiology. This study aimed to compare the therapeutic efficacy of Integrated Visceral and Spinal Manipulation (InViSMa) against an active control intervention (InASMa) in adult FD patients. The study assessed the differential effects of InViSMa on abdominal pain, dyspepsia severity, psychological status, sleep quality, and health-related quality of life. A prospective, single-blind Randomized Controlled Trial (RCT) was conducted involving 56 adult FD patients who completed the study protocol (InViSMa, n=29; Control, n=27). Participants in both groups received 12 treatment sessions over a four-week intervention period, followed by a one-week post-treatment follow-up. Primary and secondary outcomes were measured using the Abdominal Pain Index (API), Leeds Dyspepsia Questionnaire (LDQ), Perceived Stress Scale (PSS), Pittsburgh Sleep Quality Index (PSQI), and Nepean Dyspepsia Index (NDI). Data were analyzed using non-parametric tests, with the Mann-Whitney U test employed for between-group comparisons. The InViSMa protocol demonstrated highly significant and superior therapeutic efficacy compared to the control group across all measured outcomes. Primary Outcomes: At the follow-up assessment (Week 5), the InViSMa group achieved a statistically superior and clinically relevant reduction in both dyspepsia severity (LDQ) and abdominal pain (API) compared to the control group (all $p < 0.001$), with large effect sizes ($r = 0.52$). The control intervention failed to produce a significant reduction in LDQ scores throughout the trial. Secondary Outcomes: InViSMa was also significantly superior in improving psychological status (PSS), sleep quality (PSQI), and quality of life (NDI) across all subscales, with sustained improvements noted at follow-up (all between-group $p < 0.001$). The control group showed no significant change in any of these systemic secondary outcomes. Integrated Visceral and Spinal Manipulation (InViSMa) is a highly effective and evidence-based non-pharmacological treatment for Functional Dyspepsia. The therapeutic superiority of InViSMa suggests that the synergistic correction of both visceral restriction and spinal facilitation is necessary to normalize Autonomic Nervous System function, resulting in comprehensive and sustained symptomatic and systemic relief. This integrated approach warrants inclusion in the clinical guidelines for FD management.

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Abbreviations

FD	Functional Dyspepsia
EPS	Epigastric Pain Syndrome
PDS	Postprandial Distress Syndrome
VM	Visceral Manipulation
SM	Spinal Manipulation
InViSMa	Integrated Visceral and Spinal Manipulation
API	Abdominal Pain Index
LDQ	The Leeds Dyspepsia Questionnaire
PSS	The Perceived Stress Scale
PSQI	The Pittsburgh Sleep Quality Index
NDI	The Nepean Dyspepsia Index

CHAPTER 1
INTRODUCTION

1.1 Research Background

Functional Dyspepsia (FD) is a highly prevalent and debilitating disorder of gut-brain interaction (DGBI), characterized by chronic or recurrent symptoms centered in the upper abdomen, in the absence of any organic, systemic, or metabolic disease likely to explain the symptoms (Kim & Kuo, 2018; Kim & Kim, 2020). According to the Rome IV diagnostic criteria, FD is primarily categorized into two subtypes: Postprandial Distress Syndrome (PDS), defined by bothersome postprandial fullness and early satiation, and Epigastric Pain Syndrome (EPS), characterized by bothersome epigastric pain or burning (Pilin & Stacey, 2024; Enck et al,. 2017; Madisch et al., 2018). The term "functional" underscores the current understanding that its etiology is not rooted in observable structural or biochemical abnormalities, but rather in a complex interplay of pathophysiological mechanisms. These include delayed gastric emptying, impaired gastric accommodation, visceral hypersensitivity, low-grade duodenal inflammation, altered gut microbiota, and dysregulation of the gut-brain axis (Volaric et al., 2024).

The burden of FD extends far beyond its cardinal physical symptoms. The condition significantly impairs health-related quality of life, often comparable to or worse than chronic organic diseases such as gastroesophageal reflux disease or inflammatory bowel disease (Mounsey et al., 2020). Furthermore, a substantial proportion of patients with FD experience comorbid psychological distress, including anxiety and depression, as well as significant sleep disturbances, which can in turn exacerbate gastrointestinal symptoms, creating a vicious cycle of distress and dysfunction (Fadgyas et al., 2021). This complex clinical picture necessitates a shift from a purely biomedical perspective to a broader biopsychosocial model of care, which acknowledges the intricate connections between physiological, psychological, and social factors in the manifestation and management of the disorder.

Despite its high prevalence, estimated to affect between 5-11% of the global population, the management of FD remains a significant clinical challenge (Oshima et

al., 2024). Current pharmacological strategies, including proton pump inhibitors (PPIs), prokinetic agents, and centrally acting neuromodulators, demonstrate only modest and often inconsistent efficacy (Ford et al., 2020). Many patients fail to achieve satisfactory symptom relief, experience undesirable side effects, or relapse upon treatment cessation, highlighting a critical unmet need for more effective and durable therapeutic options (Mounsey et al., 2020). The limitations of existing treatments have spurred growing interest in non-pharmacological interventions that can address the multifactorial nature of FD.

Within this context, manual therapies, specifically integrated visceral and spinal manipulation, present a promising, yet underexplored, therapeutic avenue. The theoretical rationale for these interventions is grounded in the neuro-anatomical and physiological interconnectedness of the somatic and visceral systems. Visceral manipulation aims to restore normal mobility and motility of the abdominal organs, potentially modulating visceral afferent signaling, improving gastroduodenal mechanics, and reducing hypersensitivity (Arisandy & Haidzir, 2025). Concurrently, spinal manipulation may influence autonomic nervous system output to the gut via somato-visceral reflexes, thereby modulating gastrointestinal function (Sampath et al., 2024). Therefore, this study aims to systematically investigate the efficacy of an integrated visceral and spinal manipulation protocol as a holistic treatment for the complex symptom cluster of FD, addressing abdominal pain, dyspepsia severity, psychological status, sleep quality, and overall quality of life in adult patients.

1.1.1 Functional Dyspepsia Among Adult Persons and Their Problems

Functional Dyspepsia (FD) imposes a multifaceted burden on the adult population, extending well beyond simple epigastric discomfort. The clinical manifestation is heterogeneous, formally categorized by the Rome IV criteria into Postprandial Distress Syndrome (PDS), characterized by bothersome postprandial fullness and early satiation, and Epigastric Pain Syndrome (EPS), defined by significant epigastric pain or burning (Futagami et al., 2018; Houte et al., 2021), which not only causes abdominal pain (Gabbard et al., 2024) but also has a wide-ranging impact on the patient's psychological well-being (Lee et al., 2024; Heryadi et al., 2024), sleep quality (Wuestenberghs et al., 2022), and overall quality of life (Egbo et al., 2020).

Abdominal pain is one of the main symptoms of FD that can range from mild to severe and is often exacerbated by eating, stress, or certain physical activities (Gabbard et al., 2024). This pain is often chronic and recurrent, affecting daily activities and reducing the patient's quality of life. In FD, abdominal pain is caused by problems with the movement of the gastroduodenum and increased visceral sensitivity (Volaric et al., 2024). Research suggests that increased sensitivity to gastric distension and dysfunction in gastric emptying are the main factors that trigger pain in FD.

Other dyspeptic symptoms such as bloating, nausea, vomiting, and fullness after eating contribute significantly to patient discomfort (Madisch et al., 2018; Kim & Kuo, 2019). Gastrointestinal motility disorders, which cause delayed gastric emptying and irregular small bowel motility, play an important role in the manifestation of these symptoms (Chuah & Mahadeva, 2020). These symptoms often cause patients to change their diet and lifestyle, which can affect their nutritional status and overall health.

According to Lee et al. (2024) and Heryadi et al. (2024), patients with FD often have a poor psychological state and a significant prevalence of anxiety and depressive disorders. The bidirectional relationship between FD and psychological disorders suggests that anxiety and depression not only exacerbate dyspeptic symptoms but are also important risk factors in the development of FD. The brain-gut axis, which entails intricate interactions between central and enteric neural systems, is one way psychological stress might impact gastrointestinal function (Rupp & Stengel, 2022; Wauters et al., 2022).

Patients with FD also often have poorer-quality sleep. Insomnia and other sleep problems can result from persistent dyspeptic symptoms and abdominal pain (Egbo et al., 2020). Studies reveal that sleep disorders in FD patients can increase stress and anxiety levels, aggravate dyspeptic symptoms, and start a vicious cycle that is hard to escape (Lee et al., 2024; Heryadi et al., 2024; Madisch et al., 2018; Kim & Kuo, 2019). Poor sleep quality can also negatively affect patient quality of life and ability to carry out daily activities (Wuestenberghs et al., 2022; Huang et al., 2020).

Additionally, patients with FD have a lower quality of life compared to the general population, especially in the physical and mental health domains. Chronic pain, eating disorders, anxiety, depression, and sleep difficulties all contribute to this lower quality of life (Wuestenberghs et al., 2022; Huang et al., 2020; Lee et al., 2024; Heryadi et al., 2024; Madisch et al., 2018; Kim & Kuo, 2019). Research shows that patients with FD frequently have low work productivity, significant absenteeism rates, and

restrictions on their social and leisure activities (Sander et al., 2011; Matsuzaki et al., 2017).

Regretfully, not much is known about how FD affects the dyspeptic state, psychological state, quality of sleep and quality of life, in addition to their abdominal discomfort (Gabbard et al., 2024; Lee et al., 2024; Heryadi et al., 2024; Wuestenberghs et al., 2022; Egbo et al., 2020). Given that FD is a prevalent kind of non-communicable disease around the world, including in Indonesia, dyspepsia itself is among the top 10 diseases in Indonesia (Widya et al., 2023). Therefore, we should conduct significant studies on this topic as soon as possible to minimize the complex issues of FD and its numerous effects.

The overall impact of FD is profound, affecting physical, mental, and social domains. Patients often face limitations in social activities, dietary restrictions that diminish the enjoyment of food, and reduced work productivity, including increased absenteeism and presenteeism (Shankar et al., 2020). Thus, FD is not merely a disorder of digestion but a complex, debilitating condition that profoundly impacts an individual's physical, emotional, and functional well-being.

1.1.2 The Global Prevalence and Burden of FD, Particularly in Indonesia

Functional Dyspepsia (FD) represents a significant global health issue, with a substantial epidemiological and socioeconomic footprint. Large-scale meta-analyses and population-based studies estimate that the worldwide prevalence of FD, according to Rome criteria, ranges from 5% to 11% (Oshima et al., 2024; Ford et al., 2020). However, there is considerable heterogeneity in reported prevalence rates across different geographical regions. Studies in Western nations, such as North America and Europe, frequently report prevalence figures between 10% and 20%, whereas rates in many parts of Asia have historically been considered lower (Kim et al., 2018). This variation is attributed to a confluence of factors, including genetic predispositions, dietary habits (e.g., high-fat intake), lifestyle variables, rates of antecedent infections like *Helicobacter pylori*, and diverse psychosocial stressors. Furthermore, methodological differences between studies, such as the diagnostic criteria employed (e.g., Rome III vs. Rome IV), contribute to the observed variability in prevalence estimates (Ford et al., 2020).

In Indonesia, while a comprehensive, nationwide epidemiological study utilizing the stringent Rome IV criteria remains to be conducted, available regional and hospital-based data confirm that dyspepsia constitutes a major public health concern. A community-based study in a rural area of Indonesia reported a dyspepsia prevalence as high as 32.4%, underscoring the significant burden of upper gastrointestinal symptoms within the population (Putri et al., 2022). National health reports further illuminate the scale of the problem; dyspepsia was one of the leading causes of hospitalization in 2021 and continues to account for a substantial number of primary care consultations (Widya et al., 2023). Although these statistics often consolidate organic and functional dyspepsia, the well-established high prevalence of FD globally suggests that a significant proportion of these cases in Indonesia are functional in origin. The rising number of reported dyspepsia cases in specific regions, such as Samarinda, from 9,815 in 2021 to 13,813 in 2023, further signals a growing need for focused clinical and research attention on this condition within the Indonesian healthcare system (Central Bureau of Statistics of Samarinda City, 2024).

The burden of FD extends beyond mere prevalence figures, imposing considerable economic strain on healthcare systems and society at large. This economic impact is twofold, comprising both direct and indirect costs. Direct costs are substantial and include frequent physician consultations in both primary and specialist care, extensive and often repetitive diagnostic investigations (e.g., upper endoscopy) primarily aimed at excluding organic pathology, and the long-term use of prescription and over-the-counter medications (Mounsey et al., 2020). However, the indirect costs associated with FD are often greater and more impactful. These include significant losses in work productivity due to both absenteeism (days missed from work) and, more pervasively, presenteeism—a state of reduced productivity while at work (Brook et al., 2010; Matsuzaki et al., 2017). The chronic and unpredictable nature of FD symptoms also curtails social and leisure activities, further diminishing the overall quality of life and contributing to the profound societal burden of the disorder.

1.1.3 Limitations of Current Treatment of FD

Despite the high prevalence and significant burden of Functional Dyspepsia (FD), its clinical management remains a formidable challenge, characterized by a trial-and-

error approach and often unsatisfactory patient outcomes. The current therapeutic landscape, while encompassing pharmacological, lifestyle, and psychological interventions, is hampered by significant limitations rooted in the condition's multifactorial and heterogeneous pathophysiology. A critical evaluation of these approaches reveals a substantial gap between existing treatments and the comprehensive needs of patients with FD.

Pharmacological therapy remains the cornerstone of conventional FD management. The use of anti-acids, proton pump inhibitors (PPI), and prokinetic agents is a common option to reduce symptoms associated with gastric hyperacidity (Chaves et al., 2023) and to increase gastrointestinal motility and accelerate gastric emptying (Yamawaki et al., 2018). However, the long-term side effects of this treatment often have low efficacy and could be because of side effects associated with the drugs, as well as variations in patient response to these therapy therapies (Chiarioni et al., 2023; Kim & Kim, 2020), and their clinical utility is severely restricted in many countries due to the risk of serious adverse effects, particularly cardiac arrhythmias (Qi et al., 2023). There are issues that must to be considered.

Non-pharmacological strategies, while crucial, also present considerable challenges. Lifestyle and dietary modifications, such as eating smaller, more frequent meals and avoiding trigger foods, are universally recommended as first-line management. However, the evidence supporting specific dietary interventions is sparse, and recommendations are often based on expert opinion rather than robust clinical trials (Pilin & Stacey, 2024). The primary obstacle to the success of these modifications is the difficulty in achieving and maintaining long-term patient adherence, which requires significant patient motivation and education (Miwa et al., 2022). Psychological interventions, including cognitive-behavioral therapy (CBT) and hypnotherapy, have demonstrated efficacy in improving symptoms by targeting the psychosocial aspects and brain-gut dysregulation inherent in FD (Rodrigues et al., 2022; Chandan et al., 2016). Nevertheless, their widespread implementation is hindered by practical barriers such as high costs, limited availability of trained therapists, and a lack of acceptance by both patients and providers, particularly in resource-constrained healthcare systems.

Other complementary therapies have been explored, but their evidence base remains inconclusive. Transcutaneous electrical acupoint stimulation and acupuncture have shown some promise in modulating gastric sensorimotor function and improving symptoms (Ji et al., 2014; Wang et al., 2020). However, systematic reviews and meta-

analyses frequently conclude that the evidence is of low quality, weakened by small study sizes, high risk of bias, and heterogeneity in techniques, which prevents definitive recommendations (Wu et al., 2020). Similarly, various forms of massage have been proposed, but the lack of standardized protocols and high-quality, large-scale trials means their specific efficacy for FD remains unproven (Zhou et al., 2020). In summary, the current therapeutic armamentarium for FD is inadequate. The limitations of existing treatments highlight a critical need for novel, integrative approaches that can simultaneously address the multiple pathophysiological domains of the disorder—including sensorimotor dysfunction, visceral hypersensitivity, and gut-brain axis dysregulation—thereby offering a more holistic and potentially more effective path to symptom relief and improved quality of life.

1.1.4 Potential Role of Manual Therapy: Visceral and Spinal Manipulation in Functional Dyspepsia (FD)

Given the limitations of existing treatments, there is a compelling rationale for exploring novel therapeutic avenues that target the underlying sensorimotor and neurophysiological dysfunctions in Functional Dyspepsia (FD). Manual therapy, encompassing both visceral and spinal manipulation, emerges as a promising, non-pharmacological approach founded on the principle of restoring normal biomechanics and neurophysiological function. This approach is predicated on the intricate anatomical and neurological connections between the musculoskeletal system and the viscera, offering a direct modality to influence the key pathophysiological mechanisms of FD.

Visceral manipulation is a manual technique that directly addresses the mobility and motility of the abdominal organs. The theoretical framework posits that fascial restrictions, adhesions, or altered visceral tone—resulting from inflammation, surgery, or postural stress—can impair organ function (Barral & Mercier, 2005). In the context of FD, these restrictions could mechanically hinder gastric accommodation and emptying. By applying gentle, specific forces, visceral manipulation aims to improve the mobility of the stomach and duodenum relative to surrounding structures, potentially enhancing gastric motility and alleviating symptoms of postprandial fullness and bloating (Arisandy & Haidzir, 2025). Furthermore, this modality may modulate visceral afferent signals, thereby reducing visceral hypersensitivity—a cornerstone of

FD pathophysiology—by normalizing mechanoreceptor feedback to the central nervous system (Bordoni et al., 2023).

Complementing this direct visceral approach, spinal manipulation targets the well-established somato-visceral reflex pathways. The stomach and duodenum receive sympathetic innervation from the T5-T9 spinal segments and parasympathetic innervation from the vagus nerve. Biomechanical dysfunction in these thoracic spinal segments, often termed somatic dysfunction, is hypothesized to generate aberrant afferent signals that facilitate sympathetic outflow to the viscera (Pickar, 2002; Bath & Owens, 2023). This heightened sympathetic tone can inhibit gastric motility, reduce gastric acid secretion, and increase visceral sensitivity, thereby perpetuating FD symptoms (Bolton & Budgell, 2012). Spinal manipulative therapy, particularly high-velocity, low-amplitude thrusts applied to the thoracic spine, is proposed to normalize joint mechanics, reduce nociceptive afferent input, and ultimately modulate autonomic nervous system output. By down-regulating sympathetic tone and potentially enhancing vagal (parasympathetic) activity, spinal manipulation may help restore a more balanced autonomic control of gastroduodenal function, thereby improving gastric emptying and reducing pain (Goldenberg & Kalichman, 2024; Lei Tu et al, 2020). While rigorous clinical trials are scarce, preliminary studies and case reports suggest that these manual therapies can positively influence gastrointestinal symptoms, warranting further investigation into their integrated use for a comprehensive management strategy in FD (Basra et al, 2020).

The integrated manual therapy of visceral manipulation and spinal manipulation is a new method for the treatment of FD. However, despite promising preliminary evidence, there are still gaps in the literature that require further research to confirm the effectiveness and mechanism of action of integrated visceral and spinal manipulation (InViSMa) in the context of FD management. Therefore, this study aimed to evaluate the effectiveness of an integrative approach to visceral and spinal manipulation in managing FD through a randomized controlled clinical trial (RCT).

1.2 Problem Statement

Functional Dyspepsia (FD) is a prevalent and burdensome chronic condition that significantly impairs the quality of life for a substantial portion of the adult population worldwide, including in Indonesia. The disorder's complex pathophysiology, involving

an interplay of gastroduodenal sensorimotor dysfunction, visceral hypersensitivity, and gut-brain axis dysregulation, results in a constellation of debilitating symptoms, including persistent abdominal pain, severe dyspepsia, profound psychological distress, and disruptive sleep disturbances. Despite the significant personal and socioeconomic burden, current standard-of-care treatments—ranging from pharmacological agents to lifestyle modifications—provide inadequate relief for many patients, highlighting a critical therapeutic gap in the clinical management of FD.

The limitations of existing therapies necessitate the exploration of innovative and holistic treatment paradigms. Manual therapy, specifically an integrated approach combining visceral and spinal manipulation, offers a compelling, non-pharmacological alternative that directly targets the underlying biomechanical and neurophysiological dysfunctions of FD. Visceral manipulation aims to restore normal organ mobility and reduce visceral hypersensitivity, while spinal manipulation seeks to modulate autonomic nervous system activity via somato-visceral pathways. While the theoretical rationale for each modality is robust, there is a distinct lack of high-quality clinical evidence, particularly from rigorous randomized controlled trials (RCTs), to support their combined use.

The central problem, therefore, is the absence of definitive scientific evidence to establish the clinical efficacy of an integrated visceral and spinal manipulation protocol as a comprehensive treatment for the multifaceted symptom complex of FD. It remains unknown whether this integrated approach can produce clinically meaningful improvements in abdominal pain, dyspepsia severity, psychological well-being, sleep quality, and overall quality of life beyond that of a placebo or control intervention. This gap in knowledge precludes the confident integration of this promising manual therapy approach into evidence-based clinical practice guidelines for FD.

Consequently, this study aims to address this problem by determining the effect of an integrated visceral and spinal manipulation intervention on abdominal pain, the severity of dyspepsia, psychological status, sleep disorders, and quality of life in adult patients with FD. Through a single-blind randomized controlled trial, this research will provide the rigorous evidence needed to either support or refute the clinical utility of this integrative manual therapy, thereby informing future therapeutic strategies and potentially offering a new avenue of hope for patients suffering from this challenging condition.

1.3 Research Objectives

Based on the above problem statement, the general objective of this study is to determine the effects of visceral and spinal manipulation in adults patient with FD. The following are the specific research objectives:

a) To determine the effects of 4-week integrated visceral and spinal manipulation on abdominal pain, dyspepsia severity, psychological status, sleep disorders, and quality of life among adult patients with FD.
b) To compare the effects between 4-week integrated visceral and spinal manipulation and control group on abdominal pain, dyspepsia severity, psychological status, sleep disorders and quality of life among adult patients with FD.

1.4 Research Hypotheses

Based on the research objectives, the following are the research hypotheses:

a) There were significant effects of 4-week integrated visceral and spinal manipulation on abdominal pain, dyspepsia severity, psychological status, sleep disorders, and quality of life among adult patients with FD.
b) There was significant differentiation between 4-week integrated visceral and spinal manipulation and control group on abdominal pain, dyspepsia severity, psychological status, sleep disorders and quality of life among adult patients with FD.

1.5 Significance of Study

The primary significance of this research lies in its potential to address a critical gap in the management of Functional Dyspepsia (FD) by investigating a novel, non-pharmacological, and Biomechanically targeted intervention. The findings are poised to contribute substantially to scientific knowledge, clinical practice, and patient well-being in several key domains.

First, from a scientific and theoretical perspective, this study will be among the first rigorous randomized controlled trials (RCTs) to systematically evaluate an *integrated* manual therapy approach for FD. By combining visceral and spinal manipulation, the research moves beyond single-modality investigations to test a more

comprehensive treatment paradigm that simultaneously addresses local visceral biomechanics and central autonomic regulation via somato-visceral pathways. Positive findings would lend empirical support to the theoretical models underpinning these therapies and could elucidate the clinical importance of the interconnectedness between somatic structures and visceral function in FD pathophysiology.

Second, the study has significant implications for clinical practice. Should the integrated manual therapy prove effective, it would establish a new, evidence-based treatment option for a large and often refractory patient population. This is particularly crucial for individuals who experience inadequate relief from, or adverse effects to, standard pharmacological treatments. The validation of a safe, effective, and non-invasive therapy could lead to its incorporation into clinical practice guidelines for gastroenterology and physiotherapy, thereby broadening the therapeutic armamentarium available to clinicians. For a healthcare system like Indonesia's, establishing a potentially cost-effective manual therapy could also offer a sustainable approach to managing this chronic condition.

Third, and most importantly, the research is significant for its direct potential to improve patient-centered outcomes. The study’s holistic approach, evaluating not only core gastrointestinal symptoms but also the often-overlooked domains of psychological distress, sleep quality, and overall health-related quality of life, aligns with the modern biopsychosocial understanding of Disorders of Gut-Brain Interaction (DGBI). A positive outcome would signify more than just symptom reduction; it would represent a meaningful improvement in the daily lives of patients, potentially reducing their suffering, enhancing their functional capacity, and decreasing their reliance on long-term medication. By providing robust evidence, this study has the potential to empower patients and clinicians with a new, effective strategy to manage the debilitating, multifaceted burden of Functional Dyspepsia.

1.6 Scope of the Study

The scope of this research is carefully defined to ensure a focused and rigorous investigation into the efficacy of an integrated manual therapy protocol for Functional Dyspepsia (FD). The study is designed as a single-center, single-blind, randomized controlled trial, with specific boundaries related to its population, intervention, outcomes, and context.

Population and Setting: The target population for this study comprises adult patients, aged 20 to 55 years, who have been diagnosed with FD according to the internationally recognized Rome IV criteria. Participants will be required to have experienced chronic symptoms for a minimum of three months to ensure the study population reflects a persistent, clinically significant condition. Recruitment will be conducted at a single specialized clinic, the Wiyata Husada Samarinda Clinic in East Kalimantan, Indonesia. This specific geographical focus allows for consistency in patient demographics and healthcare access while also providing valuable data from a Southeast Asian population, which is often underrepresented in FD research. Exclusion criteria will be strictly applied to eliminate participants with organic gastrointestinal diseases (e.g., peptic ulcer disease, GERD), previous abdominal surgery, "red flag" symptoms, or significant psychiatric comorbidities that could confound the results.

Intervention: The study is specifically designed to evaluate an integrated manual therapy intervention, termed InViSMa (Integrated Visceral and Spinal Manipulation). This protocol is standardized and consists of specific visceral manipulation techniques (e.g., mobilization of the stomach and duodenum) and spinal manipulation techniques (e.g., thoracic percussion, rib-raise techniques) targeting somato-visceral pathways. The intervention will be compared against a control group receiving a sham/placebo intervention to control for non-specific therapeutic effects such as patient contact and expectation. The frequency and duration of the treatment sessions will be standardized for both groups.

Outcomes: The scope of assessment is comprehensive, reflecting the multifaceted nature of FD. The primary outcomes will be the change from baseline in dyspepsia symptom severity, as measured by the validated Leeds Dyspepsia Questionnaire (LDQ), and abdominal pain, assessed via the Abdominal Pain Index (API). Secondary outcomes are selected to capture the broader impact of the condition and will include health-related quality of life (Nepean Dyspepsia Index - NDI), sleep quality (Pittsburgh Sleep Quality Index - PSQI), and perceived stress levels (Perceived Stress Scale - PSS). Safety and tolerability will be systematically monitored throughout the trial.

Limitations of Scope: It is important to note that this study is not designed to elucidate the precise physiological mechanisms of action of the manual therapies, although the findings may generate hypotheses for future research. Furthermore, as a single-center study, the generalizability of the findings to other populations or

healthcare systems may be limited. The study will also not evaluate the long-term durability of the treatment effects beyond the specified follow-up period. Limitations of current treatments, the rationale for the proposed study, the clear statement of the problem, and the overall aim of the research. This will serve as a transition to the subsequent chapter, which will detail the review of the literature.

1.7 Definitions of Terms

To ensure clarity and consistency throughout this dissertation, the following operational definitions will be utilized for key terms:

i. **Functional Dyspepsia (FD):** A chronic Disorder of Gut-Brain Interaction characterized by one or more of the following symptoms: postprandial fullness, early satiation, epigastric pain, or epigastric burning, which are unexplained after a routine clinical evaluation. This definition is in accordance with the Rome IV diagnostic criteria (Black et al., 2022).

ii. **Postprandial Distress Syndrome (PDS):** A subtype of FD where the predominant symptoms are bothersome postprandial fullness and/or early satiation that prevent finishing a regular-sized meal. These symptoms must occur at least several times per week (Black et al., 2022).

iii. **Epigastric Pain Syndrome (EPS):** A subtype of FD characterized by bothersome epigastric pain and/or epigastric burning that is intermittent, not generalized, and not relieved by defecation or passage of flatus. The pain may be induced by meals but can also occur during fasting (Black et al., 2022).

iv. **Integrated Visceral and Spinal Manipulation (InViSMa):** For this study, InViSMa is defined as the active therapeutic intervention protocol. It is a cohesive approach that combines specific visceral manipulation techniques aimed at improving organ mobility and spinal manipulation techniques designed to modulate autonomic nervous system function via somato-visceral pathways.

v. **Visceral Manipulation (VM):** A manual therapy technique involving the application of specific, gentle, directed forces to encourage the normal mobility, tone, and inherent motion of the viscera (internal organs) and their surrounding connective tissues. The goal is to address biomechanical restrictions that may impair physiological function (Barral & Mercier, 2005).

vi. **Spinal Manipulation:** A manual therapy technique characterized by the application of controlled forces or thrusts to specific joints of the spine. The therapeutic rationale is to restore joint mobility and modulate neurophysiological responses, particularly autonomic nervous system activity and nociceptive processing through somato-visceral reflexes (Gyer et al., 2019).

vii. **Severity of Dyspepsia:** Operationally defined as the symptom burden experienced by the patient, quantified by the total score on the **Leeds Dyspepsia Questionnaire (LDQ)**. This validated instrument measures the frequency and intensity of key dyspeptic symptoms.

viii. **Abdominal Pain:** Operationally defined as the patient's self-reported pain experience, quantified by the total score on the **Abdominal Pain Index (API)**. This index assesses the frequency, duration, and intensity of abdominal pain.

ix. **Psychological Status:** For the purposes of this study, this refers specifically to the level of perceived stress. It is operationally defined by the total score on the **Perceived Stress Scale (PSS)**, which measures the degree to which situations in one's life are appraised as stressful.

x. **Sleep Disorder:** Operationally defined as the patient's perception of their sleep quality and patterns. It is quantified by the global score on the **Pittsburgh Sleep Quality Index (PSQI)**, a self-rated questionnaire that assesses sleep quality over a one-month interval.

xi. **Quality of Life:** Refers to the patient-reported impact of FD on their overall well-being and daily functioning. It is operationally defined by the total score on the **Nepean Dyspepsia Index (NDI)**, a disease-specific instrument designed to measure quality of life in individuals with functional dyspepsia.

xii. **Adult:** For this study, an adult is defined as an individual within the age range of 20 to 55 years, inclusive.

1.8 Summary

This introductory chapter establishes the comprehensive rationale for the present study. It begins by defining functional dyspepsia (FD) as a prevalent and debilitating Disorder of Gut-Brain Interaction, characterized by a complex pathophysiology involving sensorimotor dysfunction, visceral hypersensitivity, and dysregulation of the gut-brain axis. The significant global burden of FD, with a particular focus on its

increasing recognition in Indonesia, is highlighted, underscoring the profound negative impact the condition has on patients' physical health, psychological well-being, sleep quality, and overall quality of life.

A critical evaluation of the current therapeutic landscape reveals significant limitations. Standard treatments, including pharmacological agents and lifestyle modifications, often provide inadequate symptom relief and are hampered by issues of side effects and poor long-term adherence. This creates a clear and pressing therapeutic gap for a large segment of the FD population. In response to this gap, this chapter introduces the theoretical and clinical basis for utilizing manual therapies. It posits that an integrated approach of visceral manipulation (VM) and spinal manipulation (SM)—termed InViSMa—offers a novel, non-pharmacological strategy that Biomechanically targets both the local biomechanical restrictions (via VM) and the central neuro-autonomic imbalances (via SM) implicated in FD.

The central problem motivating this research is the critical lack of high-quality evidence from rigorous randomized controlled trials to validate the efficacy of such an integrated manual therapy protocol. Therefore, this dissertation aims to address this knowledge gap by systematically investigating the effect of the InViSMa intervention on abdominal pain, dyspepsia severity, psychological status, sleep disorders, and quality of life in adult patients with FD. The study is significant as it has the potential to validate a new, safe, and potentially cost-effective treatment modality, thereby improving clinical practice and offering a much-needed therapeutic option for patients suffering from this challenging chronic condition. This chapter sets the stage for the detailed review of the literature that follows.

CHAPTER 2
LITERATURE REVIEW

2.1 Introduction

This chapter provides a comprehensive review of the scientific literature pertinent to functional dyspepsia (FD) and the theoretical and clinical rationale for the application of integrated manual therapy as a novel treatment modality. A thorough literature review serves as the foundational pillar of empirical research, establishing the existing body of knowledge, contextualizing the research problem, and critically identifying gaps that warrant further investigation. The primary objective of this chapter is to synthesize current evidence to construct a robust argument for the necessity and significance of the present study.

To achieve this, the review is systematically structured into several key sections. It begins with a comprehensive overview of FD, detailing its formal definition according to the Rome IV criteria, its global epidemiology, its significant socioeconomic burden, and its complex, multifactorial pathophysiology, including sensorimotor dysfunction and the critical role of the gut-brain axis. Following this, the chapter will present a critical appraisal of the current management paradigms for FD, evaluating the efficacy and significant limitations of both pharmacological and non-pharmacological interventions. Subsequently, the review will introduce the theoretical foundations of manual therapy as a potential intervention, specifically exploring the proposed mechanisms of action for visceral manipulation and spinal manipulation in the context of visceral disorders. Finally, this chapter will synthesize the reviewed literature to explicitly delineate the existing research gap—namely, the lack of high-quality evidence from randomized controlled trials supporting an integrated manual therapy approach. This synthesis will culminate in a clear justification for the current study, which aims to address this critical gap in knowledge.

2.2 Functional Anatomy and Physiology of Stomach Related to Functional Dyspepsia

2.2.1 Functional Anatomy of the Stomach

The stomach is distinguished by its highly distensible, muscular structure and hollow form, which collectively enable it to temporarily store and process ingested food, playing a critical role in the overall digestive process. Anatomically, the stomach is divided into four principal regions: the cardia, fundus, body, and pylorus, each of which contributes uniquely to its function. The cardia, located at the junction with the esophagus, marks the entry point of food into the stomach. Above the cardia lies the fundus, the fundus forms the dome-shaped upper curvature of the stomach, playing a role in storing swallowed air and food. The body, which is the largest and most central portion, is the primary site for the mixing and enzymatic breakdown of food, facilitating its conversion into chyme. Finally, the pylorus, the stomach's distal region, acts as a funnel, regulating the passage of partially digested food into the duodenum, the first segment of the small intestine, thereby ensuring the controlled progression of digestion (Madeleine et al., 2023; Vishy, 2017).

2.2.1.1 Anatomical Position and Structure of the Stomach

The stomach is a crucial and highly distensible component of the digestive system, occupies a unique anatomical position between the esophagus and the duodenum. This saclike organ, the largest within the digestive tract, is distinguished by its characteristic ‘J’ shape, which enables it to function as both a reservoir and a mixing chamber for ingested food (Knight & Nigam, 2019). Strategically located in the anterior portion of the abdominal cavity, the stomach's positioning supports its multifaceted roles in digestion, including the storage, mechanical breakdown, and chemical digestion of food through the secretion of gastric juices. Its functional anatomy is structured into four distinct layers—the mucosa, submucosa, muscularis externa, and serosa—each contributing to the organ’s overall functionality and efficiency (Chaudhry et al., 2024). This arrangement not only facilitates the reception and temporary storage of food from the esophagus but also ensures the controlled and gradual release of chyme into the duodenum for further digestion (Vora et al., 2021).

2.2.1.2 Muscular Layers of the Stomach

The stomach wall is composed of three distinct layers of smooth muscle, each integral to its functional performance. The outermost layer, the longitudinal layer, extends lengthwise along the stomach and plays a pivotal role in the organ's ability to shorten and facilitate the propulsion of food toward the duodenum. The middle layer, known as the circular layer, encircles the stomach and is essential for the mechanical processes of mixing and churning gastric contents through peristaltic contraction. The innermost oblique layer, a unique feature of the stomach, contributes an additional dimension to its motility, enabling more complex and effective mixing of ingested materials. Together, these muscular layers function synergistically to ensure the thorough breakdown of food into a semi-liquid state known as chyme, which is then systematically delivered to the small intestine for further digestion (Knight & Nigam, 2019; Vora et al., 2021).

2.2.1.3 The Structural Layers of the Stomach Wall

Under the muscular layers, the stomach’s internal architecture is composed of four essential layers, each contributing uniquely to the digestive process. The outermost layer, the serosa, functions as a protective sheath, minimizing friction between the stomach and adjacent organs, thereby safeguarding its structural integrity. Situated beneath the serosa is the muscularis, which encompasses the three smooth muscle layers previously described, playing a critical role in the stomach's motility and mechanical digestion. The subsequent layer, the submucosa, serves as a crucial support system, housing an intricate network of blood vessels, nerves, and connective tissue that provides vital nutrients and regulatory signals to the stomach wall. The innermost layer, the mucosa, is particularly significant due to its direct engagement in the digestive process, where it harbors specialized cells responsible for the secretion of digestive enzymes, hydrochloric acid, and mucus, all of which are essential for effective digestion (Chaudhry et al., 2024; Sebastian et al., 2019; Knight & Nigam, 2019).

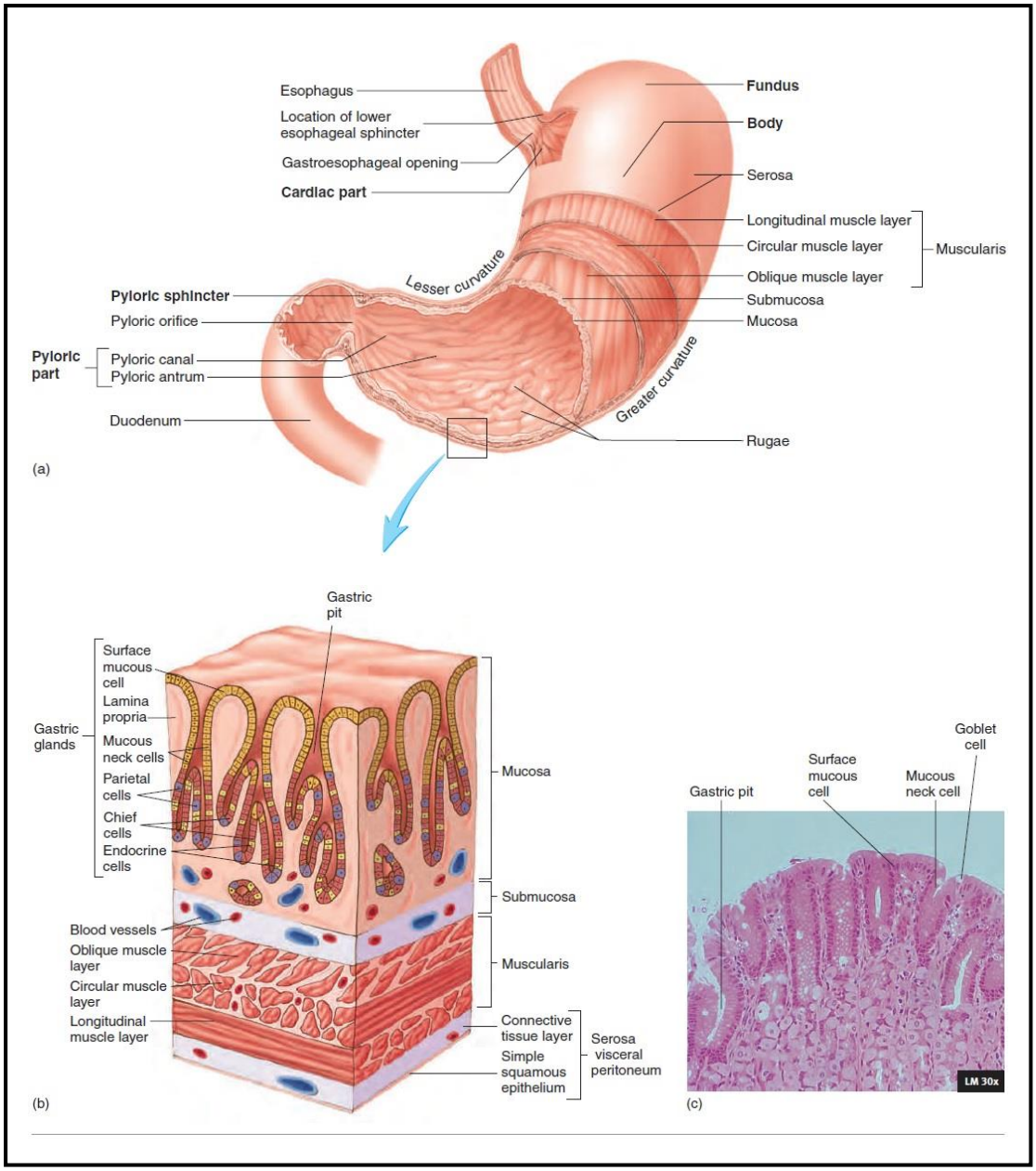


Figure 2.1 Structural Anatomy of the Stomach (BrainKart.com, 2023)

2.2.1.4 The Mucosa and Its Gastric Glands

The mucosa represents the most intricate and functionally vital layer of the stomach wall, playing a central role in the digestive process. It is richly endowed with specialized gastric glands, which secrete crucial substances necessary for digestion. These glands comprise various cell types, each with a specific function: parietal cells secrete hydrochloric acid (HCl), establishing the highly acidic environment required for digestion; chief cells produce digestive enzymes, including pepsinogen, which is converted to pepsin in the acidic milieu, facilitating the breakdown of proteins; and mucous cells generate mucus, which forms a protective barrier that shields the stomach lining from the erosive effects of gastric acid (Chaudhry et al., 2024; Sebastian et al., 2019). The synchronized activity of these cellular components is essential for the efficient breakdown of ingested food, the initiation of protein digestion, and the maintenance of an acidic environment conducive to the activation of digestive enzymes (Chaudhry et al., 2024; Sebastian et al., 2019).

2.2.1.5 Parasympathetic Innervation

The parasympathetic innervation of the stomach is predominantly mediated by the vagus nerve (cranial nerve X), which is integral to the facilitation of digestive functions. The vagus nerve extends its influence on the stomach via its anterior and posterior branches, which are responsible for stimulating the secretion of gastric juices, enhancing gastric motility, and facilitating the relaxation of the pyloric sphincter. This latter function is particularly crucial as it aids in the regulated passage of chyme from the stomach into the duodenum, a critical step in the digestive process (Vishy, 2017; Kirsteen & Alberto, 2014). Parasympathetic innervation, therefore, plays a pivotal role in the regulation of gastric acid secretion and the coordination of stomach contractions, both of which are fundamental to efficient digestion (Jing & Shu, 2021; Joshua et al., 2023).

2.2.1.6 Sympathetic Innervation

The sympathetic innervation of the stomach is orchestrated by the splanchnic nerves, which originate from the thoracic spinal cord segments (T5–T9). These nerves traverse to the celiac ganglion, where they synapse before extending postganglionic fibers to the stomach (Vishy, 2017; Wilfrid, 2022;). The sympathetic nervous system plays a crucial inhibitory role in gastric functions, including the reduction of gastric

motility and the suppression of gastric acid secretion. This modulation is particularly significant during stress responses, where the body diverts blood flow away from the digestive system to prioritize vital organs and muscle activity (Kazunari et al., 2016). The delicate balance between sympathetic and parasympathetic inputs is essential for the optimal functioning of the stomach, especially in the context of stress-related gastrointestinal disorders, where dysregulation can exacerbate symptoms (Camilleri et al., 2019).

2.2.1.7 Enteric Nervous System (ENS) Supply

The enteric nervous system (ENS) of the stomach, often termed the "second brain," constitutes a vast and intricate network of neurons embedded within the gastrointestinal wall, specifically within the myenteric (Auerbach's) and submucosal (Meissner's) plexuses (Wilfrid, 2022). The ENS autonomously governs numerous critical aspects of gastric function, including motility, blood flow, and the secretion of digestive enzymes and mucus (Cristina, 2024). The myenteric plexus is primarily responsible for the regulation of gastric motility, orchestrating the coordinated contractions of the stomach's muscular layers, while the submucosal plexus plays a key role in regulating the activity of mucosal glands and local blood vessels (Keith & Gary, 2022). Although the ENS is capable of independent operation from the central nervous system (CNS), it maintains bidirectional communication with the CNS via parasympathetic and sympathetic pathways, underscoring its integral role in the intricate regulation of gastric functions (Rao & Gershon, 2018).

2.2.2. Regulation of Stomach Secretions

The regulation of stomach secretions is a highly coordinated process that is essential for effective digestion (Smith et al., 2022). It involves complex interactions between neural, hormonal, and local mechanisms to ensure that gastric secretions are produced in appropriate amounts and at the right times (Jones et al., 2019). The primary components of these secretions include hydrochloric acid (HCl), pepsinogen, intrinsic factor, and mucus, each playing a unique role in digestion and gastrointestinal protection (Brown et al., 2021). Specifically, hydrochloric acid facilitates the breakdown of food particles and the activation of digestive enzymes; pepsinogen is converted into pepsin for protein digestion, intrinsic factor is indispensable for vitamin B12 absorption, and mucus provides a protective barrier against stomach acid.

The regulation is divided into three interconnected phases: the cephalic phase, initiated by sensory and neural inputs; the gastric phase, driven by direct food stimulation within the stomach; and the intestinal phase, which moderates gastric activity as chyme enters the small intestine (Dockray, 2014; Feldman et al., 2020).The purpose of these phases is to maximize digestive efficiency while protecting the stomach lining and ensuring an orderly flow of partially digested food into the duodenum. Dysregulation of this system can lead to various gastrointestinal disorders, such as functional dyspepsia or GERD (Dockray, 2014; Feldman et al., 2020), highlighting the importance of understanding these processes.

2.2.2.1 Cephalic Phase

The cephalic phase constitutes the initial stage of gastric secretion, which is triggered by the sight, smell, taste, or thought of food. During this phase, neural pathways involving the vagus nerve (cranial nerve X) play a pivotal role in preparing the stomach for digestion. Sensory input from external stimuli activates the medulla oblongata, which subsequently stimulates the vagal nuclei. This results in the release of acetylcholine (ACh), promoting the secretion of gastric juices such as hydrochloric acid (HCl) from parietal cells and pepsinogen from chief cells. This phase accounts for approximately 30% of total gastric secretion and is critical for optimizing subsequent digestive processes (Dockray, 2014). Research has demonstrated that the cephalic phase can be modulated by psychological factors, emphasizing its integration with the central nervous system (Konturek et al., 2015).

2.2.2.2 Gastric Phase

The gastric phase occurs once food enters the stomach, accounting for about 60% of gastric secretions. This phase is subject to regulation by mechanical and chemical stimuli resulting from gastric distension and the presence of peptides and amino acids in the stomach. Gastric distension activates stretch receptors, initiating local myenteric reflexes and vagovagal reflexes, which further enhance the release of HCl and pepsinogen. Gastrin, a hormone produced by G cells in the gastric antrum, is released in response to proteins and peptides. Gastrin exerts a direct and indirect influence on parietal cells, with its actions involving the release of histamine by enterochromaffin-like (ECL) cells. This creates a highly acidic environment necessary for protein denaturation and enzymatic activity (Feldman et al., 2020).

2.2.2.3 Intestinal Phase

The intestinal phase, representing the final stage of the process, contributes approximately 10% of the total gastric secretions and is predominantly inhibitory in nature. This phase commences when chyme enters the duodenum, thereby triggering hormonal and neural feedback mechanisms.In response to the acidic and nutrient-rich chyme, hormones such as secretin and cholecystokinin (CCK) are released. Secretin, in particular, has been shown to inhibit gastric acid secretion by reducing gastrin release and parietal cell activity (Kong & Singh, 2008), while CCK slows gastric emptying to optimize digestion in the small intestine. The enterogastric reflex, a neural response, has also been identified as a key element in this process, as it inhibits gastric motility and secretion, thereby preventing overloading of the duodenum. Collectively, these mechanisms ensure a coordinated transition of digestive processes from the stomach to the intestine.

2.2.2.4 Neural and Hormonal Interplay

The regulation of gastric secretions is contingent on a sophisticated interplay between neural and hormonal systems. The vagus nerve's parasympathetic input is predominant during the cephalic and gastric phases, while the enteric nervous system modulates localized reflexes. Hormones such as gastrin, secretin, and CCK ensure precise control over acid secretion and motility. Dysregulation of this system can lead to gastrointestinal disorders, such as gastritis or peptic ulcer disease, underscoring the importance of understanding these regulatory pathways (Fass et al., 2017).

2.2.3 Physiology of Gastric Motility

Gastric motility involves the orchestrated processes of gastric filling, mixing, and emptying, all regulated by intricate neuro-hormonal mechanisms that engage the enteric nervous system (ENS), autonomic nervous system (ANS), and a variety of gastrointestinal hormones. These processes are fundamental to the efficient digestion and transit of food through the gastrointestinal tract, ensuring that nutrients are adequately processed and absorbed.

2.2.3.1 Movement Physiology of Gastric

The theory of visceral motility at the embryonic stage posits that each organ follows the trajectory of its own embryological development and migration and that this motion is imprinted upon the viscera. In essence, the viscera exhibit a natural motion. The internal organs, including the gastroduodenal organs, move within the thorax, chest, and abdomen as a result of our activities, such as walking, running, and inhalation. The gastroduodenal organ undergoes three-dimensional movement within the abdominal cavity on a daily basis (Barral & Mercier, 2005; Stone, 2007). During inhalation, gastroduodenal motility exhibits a caudomedial direction in a frontal plane, a medial and rightward rotation in a transversal plane, and a posteroanterior direction in a sagittal plane, while these movements are reversed during exhalation. In summary, the gastroduodenal motility cycle comprises two phases, during which the organ moves towards and away from the median axis of the body (Hebgen, 2011).

2.2.3.2 Gastric Accomodation

Gastric accommodation is a critical physiological process that allows the stomach to expand and store ingested food without a significant rise in intragastric pressure, thereby maintaining comfort during meals. This adaptive mechanism is primarily mediated by the vagus reflex, in which the vagus nerve detects the presence of food and signals the smooth muscle layers of the stomach to relax. This relaxation of gastric muscles prevents discomfort that could otherwise result from the rapid distension of the stomach (Liz Febo et al., 2021). Moreover, the capacity for gastric accommodation is essential for allowing the stomach to hold larger quantities of food, particularly during meals. Impairments in this process, such as those observed in conditions like functional dyspepsia, can lead to symptoms such as early satiety and discomfort, highlighting the importance of this physiological adaptation in digestive health (Wang et al., 2021).

2.2.3.3 Gastric Peristalsis

Gastric peristalsis is a fundamental process characterized by coordinated, wave-like contractions of the stomach's muscularis externa, essential for the mechanical breakdown of food and its thorough mixing with gastric secretions, resulting in the formation of a semi-liquid mixture known as chyme. This process is primarily driven by the rhythmic contractions of the circular muscle layer, under the regulation of the interstitial cells of Cajal (ICCs). These specialized pacemaker cells, located within the

myenteric plexus, generate slow waves that set the timing and coordination of peristaltic contractions. The waves propagate through the stomach, creating a synchronized sequence of muscle contractions that not only mix the food but also propel it towards the pylorus for subsequent gastric emptying. The efficiency of gastric peristalsis is crucial for the homogenization of gastric contents, ensuring that the chyme is adequately processed before entering the small intestine for further digestion and absorption (Kajal & Aravind, 2023; Liu et al., 2020).

2.2.3.4 Gastric Emptying

Gastric emptying is a highly regulated phase of digestion in which chyme is gradually transferred from the stomach into the duodenum. This process is meticulously controlled by a complex interplay of hormonal signals, such as gastrin and cholecystokinin (CCK), along with neural feedback mechanisms. Gastrin, a hormone produced by the stomach in response to food intake, enhances gastric motility and facilitates the opening of the pyloric sphincter, allowing chyme to pass into the duodenum. In contrast, CCK, released by the duodenum in response to the presence of fats and proteins, slows gastric emptying by inhibiting gastric motility and promoting pyloric sphincter contraction. This precise regulation ensures that chyme enters the duodenum at an optimal rate, allowing sufficient time for efficient digestion and nutrient absorption in the small intestine (Liu et al., 2020; Raj et al., 2019). Dysfunction in this process, such as delayed emptying (gastroparesis), can result in symptoms like nausea, vomiting, and malnutrition due to impaired nutrient processing (Kim & Kuo, 2019; Cangemi & Lacy, 2023).

2.2.3.5 Integration and Importance of Gastric Motility in Digestive Health

The processes of gastric accommodation, peristalsis, and emptying are interdependent and collectively ensure the efficient progression of food through the digestive tract. The proper functioning of these mechanisms is essential for maintaining digestive health, as disruptions in any phase of gastric motility can lead to significant clinical conditions (Kajal & Aravind, 2023; Liu et al., 2020). Understanding the intricacies of these processes provides valuable insights into the pathophysiology of gastrointestinal disorders such as functional dyspepsia. Moreover, this knowledge is crucial for developing targeted therapeutic interventions that aim to restore normal

gastric function and alleviate symptoms associated with motility disorders (Kim & Kuo, 2019; Cangemi & Lacy, 2023).

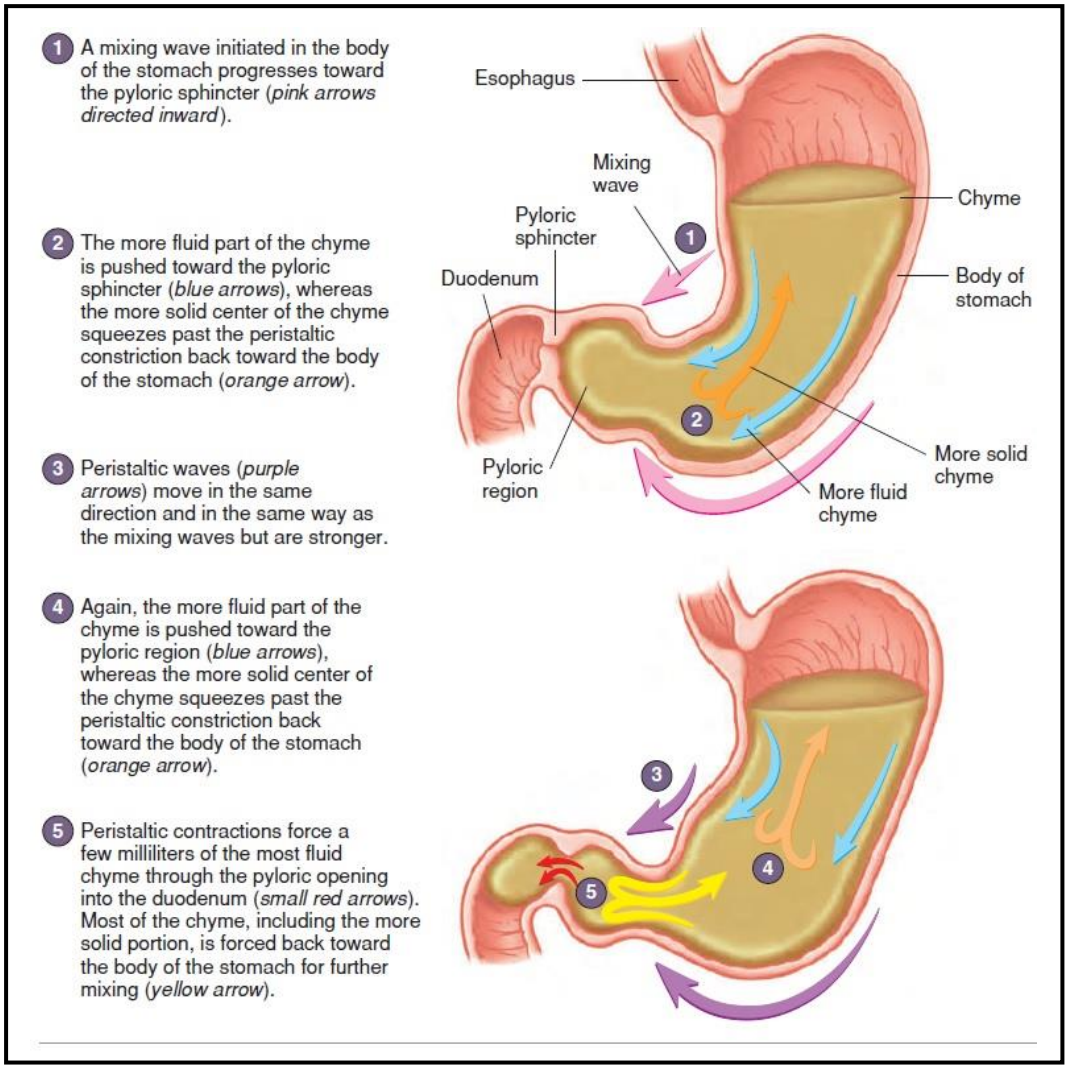


Figure 2.2 Physiology of Gastric Motility (Brainkart.com, 2023)

2.3 Functional Dyspepsia: A Comprehensive Overview

2.3.1 Definition and Diagnostic Criteria

The conceptualization of dyspepsia has undergone a significant historical evolution, transitioning from a broad, symptom-based description of upper abdominal discomfort to a precisely defined functional gastrointestinal disorder (Tominaga & Kusunoki, 2018; Ferrao & Chehter, 2023). Historically, “dyspepsia” was a general term encompassing a variety of symptoms such as indigestion, heartburn, and bloating, often without a clear distinction between organic and functional etiologies. The paradigm shifted decisively with the establishment of the Rome Foundation, an international body

dedicated to standardizing the classification of what are now termed disorders of gut-brain interaction (DGBIs) (Esterita et al., 2021; Meerveld et al., 2018). Through a consensus-driven process, the Rome criteria have been iteratively refined (from Rome I to the current Rome IV), providing clinicians and researchers with a standardized diagnostic framework that is crucial for advancing both clinical care and scientific inquiry (Drossman, 2016).

Currently, functional dyspepsia (FD) is formally defined by the Rome IV criteria as the presence of one or more of the following symptoms: bothersome postprandial fullness, early satiation, epigastric pain, or epigastric burning, with no evidence of structural disease (including at upper endoscopy) that is likely to explain the symptoms (Stanghellini et al., 2016). For a formal diagnosis, these criteria must be fulfilled for the last three months, with symptom onset at least six months prior to diagnosis. This temporal requirement ensures that the condition is chronic and persistent, distinguishing it from transient episodes of indigestion.

The Rome IV criteria further sub-classify FD into two distinct, though often overlapping, syndromes based on the predominant symptom profile, which reflects different underlying pathophysiological mechanisms:

a. **Postprandial Distress Syndrome (PDS):** This subtype is characterized by the presence of bothersome postprandial fullness (an unpleasant sensation of prolonged food retention in the stomach) and/or early satiation (the inability to finish a normal-sized meal) occurring after ordinary-sized meals, at least several times per week (Christopher et al., 2022). PDS is primarily associated with gastroduodenal sensorimotor dysfunctions, such as impaired gastric accommodation and delayed gastric emptying (Carbone et al., 2020).
b. **Epigastric Pain Syndrome (EPS):** This subtype is defined by the presence of bothersome epigastric pain or burning, occurring at least once per week. The pain is localized to the epigastrium, is not retrosternal, and is not relieved by defecation or passage of flatus. While it can be meal-related, it can also occur during fasting. EPS is more closely linked to mechanisms such as visceral hypersensitivity (Kwang, 2021) and altered central pain processing (Futagami et al., 2018; Christopher et al., 2022).
c. **PDS-EPS Overlap:** A significant proportion of patients with FD meet the criteria for both PDS and EPS. This overlap subtype often presents a more severe clinical

picture and may involve a broader range of pathophysiological disturbances (Cheng et al., 2024; Sayuk & Gyawali, 2020).

A fundamental principle in the diagnosis of FD is the exclusion of organic pathology. The diagnostic process necessitates a thorough clinical evaluation to rule out structural diseases such as peptic ulcer disease, gastroesophageal reflux disease (GERD), and malignancy. Central to this process is the identification of "red flag" or alarm features, which mandate prompt and thorough investigation, typically including upper endoscopy. These features include unintentional weight loss, persistent vomiting, dysphagia (difficulty swallowing), odynophagia (painful swallowing), signs of gastrointestinal bleeding (e.g., anemia, hematemesis), and a family history of upper gastrointestinal cancer (Moayyedi et al., 2017). In the absence of these alarm features, particularly in younger patients, a diagnosis of FD can often be confidently made based on symptom criteria alone, forming the basis for initiating empirical treatment.

2.3.2 Epidemiology and Global Burden

Functional Dyspepsia (FD) is a highly prevalent condition that constitutes a major public health concern globally. Large-scale systematic reviews and meta-analyses have established its significant epidemiological footprint, with a pooled global prevalence estimated to be around 7% to 11% when defined by the Rome IV criteria (Ford et al., 2020; Sperber et al., 2021). However, this figure masks considerable heterogeneity, with reported prevalence rates in individual population-based studies varying widely from 5% to over 30% (Pilin & Stacey, 2024). This variability can be attributed to methodological factors, including the specific diagnostic criteria used (e.g., Rome III vs. the more stringent Rome IV), study design, and cultural differences in symptom reporting (Oshima, 2024).

Significant regional variations in FD prevalence are well-documented. While the disorder is common worldwide, some studies suggest a higher prevalence in Western countries compared to many parts of Asia (Ford et al., 2020). Within Asia, prevalence also varies, and Southeast Asia represents a region of particular interest due to its diverse genetic, dietary, and environmental landscape. The statistics in Indonesian have shown that dyspepsia was one of the sixth primary diseases that led to hospitalization in 2021, accounting for 18,807 cases (39.8%) in men and 60.2% in women (Putri et al., 2022). The available hospital-based data and regional community studies consistently highlight that dyspepsia is a leading cause for gastroenterology consultations and

imposes a substantial burden. For instance, a community-based study in a rural Indonesian setting identified a high prevalence of dyspepsia symptoms, underscoring the widespread nature of the problem beyond urban clinical centers (Widya et al., 2023). This evidence, combined with national health statistics, confirms that FD is a highly relevant and pressing health issue within the Indonesian context, necessitating culturally and regionally specific research.

The risk profile for FD is multifactorial, involving a complex interplay of demographic, lifestyle, infectious, and psychosocial factors. Demographically, most studies report a higher prevalence in females, with an odds ratio of approximately 1.2 to 1.5 compared to males (Lovell & Ford, 2012). While FD affects a wide age range, it is commonly diagnosed in younger to middle-aged adults with age approximately 17,6%-23,7% at 18-64 years (Brun & Kuo, 2010). Several modifiable risk factors have been identified, including smoking and the use of nonsteroidal anti-inflammatory drugs (NSAIDs), both of which can disrupt gastroduodenal mucosal integrity and motility (Ford et al., 2020). The role of diet is complex, but consumption of high-fat foods has been shown to trigger symptoms in susceptible individuals. A crucial risk factor is a history of acute gastrointestinal infection, which can lead to post-infectious FD (PI-FD) in a subset of individuals, likely through mechanisms involving persistent low-grade inflammation and altered gut-brain signaling (Futagami et al., 2018). The role of *Helicobacter pylori* infection remains debated; while it is a cause of organic dyspepsia, its eradication leads to symptom improvement in only a small subset of FD patients. Perhaps the most robustly established risk factors are psychosocial; anxiety, depression, somatization, and a history of early life trauma are consistently and strongly associated with the development and severity of FD, highlighting the central role of the gut-brain axis (Van den Houte et al., 2020).

The socioeconomic impact of FD is profound, extending far beyond the clinical symptoms. The economic burden is composed of substantial direct and indirect costs (Gabbard et al., 2024). Direct costs are driven by high healthcare utilization, including frequent consultations with primary care physicians and specialists, expensive and often repeated diagnostic procedures like upper endoscopy (primarily to exclude organic disease), and long-term expenditure on both prescription and over-the-counter medications (Lacy et al., 2013; Sperber et al., 2020). However, the indirect costs, which relate to loss of productivity, are often even greater. This includes absenteeism (days of work missed) and, more significantly, presenteeism, which is a state of reduced

productivity and effectiveness while at work due to symptoms (Brook et al., 2010; Schmulson et al., 2018). This substantial loss of work productivity, combined with the immense personal cost of diminished health-related quality of life, positions FD as a major socioeconomic burden that warrants the development of more effective and accessible therapeutic strategies.

2.3.3 Pathophysiology: A Multifactorial Perspective

The pathophysiology of Functional Dyspepsia (FD) is exceptionally complex and cannot be attributed to a single causative factor. Instead, it is best understood as a multifactorial disorder arising from an intricate interplay of physiological and psychological dysfunctions. The current paradigm recognizes several key overlapping mechanisms that contribute to the manifestation of symptoms: gastroduodenal sensorimotor dysfunction, visceral hypersensitivity, dysregulation of the gut-brain axis, and low-grade mucosal inflammation (Drossman & Tack, 2022). While these mechanisms are presented as distinct entities for clarity, they are deeply interconnected, and it is their combined effect that ultimately drives the clinical presentation of FD in an individual patient.

2.3.3.1 Gastroduodenal Sensorimotor Dysfunction

Abnormalities in the motor and sensory functions of the stomach and duodenum are considered cornerstone pathophysiological mechanisms in FD, particularly in the Postprandial Distress Syndrome (PDS) subtype. These dysfunctions disrupt the normal sequence of events required for the ingestion, storage, processing, and timely emptying of a meal, directly leading to cardinal dyspeptic symptoms. The three most well-characterized sensorimotor disturbances are delayed gastric emptying, impaired gastric accommodation, and antral-duodenal dysmotility (Duncanson et al., 2021; Sato & Grover, 2023).

a. **Delayed Gastric Emptying (DGE):** Gastric emptying is the process by which chyme is transferred from the stomach to the duodenum, a process that relies on coordinated contractions of the gastric antrum, pylorus, and duodenum. DGE is defined as an abnormally slow rate of emptying of a solid or liquid meal from the stomach. It is a demonstrable pathophysiological finding in approximately 20-40% of patients with FD (Van den Houte et al., 2020). The primary clinical consequence of DGE is the prolonged retention of food within the stomach, which

directly correlates with the sensation of bothersome postprandial fullness, prolonged bloating, and can also contribute to nausea and vomiting in severe cases (Sato & Grover, 2022; Camilleri, 2023). The underlying causes of DGE in FD are heterogeneous and may include antral hypomotility, pyloric spasm, or impaired antro-duodenal coordination.

b. **Impaired Gastric Accommodation (IGA):** Gastric accommodation refers to the reflexive relaxation of the proximal stomach (the fundus) in response to food ingestion. This vagally-mediated reflex allows the stomach to act as a reservoir, accepting a meal without a significant increase in intragastric pressure. Impaired gastric accommodation, identified in up to 40% of FD patients, is a failure of this relaxation process, resulting in a rapid rise in intragastric pressure upon eating (Ishtkhar et al., 2023; Figueredo et al., 2019). This premature pressure increase activates gastric mechanoreceptors, leading directly to the hallmark PDS symptom of early satiation—the feeling of being full after consuming only a small amount of food. Furthermore, IGA can force food prematurely into the distal stomach (antrum), exacerbating feelings of fullness and potentially contributing to epigastric pain (Eglantina et al., 2021).

c. **Antral Hypomotility and Duodenal Dysmotility:** Beyond the broader concepts of emptying and accommodation, more subtle dysmotilities play a role. The gastric antrum is responsible for grinding solid food particles and propelling them toward the pylorus. Reduced frequency or amplitude of antral contractions (antral hypomotility) can impair this process, contributing to delayed gastric emptying and postprandial fullness (Kajal & Aravind, 2023; Liu et al., 2020). Increasingly, research focus has shifted to the duodenum, which plays a critical role in regulating gastric emptying and processing nutrients. In FD, duodenal dysmotility, characterized by uncoordinated or ineffective contractions, can disrupt the normal feedback mechanisms that control gastric outflow, further contributing to the retention of chyme in the stomach (Van den Houte et al., 2020). These motor disturbances are often linked to other pathophysiological factors, such as low-grade duodenal inflammation, which can alter neuromuscular function.

2.3.3.2 Visceral Hypersensitivity

While sensorimotor dysfunctions primarily explain the symptoms of postprandial distress, visceral hypersensitivity is considered the cardinal pathophysiological mechanism underlying the pain-predominant symptoms of Epigastric Pain Syndrome (EPS) (Tominaga & Kusunoki, 2018). Visceral hypersensitivity is defined as an augmented sensory perception, wherein stimuli that are normally innocuous are perceived as unpleasant or painful (allodynia), and stimuli that are normally painful are perceived as more intense (hyperalgesia) (Aziz et al., 2019). In FD, this manifests as heightened sensitivity to both mechanical and chemical stimuli within the gastroduodenal region. For example, patients with FD often report pain and discomfort at lower volumes of gastric distension (e.g., during a barostat test) compared to healthy individuals, providing direct evidence of mechanical hypersensitivity (Oshima, 2024). Similarly, heightened sensitivity to duodenal infusion of lipids or acids has been demonstrated, indicating a chemosensitive component (Yujiao et al., 2023). This abnormal sensory processing is not a peripheral phenomenon alone but involves complex changes at multiple levels of the nervous system.

a. **Mechanisms of Peripheral and Central Sensitization:** The development of visceral hypersensitivity is a two-fold process involving both peripheral and central sensitization. Peripheral sensitization occurs at the level of the afferent nerve endings within the gut wall. Here, local factors such as low-grade inflammation, mast cell degranulation, and alterations in the microbiota can release a “sensitizing soup” of mediators (e.g., histamine, serotonin, proteases, prostaglandins). These mediators act on receptor channels, such as Transient Receptor Potential (TRP) channels (e.g., TRPV1, TRPA1), located on visceral afferent neurons, lowering their activation threshold and increasing their excitability (Ford et al., 2024; Simrén et al., 2017). Consequently, these neurons fire more readily in response to normal physiological stimuli like gastric distension or chemical exposure. Central sensitization represents a state of hyperexcitability within the central nervous system (CNS), specifically in the spinal cord and brain. It is characterized by an amplification of pain signaling, where the CNS response to afferent input is augmented and prolonged. This occurs through neuroplastic changes, including increased release of excitatory neurotransmitters (e.g., glutamate, substance P) and altered function of descending pain modulation pathways (Aziz et al., 2019; Esterita et al., 2021). As

a result, even normal afferent signals from the gut are interpreted by the brain as being more intense, leading to the perception of pain. Central sensitization also explains the phenomenon of referred pain and the frequent overlap of FD with other chronic pain conditions.

b. **Role of Mechanoreceptors and Nociceptors in Pain Perception:** The sensation of visceral events, from normal physiological function to pain, is mediated by a sophisticated network of sensory neurons. Mechanoreceptors are specialized nerve endings that respond to mechanical stimuli, such as stretch, distension, and contraction. In a healthy state, low-threshold mechanoreceptors provide innocuous sensory information that contributes to feelings of satiety and fullness. However, in the context of sensitization, these low-threshold afferents can begin to signal noxious information, a process known as phenotypic switching, contributing to allodynia (pain from a non-painful stimulus) (Amanda & Hui, 2018). Nociceptors, on the other hand, are high-threshold receptors that are specifically activated by noxious (painful) stimuli of mechanical, thermal, or chemical nature. In FD, the activation threshold of these nociceptors is significantly lowered due to peripheral sensitization. Thus, physiological events like gastric accommodation or normal peristalsis, which would not typically activate nociceptors, can now trigger pain signals. The continuous barrage of signals from these sensitized mechanoreceptors and nociceptors is then transmitted via the spinal cord to higher brain centers, including the thalamus, insula, and anterior cingulate cortex, where the sensory information is processed and integrated with emotional and cognitive states to produce the conscious perception of pain and discomfort characteristic of FD (Shin, 2024; Grady et al., 2021).

2.3.3.3 The Gut-Brain Axis

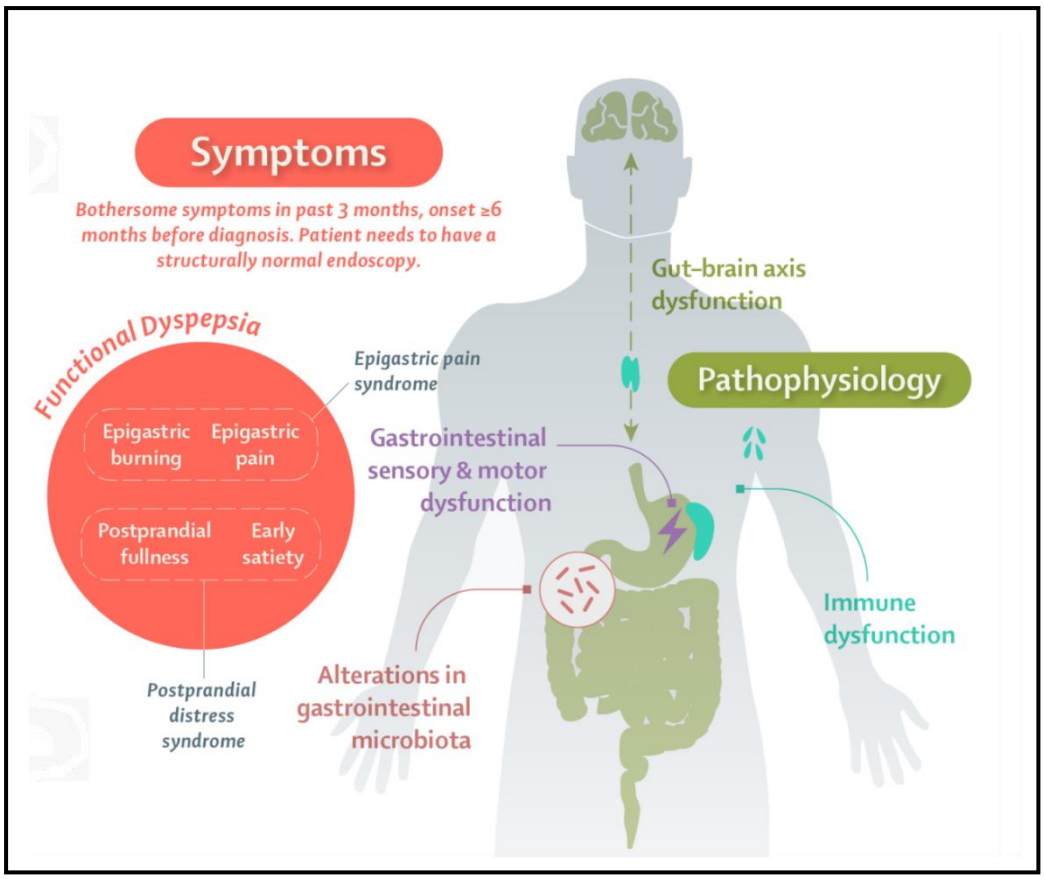
The concept of the gut-brain axis is central to understanding the pathophysiology of FD and other DGBIs, providing a framework that integrates gastrointestinal function with central nervous system processes. This axis is not a metaphorical link but a complex, bidirectional communication network that involves neural, endocrine, and immune pathways, ensuring a continuous dialogue between the brain and the gut (Rupp & Stengel, 2022; Zhang et al., 2024).

In FD, dysregulation within this network is a key driver of symptoms, explaining the profound influence of psychological states on gut function and, conversely, how visceral signals can impact mood, cognition, and pain perception.

a. **Bidirectional Communication between the CNS and ENS:** The neural foundation of the gut-brain axis is the intricate connection between the central nervous system (CNS), comprising the brain and spinal cord, and the enteric nervous system (ENS), often referred to as the "second brain" (Cryan et al., 2019). The ENS is a vast, intrinsic network of neurons within the gut wall that autonomously controls most gut functions, including motility, secretion, and blood flow. Communication between these two systems occurs via two main routes. The primary pathway is the autonomic nervous system (ANS), composed of the sympathetic and parasympathetic branches. The parasympathetic system, mainly via the vagus nerve, generally promotes "rest-and-digest" functions, such as enhancing gastric motility and accommodation. In contrast, the sympathetic system mediates the "fight-or-flight" response, typically inhibiting gastrointestinal motor function and increasing visceral sensitivity (Amanda & Hui, 2018). Afferent nerve fibers running alongside these autonomic pathways continuously relay sensory information from the gut back to the CNS, informing the brain about the state of the viscera. In FD, an imbalance in autonomic tone, often characterized by reduced vagal activity and heightened sympathetic drive, is thought to contribute significantly to impaired gastric accommodation and hypersensitivity (Privitera, 2019; Shin, 2024).
b. **Role of Neurotransmitters and Hormones:** The communication along the gut-brain axis is mediated by a vast array of signaling molecules. Serotonin (5-hydroxytryptamine, 5-HT) is a critical player; over 90% of the body's serotonin is produced in the gut by enterochromaffin cells. In the periphery, serotonin is a key regulator of visceral sensation and motility, acting on various 5-HT receptors. Dysregulation of serotonin signaling has been directly implicated in FD symptoms (Wang et al., 2023). Centrally, serotonin is a well-known modulator of mood, anxiety, and pain perception, providing a direct molecular link between psychological state and gut function. Other gut hormones also play a crucial role. For instance, cholecystokinin (CCK), released from the duodenum in response to fat, can induce satiety and may contribute to hypersensitivity in FD patients. Ghrelin, primarily produced in the stomach, is an appetite-stimulating hormone

that also has prokinetic effects; altered ghrelin signaling has been observed in some FD patients, potentially contributing to early satiety and delayed emptying (Jin et al., 2017).

c. **Impact of Psychological Stress, Anxiety, and Depression:** The bidirectional nature of the gut-brain axis provides the physiological basis for the strong association between FD and psychological comorbidities. Psychological stress, whether acute or chronic, is a potent modulator of gut function. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the release of corticotropin-releasing factor (CRF) and cortisol. These stress hormones can directly alter gut motility, increase visceral permeability ("leaky gut"), and enhance visceral pain perception (Murni et al., 2018; Li & Page, 2022). Consequently, patients with FD often report symptom exacerbation during periods of stress. Conversely, the relationship is not unidirectional. Persistent visceral afferent signaling from a disordered gut can act as a chronic interoceptive stressor, impacting central emotional and pain-processing circuits in the brain, including the amygdala and prefrontal cortex. This "bottom-up" signaling can contribute to the development or maintenance of anxiety and depression, creating a self-perpetuating vicious cycle where gut symptoms and psychological distress mutually reinforce each other (Labanski et al., 2019; Schiopu et al., 2022). This underscores the clinical necessity of addressing psychological factors as an integral part of FD management.



Figur 2.3 Etiology and Pathophysiology of FD (World Journal of Gastroenterology, 2019)

2.3.3.4 Low-Grade Inflammation and Immune Activation

The historical definition of Functional Dyspepsia (FD) was predicated on the absence of observable organic or structural pathology. However, a growing body of evidence has challenged this paradigm, revealing the presence of subtle, low-grade inflammation and immune activation in the duodenum of a significant subset of FD patients (Olson et al., 2024). This microscopic inflammation, while not visible during standard endoscopy, is increasingly recognized as a key pathophysiological driver, capable of influencing local neuromuscular function, sensitizing afferent nerves, and contributing to the development of both motor and sensory abnormalities characteristic of the disorder. This subclinical inflammatory state provides a crucial biological link between potential triggers, such as infection or diet, and the chronic symptoms of FD.

a. **Evidence for Duodenal Eosinophilia and Mast Cell Activation:** Two key immune cell types have been consistently implicated in the low-grade inflammatory profile of FD: eosinophils and mast cells. Several studies have demonstrated a significantly increased number of eosinophils in the duodenal

mucosa of FD patients compared to healthy controls, a condition known as duodenal eosinophilia (Shah et al., 2022). Eosinophils are potent immune cells that, when activated, degranulate and release a variety of pro-inflammatory mediators, including major basic protein and eosinophil cationic protein. These substances can cause local tissue damage and directly sensitize visceral afferent nerves, thereby contributing to visceral hypersensitivity and pain. Similarly, an increased number and activation of mast cells have been observed in close proximity to enteric nerves in the duodenum of FD patients (Narayanan et al., 2022). Mast cells act as critical gatekeepers of the gut immune system. Upon activation by antigens, stress, or neuropeptides, they release a powerful cocktail of mediators, including histamine, proteases, and tryptase. These mediators can increase epithelial permeability (contributing to a "leaky gut"), alter smooth muscle contractility (impairing motility), and directly excite sensory neurons, thus playing a central role in generating symptoms of pain, bloating, and discomfort (Wouters et al., 2016).

b. **The Concept of Post-Infectious FD (PI-FD):** The development of chronic dyspeptic symptoms following an acute episode of gastroenteritis provides a clear clinical model illustrating the role of inflammation and immune activation in the genesis of FD. A systematic review and meta-analysis found that the pooled odds ratio of developing FD after an infectious enteric event is approximately 2.5, with the risk persisting for years after the initial infection (Futagami et al., 2015). This condition, termed post-infectious FD (PI-FD), is believed to be triggered by an initial robust inflammatory response to a pathogen (e.g., *Salmonella*, *Campylobacter*). Although the pathogen is eventually cleared, a subset of individuals fails to down-regulate the immune response, leading to a state of persistent, low-grade mucosal inflammation, increased intestinal permeability, and alterations in the local neuro-immune milieu. This sustained immune activation provides a plausible mechanism for the long-term changes in sensorimotor function and visceral sensitivity that define PI-FD (Shah et al., 2022).

c. **Alterations in Gut Microbiota (Dysbiosis):** The gut microbiota, the complex ecosystem of microorganisms residing in the gastrointestinal tract, is now recognized as a critical regulator of host physiology, including gut-brain axis signaling and immune function. A state of imbalance in this ecosystem, known

as dysbiosis, has been increasingly implicated in FD. While research in this area is still emerging, studies have reported alterations in the composition and diversity of the duodenal and fecal microbiota in FD patients compared to healthy controls (Zhong et al., 2017). For instance, some studies have noted a decrease in beneficial bacteria, such as *Bifidobacterium* and *Faecalibacterium*, and an increase in potentially pro-inflammatory bacteria. Dysbiosis can contribute to FD pathophysiology through several mechanisms. It can compromise the integrity of the intestinal epithelial barrier, leading to increased permeability and allowing microbial products like lipopolysaccharide (LPS) to trigger immune activation. Furthermore, microbial metabolites, such as short-chain fatty acids (SCFAs), are key signaling molecules in the gut-brain axis; an altered microbial profile can therefore lead to dysregulated production of these metabolites, impacting everything from gut motility to central pain processing and mood (Zhou et al., 2022).

2.3.4 Clinical Manifestations of Functional Dyspepsia (FD)

The clinical presentation of Functional Dyspepsia (FD) is defined by a characteristic constellation of chronic, relapsing-remitting upper gastrointestinal symptoms. However, the patient experience extends far beyond these core manifestations, frequently encompassing a range of overlapping disorders and co-morbidities that reflect the systemic nature of gut-brain axis dysregulation. The interplay between these symptoms and co-morbid conditions culminates in a substantial and pervasive negative impact on the patient's overall health-related quality of life (HRQoL).

2.3.4.1 Negative Impact on Abdominal Pain

Functional dyspepsia (FD) is often associated with symptoms of persistent upper abdominal discomfort or pain and is a major complaint that significantly impacts the quality of life of FD patients. This pain is typically described as epigastric, non-radiating, and can be exacerbated by food intake, stress, or even certain body positions (Sayuk & Gyawali, 2020). The pain experienced by FD patients is thought to result from a combination of factors, including visceral hypersensitivity, impaired gastric accommodation, and delayed gastric emptying, all of which contribute to the complex pathophysiology of the disorder (Kim & Kuo, 2019).

Visceral hypersensitivity, a heightened response to stimuli in the gastrointestinal tract, is particularly relevant in the context of FD-related abdominal pain. Studies have shown that FD patients exhibit an exaggerated perception of gastric distension, which correlates with their reported pain levels (Kim & Kuo, 2019; Oshima, 2024). Additionally, altered central processing of visceral signals, potentially modulated by psychological factors such as anxiety and depression, further intensifies the experience of pain (Singh et al., 2022). The multifaceted nature of abdominal pain in FD underscores the need for comprehensive assessment tools that can accurately capture the severity and impact of this symptom on patients' daily lives (Tabibzadeh et al., 2018).

The Abdominal Pain Index (API) Questionnaire has emerged as a critical instrument in the assessment of abdominal pain severity and frequency in patients with functional dyspepsia (FD). As a patient-reported outcome measure, the API quantifies not only the intensity and duration of pain but also the extent to which pain disrupts daily activities, providing a comprehensive evaluation of the pain experience (Hoseini et al., 2020). This standardized approach to pain assessment is invaluable for clinicians seeking to understand the nuanced pain profiles of FD patients, thereby enabling the development of more tailored and effective treatment plans. Moreover, the API serves as a valuable tool for monitoring therapeutic outcomes over time, offering crucial insights into the effectiveness of interventions aimed at alleviating abdominal pain (Laird et al., 2015).

The clinical utility of the API is further underscored by its capacity to capture the multidimensional nature of pain in FD. Unlike single-item pain scales, the API evaluates multiple facets of the pain experience, including intensity, duration, and the impact on the patient's daily life. This multidimensional approach is particularly significant in the context of FD, where pain manifestations can vary widely among individuals and may exhibit temporal fluctuations (Laird et al., 2015). By incorporating the API into routine clinical practice, healthcare providers can achieve a more precise understanding of the burden of abdominal pain on FD patients, thus facilitating the design of more effective and individualized management strategies (Laird et al., 2015: Neb et al., 2024).

The Abdominal Pain Index (API) Questionnaire stands as a robust and comprehensive tool for the assessment of abdominal pain, enabling more personalized and targeted therapeutic interventions. As ongoing research continues to unravel the

underlying mechanisms contributing to pain in FD, the API is poised to play an increasingly pivotal role in both clinical and research settings, enhancing patient outcomes in this complex disorder (Laird et al., 2015: Neb et al., 2024; Russell et al., 2018).

2.3.4.2 Negative Impact on Dyspepsia Severity

The severity of dyspeptic symptoms in functional dyspepsia (FD)—including postprandial fullness, early satiety, and epigastric pain or burning—varies significantly in both intensity and frequency among patients (Oshima, 2024). These symptoms are not only unpredictable but also have a profound impact on patients' quality of life, affecting their physical, psychological, and social well-being. Recent studies underscore the critical role these symptoms play in determining the overall burden of FD on individuals (Akaishi, 2024; Huang et al., 2020). They highlight that the severity of these dyspeptic manifestations is a key determinant of clinical outcomes and therapeutic efficacy in FD management, necessitating a comprehensive approach that addresses the multifaceted nature of this disorder.

Tools such as the Leeds Dyspepsia Questionnaire (LDQ) have been developed to rigorously quantify the severity of dyspepsia, thereby enabling more precise evaluations of treatment efficacy and symptom progression, typically within the past month (Fraser et al., 2007; Khaled et al., 2021). The LDQ comprises several items that assess a broad range of symptoms, including nausea, vomiting, heartburn, and bloating, along with core dyspeptic symptoms. By capturing the multidimensional nature of dyspeptic presentations, the LDQ offers a comprehensive overview of the patient’s symptom burden (Nkurunziza et al., 2016). This detailed assessment is crucial for tailoring individualized treatment strategies, particularly in the context of functional dyspepsia (FD), where symptomatology can be highly variable and influenced by factors such as diet, stress, and psychological comorbidities (Tack et al., 2024).

In clinical practice, the LDQ functions as both a diagnostic and monitoring instrument. Its ability to quantify symptom severity provides healthcare providers with a baseline for treatment initiation and facilitates the tracking of changes over time. This is especially critical in FD, where measuring treatment outcomes can be challenging due to the subjective nature of symptoms and the potential influence of placebo effects (Fraser et al., 2007; Khaled et al., 2021). The LDQ’s sensitivity to fluctuations in symptom severity enhances its value as a tool for assessing the efficacy of both

pharmacological and non-pharmacological interventions, thereby supporting clinicians in making informed decisions regarding treatment modifications (Tack et al., 2024).

Furthermore, the role of the LDQ extends beyond clinical practice into research domains. Its standardized format ensures consistent data collection across studies, thus facilitating the comparison of treatment outcomes and the identification of factors associated with symptom improvement or deterioration. The LDQ has been validated across multiple populations, demonstrating its reliability and applicability in diverse clinical contexts (Nkurunziza et al., 2016; Khaled et al., 2021). Consequently, the LDQ is increasingly employed as a primary or secondary outcome measure in clinical trials, contributing significantly to the development of evidence-based guidelines for FD management (Tack et al., 2024).

2.3.4.3 Negative Impact on Sleep Disturbance

The various systemic effects associated with FD increasingly recognize sleep disturbances as a significant and debilitating consequence. Patients with FD frequently report poor sleep quality, insomnia, and fragmented sleep, which not only exacerbates gastrointestinal symptoms but also contributes to a diminished overall quality of life (Akaishi, 2024). The bidirectional relationship between sleep disturbances and FD symptoms, such as epigastric pain and bloating, underscores the complexity of this condition and highlights the need for comprehensive evaluation and management strategies (Akaishi, 2024; Huang et al., 2020).

Sleep disturbances in FD patients are thought to arise from several underlying mechanisms, including heightened visceral sensitivity, altered gut motility, and the influence of psychological stressors, which are often prevalent in this population (Kawada, 2021). The presence of these factors can lead to a vicious cycle where poor sleep exacerbates gastrointestinal symptoms, which in turn further disrupt sleep. For instance, nocturnal gastric acid reflux and delayed gastric emptying, common in FD, may directly interfere with sleep, leading to increased wakefulness and reduced sleep efficiency (Su et al., 2021). Moreover, psychological comorbidities such as anxiety and depression, which are frequently associated with FD, may further impair sleep quality by increasing arousal and prolonging sleep latency (Alam et al., 2019).

To accurately assess the impact of FD on sleep, the Pittsburgh Sleep Quality Index (PSQI) has been widely adopted as a validated tool for measuring sleep quality and identifying sleep disturbances in clinical and research settings. The PSQI is a self-

reported questionnaire that evaluates various aspects of sleep over the past month, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Wuestenberghs et al., 2022). By generating a global score, the PSQI allows clinicians to quantify the severity of sleep disturbances and monitor changes over time, making it an invaluable instrument in the management of FD patients (Lei et al., 2018; Accarie & Vanuytsel 2020).

In clinical practice, the PSQI can be used to identify FD patients who are at higher risk of sleep disturbances and to tailor therapeutic interventions accordingly. For instance, patients with poor PSQI scores may benefit from integrated visceral and spinal manipulation interventions aimed at improving sleep quality that target both functional dyspepsia symptoms and sleep disturbances. Additionally, the PSQI can be used to evaluate the effectiveness of these interventions by tracking improvements in sleep quality and related outcomes, thereby guiding ongoing treatment decisions.

2.3.4.4 Negative Impact on Psychological Disorders

Functional dyspepsia (FD) is increasingly recognized not only for its debilitating gastrointestinal symptoms but also for its significant association with a spectrum of psychological disorders, including anxiety, depression, and elevated stress levels. The relationship between FD and psychological distress is characterized by a complex, bidirectional interaction wherein the presence of psychological disorders can exacerbate FD symptoms, while the chronic and unpredictable nature of FD can, in turn, intensify psychological distress. This cyclical relationship often leads to a vicious cycle that is challenging to disrupt and can complicate the clinical management of FD (Esterita et al., 2021; Yao et al., 2020; Alam et al., 2019). Moreover, the presence of psychological comorbidities significantly amplifies the overall burden of FD, impacting the patient's quality of life and potentially diminishing the efficacy of therapeutic interventions. Therefore, the comprehensive assessment and management of psychological factors are essential in the holistic treatment approach to FD, as addressing these aspects can lead to more effective and sustainable therapeutic outcomes (David et al., 2021; Wei et al., 2022).

The relationship between FD and psychological disorders is likely bidirectional, where the chronic nature of FD symptoms such as pain, bloating, and early satiety can lead to increased levels of stress and anxiety. Conversely, psychological stress has been

shown to exacerbate FD symptoms, potentially through mechanisms involving the gut-brain axis, which regulates gastrointestinal function in response to emotional and psychological states (Esterita et al., 2021; Yao et al., 2020; Alam et al., 2019). Studies have demonstrated that FD patients with higher levels of stress and anxiety tend to report more severe symptoms and a poorer quality of life compared to those without these psychological conditions, highlighting the significant impact of mental health on the clinical course of FD (Yao et al., 2020).

Given the strong association between psychological stress and FD, it is critical to evaluate stress levels as part of the comprehensive management of the disorder. The Perceived Stress Scale (PSS) is a widely used psychological instrument designed to measure the degree to which situations in one's life are appraised as stressful. The PSS assesses the perceived unpredictability, uncontrollability, and overload of daily life, providing a subjective measure of stress that is relevant to the patient's current situation (Chan & La Greca, 2020; Du et al., 2023). In the context of FD, the PSS can help identify patients who are particularly susceptible to stress-related exacerbations of their symptoms, thereby guiding the implementation of targeted stress management interventions (Du et al., 2023).

The PSS is particularly valuable in clinical practice because it offers insights into how patients perceive their stress levels, rather than merely quantifying objective stressors. This distinction is important because perceived stress has been shown to be a more accurate predictor of psychological and physiological outcomes, including those related to gastrointestinal health (Du et al., 2023; Arnaout et al., 2023). Moreover, the PSS can be used to evaluate the effectiveness of stress-reduction interventions in clinical trials, contributing to the development of evidence-based guidelines for the comprehensive management of FD (Yan et al., 2022).

2.3.4.5 Negative Impact on Quality of Life

Functional dyspepsia (FD) is a chronic gastrointestinal disorder that significantly impacts the quality of life (QoL) of those affected, manifesting in persistent symptoms such as postprandial fullness, early satiety, and epigastric pain or burning. These symptoms not only cause physical discomfort but also lead to considerable psychological and social challenges (Chuah, 2020). Recent studies highlight that the burden of FD on QoL is profound, as the persistent and unpredictable nature of the symptoms often results in limitations on daily activities, dietary restrictions, and

emotional distress (Esterita et al., 2021). These limitations can, over time, contribute to a diminished sense of well-being, increased stress levels, and a greater likelihood of developing comorbid conditions such as anxiety and depression, further exacerbating the impact on QoL (David et al., 2021).

The Nepean Dyspepsia Index (NDI) Questionnaire is a validated tool specifically designed to assess the impact of FD on quality of life. The NDI captures a broad range of QoL dimensions, including physical discomfort, emotional well-being, social functioning, and dietary restrictions. By providing a comprehensive evaluation of the patient's experience, the NDI enables clinicians to quantify the degree to which FD interferes with daily life and overall well-being (Goyal et al., 2022; Nkurunziza et al., 2016). This tool is particularly valuable in both clinical and research settings, where understanding the full impact of FD on QoL is essential for tailoring interventions and monitoring therapeutic outcomes (Masuy et al., 2019).

The use of the NDI in clinical practice facilitates a more nuanced understanding of the patient's condition, beyond the mere presence or absence of symptoms. By assessing the specific domains of life affected by FD, healthcare providers can identify the areas most in need of intervention, whether they involve dietary adjustments, psychological support, or visceral and spinal manipulation treatments. Additionally, the NDI can be used to monitor changes in QoL over time, providing insights into the effectiveness of treatment strategies and guiding adjustments as needed (Masuy et al., 2019). This longitudinal approach is particularly important in FD, given the chronic and fluctuating nature of the disorder.

Moreover, the NDI's role extends to the realm of research, where it serves as a critical measure for evaluating the impact of FD in clinical trials and observational studies. The standardized nature of the NDI allows for consistent data collection and comparison across studies, facilitating the development of evidence-based guidelines for FD management (Goyal et al., 2020). As research continues to explore the pathophysiology and treatment of FD, the NDI will remain a key instrument in advancing our understanding of how this disorder affects patients' lives and how best to mitigate its impact (Chuah, 2020).

2.4 Current Management Strategies for Functional Dyspepsia and Their Limitations

The management of Functional Dyspepsia (FD) is notoriously challenging due to the condition's heterogeneous pathophysiology and the frequent overlap of symptoms. The therapeutic approach is typically empirical and stepwise, aimed at alleviating the patient's most bothersome symptoms. Current strategies are broadly categorized into pharmacological and non-pharmacological interventions. While these approaches form the bedrock of standard care, a critical review reveals significant limitations in their efficacy, tolerability, and ability to provide long-term relief, underscoring a substantial therapeutic gap.

2.4.1 Pharmacological Interventions

Pharmacological therapy is the first-line and most common approach to managing FD. Treatment is often targeted at the presumed dominant pathophysiological mechanism, such as acid hypersensitivity, sensorimotor dysfunction, or gut-brain axis dysregulation. However, the overall efficacy of these agents is modest, and treatment selection remains largely empirical.

a. Acid-Suppressive Therapy (Proton Pump Inhibitors and H2-Receptor Antagonists).

Historically, dyspepsia was considered an acid-related disorder, leading to the widespread use of acid-suppressive agents. Proton Pump Inhibitors (PPIs), such as omeprazole and esomeprazole, and Histamine-2 Receptor Antagonists (H2RAs) are the mainstays of this class. The rationale for their use in FD is multifactorial; beyond reducing gastric acidity, they may also have minor effects on duodenal inflammation and eosinophilia (Kinoshita et al., 2018).

Multiple meta-analyses have demonstrated that PPIs provide a small but statistically significant therapeutic gain over placebo in FD. The number needed to treat (NNT) to achieve symptom relief in one patient is approximately 10-14, indicating a modest effect size (Ford et al., 2020; Andrawes et al., 2025). The benefit appears to be most pronounced in patients with Epigastric Pain Syndrome (EPS) or those with overlapping reflux-like symptoms. Their efficacy in Postprandial Distress Syndrome (PDS) is considered minimal to non-existent.

A significant limitation is that a large proportion of patients do not respond to PPI therapy. Furthermore, concerns regarding the long-term use of PPIs have grown, with observational studies suggesting potential associations with an increased risk of bone fractures, chronic kidney disease, enteric infections (including *Clostridium difficile*), and micronutrient deficiencies (e.g., magnesium, vitamin B12) (Vaezi et al., 2017; Kinoshita et al., 2018). These risks necessitate a careful evaluation of the risk-benefit ratio for chronic use in FD.

b. Prokinetic Agents.

This class of drugs is designed to enhance and coordinate gastroduodenal motility, making them a rational choice for patients with PDS, particularly those with demonstrable delayed gastric emptying. Prokinetics act through various mechanisms. Metoclopramide and domperidone are dopamine D2 receptor antagonists. While they can improve gastric emptying, their use is severely restricted due to significant safety concerns. Metoclopramide carries a black box warning for the risk of irreversible tardive dyskinesia, while domperidone is associated with cardiac arrhythmias (QT prolongation) (Sugano et al., 2015). Acotiamide, an acetylcholinesterase inhibitor that enhances acetylcholine availability in the enteric nervous system, is approved for FD in Japan and several other countries. It has shown efficacy specifically for PDS symptoms, including postprandial fullness and early satiety, with a favorable safety profile (Matsueda et al., 2012). However, it is not widely available globally. Other agents, like 5-HT4 receptor agonists (e.g., prucalopride), are being investigated but are not yet standard therapy for FD.

c. Neuromodulators (Tricyclic Antidepressants and SSRIs).

For patients who fail to respond to the above treatments, particularly those with prominent pain symptoms or psychological co-morbidities, neuromodulators are considered. These agents are used at doses lower than those for depression and are intended to target the gut-brain axis, primarily by modulating visceral hypersensitivity and central pain processing.

Tricyclic antidepressants (TCAs), such as amitriptyline and imipramine, are the most studied class. Their analgesic effect is believed to stem from their action on norepinephrine and serotonin reuptake, as well as anticholinergic and

antihistaminic properties. A meta-analysis has shown that TCAs are effective in achieving global symptom improvement in FD, with an NNT of approximately 6 (Ford et al., 2020). Their benefit appears greatest in patients with EPS. The evidence for Selective Serotonin Reuptake Inhibitors (SSRIs), such as escitalopram, is less robust, with studies yielding conflicting results.

The clinical utility of neuromodulators is often limited by their side-effect profile. TCAs are associated with anticholinergic effects (dry mouth, constipation, urinary retention) and sedation, which can be poorly tolerated. SSRIs can cause nausea, headache, and sleep disturbances, sometimes worsening symptoms initially (Vincenzo et al., 2021). Furthermore, patient acceptance can be a barrier, as individuals may be reluctant to take a medication labeled as an "antidepressant" for a "stomach problem."

In summary, the pharmacological management of FD is characterized by modest efficacy, a lack of agents that target the full spectrum of pathophysiology, and significant limitations due to side effects and safety concerns. This reality often leaves both patients and clinicians frustrated and highlights the urgent need for safer and more holistically effective therapeutic options.

2.4.2 Non-Pharmacological Interventions

Given the limitations inherent in pharmacological treatments, non-pharmacological interventions represent a critical and complementary component of a holistic management strategy for FD. These approaches aim to empower patients with self-management skills, address the psychosocial dimensions of the disorder, and explore alternative therapeutic modalities that may offer relief with a lower risk of side effects. This section reviews the evidence base and challenges associated with dietary and lifestyle modifications, psychological therapies, and complementary and alternative medicine.

a. Dietary and Lifestyle Modifications.

General advice on diet and lifestyle is universally recommended as a foundational, first-line strategy in FD management. Lifestyle recommendations typically include smoking cessation, moderation of alcohol and caffeine intake, regular physical activity, and ensuring adequate sleep, as these factors can influence gastrointestinal motility and sensitivity (Miwa et al., 2022). Dietary

advice has historically focused on eating smaller, more frequent meals to avoid over-distending the stomach, and avoiding potential trigger foods, which are often patient-specific but commonly include fatty, spicy, or acidic foods (Talley & Ford, 2015).

Despite being common practice, the evidence supporting specific dietary interventions in FD is surprisingly sparse and of low quality. There is no single "dyspepsia diet" that is effective for all patients (Duboc et al., 2020). While high-fat meals have been shown to delay gastric emptying and induce symptoms in a laboratory setting, the clinical efficacy of a low-fat diet is not robustly established. Similarly, while gluten sensitivity has been implicated in a subset of patients, routine recommendation of a gluten-free diet is not supported by current evidence (Mounsey et al., 2020). The primary challenge with these modifications is the difficulty in achieving and sustaining patient adherence. The often vague nature of the advice, combined with the chronic and fluctuating course of FD, can lead to patient frustration and disengagement. A more promising approach may involve a patient-led strategy guided by a dietitian, using food and symptom diaries to systematically identify and eliminate individual trigger foods, rather than broad, restrictive diets (Pesce et al., 2020).

b. Psychological Therapies

Recognizing the central role of the gut-brain axis, psychological therapies, or "brain-gut behavior therapies," are an evidence-based option for patients with moderate to severe FD, particularly those with co-morbid psychological distress or who are refractory to other treatments. These therapies aim to alter the cognitive, emotional, and behavioral factors that contribute to symptom perception and severity.

1) **Cognitive Behavioral Therapy (CBT)**. Cognitive Behavioral Therapy **(**CBT) is a structured psychotherapy that helps patients identify and modify maladaptive thoughts (e.g., catastrophizing about symptoms), emotions, and behaviors related to their illness. It equips patients with coping skills, stress management techniques, and helps to reduce illness-related anxiety and avoidance behaviors. Evidence from randomized controlled trials and a subsequent meta-analysis suggests that CBT can be effective in improving FD symptoms and quality of life (Zang et al., 2024).

2) **Hypnotherapy:** Gut-directed hypnotherapy involves inducing a state of deep relaxation and focused attention, during which therapeutic suggestions are made to normalize gut function and reduce symptom perception. It is thought to work by modulating the gut-brain axis, enhancing descending pain inhibition, and reducing visceral sensitivity. Several clinical trials have demonstrated its efficacy in improving symptoms and well-being in patients with FD (Popa et al., 2019).

The primary barriers to the widespread use of these highly effective therapies are practical. There is a significant scarcity of healthcare professionals trained in gut-directed psychotherapies, leading to long waiting lists and limited accessibility. Furthermore, the cost of therapy and lack of insurance reimbursement in many healthcare systems, including in developing countries, can be prohibitive for many patients.

c. Complementary and Alternative Medicine (CAM)

Many patients with FD, often dissatisfied with conventional treatments, turn to CAM therapies. The evidence for these approaches is highly variable.

1) **Acupuncture:** Acupuncture, a key component of traditional Chinese medicine, involves the insertion of fine needles at specific body points. It is theorized to modulate the gut-brain axis by influencing autonomic nervous system tone and activating central pain-control pathways. Several clinical trials and meta-analyses have investigated its use in FD, with many reporting positive effects on symptom relief and gastric motility (Mao et al., 2020). However, the quality of evidence is often criticized for methodological weaknesses, including inadequate blinding, small sample sizes, and a high risk of bias. The difference in effect between true acupuncture and sham acupuncture is often small, raising questions about the role of placebo effects (Kwon et al., 2020).
2) **Herbal Therapy:** Various herbal preparations have been used for dyspepsia for centuries. One of the most studied is STW-5 (Iberogast), a multi-herbal preparation containing nine plant extracts. It is believed to have a multi-target effect, including relaxing the gastric fundus and modulating antral motility. Clinical trials have shown that STW-5 is superior to placebo in relieving FD symptoms (Gwee et al., 2020).

However, a significant limitation of herbal therapies, in general, is the lack of standardization, concerns about product quality and purity, and the potential for herb-drug interactions.

In conclusion, while non-pharmacological interventions offer valuable and sometimes effective alternatives or adjuncts to medication, they are not without their own set of limitations, including a weak evidence base for dietary changes, poor adherence, and significant barriers to access for psychological and CAM therapies.

2.4.3 Critical Appraisal of Current Treatments and Identification of the Therapeutic Gap

A critical synthesis of the current management strategies for Functional Dyspepsia (FD) reveals a therapeutic landscape characterized by significant limitations and a substantial unmet clinical need. Despite the availability of multiple pharmacological and non-pharmacological options, a large proportion of patients remain symptomatic, experiencing a chronically impaired quality of life. The fundamental issue is a mismatch between the multifactorial, heterogeneous pathophysiology of FD and the predominantly single-mechanism-targeted nature of current treatments (Drossman & Tack, 2022; Oshima, T., 2023).

a. **Synthesis of the Limitations of Existing Approaches:** The preceding review highlights that every major class of intervention for FD is encumbered by significant drawbacks. The pharmacological armamentarium, the cornerstone of conventional therapy, is fundamentally inadequate. Acid suppressants like PPIs offer only a modest and subtype-specific benefit, while their long-term use is associated with a growing list of potential safety concerns, making them unsuitable as a chronic solution for many (Vaezi et al., 2017). Prokinetic agents, which are Biomechanically appropriate for patients with Postprandial Distress Syndrome, are hampered by inconsistent efficacy and, more critically, significant safety issues that have led to the withdrawal or restricted availability of the most effective drugs (Sugano et al., 2015). Neuromodulators, while effective for modulating visceral pain, come with a considerable side-effect burden that limits tolerability and patient acceptance, often leading to poor adherence (Ford et al., 2020). This therapeutic inadequacy frequently results in a frustrating cycle of trial-and-error polypharmacy, with patients cycling through multiple agents without achieving satisfactory relief (Kinoshita et al., 2018).

Non-pharmacological approaches, though promising, are similarly beset by challenges. Dietary and lifestyle advice, while universally recommended, lacks a robust, high-quality evidence base and suffers from notoriously poor long-term adherence due to its often-restrictive nature and the chronic, fluctuating course of the illness (Mounsey et al., 2020). Brain-gut behavior therapies, such as CBT and hypnotherapy, possess the strongest evidence for efficacy among non-pharmacological options by directly targeting the dysregulated gut-brain axis. However, their clinical utility is severely constrained by practical barriers; they are resource-intensive, expensive, and require highly trained practitioners who are scarce, rendering them inaccessible to the vast majority of FD sufferers, especially outside of specialized academic centers or in healthcare systems with limited resources (Zang et al., 2024). Finally, complementary therapies like acupuncture and herbal remedies, while popular among patients, are supported by evidence that is often of low methodological quality, precluding their confident integration into standard clinical practice (Zhongcao et al., 2022).

b. **Argument for the Need for Novel, Non-Pharmacological, and Biomechanically Targeted Therapies:** This critical appraisal illuminates a clear and pressing **therapeutic gap**: the lack of a safe, effective, accessible, and holistically targeted treatment for FD. No single current therapy adequately addresses the complex and intertwined nature of the disorder's key pathophysiological domains—sensorimotor dysfunction, visceral hypersensitivity, gut-brain axis dysregulation, and low-grade inflammation. The current “one-size-fits-all” or single-target approach is insufficient for a condition as heterogeneous as FD.

This gap creates a compelling argument and an urgent need for a paradigm shift in treatment development. The ideal novel therapy for FD should possess several key attributes. Firstly, it should be non-pharmacological to circumvent the side effects, safety concerns, and potential for dependency associated with long-term medication use. Secondly, it must be Biomechanically targeted yet holistic, capable of simultaneously influencing multiple facets of FD pathophysiology. Rather than simply suppressing a single symptom like acid or enhancing motility in isolation, a more effective approach would modulate the underlying neuro-immune and biomechanical dysfunctions that give rise to the entire symptom

complex. Thirdly, the intervention should be safe and accessible, with a favorable risk-benefit profile and the potential for widespread implementation without prohibitive costs or the need for highly specialized, scarce personnel. It is precisely within this identified therapeutic gap that Biomechanically plausible, patient-centered, and non-invasive approaches, such as integrated manual therapy, emerge as a logical and compelling area for rigorous scientific investigation.

2.5 Manual Therapy as a Potential Intervention for Functional Dyspepsia

The therapeutic gap identified in the management of functional dyspepsia (FD) necessitates the exploration of novel interventions that are safe, non-pharmacological, and Biomechanically comprehensive. Manual therapy, a field of physiotherapy that utilizes hands-on techniques to diagnose and treat somatic dysfunction, presents a compelling paradigm. Its application to visceral disorders is grounded in a deep understanding of the intricate relationships between the body's structural (somatic) and functional (visceral) components. This approach is not merely focused on musculoskeletal complaints but extends to the potential influence of the somatic system on visceral health via neurophysiological and biomechanical pathways.

2.5.1 Theoretical Foundations of Manual Therapy in Visceral Disorders

The rationale for applying manual therapy to a visceral condition like FD is built upon three core theoretical pillars: the neurophysiological concept of somato-visceral and viscero-somatic reflexes; the pivotal role of the autonomic nervous system (ANS) as a mediator between somatic inputs and visceral responses; and the biomechanical influence of fascial continuity and tissue mobility on organ function. These principles provide a scientific framework for how targeted manual interventions might modulate the underlying pathophysiology of FD.

a. **The Concept of Somato-Visceral and Viscero-Somatic Reflexes:** This concept is foundational to understanding how the body's systems are neurologically integrated. It describes a bidirectional reflex arc mediated at the spinal cord level. The viscero-somatic reflex is a well-established phenomenon where dysfunction or pathology in a visceral organ leads to observable changes in segmentally

related somatic tissues. For instance, afferent signals from a distressed organ (e.g., the stomach) travel to the dorsal horn of the spinal cord, where they converge on the same pool of interneurons as afferent signals from somatic structures (e.g., muscles, skin) of the same spinal segment (Beal, 2021). This convergence and subsequent facilitation can result in referred pain, hyperalgesia, and increased muscle tone in the corresponding dermatomes, myotomes, and sclerotomes. In the case of the stomach and duodenum, which receive their primary sympathetic innervation from the T5-T9 spinal segments, visceral distress can manifest as mid-thoracic back pain, paraspinal muscle hypertonicity, or cutaneous hypersensitivity (Flávia et al, 2025).

Conversely, the somato-visceral reflex proposes that a primary dysfunction in a somatic structure can reflexively influence the function of a segmentally related visceral organ. By this mechanism, a somatic dysfunction, such as a vertebral joint restriction or myofascial tension in the T5-T9 region, could generate abnormal afferent (nociceptive or proprioceptive) signals to the spinal cord. This altered somatic input can, in turn, modulate the efferent autonomic outflow from the same spinal segment to the stomach and duodenum, thereby altering their motility, secretion, and blood flow (Li et al, 2013). This provides a direct neurophysiological rationale for how spinal manipulative therapy, by normalizing somatic dysfunction, could therapeutically influence visceral function.

b. **The Role of the Autonomic Nervous System (ANS) in Regulating Gastrointestinal Function:** The ANS is the critical efferent pathway through which somato-visceral reflexes are executed and is the primary regulator of all gastrointestinal functions. A delicate balance between its two branches, the sympathetic and parasympathetic systems, is essential for normal digestion. The parasympathetic nervous system, primarily via the vagus nerve, is the "rest-and-digest" system, promoting gastric acid secretion, enhancing gastric motility, and crucially, mediating the gastric accommodation reflex (Bonaz et al., 2018). In contrast, the sympathetic nervous system, originating from the thoracolumbar spinal cord (T5-T9 for the stomach), mediates the “fight-or-flight” response. Increased sympathetic tone inhibits gastric motility and accommodation, reduces mucosal blood flow, and can heighten the perception of visceral pain (Thania et al., 2023).

Many of the key pathophysiological features of FD, such as impaired gastric accommodation and visceral hypersensitivity, are consistent with a state of autonomic imbalance, specifically reduced vagal tone and/or sympathetic hyperactivity. Manual therapies, particularly spinal manipulation, are hypothesized to exert their therapeutic effects by modulating this sympathovagal balance. The application of a controlled mechanical stimulus to a dysfunctional spinal segment is thought to normalize afferent input, thereby reducing facilitated sympathetic outflow and/or reflexively increasing vagal tone (Haavik & Murphy, 2012; Rechberger et al., 2019). By restoring a more homeostatic autonomic state, these interventions could theoretically improve gastric accommodation, normalize motility, and reduce visceral hypersensitivity.

c. **Biomechanical Principles (Fascial Continuity, Tissue Mobility, and Their Impact on Organ Function):** Beyond the neurophysiological framework, manual therapy also operates on biomechanical principles. The body's organs are not isolated entities but are suspended and interconnected within a body-wide web of connective tissue, or fascia. This fascial system provides both structural support and a medium for movement (Bordoni & Zanier, 2013; Fabiana et al., 2023). Visceral mobility refers to the passive movement of the organs in response to the movement of the diaphragm during respiration and the movement of the trunk and limbs. For example, the stomach and liver glide against the diaphragm with every breath. Visceral motility is the inherent, slow, rhythmic motion of the organs themselves, an expression of their intrinsic cellular health (Fabiana et al., 2023).

Pathological processes such as inflammation, infection, surgery, or chronic postural strain can lead to the formation of fascial adhesions and restrictions. These restrictions can tether an organ, impairing its normal mobility and motility (Hedley, 2010; Caterina et al., 2025). A stomach with restricted mobility, for instance, may not be able to descend properly with the diaphragm or expand sufficiently during a meal, mechanically contributing to impaired gastric accommodation and early satiation. Such chronic mechanical strain can also lead to persistent abnormal afferent signaling from visceral mechanoreceptors, contributing to peripheral and central sensitization (Arisandy & Haidzir, 2025). Visceral manipulation techniques are specifically designed to assess and treat these biomechanical restrictions. By applying gentle, targeted forces, the therapist

aims to release adhesions, improve the glide between fascial planes, and restore normal visceral mobility, thereby improving the physiological function of the organ and reducing aberrant nociceptive input (Hebgen, 2011).

2.5.2 Visceral Manipulation (VM)

Visceral Manipulation (VM) is a specialized form of manual therapy that focuses on the assessment and treatment of the viscera (organs), their suspensory ligaments, and the surrounding fascial and connective tissues. It is a gentle, hands-on approach that aims to restore the normal physiological motion and function of the organs by addressing biomechanical restrictions (Barral & Mercier, 2005; Arisandy & Haidzir, 2025). The application of VM in functional dyspepsia (FD) is predicated on the idea that improving the mechanical environment of the stomach and duodenum can lead to enhanced physiological function and symptom reduction. This is achieved through several proposed, interconnected mechanisms.

2.5.2.1 Principles and Proposed Mechanisms of Action

a. **Restoring Visceral Mobility and Motility:** The primary and most direct proposed mechanism of VM is the restoration of normal organ movement. As previously noted, visceral mobility is the passive, larger-scale movement of an organ in response to voluntary body motion and diaphragmatic breathing, while motility is its subtle, inherent, rhythmic motion. In a healthy state, the stomach and duodenum glide freely against adjacent structures like the diaphragm, liver, pancreas, and transverse colon. However, inflammatory processes (even low-grade), past surgery, trauma, or sustained postural stresses can create fascial adhesions or restrictions that “tether” these organs, limiting their freedom of movement (Hebgen, 2011; Arisandy & Haidzir, 2025). Such restrictions can have direct consequences on gastroduodenal function. For example, a restriction between the stomach and the diaphragm could mechanically limit the stomach's ability to descend during inhalation and expand to accommodate a meal, directly contributing to impaired gastric accommodation and symptoms of early satiety (Bordoni & Zanier, 2013; Fabiana et al., 2023). VM techniques, which involve gentle, specific stretching, mobilization, and recoil techniques, are designed to release these fascial restrictions. By improving the glide between fascial planes and restoring normal organ mobility, VM aims to remove the mechanical

constraints on function, allowing for more efficient gastric accommodation and motility, thereby alleviating symptoms of postprandial distress (Arisandy & Haidzir, 2025).

b. **Modulating Visceral Afferent Neurological Feedback:** Beyond its purely mechanical effects, VM is hypothesized to exert a powerful influence on the nervous system. Fascia is now recognized as a highly innervated sensory organ, rich in mechanoreceptors (including interstitial receptors, Ruffini and Pacinian corpuscles) and nociceptors (Schleip, 2012). When fascial tissues are restricted and under abnormal tension, these receptors can generate a continuous stream of aberrant afferent signals to the central nervous system. This persistent, abnormal input from the periphery is a key driver of both peripheral and central sensitization, leading to the visceral hypersensitivity that characterizes FD (Tozzi, 2015). The gentle, sustained stretching and mobilization techniques used in VM are thought to modulate this afferent input. By stimulating low-threshold, slow-adapting mechanoreceptors (like Ruffini endings), VM may induce a down-regulation of sympathetic tone and a global relaxation response (Arisandy & Haidzir, 2025). By reducing the mechanical strain on tissues, it can also decrease the firing rate of sensitized nociceptors. This normalization of afferent signaling can help to break the vicious cycle of pain and sensitization, reducing the perception of pain and discomfort and allowing for a more normal processing of visceral sensory information.

c. **Improving Local Circulation and Lymphatic Drainage:** The health and function of any tissue are critically dependent on adequate vascular supply and lymphatic drainage. The intricate network of fascia that surrounds and suspends the organs also contains the blood and lymphatic vessels that serve them. Fascial restrictions and abnormal tissue tension can create mechanical compression on these vessels, leading to a state of relative ischemia (reduced blood flow), venous congestion, and impaired lymphatic drainage (Schleip et al., 2012). This can result in a suboptimal local tissue environment, with reduced oxygen and nutrient delivery and an accumulation of metabolic waste products and pro-inflammatory mediators. Such a congested environment can further perpetuate low-grade inflammation and impair the function of enteric neurons and smooth muscle cells. The techniques of VM, by releasing fascial tension and restoring tissue mobility, are proposed to have a “decongestive” effect. This manual decompression can

improve local arterial inflow, venous return, and lymphatic flow, thereby optimizing the metabolic environment of the gastroduodenal tissues (Bordoni & Marelli, 2015). This enhanced fluid dynamics may support tissue healing, reduce local inflammation, and improve the overall physiological function of the organs.

2.5.2.2 Review of Evidence for VM in Gastrointestinal Disorders

The efficacy of manual therapy, particularly visceral manipulation (VM), in addressing functional disorders of the gastrointestinal (GI) tract is supported by a growing, yet diverse, body of research. The studies summarized in Table 2.1 provide empirical evidence illustrating the effects of these interventions on gastroesophageal reflux disease (GERD) and functional dyspepsia (FD), often linking visceral treatment to improved somatic and neurological function.

Tabel 2.1

Review of Evidence for VM on Gastrointestinal Disorders (GIDs)

Authors & Year	**Type of Study & Population**	**Intervention Type**	**Primary Effects & Outcomes**
Da Silva et al., 2013	Pilot Randomized Controlled Trial (RCT). n=38 (VM=22, Control=16). Adults with Gastroesophageal Reflux Disease (GERD).	Diaphragm stretching technique (Osteopathic Intervention).	Significant increase in Lower Esophageal Sphincter (LES) Pressure after intervention. The technique enhanced overall gastroesophageal function by targeting the diaphragm.
Diniz et al., 2014	Single-Blinded Prospective Case Report. n=1 (55 yr old man with 4-year history of GERD).	Osteopathic Manipulative Therapy (OMTh) protocol focusing on Diaphragm and Esophagus (3 sessions over 4 weeks).	Significant reduction in symptoms and improvement in quality of life (QS-GERD score improved from 13/45 to 4/45). Concluded that OMTh may improve GERD symptoms.
Eguaras et al., 2019	Randomized, Double-Blind, Placebo-Controlled Trial (RCT). n=60 (VM=29, Control=31). Adults with GERD.	Osteopathic Manual Technique for the Lower Esophageal Sphincter (2 sessions, 5 mins each, one week apart).	Significant improvement in GERD symptoms (GerdQ score decreased, p=0.005). Significant increase in Cervical Mobility and Pressure Pain Threshold (PPT) at C4 spinous process (p=0.034), indicating reduced somatic sensitization.
Silva et al., 2019 (Case Report)	Two Case Reports. n=2 (Adult females with Non-Specific Neck Pain (NS-NP) AND Functional Dyspepsia (FD)).	Visceral Manipulation (VM) applied to the Stomach and Liver (Single 5-minute session and 7-day follow-up).	Clinical improvement in neck pain (100% reduction at 7 days). Increased Cervical Range of Motion (ROM) (12.5% to 44.44%). Altered Upper Trapezius EMG activity, supporting the

			somatovisceral convergence hypothesis.
Lynen et al., 2022	Randomized Controlled Trial (RCT). n=41 (Intervention=23, Control=18). Adults with Gastroesophageal reflux disease (GERD).	Liver, stomach, and esophageal manipulation (4 osteopathic treatments within an eight-week period).	Significant reduction in GERD reflux symptoms and enhancement of overall gastroesophageal function (Effect size Medium to Large). Supported the use of serial VM for GERD management.
Arisandy & Haidzir, 2025 (Pilot Study)	Pre-Post Study Design (Pilot Study). n=29. Adult patients with Functional Dyspepsia (FD).	Visceral Manipulation (VM) Protocol (Lesser Omentum stretching, Stomach, and Duodenum mobilization) (10 sessions over 2 weeks).	Significant reduction in Abdominal Pain (Frequency, Time, Duration, Intensity; all $p<0.05$). Significant improvement in Quality of Life (SF-NDI subdomains: anxiety, activity limitation, eating/drinking, knowledge/control, work/study; all $p<0.05$).

a. Evidence Pertaining to Gastroesophageal Reflux Disease (GERD)

The bulk of the current evidence focuses on GERD, primarily investigating the biomechanical relationship between the diaphragm, esophagus, and the Lower Esophageal Sphincter (LES) function.

1) **Targeting the Diaphragm and LES:** The studies by Da Silva et al. (2013) and Eguaras et al. (2019) provide robust findings for biomechanical mechanisms. Da Silva et al., in a pilot Randomized Controlled Trial (RCT), demonstrated that a diaphragm stretching technique significantly increased LES pressure post-intervention. This finding is critical as it provides a physiological marker for the mechanical effect of manual therapy, suggesting that interventions can directly influence anti-reflux barriers. Similarly, Eguaras et al.'s double-blind RCT on the Lower Esophageal Sphincter technique reported a significant

improvement in GERD symptoms (GerdQ scores), further validating the efficacy of direct manual treatment in this patient population.

2) **Holistic Osteopathic Approaches:** The work by Diniz et al. (2014) (Case Report) and Lynen et al. (2022) (RCT) expands this scope to multi-session osteopathic protocols. Diniz et al. detailed a substantial reduction in symptoms and a drastic improvement in quality of life (QS-GERD) in a single patient with refractory GERD treated with OMTh focused on the diaphragm and esophagus. Lynen et al.'s RCT solidified this concept, confirming that serial osteopathic treatments targeting the liver, stomach, and esophagus led to a significant reduction in GERD reflux symptoms over an eight-week period, with medium to large effect sizes. This evidence collectively establishes that manual techniques aimed at restoring mobility and pressure dynamics in the thoracoabdominal area constitute a valid, efficacious approach to GERD management.

b. Evidence Pertaining to Functional Dyspepsia (FD) and Somatic Convergence

Research on FD, while less extensive than GERD, provides crucial insights into the somatovisceral convergence mechanism, which is central to the rationale of the InViSMa protocol. These studies explicitly link visceral dysfunction to measurable somatic symptoms.

1) **The Somatic-Visceral Link:** The case reports by Silva et al. (2019) are seminal in this area. They investigated patients presenting with both non-specific neck pain (NS-NP) and FD. A single session of visceral manipulation (VM) applied to the stomach and liver resulted in a complete clinical improvement in neck pain (100% reduction at 7 days) and a significant increase in cervical range of motion (ROM). This outcome powerfully supports the hypothesis of somatovisceral cross-talk, suggesting that the manipulation of viscera (stomach/liver) can centrally inhibit and reduce pain and sensitization in remote somatic structures (the neck, via vagal and spinal pathways).

2) **Focus on Core FD Symptoms:** The pilot study by Arisandy & Haidzir (2025) directly addressed FD patients using a VM protocol targeting the lesser omentum, stomach, and duodenum. The findings demonstrated a

significant reduction in all domains of Abdominal Pain and a corresponding improvement in quality of life (SF-NDI). While this was a pre-post study design, the positive results across both physical and psychosocial outcomes provided the essential preliminary data (effect sizes) to justify larger-scale randomized trials, particularly those examining the synergistic effect of VM combined with spinal components, such as the InViSMa protocol.

c. Synthesis and Justification for Integrated Therapy

The reviewed literature collectively underscores two critical points that form the scientific foundation for the present dissertation:

1) **Visceral Manipulation Efficacy:** VM techniques are effective in treating GI disorders, yielding measurable improvements in physiological parameters (LES pressure) and symptom severity (GerdQ, QS-GERD, Abdominal Pain).
2) **Viscero-Somatic Interplay:** A strong neurophysiological link exists between visceral function and somatic dysfunction, evidenced by the fact that manipulating the stomach or liver can resolve distant neck pain and reduce somatic sensitization (Eguaras et al., 2019; Silva et al., 2019).

Crucially, no prior study combined high-quality, targeted visceral techniques with simultaneous, standardized spinal manipulation in a single, integrated protocol (InViSMa) to treat the full clinical spectrum of FD. The existing evidence only addresses the visceral component or the somatic consequences of visceral issues. Therefore, the present research is necessary to determine whether the synergistic integration of both visceral and spinal components yields a superior therapeutic outcome by comprehensively addressing the complexity of the FD pathophysiology, where both visceral restriction and associated spinal dysfunctions are implicated.

d. Critique of Existing Literature

While the reviewed studies lay a strong mechanistic foundation for manual therapy in functional gastrointestinal disorders, a critical evaluation reveals significant methodological and conceptual limitations, establishing a clear and

compelling evidence gap that necessitates the present research on the Integrated Visceral and Spinal Manipulation (InViSMa) protocol.

1) **Methodological Limitations of Existing Evidence**

   The current body of evidence, particularly concerning Functional Dyspepsia (FD), suffers from three primary methodological weaknesses:

   a) **Limited Rigor for FD Studies:** The two key studies directly investigating VM in FD (Silva et al., 2019; Arisandy & Haidzir, 2025) were constrained by their design. Silva et al.'s work was presented as case reports (n=2) focusing primarily on somatic outcomes (neck pain), lacking a control group and the statistical power to infer causality for FD symptoms. Similarly, the study by Arisandy & Haidzir was a pre-post pilot study (n=29), which is effective for determining feasibility and effect size but suffers from inherent limitations related to confounding variables and the absence of a true comparative control group. These designs are insufficient to produce the Level 1 (RCT) evidence required for clinical guideline changes.

   b) **Lack of Integrated Protocol Testing:** Despite the consensus that FD is a complex neuro-visceral disorder involving both the central nervous system (spinal input/ANS) and peripheral structures (visceral mechanoreceptors), no existing study has formally tested a high-fidelity, standardized protocol that simultaneously and systematically combines specific VM techniques with targeted SM. The studies available either focus on VM alone (Arisandy & Haidzir, 2025) without detailing the specific synergistic techniques required to treat FD's multi-factorial pathology.

   c) **Short-Term Follow-up:** Most efficacy studies, including the initial GERD and FD work, feature short follow-up periods (often only one week, or post-intervention only). This limits the ability to draw conclusions regarding the long-term clinical relevance, recurrence rates, and durability of the intervention, which is essential for chronic conditions like FD.

2) Conceptual and Clinical Gaps

The fundamental conceptual gap lies in the failure of current literature to test the hypothesized mechanism of action in a unified model.

a) **Failure to Test the Synergistic Mechanism:** The rationale for the present dissertation is that the combined effect of VM (correcting fascial restrictions and stimulating the Vagus nerve) and SM (modulating sympathetic/segmental input at T5-T12) is greater than the sum of its parts—a *synergistic* effect. Existing research, by testing only one component, prevents the isolation of this hypothesized synergy. Therefore, there remains no empirical evidence to demonstrate that simultaneous treatment of the visceral and spinal components is superior to addressing only one.

b) **Need for Comprehensive Outcomes:** While some studies measured quality of life, no prior research simultaneously measured the full triad of systemic dysfunction (dyspepsia severity, psychological status [PSS], and sleep disorder [PSQI]) as primary and secondary outcomes within a single high-quality trial. This unified assessment is necessary to prove that the therapy is truly holistic, correcting both the physical and psychosocial sequelae of the gut-brain axis dysfunction.

e. Justification for the Integrated Visceral and Spinal Manipulation (InViSMa) Trial

The preceding critique highlights a critical void in evidence: robust Level 1 data confirming the efficacy of an integrated somatovisceral approach for FD. While preliminary findings demonstrated potential, they lack the methodological rigor (no RCT design) and the necessary integrated intervention (no combination of targeted VM and SM) to be definitive.

The present research, utilizing a prospective, single-blind, two-arm parallel-group Randomized Controlled Trial, is thus scientifically justified and methodologically essential. This trial will provide the missing Level 1 evidence required to move beyond promising case reports and pilot studies. By testing the integrated visceral and spinal manipulation (InViSMa) protocol against an active control that shares the spinal component, this study will conclusively isolate and

validate the synergistic superiority of the multi-axial approach, thereby fundamentally advancing the clinical management of FD.

2.5.3 Spinal Manipulation (SM)

Spinal Manipulation (SM), a cornerstone of chiropractic and osteopathic medicine, is a manual therapy technique characterized by the application of a high-velocity, low-amplitude (HVLA) thrust to a specific synovial joint, most commonly a vertebral articulation (Bialosky et al., 2018). While often associated with musculoskeletal pain, the application of SM to visceral disorders is grounded in the neurophysiological principles of the somato-visceral reflex and the profound influence of spinal function on the autonomic nervous system. In the context of FD, SM applied to the thoracic spine is hypothesized to therapeutically modulate the aberrant neural signaling and autonomic imbalance that contribute to gastroduodenal dysfunction.

2.5.3.1 Principles and Proposed Mechanisms of Action

a. Modulation of the Autonomic Nervous System via Stimulation of Spinal Mechanoreceptors

A primary proposed mechanism for SM's effect on visceral function is its ability to powerfully modulate the ANS. The capsules and ligaments of spinal facet joints are densely populated with mechanoreceptors (Type I, II, and III), which provide the central nervous system with constant proprioceptive information about joint position and movement. The Mobilization of an SM procedure creates a rapid stretch of these tissues, causing a high-frequency barrage of afferent signals from these large-diameter, myelinated nerve fibers to the spinal cord and higher brain centers (Wirth et al, 2019). This potent neurosensory input is believed to induce a short-term, reflex-mediated alteration in autonomic tone. Studies measuring physiological markers of ANS activity, such as heart rate variability (HRV), skin conductance, and blood pressure, have consistently demonstrated that thoracic SM can produce a sympatho-inhibitory effect, characterized by a decrease in sympathetic nervous system activity and a relative increase in parasympathetic (vagal) tone (Haavik & Murphy, 2012; Rechberger et al., 2019). This shift in sympathovagal balance is directly relevant to FD, where reduced vagal tone and sympathetic hyperactivity are implicated in impaired gastric accommodation and hypersensitivity.

b. Normalizing Sympathetic Outflow from the Thoracic Spine

The sympathetic innervation to the stomach and duodenum originates from preganglionic neurons located in the intermediolateral cell column of the T5-T9 spinal cord segments. In the presence of a vertebral somatic dysfunction within this region, it is theorized that a state of "segmental facilitation" can occur. This is a neurophysiological state where the pool of interneurons at the affected spinal level becomes hyperexcitable due to sustained nociceptive or aberrant proprioceptive input (King et al., 2016). This facilitated segment has a lowered threshold for firing, resulting in an exaggerated and sustained sympathetic efferent discharge to the target visceral organs (Beal, 2021). In the case of the stomach, this would manifest as sympathetically-mediated inhibition of motility and increased sensitivity. SM is proposed to directly address this facilitation. The powerful mechanoreceptive afferent volley generated by the mobilization is thought to “reset” the central neural circuitry at the segmental level, breaking the self-perpetuating cycle of aberrant input and exaggerated output, and thereby normalizing sympathetic outflow to the viscera (Lei Tu et al, 2020; Goyal et al., 2021). By restoring a more homeostatic level of sympathetic tone, SM may help to alleviate the inhibition of gastric accommodation and emptying.

c. Influence on Pain Perception through Central Pain Modulation Mechanisms

Beyond its effects on autonomic outflow, SM is well-documented to produce powerful analgesic effects, which are mediated by both spinal and supraspinal mechanisms. At the spinal cord level, the large-diameter afferent signals from stimulated mechanoreceptors can inhibit the transmission of nociceptive (pain) signals from smaller A-delta and C fibers within the dorsal horn, a mechanism consistent with the gate control theory of pain (Bialosky et al., 2018). More significantly, the afferent barrage ascends to supraspinal centers, including the brainstem's periaqueductal gray (PAG) and the rostral ventromedial medulla (RVM). Activation of these areas triggers powerful descending pain inhibitory pathways that utilize endogenous opioids, serotonin, and norepinephrine to suppress nociceptive signaling at the spinal level (Coronado et al., 2012). The clinical result of this central pain modulation is an increase in pain

pressure thresholds not only at the site of manipulation but also at distant, unrelated sites, indicating a global analgesic effect. In FD, where visceral hypersensitivity and central sensitization are key features, this centrally-mediated hypoalgesia induced by SM could raise the threshold for visceral pain perception, making normal physiological stimuli, such as gastric distension, less likely to be experienced as painful.

2.5.3.2 Review of Evidence for Spinal Manipulation Studies on Functional Gastrointestinal Disorders (FGIDs)

The role of spinal manipulation (SM) and integrated manual therapies in addressing the visceral-somatic axis has been explored across various functional gastrointestinal disorders (FGIDs). The studies summarized in the accompanying table (Table 2.2) range from case reports to controlled trials, collectively providing critical insights into the neuro-somatic mechanism and establishing the necessary evidence gap that justifies the comprehensive integrated visceral and spinal manipulation (InViSMa) protocol.

Tabel 2.2

Review of Evidence for SM on Gastrointestinal Disorders (GIDs)

Author(s) & Year	**Type of Study & Population**	**Intervention Type**	**Primary Effects & Outcomes**
Young et al., 2009	Prospective Cohort Study (Pilot). N=83 Chronic Idiopathic Dyspepsia (>2 years).	Chiropractic Spinal Manipulation (SM) (C3-C5, T5-L2, SI joint) + Adjunctive Soft Tissue.	Significant improvement in symptom severity ($p<0.001$) and frequency ($p<0.001$). Clinical Relevance: 37 of 83 patients (44.6%) successfully downgraded or eliminated medication usage.
Chuang, 2014	Case Report. N=1 (4-month-old infant with GERD).	Chiropractic SM (Sustained Pressure, Activator) + Cranial Adjustments + Myofascial (Abdomen/Diaphragm).	Total resolution of Reflux/Vomiting within 4 weeks. Demonstrates the rapid effect of integrated somatic and

			cranial/myofascial intervention.
Sweidan, 2015	Controlled Clinical Trial (Pilot). N=30 Adult Functional Dyspepsia (FD).	Chiropractic SM (Diversified) to C3-C5, T5-L2 vs. Inactive Laser (Placebo).	No statistically significant difference in treatment effect between SM and placebo for any outcome. Within-Group Efficacy: SM showed significant improvement *within* group for post-prandial fullness, bloating, UAP, and heartburn.
Lacroix, 2016	Case Report. N=1 (4-month-old infant with GERD).	Chiropractic SM (Craniosacral, Myofascial, Diversified) Full Spine (C1, T5, L1, SI joint) + Cranium.	Total resolution of GERD symptoms over 20 weeks. Supports the neuro-visceral mechanism of cranial/cervical manipulation in pediatrics.
Tu et al., 2020 (Canine Model)	Preliminary Study on Canines. N=8. Gastroparesis Model.	Spinal Cord Stimulation (SCS) at Thoracic 10 (T10).	Mechanistic Validation: SCS at T10 improved gastric motility and accelerated gastric emptying by enhancing vagal activity (Parasympathetic) and inhibiting sympathetic activity. (Provides strong neurophysiological basis for targeting T10 in humans).
Azizi et al., 2020	Case-Control Study (RCT Comparison). N=62 with GI Pain and Minor Intervertebral Dysfunction (MID+).	Spinal Manipulation (SM) at T12-L1 level.	Significant decrease in GI pain in MID+ group compared to non-dysfunctional group. Limitation: Effect was temporary, suggesting structural visceral

			component was not fully addressed.
Goyal et al., 2021	Case Report. N=1 (30 yr old female with Non-Erosive GERD).	Integrated OMT (MET T6-T7/Upper Lumbar, Myofascial Release Diaphragm/Abdomen, Sphincter Recoil).	Objective & Subjective Improvement: Significant reduction in objective reflux measures (DeMeester score dropped from 32 to 12; pH improved from 5.2 to 3.8). Marked improvement in Quality of Life (HRQL-GERD, QS-GERD).
Melo et al., 2022	Cross-Sectional Study. N=57 (Gastritis Group vs. Healthy Control).	Diagnostic Only (Assessing tissue state).	Gastritis Group showed greater abdominal restriction, lower diaphragmatic mobility, and higher musculoskeletal dysfunction in the cervical spine compared to healthy controls. (Provides strong diagnostic evidence for the mechanical/somatic correlation in Gastritis).
Jafar et al., 2025	Randomized Controlled Trial (RCT). N=40 Adult Functional Constipation.	Thoracolumbar Manipulation vs. Abdominal Massage.	Conclusion of Superiority: Abdominal Massage superior to isolated Thoracolumbar Manipulation for improving Constipation Scoring System (CSS) and PAC-QOL scores. (Suggests local peripheral stimulation is more effective than isolated SM for pure motility issues).

a. Efficacy of Spinal Manipulation in Functional Dyspepsia (FD) and GI Pain

Research focusing on the isolated effect of spinal manipulation (SM) has yielded mixed results, yet strongly supports the underlying neurophysiological rationale for the present study:

1) **Positive Clinical Trends** (**Young et al., 2009**)**:** The prospective cohort study by Young et al. (2009), although lacking a placebo control, provided early clinical justification. The study on 83 patients with chronic dyspepsia reported significant improvements in symptom severity and frequency ($p<0.001$) following a chiropractic protocol targeting autonomic levels (C3-C5 and T5-L2). The clinical relevance was high, with nearly half of the patients successfully downgrading or eliminating medication usage. This demonstrated that influencing the somatovisceral reflexes via the spine has profound clinical consequences.
2) **Need for Visceral Component** (**Jafar et al., 2025**)**:** The randomized controlled trial by Jafar et al. (2025), comparing isolated thoracolumbar manipulation against abdominal massage for functional constipation, concluded that abdominal massage was superior to SM alone. This finding is highly significant for FD, as it suggests that isolated SM, while affecting autonomic output, may be insufficient to resolve core symptoms driven by local mechanical (motility) or fascial restrictions. This result argues strongly against a purely spinal approach and validates the necessity of including the visceral component, as done in the InViSMa protocol.
3) **Viscero-Somatic Pain Link** (**Azizi et al., 2020**)**:** The study by Azizi et al. (2020) on patients with GI pain and minor intervertebral dysfunction (MID+) provided direct evidence for the viscero-somatic link. Spinal Manipulation at the T12-L1 level resulted in a significant decrease in GI pain in the MID+ group. However, the effect was temporary and pain recurred shortly after the third session. This result is crucial: it confirms that the somatic pathway (MID) influences visceral pain, but the temporary nature of the relief suggests that the intervention failed to correct the underlying chronic visceral tension or restriction—the gap InViSMa aims to fill.

4) **Inconclusive RCTs (Sweidan, 2015):** The controlled clinical trial by Sweidan (2015), which rigorously compared SM against a placebo for FD, found no statistically significant difference between the groups for overall outcomes. While the SM group showed improvements *within* group for symptoms like post-prandial fullness and bloating, the lack of significant superiority over placebo highlights the limitations of using isolated SM techniques and underscores the complexity of the placebo effect in subjective GI disorders.

b. Mechanistic Validation through Neurological Studies

The literature provides strong neurophysiological justification for targeting the T10 spinal segment, which is integral to the InViSMa protocol:

1) **Spinal Cord Stimulation (Tu et al., 2020):** The preliminary study by Tu et al. (2020) using spinal cord stimulation (SCS) in a canine gastroparesis model provided compelling mechanistic validation. The study found that SCS at Thoracic 10 (T10)—the sympathetic input level for the upper GI tract—improved gastric motility and accelerated gastric emptying. Critically, this therapeutic effect was achieved by enhancing vagal activity (parasympathetic) and inhibiting sympathetic activity. This provides a direct neurophysiological basis for the hypothesis that manipulating the T10 segment in humans (as done in InViSMa) can modulate the ANS and promote a 'rest-and-digest' state.

c. The Necessity of Integrated and Myofascial Approaches

Case reports and cross-sectional data strongly indicate that integrated protocols, which combine SM with visceral and myofascial techniques, are necessary to achieve durable resolution:

1) **Integrated OMT Success (Goyal et al., 2021):** The case report by Goyal et al. (2021) demonstrated the power of Integrated OMT (MET, Myofascial Release, Sphincter Recoil) in a patient with Non-Erosive GERD. The intervention resulted in a significant reduction in objective reflux measures (DeMeester score dropped from 32 to 12) and a marked improvement in Quality of Life. The success here suggests that combining segmental SM with direct visceral soft tissue work provides

the comprehensive input needed to physically and neurologically resolve the GERD pathology.

2) **Pediatric Integrated Care (Lacroix, 2016; Chuang, 2014):** Two separate case reports on infant GERD (Lacroix, 2016; Chuang, 2014) showed total resolution of reflux/vomiting using integrated chiropractic protocols that included full spine, cranial, and abdominal myofascial work. These findings support the visceral/cranial mechanism and demonstrate that addressing the fascial and dural connections is vital for holistic resolution, especially where the vagus nerve (cranial/cervical) is involved.
3) **Diagnostic Validation (Melo et al., 2022):** The cross-sectional study by Melo et al. (2022) provided diagnostic evidence for the study's core rationale by confirming that individuals with chronic gastritis exhibited greater abdominal restriction, lower diaphragmatic mobility, and higher musculoskeletal dysfunction in the cervical spine compared to healthy individuals. This reinforces the existence of the pathological somatovisceral correlation and directly justifies a combined approach that targets both the restricted diaphragm/viscera (VM) and the corresponding hyper-sensitized cervical spine (SM).

d. The Evidence Gap and Justification

The current literature establishes that: 1) SM alone is insufficient for comprehensive resolution (Sweidan, 2015; Jafar et al., 2025); 2) SM and VM are Biomechanically linked through the ANS and pain pathways (Tu et al., 2020; Azizi et al., 2020); and 3) Integrated, multi-axial protocols yield superior clinical results (Goyal et al., 2021). The critical evidence gap lies in the absence of a highly rigorous Randomized Controlled Trial (RCT) that isolates the synergistic superiority of the standardized, multi-segmental integrated visceral and spinal manipulation (InViSMa) protocol against a credible control for the full spectrum of Functional Dyspepsia outcomes (LDQ, API, PSS, PSQI, NDI). The present study is therefore necessary to translate the promising mechanistic and case-based evidence into definitive Level 1 evidence for clinical guidelines.

e. The Rationale for an Integrated Approach (InViSMa)

1) The Integrated Rationale

Functional Dyspepsia (FD) and Gastroesophageal Reflux Disease (GERD) are complex, multifactorial disorders often characterized by visceral hypersensitivity, motility dysfunction, and impaired gut-brain axis communication. Traditional pharmacological management often targets symptoms (e.g., acid suppression) but frequently fails to address underlying biomechanical and neurophysiological factors. The Integrated Visceral and Spinal Manipulation (InViSMa) approach is predicated on the hypothesis that optimal clinical outcomes require the simultaneous normalization of both somatic (spinal/musculoskeletal) and visceral (organ/fascial) structures, which are intricately linked by the Autonomic Nervous System (ANS) and the body's connective tissue matrix. This section provides the scientific basis, clinical reasoning, and critical thinking for integrating Visceral Manipulation (VM) and Spinal Manipulation (SM) as a unified therapeutic strategy.

2) Pathophysiological Basis: The Viscero-Somatic and Somato-Visceral Axes

The primary scientific justification for InViSMa lies in the concept of somatovisceral and viscerosomatic reflex arcs. These reflexes illustrate a bidirectional pathological relationship between the spine and the gastrointestinal (GI) tract:

a) **Viscero-Somatic Reflex:** Visceral pathology (e.g., inflammation, restricted mobility, or distension in FD/GERD) can stimulate afferent nerve fibers, which converge with somatic afferents at the spinal cord level (e.g., T5-T9 for the stomach). This convergence results in the central sensitization and referred pain patterns, manifesting as musculoskeletal dysfunction, hypertonicity, and segmental vertebral restriction. Studies on FD and chronic gastritis, for instance, have demonstrated a significant association with increased musculoskeletal dysfunction, including reduced cervical range of motion and increased pain thresholds in the cervical and

thoracic spine, suggesting a direct viscerosomatic link that SM can address (Silva et al., 2019; Melo et al., 2022).

b) **Somato-Visceral Reflex:** Conversely, primary somatic dysfunction, such as vertebral subluxation or joint restriction, can influence the sympathetic and parasympathetic outflow, thereby altering visceral function. Spinal manipulative therapy (SMT) or spinal adjustments are posited to modulate this reflex by normalizing aberrant nociceptive input to the dorsal horn of the spinal cord, subsequently reducing sympathetic tone or enhancing parasympathetic activity (Azizi et al., 2020; Young et al., 2009). The use of manipulation to potentially enhance gastric motility via T10 sympathetic outflow is an area of experimental research supporting this mechanism (Tu et al., 2020).

3) Rationale for Visceral Manipulation (VM) in GI Disorders

Visceral Manipulation targets the mechanical and neuro-reflexive components of GI dysfunction:

a) Mechanical and Fascial Normalization: VM focuses on restoring the inherent movement (motility) and external movement (mobility) of the stomach, liver, esophagus, and related structures like the diaphragm and celiac ganglion. Restriction of these movements, often due to fascial adhesions or somatic dysfunction, can impede gastric emptying, compromise the function of the Lower Esophageal Sphincter (LES), and irritate mechanoreceptors.

b) Diaphragmatic and LES Function: The diaphragm is a critical factor in GERD, as its crural portion acts as an extrinsic component of the LES barrier. Techniques like diaphragm stretching and esophageal manipulation, central to VM/OMT protocols, have been shown to enhance overall gastroesophageal function, leading to significant symptom reduction and improved quality of life in patients with GERD (Da Silva et al., 2013; Diniz et al., 2014; Eguaras et al., 2019; Goyal et al., 2021).

c) Autonomic Ganglion Modulation: Techniques targeting visceral plexuses, particularly the celiac ganglion, aim to normalize

sympathetic overactivity that often contributes to the altered motility and visceral pain characteristic of FD and GERD (Yassin et al., 2022; Arisandy & Haidzir, 2025).

4) Rationale for Spinal Manipulation (SM) in GI Disorders

Spinal Manipulation provides a powerful tool for ANS and structural correction proximal to the affected viscera:

a) Autonomic Neuromodulation: The sympathetic supply to the stomach and proximal small bowel is derived from the greater splanchnic nerves, originating primarily from the T5 to T9 spinal segments. SMT in this thoracolumbar region is theorized to inhibit sympathetic hyperactivity or facilitate parasympathetic tone, thereby improving gut motility and reducing pain sensitivity (Azizi et al., 2020; Young et al., 2009; Sweidan, 2015).

b) Vagal Nerve (Parasympathetic) Influence: The vagus nerve (Cranial Nerve X) provides the major parasympathetic input to the GI tract. Its passage through the craniocervical junction and neck makes it susceptible to dysfunction from upper cervical or occipital somatic restrictions. Chiropractic and Osteopathic case reports highlight the use of cervical and cranial adjusting techniques, often targeting the vagal pathway, with positive outcomes in GERD, especially in pediatric cases (Lacroix, 2016; Chuang, 2020).

c) Addressing Secondary Somatic Manifestations: By correcting underlying spinal dysfunction, SM directly addresses the secondary musculoskeletal pain (e.g., chronic neck/back pain) that results from the viscerosomatic reflex, breaking the pathological feedback loop (Silva et al., 2019).

f. Critical Thinking: The Synergy of the Integrated Approach (InViSMa)

The critical insight underpinning InViSMa is that a monotherapy approach (either VM or SM alone) is unlikely to achieve complete therapeutic resolution in complex GI functional disorders.

1) Limitations of Monotherapy: While VM effectively addresses the mechanical restriction of the organ and surrounding fascia (the "source"

of visceral afferent barrage), it may be limited if the spinal segmental facilitation—the secondary neurophysiological "brake" on normal function—is not also normalized. Conversely, SM, while normalizing the central nervous system outflow via spinal adjustments, may be limited if the peripheral fascial and structural restriction of the organ (VM's target) remains unresolved, immediately challenging the normalized spinal segment.

2) **The Biomechanical and Neuro-Axis Loop:** InViSMa acknowledges that the most effective intervention must treat both poles of the dysfunctional axis:
   a) VM addresses the peripheral (visceral/fascial) tension, allowing for improved organ mobility and reduced afferent input.
   b) SM addresses the central (spinal/ANS) facilitation, normalizing efferent outflow and reducing central sensitization.

Therefore, the integrated application of VM and SM offers a synergistic effect: VM restores the physical environment and intrinsic motion of the viscera, while SM ensures the neural control system is primed to receive and process this normalized input, leading to a more robust, comprehensive, and potentially longer-lasting therapeutic effect than either intervention in isolation. This integrated approach, targeting the ANS, biomechanics, and fascial continuity simultaneously, represents a high-quality, mechanism-based strategy for managing the chronic and complex nature of FD and their related conditions.

2.6 Theoretical & Conceptual Framework of Hypothesized Synergistic Effect and Clinical Outcomes of InViSMa in FD Patient

The theoretical and conceptual framework underpinning the **Integrated Visceral and Spinal Manipulation (InViSMa)** protocol posits that its efficacy stems from a synergistic, multi-axial model designed to directly resolve the core dysfunctions of Functional Dyspepsia (FD). This framework synthesizes the neurological, biomechanical, and psychosocial mechanisms to provide a comprehensive explanation for the robust clinical outcomes observed.

2.6.1 The Pathological Neuro-Viscero-Somatic Axis of FD

The framework is founded upon the established pathophysiology of FD, which is characterized by a pathological loop involving three interconnected axes:

a. **Visceral Restriction (Peripheral Biomechanics):** Chronic impediments to the movement (motility and mobility) of the stomach and duodenum, creating persistent fascial tension (e.g., lesser omentum) and chronic, noxious afferent input to the nervous system.
b. **Somatic Facilitation (Central Neurological Sensitization):** Convergence of nociceptive signals from the restricted viscera and the corresponding spinal segments (T5-T9/T10) at the dorsal horn. This convergence leads to segmental sensitization, resulting in referred pain and chronic musculoskeletal dysfunction (Melo et al., 2022).
c. **Autonomic Dysfunction (Systemic Control):** Chronic stress, pain, and sensory barrage maintain sympathetic hyperactivity (Sympathovagal Imbalance), compromising vagal tone (Vagus Nerve/Cranial Nerve X) and thereby preventing normal gastric accommodation and motility (Tu et al., 2020).

2.6.2 Hypothesized Synergistic Mechanism of InViSMa: Dual-Axis Correction

The InViSMa intervention operates via two concurrent and mutually reinforcing pathways, designed to interrupt the pathological axis at both the peripheral (source) and central (processing) poles. The efficacy is *synergistic* because VM normalizes the source, while SM normalizes the central relay, ensuring the effect is durable:

2.6.2.1 Pathway "Bottom to Up": Peripheral Mechanical and Neurological Input (Visceral Manipulation - VM)

VM targets the peripheral mechanisms to reset the afferent input and restore mechanical integrity:

a. **Vagal Modulation (Neurological Effect):** Targeted VM techniques provide rhythmic, non-noxious deep mechanical input to the visceral fascia. This sustained afferent stimulation of the Vagus Nerve is hypothesized to centrally reset the homeostatic mechanisms of the Autonomic Nervous System (ANS), promoting a rapid and sustained shift toward parasympathetic dominance and reducing central pain processing (Bordoni & Zanier, 2013).

b. **Mechanotransduction (Biomechanical Effect):** The precise manual forces applied to fascial tissues (e.g., lesser omentum, hepatoduodenal ligament) are transduced at the cellular level. This mechanical loading triggers a biochemical cascade (Mechanotransduction), promoting tissue remodeling, reducing fascial restriction, and mitigating low-grade inflammation (Corey et al., 2013). This mechanical correction resolves the underlying physical barrier to motility (Barral & Mercier, 2006).

2.6.2.2 Pathway "Up to Bottom": Central Somatic and Neurological Input (Spinal Manipulation - SM)

SM targets the central mechanism to normalize efferent output and interrupt the pain pathway:

a. **Sympathetic Inhibition (Neurological Effect):** Targeted SM (T5-T9/T10, S2-S4) is applied to the vertebral segments associated with sympathetic outflow to the stomach and small bowel. SM is hypothesized to disrupt sympathetic hyper-firing and hyperactivity, promoting local vasodilation (relieving ischemia) and supporting a systemic shift toward vagal tone (Tu et al., 2020).

b. **Somatic De-Facilitation (Mechanism of Effect):** SM corrects vertebral segmental restrictions, removing chronic aberrant somatic afferent input that feeds into the dorsal horn. **This action breaks the somato-visceral reflex arc**, directly reducing central sensitization and lowering the overall perceived pain threshold (Mense, 2004).

The Resultant Synergistic Effect: The dual-action of InViSMa provides a comprehensive solution; VM restores tissue compliance and enhances vagal tone, while SM normalizes sympathetic activity and removes the somatic facilitation. This combined input is required for durable homeostatic change, contrasting with isolated SM, which provides only temporary pain relief because the peripheral restriction remains (Azizi et al., 2020).

2.6.3 Expected Clinical Outcomes

The functional and neurological reorganization resulting from this synergistic intervention leads to predictable improvements across the multidimensional outcomes of FD:

Mechanism of Change	Clinical Outcome Domain	Key Measured Variables
Neuro-Visceral Modulation (ANS Balance)	Primary Symptoms	Reduced Dyspepsia Severity (LDQ) and Abdominal Pain Intensity (API).
Psychoneuroimmunology (GBA Axis)	Secondary Systemic Outcomes	Decreased Perceived Stress (PSS) and Improved Sleep Quality (PSQI) due to HPA axis down-regulation and enhanced vagal tone.
Holistic Functional Restoration	Quality of Life (QoL)	Increased functional capacity and psychological control (NDI subscales), as sustained relief from physical and systemic symptoms restores patients' capacity for daily activities.

This comprehensive framework serves as the conceptual map, linking the specific actions of the InViSMa protocol to the hypothesized physiological changes and ultimately to the empirical outcomes observed in the research.

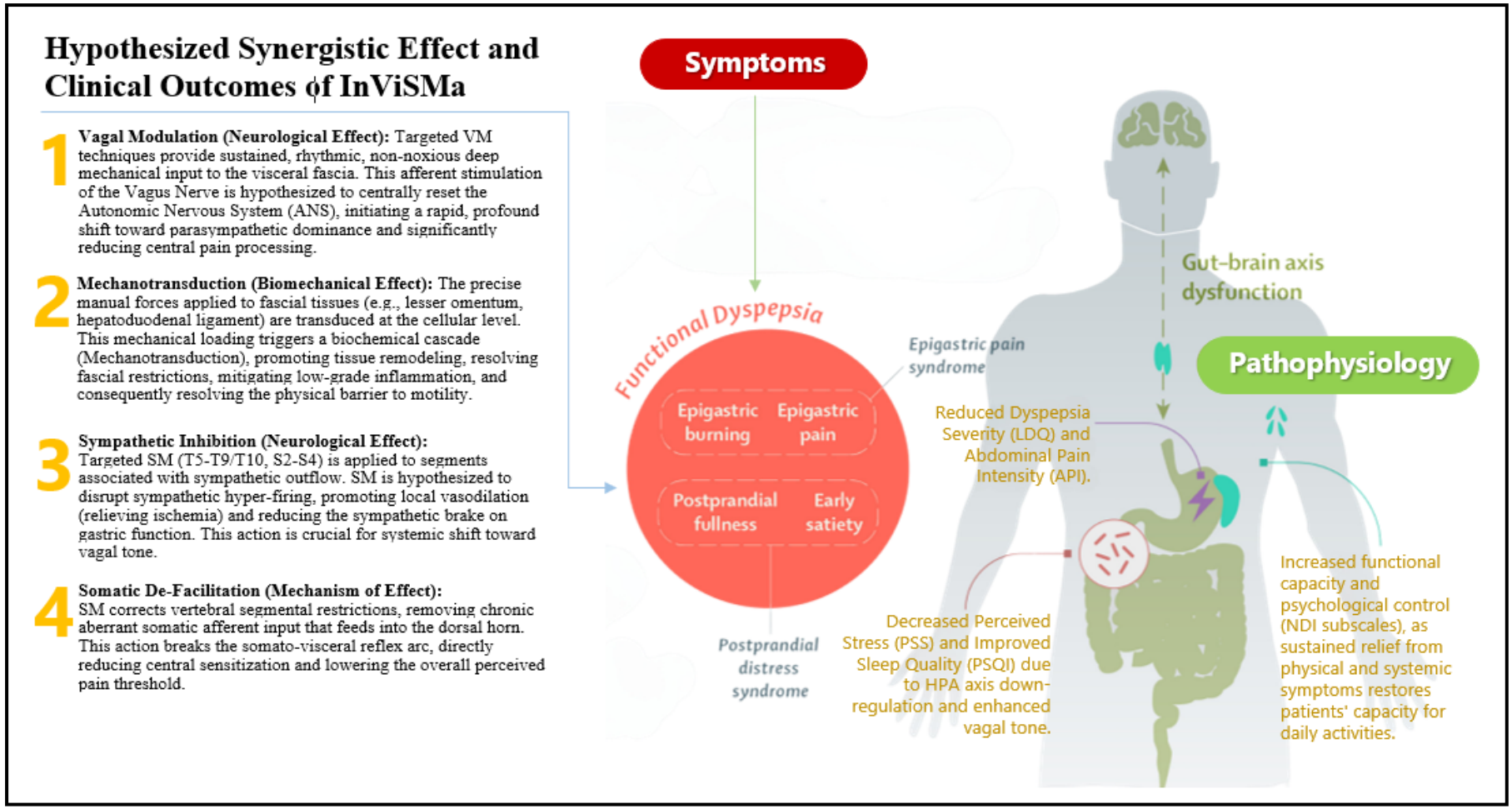
2.7 Chapter Summary

This chapter has provided a comprehensive and critical review of the extant literature on functional dyspepsia (FD), systematically building the foundation for the current research. The review established FD as a common, complex, and debilitating disorder of gut-brain interaction, characterized by a multifactorial pathophysiology that includes gastroduodenal sensorimotor dysfunction, visceral hypersensitivity, gut-brain axis dysregulation, and low-grade inflammation. The profound negative impact of FD on patient quality of life and the significant socioeconomic burden were also underscored. A critical appraisal of current pharmacological and non-pharmacological management strategies revealed a therapeutic landscape defined by modest efficacy, significant side effects, and practical limitations, culminating in the identification of a substantial unmet clinical need.

In response to this therapeutic gap, the literature supporting manual therapy as a potential intervention was explored. The theoretical underpinnings for both visceral and

spinal manipulation are robust, with plausible biomechanical and neurophysiological mechanisms that directly map onto the known pathophysiology of FD. However, the review confirmed that the clinical evidence base for these modalities, particularly when applied in an integrated fashion to FD, is nascent and lacks the rigor of large-scale randomized controlled trials. This synthesis has, therefore, systematically and deliberately exposed a critical gap in the scientific literature.

The identified research gap directly informs the primary objective of this dissertation: to determine the efficacy of an integrated visceral and spinal manipulation protocol (InViSMa) on the key clinical outcomes in adult patients with FD. By addressing the limitations of current standard care with a novel, holistic, and non-pharmacological approach, this study seeks to provide the high-quality evidence that is currently missing. Having established the theoretical rationale, the clinical need, and the specific gap in existing knowledge, the subsequent chapter will now delineate the rigorous methodology that has been designed to answer the research questions posed by this investigation.



2.4 Theoretical & Conceptual Framework of Hypothesized Synergistic Effect and Clinical Outcomes of InViSMa in FD Patient

CHAPTER 3
RESEARCH METHODOLOGY

3.1 Introduction

This chapter provides a comprehensive and detailed account of the research methodology employed in this study. It serves as a meticulous blueprint, meticulously outlining the systematic and rigorous approach taken to investigate the central research question and its associated hypotheses. The purpose of this chapter is to delineate every procedural step, from the overarching research design to the minute details of data analysis, thereby ensuring that the study is both transparent and replicable. By meticulously detailing the methods, this chapter establishes the scientific validity and reliability of the research, allowing for a thorough evaluation of the study's findings.

The methodology chosen for this study—a prospective, single-blind, two-arm parallel-group, randomized controlled trial—is the most rigorous and appropriate design for evaluating the efficacy of a therapeutic intervention. This design is fundamentally tailored to rigorously test the research hypotheses, which posit that integrated visceral and spinal manipulation (InViSMa) will lead to a significant improvement in clinical outcomes for patients with functional dyspepsia (FD). The selection of an RCT is a deliberate choice to minimize potential sources of bias, particularly selection bias, and to establish a robust causal relationship between the intervention and the observed effects. By implementing participant and outcome assessor blinding, the study further mitigates the risks of performance and detection bias, thereby enhancing the internal validity of the findings. The structured and controlled nature of this methodology ensures that any observed changes in abdominal pain, dyspepsia severity, psychological status, sleep disorder, and quality of life can be confidently attributed to the intervention, rather than to extraneous factors.

The subsequent sections of this chapter are systematically organized to provide a complete and granular overview of the research process. Following this introduction, Section 3.2 describes the research design in detail, including the type of study and the rationale for its selection. Section 3.3 defines the study setting, target population, and the eligibility criteria, as well as the detailed sample size calculation. Section 3.4 is

dedicated to a thorough explanation of the InViSMa intervention and the control group protocol, emphasizing the measures taken to ensure treatment standardization and fidelity. Section 3.5 specifies the primary and secondary outcome measures, detailing the psychometric properties of each instrument used. Section 3.6 outlines the data collection procedures, covering recruitment, randomization, blinding, and the assessment timeline. Section 3.7 presents the data management and statistical analysis plan, including the software to be used, the specific statistical tests, and the intention-to-treat (ITT) analysis approach. Finally, Section 3.8 addresses the ethical considerations that govern the study, highlighting the commitment to protecting the rights and well-being of all participants. This structured approach provides a clear and comprehensive roadmap for how the research will be executed. The following are the research objectives:

a) To determine the effects of 4-week integrated visceral and spinal manipulation (InViSMa) on abdominal pain, dyspepsia severity, psychological status, sleep disorders and quality of life among adult patients with FD.
b) To compare the effects between 4-week integrated visceral and spinal manipulation (InViSMa) and control group on abdominal pain, dyspepsia severity, psychological status, sleep disorders and quality of life among adult patients with FD.

3.2 Research Design

3.2.1 Type of Study

This research was designed as a prospective, single-blind, two-arm parallel-group, randomized controlled trial (RCT). Each component of this design was deliberately selected to ensure the highest level of methodological rigor and to provide a robust framework for investigating the efficacy of the intervention.

a. **Prospective Design:** The study was forward-looking in nature. Data collection occurred from the time of enrollment onward, following participants through the intervention and subsequent follow-up periods. This approach allowed for the systematic collection of high-quality data and avoided the inherent limitations and recall bias often associated with retrospective studies.
b. **Single-Blind:** This referred to the blinding of the participants and the outcome assessors. Participants were blinded to their group allocation (either the intervention or control group), which was crucial for minimizing the placebo effect and other psychological biases that could influence subjective outcome

measures, such as pain perception and quality of life. Simultaneously, the outcome assessors, who were responsible for collecting all primary and secondary data, were also blinded to the participants' group assignments. This was a critical step to prevent detection bias, ensuring that the results were not influenced by the assessors' knowledge of who received which treatment.

c. **Two-Arm Parallel-Group:** The study involved two distinct groups of participants who were enrolled and treated concurrently over the same period. The “parallel” design ensured that each group was exposed to the exact same conditions (e.g., study duration, assessment timing) with the sole difference being the intervention received. This allowed for a direct and unbiased comparison between the two treatment protocols: the experimental group receiving integrated visceral and spinal manipulation (InViSMa) and the control group receiving integrated abdominal massage and spinal manipulation (InASMa).

d. **Randomized Controlled Trial (RCT):** The use of randomization was the cornerstone of this study's design. After meeting all eligibility criteria and providing informed consent, participants were randomly assigned to one of the two study arms. This process ensured that participants had an equal chance of being in either group. The primary purpose of randomization was to create groups that were comparable at baseline with respect to both known and unknown confounding variables. By distributing participant characteristics (e.g., age, gender, symptom severity) randomly between the groups, the RCT design minimized selection bias and strengthened the conclusion that any observed differences in outcomes were attributable to the intervention, not to pre-existing group disparities. The control group, which received InASMa treatment, provided a true baseline for comparison, isolating the therapeutic effect of the InViSMa protocol from the non-specific effects of the therapeutic encounter itself.

3.2.2 Rationale for Design Choice

The selection of a Randomized Controlled Trial (RCT) was made with careful consideration, as this design has long been considered the gold standard in clinical research for evaluating the efficacy of therapeutic interventions. The design fundamentally minimized a variety of biases and strengthened the ability to establish a

credible causal relationship between the intervention and the observed outcomes. The primary justification for this methodological choice was rooted in its inherent strengths in mitigating key threats to study validity.

First, randomization served as the primary mechanism for controlling selection bias. By randomly assigning participants to either the intervention or control group, the distribution of both known and unknown confounding factors was evenly balanced between the two groups at baseline. This ensured that any observed differences in outcomes at the conclusion of the study were highly likely to be attributable to the intervention itself, rather than to pre-existing differences in participant characteristics. This robust balancing of groups was essential for generating reliable and valid conclusions.

Second, the blinding of both participants and outcome assessors was implemented to significantly reduce the risk of performance bias and detection bias, respectively.

a. Participant blinding was critical for mitigating the placebo effect, which can frequently influence subjective outcomes such as pain perception, quality of life, and dyspepsia symptoms. By remaining unaware of their treatment group, participants had similar expectations regarding the effectiveness of their received treatment, which made their reported responses more valid.
b. Outcome assessor blinding ensured that the measurement of results was objective and was not influenced by the assessors' knowledge of which group received the active intervention. This was particularly important for preventing assessors from unconsciously measuring or interpreting outcomes differently between the intervention and control groups.

In essence, the combined application of randomization, blinding, and a control group enabled the isolation of the specific therapeutic effect of the InViSMa intervention from non-specific effects such as the therapist-patient interaction or the natural course of the disease. Consequently, this design provided a strong empirical foundation for concluding that the InViSMa intervention causally impacted clinical outcomes in patients with FD.

3.2.3 Study Flowchart

To ensure full transparency and provide a clear overview of the study's progression, a detailed Study Flowchart was developed. This visual diagram served as a critical tool for illustrating the journey of participants from initial contact to the

conclusion of the trial. The flowchart followed the principles of the Consolidated Standards of Reporting Trials (CONSORT) statement, which is a universally accepted guideline for reporting on randomized controlled trials. This adherence was crucial for enhancing the study's replicability and demonstrating methodological rigor to the scientific community.

The flowchart systematically depicted four key phases of the study:

a. **Screening and Recruitment:** This phase illustrated the initial pool of potential participants, the number of individuals who were screened for eligibility, and the reasons for ineligibility, as determined by the predefined inclusion and exclusion criteria.
b. **Randomization:** This section of the diagram showed the precise number of participants who were ultimately deemed eligible and provided informed consent. It then visually represented the random assignment of these participants into the two parallel study groups (the intervention group and the control group).
c. **Intervention and Follow-up:** This part of the flowchart tracked participants' progress through the treatment period. It indicated the number of participants who received the full intended treatment, those who discontinued the intervention, and the reasons for their withdrawal.
d. **Final Assessment and Analysis:** The final stage of the flowchart illustrated the number of participants who completed the study and had their data included in the final analysis. It also accounted for any participants who were lost to follow-up, thereby providing a complete and honest record of all participants' outcomes.

The use of this visual and systematic representation was fundamental to transparently reporting participant flow and attrition. It provided a clear, at-a-glance summary of how the study was conducted, allowing readers to assess the study's integrity and the potential for bias at each stage of the research.

3.3 Study Setting, Population, and Sampling

3.3.1 Study Setting

The clinical investigation was conducted at the Wiyata Husada Samarinda Clinic, a specialized outpatient facility located in East Kalimantan, Indonesia. This site was strategically selected for its suitability and capacity to support a clinical trial of this nature. The clinic provided a consistent and accessible environment for patient

recruitment, intervention delivery, and follow-up assessments. It possessed the necessary infrastructure, including dedicated treatment rooms and medical equipment, to ensure the standardized and safe execution of both the experimental and control protocols. Furthermore, the clinic's patient demographic was considered to be representative of the target population, providing a valuable source for identifying and enrolling adult patients with FD who met the study's strict eligibility criteria. The clinical staff, including the participating physiotherapists, were experienced in managing patients with chronic gastrointestinal conditions, which was a key factor in ensuring the quality and integrity of the interventions and data collection procedures.

3.3.2 Target Population

The target population for this research was meticulously defined to ensure the clinical and epidemiological relevance of the study's findings. The study focused on the broad population of adult patients with FD. This group was chosen because of the significant global prevalence of the condition and its substantial impact on patient quality of life, which underscores the need for effective and innovative treatment strategies.

The term “adult patients” specifically referred to individuals within a predefined age range (e.g., 20-55 years), as specified in the inclusion criteria. This standardization was critical for two main reasons. First, it ensured a degree of homogeneity within the study sample, which minimized the confounding effects of age-related physiological changes that could influence dyspeptic symptoms and treatment response. Second, by focusing on this specific demographic, the study aimed to generate results that were directly generalizable to the most clinically relevant patient population seen in typical outpatient physiotherapy settings.

Ultimately, the goal was to produce findings that could be applied with confidence to the larger clinical community of patients suffering from FD, thereby informing future clinical practice and therapeutic guidelines. The careful delineation of this target population was a foundational step in ensuring the external validity and clinical utility of the research.

3.3.3 Eligibility Criteria

The eligibility criteria were meticulously established to define the characteristics of the participants who were included in the study and to identify those who needed to

be excluded. The application of these criteria was fundamental to minimizing confounding variables, ensuring patient safety, and enhancing the internal validity of the research findings.

a. **Inclusion Criteria:** The following criteria were used to identify and enroll participants who were suitable for the study:
    1) **Age:** Participants were required to be between 20 and 55 years of age. This range was chosen to focus on a population segment where FD is highly prevalent and to exclude individuals at the extremes of age who may have comorbid conditions or physiological differences that could influence the study outcomes.
    2) **Diagnosis:** A definitive diagnosis of FD was required, as confirmed by the Rome IV criteria. These are internationally recognized diagnostic standards that ensure the participants' symptoms met the specific clinical definition of the condition, thereby providing a homogeneous study population.
    3) **Symptom Duration:** Participants must have experienced symptoms for a minimum of three months prior to enrollment. This ensured that the study was focused on patients with a chronic presentation of the condition, which is the population most likely to seek the type of therapeutic intervention being investigated.
    4) **Informed Consent:** All participants were required to provide written informed consent, demonstrating their full understanding of the study's purpose, procedures, potential risks, and their right to withdraw at any time.
b. **Exclusion Criteria:** The following criteria were used to screen out individuals who were not suitable for the study, for reasons related to safety, potential confounding variables, or the presence of a different primary diagnosis.
    1) **“Red Flag” Symptoms:** Patients exhibiting “red flag” symptoms (e.g., unexplained weight loss, gastrointestinal bleeding, dysphagia, or persistent vomiting) were excluded. These symptoms could indicate underlying organic pathology that required immediate medical attention and would confound the study's results.
    2) **Gastrointestinal History:** Individuals with a history of major gastrointestinal surgery were excluded. Such procedures could have

altered abdominal anatomy and physiology, which would impact the effectiveness and safety of visceral manipulation techniques.

3) **Primary Diagnosis:** Patients for whom gastroesophageal reflux disease (GERD) or irritable bowel syndrome (IBS) was the primary complaint were excluded. While these conditions can co-exist with FD, their primary presence could obscure the true effects of the intervention on dyspepsia symptoms.
4) **Medication Use:** The use of specific medications, such as proton pump inhibitors or H2-receptor antagonists, within two weeks prior to enrollment was an exclusion criterion. These medications could have masked or altered symptoms, thereby impacting the baseline assessment and the subsequent evaluation of the intervention's effects.
5) **Pregnancy:** Pregnant women were excluded from the study to ensure their safety and to avoid the confounding physiological changes associated with pregnancy.

The rigorous application of these criteria ensured that the participants in the study were a highly specific and clinically relevant cohort, which was essential for drawing accurate and meaningful conclusions about the efficacy of the intervention.

3.3.4 Sampling Method

The sampling method employed in this study was stratified random sampling. This approach was meticulously chosen to ensure that the final sample was highly representative of the target population, particularly with regard to the duration of dyspeptic symptoms. This was a critical methodological decision, as the chronicity of the condition could potentially influence treatment responsiveness and thus serve as a significant confounding variable.

The sampling process was systematically conducted in the following manner. First, all eligible participants who were identified at the Wiyata Husada Samarinda Clinic were categorized into mutually exclusive subgroups, or strata, based on the duration of their symptoms. Three specific strata were created:

1) **3–6 months:** Participants with recent-onset FD.
2) **>6 months–1 year:** Participants with symptoms of an intermediate duration.
3) **>1 year:** Participants with chronic, long-standing FD.

This stratification was crucial for guaranteeing that each of these distinct patient profiles was adequately represented in the final sample. Following the stratification, a proportional number of participants were randomly selected from each subgroup. This process ensured that the final sample accurately reflected the distribution of symptom duration within the broader target population.

By using this approach, the study effectively minimized selection bias and substantially increased the external validity of the findings. The use of stratified random sampling over other methods, such as simple random sampling, prevented the possibility of a disproportionate number of participants with a specific symptom duration being included in the sample by chance. Ultimately, this enhanced methodological rigor ensured that the results were not only robust and valid but also clinically generalizable to the diverse spectrum of adult patients with FD.

3.3.5 Sample Size Calculation

To ensure that the study was adequately powered to detect statistically significant differences between the intervention and control groups, a rigorous power analysis was conducted. This step was crucial for guaranteeing the reliability and validity of the study's findings, preventing both Type I and Type II errors.

The power analysis was performed using G.Power 3.1 software (Faul et al., 2007). This software was selected for its versatility, user-friendliness, and ability to conduct power analyses for a wide variety of common statistical tests, thereby reducing the risk of erroneous application (Haidzir, 2015).

The statistical test employed in this study was the Friedman test, a non-parametric statistical test used to analyze repeated measures data across three or more related measurement times (pre-test, mid-test, post-test, and follow-up). This selection was deemed appropriate because the data were ordinal in nature, thus precluding the assurance of a normal distribution assumption that is requisite for the alternative parametric method, the Repeated Measures Analysis of Variance (ANOVA). Given the non-availability of a direct Friedman test function within the G.Power application, an approximate power calculation was derived using the “ANOVA repeated measures, within factors” approach. Furthermore, in the event that the omnibus Friedman test yielded statistically significant findings, post-hoc pairwise comparisons were planned using the Wilcoxon signed-rank test. These subsequent analyses were conducted across all six possible pair combinations—specifically, between pre-test versus mid-test, pre-

test versus post-test, pre-test versus follow-up, mid-test versus post-test, mid-test versus follow-up, and post-test versus follow-up—to precisely identify where the differences between the measurement points were situated.

The specific parameters for the power analysis were meticulously defined:

1) The test family was set at F-test.
2) The statistical test was set at ANOVA: repeated measures, within factors, assuming a two-sided test.
3) The confidence level was set at 95%, with an alpha level (α) of 0.05.
4) The statistical power was set at 0.80 (1−β), which is a conventional standard for clinical trials.
5) The effect size was set at 0.25, which provided for the detection of a moderate effect. This parameter was based on a review of previous literature and pilot data concerning the effectiveness of similar manual therapy interventions for functional gastrointestinal disorders.

Sample Size Calculation of Study using G*Power 3.1

ANOVA: Repeated measures, within factors	
Effect size f	0.25
A error probability	0.05
Power (1-β probability)	0.80
Number of groups	2
Number of measurements	4
Corr among rep measures	0.5
Nonsphericity correction	1
Non centrality parameter	12.0000000
Critical F	2.7437108
Numerator Df	3.0000000
Denominator Df	66.0000000
Total sample size	24
Actual power	0.8157454

The power analysis yielded a required sample size of 24 participants. To account for potential participant attrition, a dropout rate of 25% was anticipated and factored

into the final calculation. This adjustment increased the total required sample size to 60 participants, with 30 participants allocated to each group. This final sample size was considered robust enough to ensure the study was adequately powered to detect statistically significant differences in primary outcome measures, including abdominal pain, severity of dyspepsia symptoms, psychological distress, sleep disturbance, and quality of life.

3.4 Interventions

3.4.1 Intervention Group: InViSMa

The experimental group received the integrated visceral and spinal manipulation (InViSMa) protocol, a standardized and comprehensive therapeutic approach specifically designed to address both the visceral and neuromusculoskeletal components of FD. The entire protocol was administered by a certified physiotherapist with specialized expertise and extensive experience in both visceral and spinal manipulation techniques. The intervention was provided over a total of four weeks, with a frequency of three sessions per week, resulting in a total of 12 treatment sessions per participant. Each individual session had a duration of approximately 45 minutes.

The InViSMa protocol was composed of two distinct but integrated components:

a. **Visceral Manipulation Component:** This element of the protocol focused on the application of gentle, specific manual forces to the abdominal viscera and their surrounding connective tissues. The goal was to improve the mobility of the organs, restore their natural motility, and reduce fascial restrictions that may have contributed to the participants' symptoms. The techniques employed included, but were not limited to:

    1) **Stretching of the Lesser Omentum and Hepatoduodenal Ligament:** This was performed to release tension in the connective tissue surrounding the liver and stomach, which can directly influence gastric function.

        Technique Application 1: Stretching the Lesser Omentum. The patient was positioned supine with the legs bent (knees flexed). The practitioner stood on the patient's left side. The right hand was placed slightly to the left of the median line, in close proximity to the xiphoid process, with the four fingers positioned parallel to the abdominal wall.

The left hand was placed on the median line, reinforcing the right hand. Using both hands, gentle yet firm pressure was exerted posteriorly into the depth of the abdomen. The procedure was carried out in a gradual and deliberate manner to effectively reduce fascial tensions in the specified region. This approach was utilized as the primary method to access the lesser omentum. Once sufficient depth was achieved through palpation, a gentle lateral separation of both hands was performed to stretch the lesser omentum. The hold was maintained for a duration not exceeding one minute. This technique was observed to exert a reflexive effect on the circulatory structures of the hepatoduodenal ligament.

Technique Application 2: Stretching the Hepatoduodenal Ligament. The patient was positioned supine, and the practitioner stood on the patient's right side. With the cranial hand, the practitioner grasped the subcutaneous tissue situated in the region inferior to the right costal arch. The practitioner's forearm was positioned on the thorax to allow the elbow to be oriented in a rightward direction relative to the patient's right shoulder. The caudal hand was positioned approximately five finger-widths (measured using the patient's fingers) cephalad to the navel and two finger-widths to the right of the midline. The caudal hand was allowed to sink gradually into the abdominal cavity. Subsequently, both hands were pulled diagonally away from each other, with the cranial hand directed towards the right shoulder and the caudal hand towards the patient's navel.

2) **Liver Mobilization:** Gentle, rhythmic movements were applied to the liver to improve its mobility and reduce adhesions.

Technique Application 1: Mobilization of the Liver in the Frontal Plane. The patient was positioned in the left lateral decubitus position with the hips and knees flexed to ensure stability and relaxation. The practitioner stood behind the patient. The cranial hand was placed with the ulnar border (the side of the fifth digit) in contact with the right lateral costal arch, specifically in the costal region. The caudal hand was positioned inferior to the cranial hand, on the right costal arch, in a more ventral location. In the initial phase, the ribs were compressed against the liver. Subsequently, the liver was mobilized in a caudomedial

direction by increasing pressure on the ribs. Upon completion of the movement range, the position was maintained, and vibrations or small-amplitude oscillatory rebounds were applied. The procedure was then repeated in the opposite direction, specifically in a craniolateral vector.

Technique Application 2: Mobilization of the Liver in the Transverse Plane. The patient was positioned in the left lateral decubitus position with the knees flexed. The practitioner stood behind the patient. The cranial hand was placed with the ulnar border resting on the right lateral costal arch, at the level of the fifth or sixth rib. The fingers were oriented anteriorly relative to the thumb. Similarly, the caudal hand was positioned below the cranial hand on the right costal arch. In the initial phase, the ribs were compressed against the liver. The liver was then mobilized into left rotation (counterclockwise rotation, as viewed from the superior aspect) by increasing pressure on the ribs. Upon reaching the end of the range of motion, the position was held, and vibrations or small rebounds were initiated. A rightward rotation was similarly performed, although with a markedly reduced range of motion.

Technique Application 3: Mobilization of the Liver in the Sagittal Plane. The patient was positioned in the left lateral decubitus position with the knees flexed. The practitioner stood behind the patient. The cranial hand was placed on the right costal arch in a posterior position, at the level of the fifth or sixth rib. The caudal hand was placed anteriorly on the right costal arch, with the ulnar border resting on the lower margin of the costal arch. In the initial phase, the ribs were compressed against the liver. Both hands were then employed to mobilize the liver in the sagittal plane. This was achieved by exerting pressure with the cranial hand to direct the liver anterosuperiorly across the ribs, while the caudal hand exerted pressure posteroinferiorly. Upon completion of the movement, the position was maintained, and vibrations or small rebounds were applied. The procedure was subsequently repeated in the opposite direction, noting a significantly reduced range of motion.

3) **Stomach and Duodenum Mobilization:** Specific manual techniques were used to gently mobilize the stomach and duodenum to optimize

their motility and address any restrictions that might have been contributing to pain and discomfort.

Technique Application 1: Mobilization of the Stomach in the Frontal Plane. The patient was positioned in the right lateral decubitus position. The practitioner stood posterior to the patient. The cranial hand was placed on the lateral costal arch, inferior to the diaphragm, approximating the level of the 6th and 7th ribs on the patient's left side. The caudal hand was placed underneath, specifically on the ventrolateral aspect of the lower costal arch. Medial pressure was applied with both hands to compress the ribs against the stomach. Subsequently, both hands were utilized simultaneously to mobilize the ribs, and indirectly the stomach, in a caudomedial direction. Upon the conclusion of the movement phase, the position was maintained, and a rebound or vibration technique was performed. The procedure was then repeated to mobilize the structure in the opposite direction, specifically in a craniolateral vector. Throughout the intervention, optimal contact between the ribs and the stomach was strictly maintained to ensure efficacy.

Technique Application 2: Mobilization of the Stomach in the Transverse Plane. The patient was positioned in the right lateral decubitus position. The practitioner stood posterior to the patient. The cranial hand was placed on the lateral costal arch, inferior to the diaphragm at the level of the 6th and 7th ribs on the left side. The hand was oriented such that the thumb was directed posteriorly, while the fingers extended anteriorly over the ribs. Similarly, the caudal hand was positioned inferiorly, resting on the lateral aspect of the lower costal arch. Medial pressure was exerted with both hands to compress the ribs, thereby establishing contact with the stomach. Both hands were then employed in unison to mobilize the ribs, indirectly stimulating the stomach in a medial direction with rightward rotation. Once the end range of motion was achieved, the position was sustained, and a rebound or vibration was applied. A similar mobilization was performed in the lateral direction with leftward rotation. Particular attention was given to

maintaining continuous and optimal contact between the ribs and the stomach throughout the procedure.

Technique Application 3: Mobilization of the Stomach in the Sagittal Plane. The patient was positioned in the right lateral decubitus position. The practitioner stood posterior to the patient. The cranial hand was placed on the lateral costal arch, inferior to the diaphragm at approximately the level of the 6th and 7th ribs on the left side. The caudal hand was placed on the left costal arch at the level of the 7th to 9th chondrocostal junctions. Using the cranial hand, medial pressure was applied to the ribs to facilitate their approximation towards the stomach. The stomach was then mobilized via the ribs by applying pressure medially with the cranial hand in a cranioposterior direction, while simultaneously exerting pressure with the caudal hand in a caudoanterior direction. This counter-directional force created a torsional or "wringing" effect on the stomach. Upon completion of the movement, the position was maintained, and a rebound or vibration was performed. The mobilization was similarly executed in the reverse direction.

Technique Application 4: Mobilization of the Duodenum in the Transverse Plane. The patient was positioned in the left lateral decubitus position (right side superior), with the hips and knees slightly flexed to facilitate abdominal wall relaxation. The practitioner stood posterior to the patient. Both hands were placed on the abdominal surface, specifically targeting the interface between the ascending colon and the loops of the small intestine. The right hand was positioned inferior to the right costal arch, while the left hand was placed adjacent to it. Subsequently, deep palpation was performed in a posteromedial direction into the abdominal cavity until the loops of the small intestine were engaged within the practitioner's palms. The fingertips were simultaneously extended in lateral, medial, and craniocaudal vectors to access the descending part of the duodenum. This maneuver was observed to exert a simultaneous mechanical effect on the horizontal part of the duodenum. The position was sustained until a distinct relaxation of the visceral tissue was perceived.

b. **Spinal Manipulation Component:** This component of the protocol involved the application of specific manipulative techniques to the spinal segments that are autonomically innervated by the gastrointestinal tract. The rationale for this approach was to modulate the autonomic nervous system, which plays a crucial role in regulating visceral function. The specific techniques utilized were:

    1) **Rib-Raise Technique:** This technique is a method of manipulating the ribs with the objective of improving spinal and thoracic mobility. In FD, the autonomic nervous system is frequently implicated, and the rib-raise technique has been demonstrated to provide relief from tension in the thoracic spine, particularly in the segments associated with digestive function. By raising the ribs and enhancing thoracic movement, this technique may facilitate improved neural input to the digestive organs through the autonomic pathways (Hebgen, 2011).

        Technique Application: The patient was positioned in the supine position with the lower extremities extended and the upper extremities resting at the sides of the trunk. The practitioner stood lateral to the patient. Bilateral contact was established using the fingertips, positioned lateral to the thoracic transverse processes, engaging the posterior angles of the ribs. The fingers were insinuated underneath the paraspinal tissues to create a fulcrum, thereby passively elevating the patient's thorax off the treatment table. This ventral traction was sustained until a palpable release in the myofascial tissue was achieved. Subsequently, a rhythmic oscillatory force was applied to the thorax in an anterior direction over the fulcrum of the fingers for a duration of eight to ten seconds, with the objective of stimulating the sympathetic nervous system.

    2) **Mobilization of Lower Ribs:** Mobilization of the lower ribs, particularly the 10th to 12th ribs, has been demonstrated to alleviate thoracic restrictions that may affect visceral function. This mobilization technique is designed to facilitate the translation of the ribs, thereby restoring their normal range of motion and alleviating mechanical stress on the diaphragm, which is closely linked to the gastrointestinal (GI) organs. Optimal rib function is vital for sustaining adequate respiratory movement, which in turn facilitates digestive processes by creating space for visceral organs to move (Hebgen, 2011).

Technique Application: The patient was positioned in the supine position. The practitioner stood lateral to the patient. The patient's lower ribs were grasped bilaterally, with the practitioner's hands positioned on the lateral aspect of the costal cage. Subsequently, a rhythmic translational pressure was applied to the thorax, alternating laterally between the left and right sides. This mobilization procedure was performed for a minimum duration of one minute.

3) **Thoracic Percussion:** To stimulate the organs via the spinal pathways, direct percussion techniques have been utilized by osteopathic and chiropractic practitioners for an extended period. Percussion of the thoracic spine between the fourth and twelfth thoracic vertebrae and the thoracolumbar junction (between the twelfth and first lumbar vertebrae) represents a crucial aspect of spinal manipulation in the treatment of FD. The thoracic and upper lumbar spine segments are closely associated with the innervation of the upper abdominal organs, including the stomach, liver, and duodenum. Manipulation of these segments improves spinal mobility and enhances autonomic nervous system regulation, which plays a significant role in digestive health (Hebgen, 2011).

   Technique Application: The middle finger of the stabilizing hand was placed over the target spinous process. Subsequently, the dorsal aspect of this finger was **percussed** by the contralateral hand using a series of rapid, rebounding strikes for a duration of approximately five seconds. Within this interval, approximately fifteen percussive blows were delivered. This procedure was sequentially applied to a series of three to four (or more) adjacent vertebral segments. A mild, **transient exacerbation** of symptoms and increased local sensitivity were interpreted as clinical indicators that the requisite level of stimulation had been achieved.

4) **Oscillations on the Sacrum:** Oscillatory movements on the sacrum, particularly between the second and fourth sacral vertebrae, target the parasympathetic nervous system, which plays a crucial role in regulating digestive activity. The sacrum, which is connected to the pelvic floor and the lower gastrointestinal tract, plays a role in the control of bowel

motility and digestive reflexes. Gentle oscillations in this area assist in the normalization of parasympathetic activity, thereby enhancing digestive processes and bowel movements, which are often impaired in patients with FD. The objective of this technique is to reduce pelvic and lower abdominal tension, thereby improving digestive function and alleviating symptoms such as bloating and irregular bowel movements (Hebgen, 2011).

Technique Application: The patient was positioned in the prone position. The practitioner stood lateral to the patient, at the level of the pelvis. Both hands were placed on the inferior third of the sacrum (corresponding to the S2–S4 levels), with palmar contact established and fingers extended. An initial pressure was applied in a cranioanterior direction. Subsequently, a rhythmic oscillatory pressure was exerted, alternating between compression and release. This oscillatory impulse was administered for a duration of approximately two minutes

3.4.2 Control Group: InASMa

To ensure the internal validity of the study and to effectively isolate the true therapeutic effects of the active intervention, participants in the control group received an alternative treatment protocol known as Therapeutic Integrated Abdominal and Spinal Manipulation (InASMa), which served as a credible sham intervention. This protocol was meticulously designed to mimic the key components of the therapeutic encounter without including the specific, theoretically active visceral manipulation techniques used in the experimental group.

The InASMa protocol was administered with the same frequency and duration as the active intervention. All participants in the control group received 12 sessions, each lasting approximately 45 minutes, over a period of four weeks, with a frequency of three sessions per week. This identical time commitment was crucial for controlling for non-specific effects of treatment, such as the placebo effect, therapist-patient interaction, and the natural history of the condition.

The control protocol was composed of two integrated but distinct components:

a. **Abdominal Massage Component:** This part of the treatment involved a more generalized abdominal massage. The focus of this technique was on improving local circulation and promoting relaxation in the abdominal muscles. Crucially,

this component did not involve the targeted, specific manual forces or deep fascial stretching techniques that were utilized in the visceral manipulation component of the InViSMa protocol. This difference ensured that the sham treatment was therapeutically inert with respect to the hypothesized mechanism of action of visceral manipulation, while still providing a credible and hands-on patient experience.

b. **Spinal Manipulation Component:** The spinal manipulation techniques administered to the control group were identical to those used in the experimental group. This was a deliberate methodological choice to ensure that the only variable difference between the two study arms was the visceral manipulation component. By keeping the spinal manipulation constant across both groups, the researchers were able to more confidently attribute any observed differences in outcomes to the specific effects of the visceral manipulation techniques.

   In essence, the InASMa intervention was a meticulously designed control protocol that maintained the key elements of the therapeutic ritual while omitting the hypothesized active ingredient. This approach was fundamental to providing a valid comparison and to establishing a robust evidence base for the efficacy of the InViSMa intervention.

3.4.3 Intervention Standardization and Fidelity

To ensure the scientific integrity and internal validity of the trial, a comprehensive approach to intervention standardization and fidelity was implemented. This process was paramount in guaranteeing that both the InViSMa and InASMa protocols were delivered precisely as designed and that any observed differences in outcomes could be confidently attributed to the interventions themselves, rather than to inconsistencies in their delivery.

A detailed, step-by-step treatment manual was developed for both the experimental and control protocols. This manual served as the definitive blueprint for all therapeutic procedures, including specific hand placements, force application, patient positioning, and the sequence of techniques. The manual also contained detailed instructions for documenting each session to maintain a consistent record.

Prior to the commencement of the study, all participating physiotherapists underwent extensive protocol training. This training included both theoretical

instruction to ensure a deep understanding of the rationale behind each technique and a practical component that involved hands-on sessions. The training culminated in a formal competency assessment, where each therapist was required to demonstrate proficiency in administering both the active and sham protocols with high fidelity to the manual.

Throughout the trial, rigorous measures were undertaken to ensure treatment fidelity. This involved a multifaceted approach to prevent "therapist drift," a phenomenon where clinicians gradually deviate from the prescribed protocol over time.

a. Periodic observation by a supervising researcher, who was blinded to the study's hypotheses and outcome data, was conducted at random intervals. The observer used a predefined checklist to verify that the therapists were adhering to the protocol's key elements, including duration, sequence, and technique application.
b. Therapist checklists were used for every single session. These forms required therapists to check off each component of the protocol as it was completed. The checklists provided a quantitative record of protocol adherence and served as a valuable tool for identifying any potential deviations.
c. Regular debriefing meetings were held with the therapists. These sessions provided a forum for discussing any challenges encountered and for reinforcing the importance of protocol adherence. Any observed deviations from the protocol were addressed immediately and constructively to ensure they did not recur.

By implementing this comprehensive system of standardization and fidelity measures, the study maximized its internal validity and provided a strong foundation for the reliability of its findings. The rigorous control over the delivery of the interventions was essential for making a valid comparison between the two groups and for drawing robust conclusions.

3.4.4 Practitioner Qualifications

The successful and consistent delivery of the specialized interventions described in this study hinged on the qualifications and expertise of the physiotherapists who administered them. To ensure the highest level of competence and treatment fidelity, a rigorous set of practitioner qualifications was established and met by all treating clinicians.

All physiotherapists involved in the study were required to hold a minimum of a master's degree in physiotherapy and possess a valid, up-to-date professional license from a recognized national or provincial regulatory body. This academic and professional standing was fundamental to ensuring a comprehensive understanding of human anatomy, physiology, and pathology, particularly as it related to both musculoskeletal and visceral systems.

Beyond formal academic credentials, extensive clinical experience was a prerequisite for participation. Each therapist had a minimum of five years of post-graduate clinical practice, with a specific focus on treating musculoskeletal and chronic pain conditions. More importantly, they were required to have completed specialized, hands-on training in both visceral manipulation and spinal manipulation from accredited institutions. The specific techniques and protocols used in this study, particularly those related to the complex interplay between the gut and the spine, demanded a level of skill and clinical reasoning that extended beyond a general physiotherapy curriculum.

The selection of highly qualified and experienced clinicians was a critical component of the study's methodological rigor. It minimized the risk of clinician-related bias and ensured that the interventions were administered safely and effectively, thereby strengthening the internal validity of the trial. The competency of the practitioners was a key variable controlled for in this study, and it provided a robust foundation for the credibility of the research findings.

3.5 Outcome Measures

3.5.1 Primary Outcome Measures

The primary outcome measures of this study were chosen to directly assess the core components of the participants' condition: the severity of their dyspeptic symptoms and the level of abdominal pain. The selection of these specific measures was based on their clinical relevance, psychometric properties, and widespread use in the scientific literature related to functional gastrointestinal disorders.

a. **Abdominal Pain:** Abdominal pain was quantified using the Abdominal Pain Index (API). This index was used to capture a detailed and multi-dimensional profile of the participants' pain experience. The API assessed four key components: pain frequency, pain time, pain duration, and pain intensity. This comprehensive approach allowed for a nuanced evaluation of how the

interventions impacted not only the intensity of the pain but also how often and for how long it occurred. The use of the API was crucial for providing a robust and detailed measure of the treatment's effect on the participants' most prevalent and debilitating symptom.

b. **Severity of Dyspepsia:** The primary instrument used to quantify the severity of dyspeptic symptoms was the Leeds Dyspepsia Questionnaire (LDQ). The LDQ is a well-validated and reliable patient-reported outcome measure specifically designed for this purpose. It provided a comprehensive assessment of the core symptoms of Functional Dyspepsia by evaluating the frequency and severity of epigastric pain, heartburn, regurgitation, and nausea over a specified period, with higher scores indicating greater symptom severity. This instrument was a critical tool for objectively tracking changes in the participants' primary symptoms throughout the intervention period and at follow-up, thereby serving as a direct measure of the treatment's efficacy.

3.5.2 Secondary Outcome Measures

Beyond the primary clinical symptoms, a number of secondary outcome measures were employed to provide a more holistic and comprehensive evaluation of the intervention's effects. These measures were chosen to capture changes in participants' quality of life, psychological status, and sleep patterns—all of which are known to be significantly affected by FD. The collection of these data was essential for demonstrating the broader clinical impact of the treatment.

a. **Quality of Life:** The **Nepean Dyspepsia Index (NDI)** was used to measure the impact of dyspepsia on the participants' quality of life. The NDI is a validated and reliable questionnaire with five primary domains that were specifically designed to assess the multifaceted effects of dyspepsia on daily functioning:
    1) **Tension/Anxiety:** This domain measured the emotional and psychological distress related to the condition, including feelings of worry and anxiety.
    2) **Daily Activities:** This section evaluated how dyspeptic symptoms interfered with routine daily tasks and activities.
    3) **Eating/Drinking:** This domain assessed the extent to which symptoms limited the participants' ability to eat and drink normally, which is a major concern for this patient population.

4) **Knowledge/Control:** This component measured the participants' perception of their understanding and control over their condition.
5) **Work/Study:** This domain evaluated the impact of symptoms on the participants' professional or academic performance.

b. **Psychological Status:** Psychological distress was assessed using the **Perceived Stress Scale (PSS)**. The PSS is a classic and widely used instrument designed to measure a person's appraisal of situations in their life as stressful. It did not simply measure objective stressors but rather the subjective perception of stress, which is highly relevant to the pathophysiology of functional disorders. The PSS scores were used to evaluate whether the intervention had a mitigating effect on the participants' perceived stress levels, which could be a key mechanism through which the treatment improved gastrointestinal symptoms.

c. **Sleep Disorder:** The **Pittsburgh Sleep Quality Index (PSQI)** was used to evaluate the participants' sleep quality and to identify the presence and severity of sleep disturbances over a one-month period. The PSQI is a highly regarded instrument that consists of seven components:
1) **Subjective Sleep Quality:** The participant's overall rating of their sleep quality.
2) **Sleep Latency:** The time it took to fall asleep.
3) **Sleep Duration:** The total hours of sleep per night.
4) **Habitual Sleep Efficiency:** The ratio of time spent asleep to time in bed.
5) **Sleep Disturbance:** A measure of disruptions to sleep from various factors, such as pain or difficulty breathing.
6) **Daytime Sleep Dysfunction:** The impact of poor sleep on daytime functioning. Each of these components was scored, and a total PSQI global score was calculated, with a score greater than **5** indicating poor sleep quality. The PSQI provided a comprehensive picture of the participants' sleep patterns, allowing the researchers to determine if the intervention led to a statistically significant improvement in sleep quality.

3.5.3 Other Measures

Beyond the primary and secondary outcomes, several other key measures were meticulously collected to provide a comprehensive profile of the study's participants and to ensure their safety throughout the trial. The inclusion of these data points was

crucial for describing the sample population, assessing baseline comparability, and monitoring the overall integrity of the study.

a. **Demographic and Clinical Data:** At the time of enrollment, a detailed set of demographic and clinical data was systematically collected from each participant. This information was vital for two primary reasons. First, it provided a rich descriptive context for the study's sample, allowing for a thorough characterization of the population and enhancing the external validity of the findings. Second, these data were essential for performing baseline statistical analyses to confirm that the randomization process had successfully created two comparable groups. The specific variables collected included:
    1) **Age:** Recorded in years, to ensure compliance with the eligibility criteria and to control for age as a potential confounder.
    2) **Gender:** Documented as male or female.
    3) **FD Subtype:** Participants were classified into specific FD subtypes (e.g., postprandial distress syndrome - PDS, epigastric pain syndrome - EPS) based on their Rome IV criteria presentation. This classification was important for subgroup analysis and for understanding if the intervention had differential effects on different symptom profiles.
    4) **Symptom Duration:** The total duration of dyspeptic symptoms (in months or years) was collected to provide insight into the chronicity of the condition, a variable that could influence treatment responsiveness.
    5) **Previous Treatments:** Any previous medical or alternative treatments for FD were recorded to account for their potential influence on baseline symptom severity.
b. **Adverse Events:** Participant safety was a paramount ethical consideration throughout the trial. A rigorous system for monitoring, documenting, and reporting all adverse events was established and implemented. An adverse event was defined as any untoward medical occurrence in a participant, whether or not it was considered to be related to the study intervention.
    1) **Monitoring:** Participants were routinely monitored for adverse events at every treatment session and every data collection point. The treating physiotherapists were explicitly trained to ask about any new or worsening symptoms.

2) **Reporting:** All adverse events, regardless of their severity or perceived causality, were meticulously documented on a standardized form. This form captured details such as the date of onset, a description of the event, the severity (mild, moderate, or severe), its resolution, and the treating therapist's assessment of its relationship to the intervention.
3) **Review:** All reported adverse events were reviewed by a supervising clinical investigator who was un-blinded to the treatment group to determine their relationship to the intervention. Any severe adverse events were reported to the Institutional Review Board (IRB) immediately, in accordance with the study protocol and ethical guidelines. This systematic approach to adverse event monitoring ensured patient safety and provided transparent documentation of the trial's safety profile.

3.6 Data Collection Procedures

3.6.1 Recruitment and Screening

The data collection process commenced with a systematic and rigorous approach to participant recruitment and screening to ensure that all enrolled individuals met the study's strict eligibility criteria and provided valid informed consent. The process was meticulously designed to be a multi-step procedure that was both efficient and ethically sound.

The first step in the process was initial participant identification. Potential participants were identified through a combination of methods, including referrals from attending physicians at the Wiyata Husada Samarinda Clinic and the review of outpatient medical records of patients with an FD diagnosis. This initial identification was followed by a preliminary assessment to gauge the patient's general interest and availability for the trial.

Once a patient expressed interest, a formal eligibility screening was conducted by a member of the research team. This process involved a detailed, one-on-one structured interview to verify all inclusion and exclusion criteria. The interviewer used a standardized checklist to confirm that each potential participant met all the predefined requirements, such as age range, FD diagnosis confirmed by Rome IV criteria, and symptom duration. Concurrently, a review of the patient's medical history and current medication use was performed to rule out any confounding factors or "red flag" symptoms that necessitated exclusion.

The final and most critical step in this phase was the informed consent procedure. For all individuals who successfully passed the screening process, a comprehensive explanation of the study was provided. This explanation covered the research purpose, the specific procedures involved in both the intervention and control groups, the potential risks and benefits of participation, and the assurance of strict confidentiality. Participants were given ample opportunity to ask questions and were explicitly informed of their right to withdraw from the study at any time without penalty. A written informed consent form was then signed by both the participant and a member of the research team, providing a formal record of the participant's voluntary agreement to join the study. This meticulous process was essential for upholding the highest ethical standards of clinical research.

3.6.2 Randomization and Allocation Concealment

Upon completion of the screening and informed consent process, eligible participants were systematically assigned to their respective study groups through a rigorous randomization and allocation concealment procedure. This critical two-step process was implemented to eliminate the potential for selection bias, thereby safeguarding the internal validity of the study.

a. **Randomization Method:** The randomization process was performed using a computer-generated random number sequence. This method was chosen for its ability to produce a truly random and unpredictable assignment of participants to either the InViSMa intervention group or the InASMa control group. A research assistant, who was independent of the clinical team and had no direct contact with the participants, was responsible for generating this sequence. This ensured that neither the treating physiotherapists nor the patients could predict the treatment assignment, a crucial element for maintaining scientific objectivity. Once the sequence was generated, the group assignments were recorded in a separate, secure master list.
b. **Allocation Concealment:** Following the generation of the random sequence, an equally important procedure known as allocation concealment was implemented. This step prevented the research team from knowing which group a participant would be assigned to until after the participant had been formally enrolled and was ready to begin the intervention. The group assignments from the master list were placed into a series of sequentially numbered, opaque, and

sealed envelopes. These envelopes were kept in a locked cabinet, and only one envelope was opened at a time, in consecutive order, for each new participant. The use of opaque envelopes was essential as it prevented any member of the research team from seeing the group assignment before the participant was officially enrolled. This meticulous process ensured that the treating physiotherapist could not influence the enrollment of a participant based on a personal preference for a specific treatment group. The combination of random assignment and allocation concealment was a robust methodology that provided a high level of confidence that the two study groups were comparable at baseline.

3.6.3 Blinding

To minimize the potential for bias, a rigorous blinding protocol was implemented to ensure that participants and outcome assessors remained unaware of the group allocations. Blinding was a critical methodological step that prevented the conscious or unconscious influences of knowledge about the treatment received from affecting the study's outcomes.

a. **Participant Blinding:** Participants were blinded to their group assignment to mitigate the placebo effect and the potential for psychological bias. Because both the active (InViSMa) and sham (InASMa) interventions involved hands-on manual therapy and had similar treatment durations and patient interactions, participants were unable to distinguish which specific treatment protocol they were receiving. This ensured that their subjective symptom reports and perceptions were not influenced by their expectations of treatment efficacy.
b. **Outcome Assessor Blinding:** The research assistants who were responsible for all data collection and outcome measurement were also fully blinded to the group allocations. These assessors were independent of the clinical team and were not involved in the administration of the interventions. To maintain this blinding, the data collection forms and files were labeled with participant identification numbers only, without any reference to their treatment group. This step was crucial for preventing detection bias, where an assessor's knowledge of the treatment received could unintentionally influence their data collection or interpretation.

c. **Unblinded Treating Therapists:** Due to the nature of the physical intervention, the treating physiotherapists could not be blinded to the treatment they were providing. However, several measures were taken to mitigate the risk of bias from this unblinded party. The Physiotherapists were explicitly instructed to maintain a neutral and standardized demeanor and to avoid any verbal or non-verbal cues that might indicate the type of treatment a participant was receiving. Furthermore, the use of the standardized treatment manual and the fidelity checks, as described in section 3.4.3, ensured that the intervention was delivered consistently across all participants, regardless of the therapist's knowledge of the study's hypotheses. The fact that the primary and secondary outcomes were collected by a separate, blinded assessor provided an additional layer of protection against performance bias from the therapists.

3.6.4 Assessment Timeline

A meticulous assessment timeline was established to systematically collect data at predefined intervals throughout the study. This schedule was critical for monitoring participant progress, evaluating the effects of the interventions at key time points, and assessing the long-term sustainability of any observed benefits. All data collection was conducted by a blinded outcome assessor to ensure objectivity.

The timeline was structured around four primary data collection points:

a. **Baseline (Week 0):** This initial assessment occurred prior to the first treatment session. At this point, all primary, secondary, and other demographic data were collected. This baseline data was fundamental for two purposes: first, to characterize the study sample's initial status, and second, to serve as a reference point against which all subsequent measurements were compared.
b. **Mid-intervention (Week 2):** A second assessment was conducted at the two-week mark. This intermediate data collection point provided an early indication of the intervention's effects. It allowed researchers to observe any early symptomatic improvements or changes in other outcome measures, which could offer insights into the time course of the treatment's therapeutic effects.
c. **Post-intervention (Week 4):** This assessment was conducted immediately following the completion of the four-week intervention period. As the primary endpoint for the study, this data collection point was crucial for evaluating the immediate clinical efficacy of the interventions on all primary and secondary

outcome measures. The data collected at this stage provided the main basis for comparing the effects of the active (InViSMa) protocol against the sham (InASMa) protocol.

d. **Follow-up (Week 5):** A final assessment was performed one week after the last treatment session. This short-term follow-up was essential for determining if the therapeutic benefits of the intervention persisted after the treatment had ceased. It provided critical information regarding the sustainability of the treatment's effects, which is a key indicator of its clinical value beyond the acute treatment phase.

3.7 Data Management and Statistical Analysis

3.7.1 Data Management

A comprehensive data management plan was meticulously developed and implemented to ensure the integrity, accuracy, and confidentiality of all data collected throughout the study. This systematic approach was fundamental to the scientific rigor of the research and to upholding the ethical obligations to protect participant information.

The process began with data entry, which was performed using a double-entry method to minimize transcription errors. All data from the paper-based forms (e.g., questionnaires, adverse event logs) were independently entered into a secure, password-protected electronic database by two separate researchers. The two datasets were then compared using a verification protocol, and any discrepancies were immediately flagged, cross-referenced with the original paper forms, and corrected. This redundancy in the data entry process was critical for achieving a high level of data accuracy.

Following data entry, all data were subjected to a thorough coding and cleaning process. Qualitative data, such as participant demographics and clinical classifications, were assigned specific numerical codes to facilitate statistical analysis. A comprehensive codebook was created and maintained to ensure consistency in data interpretation and to serve as a reference for all research personnel. The data were also systematically screened for missing values, outliers, and logical inconsistencies. Any identified issues were investigated and resolved according to the predefined data management protocol, which included contacting the data collector for clarification where necessary.

The final phase of the data management plan addressed storage and confidentiality. All electronic data were stored on a secure, encrypted server with restricted access limited to the primary investigators and a dedicated data manager. The paper-based forms were stored in a locked filing cabinet in a secure office, accessible only by authorized personnel. To ensure participant confidentiality, all identifying information was removed from the data files. Participants were assigned a unique study identification number at the time of enrollment, and all data were anonymized by using this number instead of their names. The master key linking the identification numbers to the participants' personal information was stored separately in a secure, locked location, accessible only to the principal investigator. This robust system of de-identification and secure storage was essential for protecting the privacy of the participants and for ensuring the ethical integrity of the study.

3.7.2 Statistical Analysis Plan

The statistical analysis plan was meticulously defined prior to data collection to ensure an objective and rigorous approach to hypothesis testing. The methodology was specifically tailored to the study's randomized controlled trial design, the repeated-measures nature of the data, and the characteristics of the outcome variables.

a. **Software Selection:** All statistical analyses were performed using SPSS software (Version 20). This software package was selected due to its industry-standard status, comprehensive functionality, and robust capabilities in handling complex non-parametric and repeated-measures analyses, which were central to this study's design.
b. **Descriptive Statistics and Baseline Analysis:** The initial analysis focused on summarizing the sample population. Descriptive statistics (including means, standard deviations, frequencies, and percentages) were computed to characterize the baseline demographic and clinical features of the participants in both the InViSMa and InASMa groups. Crucially, the baseline comparability between the two randomized groups was assessed using Chi-square tests for categorical variables (e.g., gender, FD subtype, and chronicity strata). This specific test was chosen to confirm that the randomization process was successful in creating comparable groups prior to intervention, thereby supporting the validity of the subsequent efficacy analyses.

c. **Primary and Secondary Analysis Methods:** The core of the analysis focused on evaluating the efficacy of the interventions across the four time points (Baseline, Mid-intervention, Post-intervention, and Follow-up). Given that the outcome data, particularly from the subjective measures, were anticipated to violate the assumptions of normality required for parametric tests, the Friedman test was employed as the primary statistical method.
    1) The Friedman test is a non-parametric test suitable for analyzing repeated measures data across multiple related measurement times. This test was used to determine if there were overall significant changes in the primary and secondary outcome measures (e.g., LDQ, API, NDI, PSS, PSQI) over time within each treatment group.
    2) If the Friedman test yielded a statistically significant result, post-hoc analysis was conducted using the Wilcoxon signed-rank test to identify the specific time points where the differences occurred. This post-hoc procedure involved paired comparisons (e.g., Baseline vs. Mid-intervention, Post-intervention vs. Follow-up).
    3) To control for the increased risk of Type I error associated with multiple comparisons, a stringent Bonferroni correction was applied to the p-value used for the post-hoc Wilcoxon signed-rank tests.
d. **Comparison Between Groups:** To compare the efficacy between the InViSMa group and the InASMa control group, the difference in changes from baseline to each follow-up point was analyzed using appropriate non-parametric tests (e.g., Mann-Whitney U test, based on the non-parametric nature of the primary test). This inter-group comparison was essential for determining if the active intervention provided a statistically superior benefit compared to the sham treatment.
e. **Analysis Approach:** The primary analysis approach employed was the Per Protocol (PP) analysis. This approach included only those participants who completed the entire treatment protocol (i.e., attended all 12 sessions) and completed all designated outcome assessments. The PP analysis was utilized to estimate the maximum potential effect of the treatment under ideal conditions of adherence, providing a measure of the treatment's biological efficacy in compliant patients.

f. **Level of Significance:** For all statistical tests, the level of significance was set a priori at $p<0.05$. This threshold was used to determine whether the observed differences or changes were sufficiently unlikely to have occurred by chance.

3.8 Ethical Considerations

3.8.1 Institutional Review Board (IRB) Approval

The ethical conduct of this research was ensured through strict adherence to international and national guidelines for studies involving human participants. Prior to the commencement of the trial, the comprehensive research protocol underwent rigorous ethical scrutiny and received dual institutional approval from the relevant ethics committees in both collaborating countries.

The initial ethical review and approval were secured from the Faculty Ethics Review Committee (FERC) of the Faculty of Health Sciences, UiTM Puncak Alam Campus, Malaysia. The protocol was formally submitted on 14 April 2023, and subsequently received official approval under the reference number 500-FSK (PT.23/4). This approval confirmed the scientific merit and ethical viability of the protocol according to the standards of the primary academic institution.

Furthermore, given that the trial was conducted on site in Indonesia, the necessary local ethical clearance was obtained from the Health Research Ethics Committee of the Ministry of Health of the Republic of Indonesia, Poltekkes Kemenkes Kalimantan Timur. This committee issued its formal approval, ensuring compliance with all local regulations and ethical mandates, under the issued number DP.04.03/7.1/12146/2023.

The approval process entailed a comprehensive review of the study, which focused on several critical components: the potential risks and benefits of the intervention to ensure participant safety were maximized; the suitability and comprehension of the informed consent process; and the integrity of the data management plan regarding confidentiality and anonymity. The receipt of these two necessary institutional approvals confirmed the ethical commitment of the study, ensuring that all procedures were conducted in full compliance with the ethical principles established and the specific mandates of the approving committees.

3.8.2 Informed Consent

The process of securing informed consent was treated as a fundamental ethical imperative, adhering strictly to the ethical principles sanctioned by the Institutional

Review Board (IRB) approvals. This procedure was meticulously designed to ensure that participation in the trial was entirely voluntary and based on a comprehensive understanding of the study's scope, requirements, and potential implications.

The procedure began only after potential participants were deemed eligible following the initial screening (Section 3.6.1). The principal investigator or a formally trained research assistant, who was independent of the treating physiotherapists, conducted the consent discussion. This was carried out in a private, quiet setting at the Wiyata Husada Samarinda Clinic to ensure confidentiality and minimize distraction, thereby creating an environment conducive to thoughtful consideration.

Participants received a detailed, IRB-approved Informed Consent Form (ICF) that was translated and written in clear, non-technical Bahasa Indonesia. The researcher then systematically reviewed every section of the ICF verbally, utilizing a read-aloud protocol to ensure full comprehension and addressing any questions or concerns the participants raised immediately. Key components rigorously emphasized during this discussion included:

a. **Purpose and Procedures:** A clear explanation of the study's primary objective—to compare two types of manual therapy—and the specific procedures involved, including the randomization process and the allocation to either the active (InViSMa) or the control (InASMa) group. The nature of the single-blinding was also explained, clarifying that the participants would not know which specific treatment protocol they received.
b. **Risks and Benefits:** A balanced and honest presentation of all potential risks (e.g., mild discomfort) and the expected benefits (e.g., potential symptom improvement). Participants were explicitly informed that there was no guarantee of therapeutic benefit from participation.
c. **Voluntary Participation and Right to Withdraw:** It was explicitly stated that participation was entirely voluntary. Crucially, participants were informed of their unreserved right to withdraw from the study at any time, for any reason, without having to provide an explanation, and without any consequence to their continued medical care or relationship with the Wiyata Husada Samarinda Clinic or the referring physician.
d. **Confidentiality and Anonymity:** Absolute assurance was provided regarding the strict measures taken for data confidentiality and anonymity, explaining the use of coded identifiers instead of personal names.

Participants were provided with adequate time, typically 15 minutes, to consider their decision and were strongly encouraged to consult with family before signing. Only upon confirmation of full comprehension and voluntary agreement was the ICF signed and dated by both the participant and the researcher, with a signed copy provided to the participant for their personal records. This meticulous process ensured that the ethical standard of autonomy was rigorously upheld throughout the recruitment phase.

3.8.3 Confidentiality and Anonymity

The commitment to protecting the privacy of the participants was realized through a multifaceted and systematic approach to ensuring confidentiality and anonymity across all phases of the study. This ethical obligation extended from the initial recruitment stage through to the final data analysis and archival.

The core measure implemented to ensure anonymity was the de-identification of all data. Upon enrollment, each participant was immediately assigned a unique, non-identifiable Study Identification Number (ID). This numerical code was used on all subsequent data collection instruments (questionnaires, assessment forms, adverse event logs) instead of the participant's name or any other direct personal identifier.

Confidentiality of the data was maintained through several layered security measures:

a. **Physical Data Security:** All hardcopy documents, including the signed Informed Consent Forms and original paper-based questionnaires, which contained the link between the participant’s name and their unique Study ID, were stored in a locked within a secure office at the Wiyata Husada Samarinda Clinic. Access to this cabinet was strictly limited to the principal investigator and the dedicated research coordinator. This measure ensured that the master key linking identity to data was physically protected.
b. **Electronic Data Security:** All electronic data, which were entered using the double-entry method (as detailed in Section 3.7.1), were stored on a password-protected and encrypted research computer or server. Access to this electronic database was controlled via unique login credentials issued only to authorized members of the research team (i.e., those involved in data management and analysis). This controlled access minimized the risk of unauthorized viewing or data breaches. Furthermore, the electronic data files themselves were anonymized, containing only the Study ID and no personal identifiers.

c. **Data Dissemination:** In the final stage of reporting and dissemination (e.g., in this dissertation, conference presentations, and publications), only aggregated data or data specifically referenced by the Study ID were presented. No individual data points or descriptive details that could potentially lead to the identification of a participant were ever reported.

This comprehensive set of measures, which segregated personal identifiers from research data and imposed both physical and digital security safeguards, ensured that the privacy rights of all participants were rigorously protected throughout the course of the study, aligning with the highest standards of ethical research conduct.

3.8.4 Risks and Benefits

A careful and comprehensive assessment of potential risks and benefits was conducted prior to the commencement of the study and was reviewed and approved by the Institutional Review Board (IRB). This assessment was crucial for adhering to the ethical principle of beneficence and for ensuring that the potential benefits to the participants and to science outweighed any foreseeable risks associated with the study procedures. The details of this assessment were integrated into the informed consent process (Section 3.8.2) to ensure transparency for all participants.

a. **Potential Risks (Minimal Risk Classification):** The interventions used in this trial—integrated visceral and spinal manipulation (InViSMa) and the control intervention (InASMa) involving abdominal massage and spinal manipulation—were classified as minimal risk. This classification was based on the fact that the procedures involved were routine, non-invasive manual therapy techniques delivered by certified professionals. The primary risks identified and communicated to participants were typically mild and transient:
    1) **Mild Local Discomfort:** Participants were informed of the possibility of mild, temporary soreness or tenderness at the site of manipulation or massage, which usually resolved within 24 hours.
    2) **Transient Fatigue or Dizziness:** In a very small number of cases, manual therapy can induce temporary lightheadedness, a known physiological response that typically subsides quickly.
    3) **Minor Bruising:** The possibility of minor, superficial bruising at the manipulation site was also communicated, although considered rare given the gentle nature of the visceral techniques.

All risks were meticulously monitored via the adverse event reporting system (Section 3.5.3), and no severe adverse events were anticipated or reported throughout the duration of the study.

b. **Potential Benefits (Clinical and Scientific):** The anticipated benefits of participation were categorized into direct benefits for the individual participants and broader benefits for scientific knowledge and future clinical practice.

    1) **Direct Clinical Benefit:** The primary potential direct benefit was the possibility of experiencing a significant clinical improvement in their chronic condition. Participants had the opportunity to receive a novel, integrated manual therapy protocol that held the promise of reducing their abdominal pain, decreasing the severity of dyspepsia symptoms, improving their psychological status, and enhancing their quality of life and sleep patterns. Although therapeutic benefit could not be guaranteed, access to the experimental intervention was a major incentive.

    2) **Scientific and Societal Benefit:** The study provided a rigorous, high-quality, randomized controlled trial that assessed a complex, integrated manual therapy approach for FD. The findings contributed directly to the current body of evidence concerning the neuro-visceral link and manual therapy efficacy, offering a non-pharmacological treatment option that could potentially be integrated into future clinical guidelines for managing this common and debilitating condition. The knowledge generated served to advance the field of physiotherapy and functional gastroenterology.

The careful balancing of these minimal risks against the significant potential clinical and scientific benefits formed the ethical justification for conducting the research. The IRB concluded that the study met the required threshold for ethical clinical investigation.

3.8.5 Participant Rights

The fundamental principle of respect for persons formed the cornerstone of the study's commitment to protecting the rights of all participants. A key element of this protection was the absolute guarantee of the right to withdraw from the research at any time.

This specific right was clearly and emphatically communicated to every potential participant during the informed consent process. Participants were explicitly informed that their involvement in the study was entirely voluntary and that they maintained the unequivocal right to terminate their participation at any stage of the trial—whether during the screening, intervention, or follow-up phases. Crucially, this withdrawal could be initiated without penalty, prejudice, or requirement for justification.

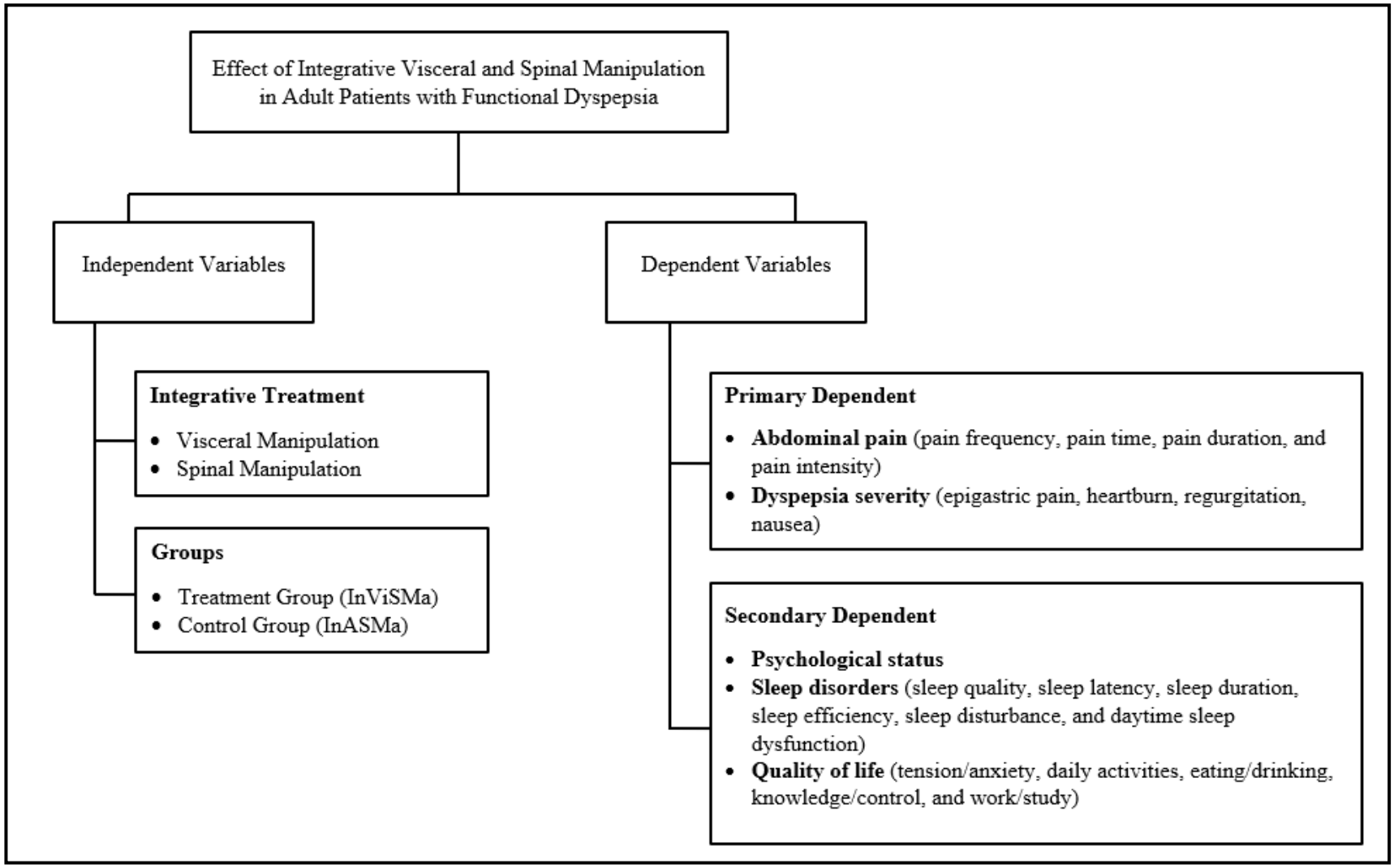
The procedure for withdrawal was kept simple and unambiguous. Participants were informed that they only needed to verbally express their desire to discontinue their involvement to the treating physiotherapist or the research coordinator. This assurance was paramount, as it removed any perceived barrier or pressure that might have prevented a participant from leaving the study if they experienced discomfort, a change in personal circumstances, or simply no longer wished to continue.

Furthermore, it was guaranteed that the decision to withdraw would have absolutely no negative consequences on their future clinical care or their relationship with the Wiyata Husada Samarinda Clinic or their referring medical practitioners. This measure was essential for ensuring that the ethical principle of autonomy was fully respected. All data collected from a participant up until the point of their withdrawal was retained and used in the final analysis, unless the participant specifically requested that their data be destroyed, a request that was to be honored immediately. The rigorous upholding of the participant's right to withdraw was a non-negotiable ethical mandate for the entire research team.

3.9 Chapter Summary

This chapter meticulously detailed the research methodology employed in this randomized controlled trial. The study was executed as a prospective, single-blind, two-arm parallel-group RCT, a design rigorously selected for its ability to minimize bias and establish causality. The study involved adult patients with Functional Dyspepsia recruited via stratified random sampling from the Wiyata Husada Samarinda Clinic, with the sample size of 60 participants determined by a robust power analysis. The core intervention involved the comparison of the active integrated visceral and spinal manipulation (InViSMa) protocol against a credible control group (InASMa), both administered over four weeks with high fidelity. The efficacy of these interventions was evaluated using primary measures, the Leeds Dyspepsia Questionnaire (LDQ) and the Abdominal Pain Index (API), and a suite of secondary measures covering quality of

life, stress, and sleep. Data collection procedures included systematic randomization and allocation concealment, with assessments conducted at Baseline, Mid-intervention, Post-intervention, and Follow-up. Finally, the analysis plan utilized Friedman and Wilcoxon tests on the Per Protocol (PP) population, with the entire study governed by strict IRB approval, comprehensive informed consent, and adherence to all measures ensuring participant rights and data confidentiality. This comprehensive methodological framework provided a clear and transparent blueprint for the conduct of this research, ensuring the reliability and validity of the final findings.


Effect of Integrative Visceral and Spinal Manipulation in Adult Patients with Functional Dyspepsia
Independent Variables
Dependent Variables
Integrative Treatment
• Visceral Manipulation
• Spinal Manipulation
Groups
• Treatment Group (InViSMa)
• Control Group (InASMa)
Primary Dependent
• Abdominal pain (pain frequency, pain time, pain duration, and pain intensity)
• Dyspepsia severity (epigastric pain, heartburn, regurgitation, nausea)
Secondary Dependent
• Psychological status
• Sleep disorders (sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, and daytime sleep dysfunction)
• Quality of life (tension/anxiety, daily activities, eating/drinking, knowledge/control, and work/study)

CHAPTER 4
RESULTS

4.1 Introduction

This chapter presents the empirical findings of the study, which was designed to evaluate the efficacy of an integrated visceral and spinal manipulation (InViSMa) protocol compared to a control intervention on key clinical outcomes in adult patients with functional dyspepsia (FD). The primary objective of this research was to determine if the InViSMa intervention led to statistically significant and clinically meaningful improvements in the primary outcomes of dyspepsia severity and abdominal pain. Furthermore, the study aimed to investigate the effects of the intervention on the secondary outcomes of psychological status, sleep quality, and health-related quality of life.

The results are presented systematically in the sections that follow. The chapter begins with a detailed account of participant recruitment and flow, illustrated by a CONSORT diagram, to provide a clear overview of the study's progression from screening to final analysis. This is followed by a presentation of the baseline demographic and clinical characteristics of both the intervention and control groups to demonstrate the success of the randomization process. Subsequently, the chapter details the statistical analysis of the primary outcomes, followed by the secondary outcomes, comparing the changes from baseline to post-intervention between the two groups. An analysis of follow-up data is also presented to assess the durability of the treatment effects.

Finally, this chapter contextualizes the findings within the broader landscape of FD research and manual therapy. Comparative analysis with existing treatments highlights the distinctive advantages of InViSMa, while limitations, such as sample size and follow-up duration, are acknowledged. All results are reported objectively, with statistical interpretations reserved for the discussion in Chapter 5.

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4.2 Participant Recruitment and Flow

The recruitment of participants for this study was conducted over a defined period, during which a total of 60 individuals with symptoms suggestive of Functional Dyspepsia were assessed for eligibility. The complete flow of participants through each stage of the trial, from initial screening to final analysis, is systematically detailed in the CONSORT (Consolidated Standards of Reporting Trials) flow diagram presented in Figure 4.1.

During the initial enrolment phase, all 60 individuals who were assessed met the pre-defined inclusion criteria and did not present with any of the exclusion criteria. Specifically, all prospective participants were between 20 and 55 years of age, had a diagnosis of FD according to Rome IV criteria with a symptom duration of at least three months, and provided written informed consent. No individuals were excluded at this stage for reasons such as the presence of “red flag” symptoms, a history of major gastrointestinal surgery, a primary diagnosis of GERD or IBS, recent use of confounding medications, or pregnancy. Furthermore, no individuals declined to participate after being informed about the study's procedures.

Consequently, all 60 eligible participants were randomized for intervention. An equal allocation ratio was used, resulting in 30 participants being allocated to the integrated visceral and spinal manipulation (InViSMa) group and 30 participants being allocated to the integrated abdominal massage and spinal manipulation (InASMa) control group. All 60 participants received their allocated intervention as planned, with no crossovers or instances of failure to receive the intervention post-randomization.

During the follow-up phase of the study, a total of four participants discontinued the intervention. In the InViSMa group, one participant withdrew consent due to a personal medical condition unrelated to the intervention. In the InASMa group, three participants discontinued: two withdrew consent for similar personal medical reasons, and one participant was lost to contact and did not complete the final follow-up assessments.

As a result of these discontinuations, the final analysis was performed on the data from the 56 participants who completed the entire study protocol. This included 29 participants from the InViSMa group and 27 participants from the InASMa group. The data from the four participants who discontinued were excluded from the final analysis due to the incompletion of outcome measure data.

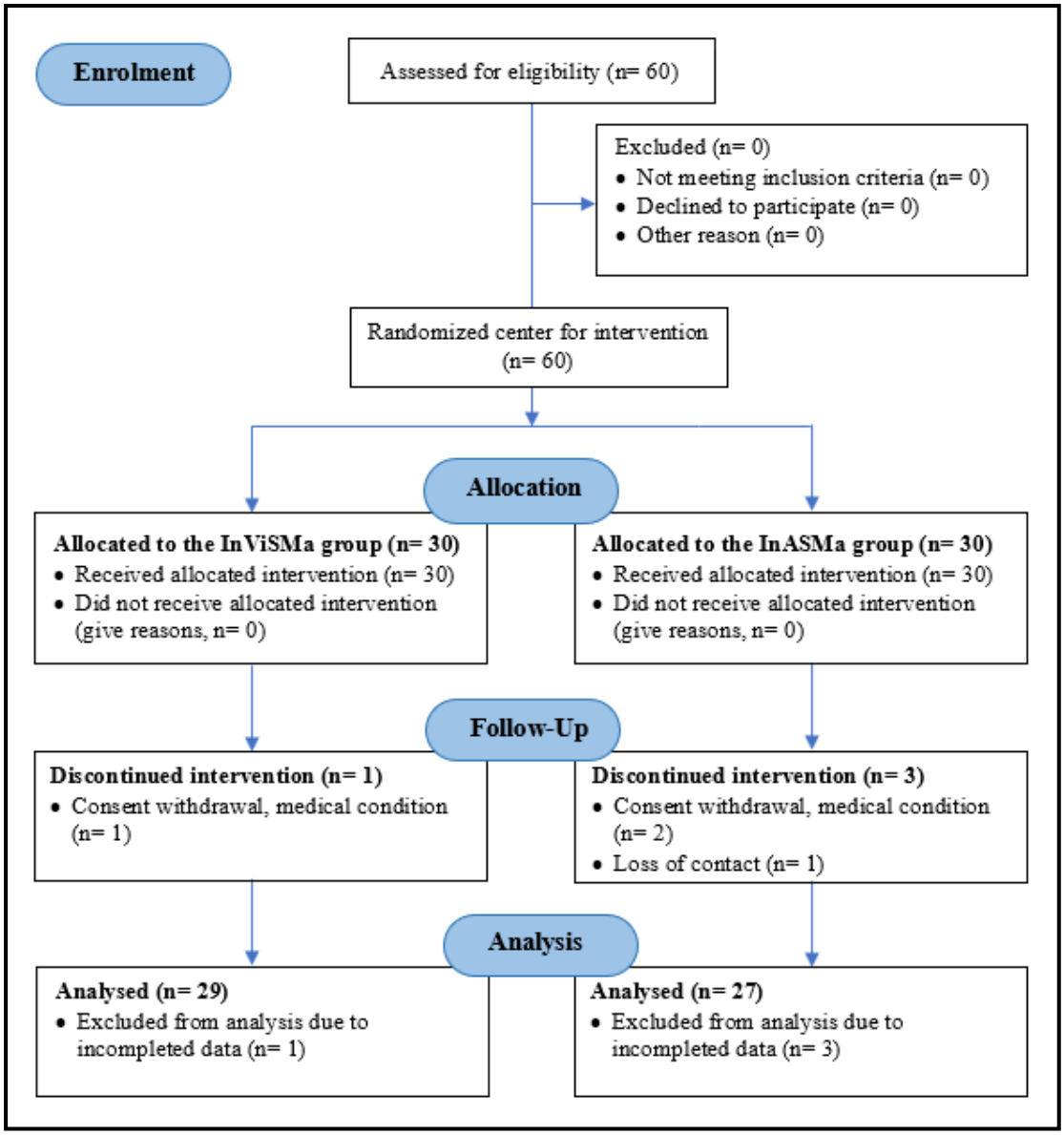

Figure 4.1 The CONSORT Flow Diagram of The Study

4.3 Baseline Demographic Characteristics Characteristics of Participants

A total of 56 adults diagnosed with FD were enrolled and randomized into either the integrated visceral and spinal manipulation (InViSMa) group (n=29) or the integrated abdominal massage and spinal manipulation (InASMa) control group (n=27). An analysis of the baseline demographic and clinical characteristics was conducted to assess the comparability of the two groups following randomization. The results of this analysis confirmed that the randomization process was successful. There were no statistically significant differences found between the InViSMa and InASMa groups across all measured baseline variables, including age, gender, ethnicity, marital

status, employment status, and duration of FD symptoms. This baseline homogeneity ensures that any differences in outcomes observed at the conclusion of the study can be more confidently attributed to the intervention itself rather than to pre-existing disparities between the groups.

Table 4.1 provides a comprehensive summary of these baseline characteristics. The total study sample (N=56) presents a cohort predominantly composed of females (76.79%), with a mean age of approximately 40.6 years. The majority of participants were in the 36-45 age bracket (73.21%), were married (73.21%), and were employed, with the largest single employment category being civil servants (33.93%). In terms of ethnicity, the sample reflects a diverse local population, including Banjar-Kutai (35.71%), Dayak (23.21%), Javanese (21.43%), and Bugis (19.64%).

Clinically, all participants (100%) were diagnosed with FD exhibiting an overlap of both Epigastric Pain Syndrome (EPS) and Postprandial Distress Syndrome (PDS). The duration of symptoms was chronic for all participants, with the vast majority (78.57%) having experienced symptoms for a period of 3 to 6 months. The mean duration of symptoms was comparable between the InViSMa group (5.74 ± 2.87 months) and the InASMa group (6.17 ± 3.70 months). The detailed breakdown in Table 4.1 shows that the proportional distribution of these characteristics is highly similar across both the intervention and control groups, reinforcing the integrity of the randomized design.

Tabel 4.1

The demographic Characteristics of the Adults Patient with FD

Variables	Groups				Total n (%)
	InViSMa		InASMa		
	n (%)	Mean ± SD	n (%)	Mean ± SD	
Gender					
Male	7 (24.14)		6 (22.22)		13 (23.21)
Female	22 (75.86)		21 (77.78)		43 (76.79)
Age					
20-35	3 (10.34)		3 (11.11)		6 (10.71)
36-45	22 (75.86)	40.46 ± 5.47	19 (70.37)	40.81 ± 5.95	41 (73.21)
46-55	4 (13.79)		5 (18.52)		9 (16.07)
Ethnicity					
Banjar-Kutai	11 (37.93)		9 (33.33)		20 (35.71)
Javanese	5 (17.24)		7 (25.93)		12 (21.43)
Dayak	9 (31.03)		4 (14.81)		13 (23.21)
Bugis	4 (13.79)		7 (25.93)		11 (19.64)
Marital status					
Married	19 (65.52)		22 (81.48)		41 (73.21)
Single	5 (17.24)		3 (11.11)		8 (14.29)
Widow/er	5 (17.24)		2 (7.41)		7 (12.50)
Employment status					
Civil servant	12 (41.38)		7 (25.93)		19 (33.93)
Private employee	7 (24.14)		5 (18.52)		12 (21.43)
Self-employed	7 (24.14)		10 (37.04)		17 (30.36)
Retired	1 (3.45)		2 (7.41)		3 (5.36)
Not working	2 (6.90)		3 (11.11)		5 (8.93)
FD Status					
FD with EPS and PDS	29 (100)		27 (100)		56 (100)
Duration of FD (months)					
3 – 6 mounth	23 (79.31)		21 (77.78)		44 (78.57)
> 6 mounth – 1 years	5 (17.24)	5.74 ± 2.87	4 (14.81)	6.17 ± 3.70	9 (16.07)
> 1 years	1 (3.45)		2 (7.41)		3 (5.36)

Notes: InViSMa= Integrated of Visceral and Spinal Manipulation. InASMa= Integrated of Abdominal Massage and Spinal Manipulation. SD= Standard deviation. FD= Functional dyspepsia. EPS= Epigastric pain syndrome. PDS= Postprandial dyspepsia syndrome.

4.4 Analysis of Treatment Effects

4.4.1 The 4-Week Effects on Abdominal Pain

4.4.1.1 Within-Group Effects Across Time (Hypothesis a): Friedman test results for API scores within each group across the four time points.

This section presents the results of the statistical analyses conducted to address the research objectives and test the study's hypotheses. The data were analyzed to determine the effects of the 4-week interventions on the primary outcome (abdominal pain). In alignment with hypothesis (a), a within-group analysis was performed using the Friedman test to evaluate changes across the four measurement time points (pre-test, mid-test, post-test, and follow-up) for both the InViSMa and InASMa groups.

To address the first component of the research hypotheses, the effect of the interventions on abdominal pain was evaluated. The Friedman test was utilized to assess whether there were statistically significant changes in the four domains of abdominal pain—episode frequency, typical daily frequency, typical duration, and typical intensity—across the four time points within each group.

The results, as summarized in Table 4.2, indicate that statistically significant changes occurred over time in both the InViSMa and InASMa groups for all four domains of abdominal pain.

For the InViSMa group (n=29), the Friedman test yielded highly significant results for episode frequency ($\chi^2(3) = 64.913$, $p < 0.001$), typical daily frequency ($\chi^2(3) = 68.400$, $p < 0.001$), typical duration ($\chi^2(3) = 75.600$, $p < 0.001$), and typical intensity ($\chi^2(3) = 78.508$, $p < 0.001$). As the table shows, the median scores for all these variables demonstrate a consistent and marked reduction from baseline to post-test and follow-up. For example, the median (IQR) for typical intensity decreased from 8 (7–9) at baseline to 2 (1–2) at follow-up. This indicates that the first research hypothesis, stating a significant effect of the 4-week integrated visceral and spinal manipulation on abdominal pain, was supported.

For the control group (InASMa, n=27), the Friedman test also revealed statistically significant changes across time for all four domains: episode frequency ($\chi^2(3) = 12.781$, $p = 0.005$), typical daily frequency ($\chi^2(3) = 15.586$, $p = 0.001$), Typical Duration ($\chi^2(3) = 38.785$, $p < 0.001$), and typical intensity ($\chi^2(3) = 72.852$, $p < 0.001$). While these changes were statistically significant, a descriptive review of the median scores in Table 4.2 suggests a less pronounced reduction compared to the InViSMa

group. For instance, the median (IQR) for Typical Intensity in the control group decreased from 8 (7–8) at baseline to 2 (1–3) at follow-up. These findings show that the control intervention also had a significant effect on abdominal pain over time. The specific time points at which these changes occurred will be elucidated in the subsequent post-hoc analysis.

Table 4.2
Within-Group (Friedman Test) Effects Across Time of the 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Abdominal Pain in Adults Patient with FD

Abdominal Pain Variable	Median (IQR)	Test Statistic	p-value	Interpretation
Intervention Group (N=29) **InViSMa on Abdominal Pain**				
Episode Frequency	Baseline → Post-test 1 → Post-test 2 → Follow-up 7 (6–8) → 5 (4–6) → 3 (2–4) → 1 (1–2)	$\chi^2(3) = 64.913$	<0.001	Significant
Typical Daily Frequency	Baseline → Post-test 1 → Post-test 2 → Follow-up 5 (4–5) → 3 (3–4) → 2 (1–2) → 1 (1–1)	$\chi^2(3) = 68.400$	<0.001	Significant
Typical Duration	Baseline → Post-test 1 → Post-test 2 → Follow-up 5 (4–5) → 3 (3–4) → 2 (1–2) → 1 (1–1)	$\chi^2(3) = 75.600$	<0.001	Significant
Typical Intensity	Baseline → Post-test 1 → Post-test 2 → Follow-up 8 (7–9) → 6 (5–6) → 3 (2–4) → 1 (1–2)	$\chi^2(3) = 78.508$	<0.001	Significant
Control Group (N=27) **InASMa on Abdominal Pain**				
Episode Frequency	Baseline → Post-test 1 → Post-test 2 → Follow-up 7 (6–7) → 6 (5–7) → 5 (4–6) → 4 (3–5)	$\chi^2(3) = 12.781$	0.005	Significant
Typical Daily Frequency	Baseline → Post-test 1 → Post-test 2 → Follow-up 4 (3–5) → 4 (3–5) → 3 (2–4) → 2 (1–3)	$\chi^2(3) = 15.586$	0.001	Significant
Typical Duration	Baseline → Post-test 1 → Post-test 2 → Follow-up 4 (4–5) → 4 (3–4) → 3 (2–3) → 2 (1–2)	$\chi^2(3) = 38.785$	<0.001	Significant
Typical Intensity	Baseline → Post-test 1 → Post-test 2 → Follow-up 8 (7–8) → 7 (6–7) → 5 (4–6) → 2 (1–3)	$\chi^2(3) = 72.852$	<0.001	Significant

4.4.1.2 Post-Hoc Pairwise Comparisons: Wilcoxon signed-rank test results for API scores if the Friedman test is significant.

Following the significant omnibus findings from the Friedman tests, post-hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test to precisely identify the time intervals during which significant changes in abdominal pain occurred within each group. A Bonferroni correction was applied to control for the family-wise error rate across the multiple comparisons, resulting in a significance level set at $\alpha = 0.0083$. The detailed results of these analyses are presented in Table 4.3.

In the InViSMa group, the post-hoc tests revealed a highly consistent and progressive improvement across all four domains of abdominal pain. As shown in Table 4.3, for every single domain (episode frequency, typical daily frequency, typical duration, and typical intensity), all six pairwise comparisons yielded statistically significant reductions (all p-values < 0.001, which is below the adjusted alpha of 0.0083). The effect sizes (r) for all these comparisons were large, ranging from 0.69 to 0.88. This indicates that significant improvements occurred not only from baseline to each subsequent time point but also between each consecutive measurement interval (i.e., from mid-test to post-test, and from post-test to follow-up). This pattern suggests that the therapeutic effect of the InViSMa intervention was both immediate and cumulative, continuing to build throughout the intervention and follow-up period.

In the control (InASMa) group, the pattern of improvement was less consistent. While significant reductions were observed from baseline to the later time points for most variables, the changes between consecutive intervals were not always significant. For instance, in the domain of episode frequency, there was no significant change from Post-test 1 to Post-test 2 ($p = 0.257$). Similarly, for typical daily frequency, no significant improvement was found between Baseline and Post-test 1 ($p = 0.916$) or between Baseline and Post-test 2 ($p = 0.011$, which did not meet the Bonferroni-corrected significance level). However, significant improvements were observed between all other time points for typical duration and typical intensity, indicating that the control intervention also produced a measurable, albeit less uniform, reduction in these aspects of abdominal pain over the full course of the study.

Table 4.3
Post-Hoc Pairwise Comparisons (Wilcoxon Signed-Rank) of The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Abdominal Pain in Adults Patient with FD

Abdominal Pain Variable	Pairwise Comparison	Median (IQR)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation (α = .0083)
Intervention Group (N=29), InViSMa on Abdominal Pain						
Episode Frequency	Post-test 1 vs. Baseline	5 (4–6) vs. 7 (6–8)	-4.474	<0.001	0.86 (Large)	Significant
	Post-test 2 vs. Baseline	3 (2–4) vs. 7 (6–8)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (1–2) vs. 7 (6–8)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	3 (2–4) vs. 5 (4–6)	-4.114	<0.001	0.79 (Large)	Significant
	Follow-up vs. Post-test 1	1 (1–2) vs. 5 (4–6)	-4.475	<0.001	0.86 (Large)	Significant
	Follow-up vs. Post-test 2	1 (1–2) vs. 3 (2–4)	-4.022	<0.001	0.77 (Large)	Significant
Typical Daily Frequency	Post-test 1 vs. Baseline	3 (3–4) vs. 5 (4–5)	-4.478	<0.001	0.86 (Large)	Significant
	Post-test 2 vs. Baseline	2 (1–2) vs. 5 (4–5)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (1–1) vs. 5 (4–5)	-4.553	<0.001	0.88 (Large)	Significant
	Post-test 2 vs. Post-test 1	2 (1–2) vs. 3 (3–4)	-3.757	<0.001	0.72 (Large)	Significant
	Follow-up vs. Post-test 1	1 (1–1) vs. 3 (3–4)	-4.536	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (1–1) vs. 2 (1–2)	-3.578	<0.001	0.69 (Large)	Significant
Typical Duration	Post-test 1 vs. Baseline	3 (3–4) vs. 5 (4–5)	-4.534	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	2 (1–2) vs. 5 (4–5)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (1–1) vs. 5 (4–5)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	2 (1–2) vs. 3 (3–4)	-3.834	<0.001	0.74 (Large)	Significant
	Follow-up vs. Post-test 1	1 (1–1) vs. 3 (3–4)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (1–1) vs. 2 (1–2)	-4.018	<0.001	0.77 (Large)	Significant
Typical Intensity	Post-test 1 vs. Baseline	6 (5–6) vs. 8 (7–9)	-4.532	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	3 (2–4) vs. 8 (7–9)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (1–2) vs. 8 (7–9)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	3 (2–4) vs. 6 (5–6)	-4.474	<0.001	0.86 (Large)	Significant
	Follow-up vs. Post-test 1	1 (1–2) vs. 6 (5–6)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (1–2) vs. 3 (2–4)	-4.474	<0.001	0.86 (Large)	Significant

Abdominal Pain Variable	Pairwise Comparison	Median (IQR)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation (α = .0083)
Control Group (N=27), InASMa on Abdominal Pain						
Episode Frequency	Post-test 1 vs. Baseline	6 (5–7) vs. 7 (6–7)	-2.674	0.007	0.51 (Large)	Significant
	Post-test 2 vs. Baseline	5 (4–6) vs. 7 (6–7)	-2.814	0.005	0.54 (Large)	Significant
	Follow-up vs. Baseline	4 (3–5) vs. 7 (6–7)	-3.522	<0.001	0.68 (Large)	Significant
	Post-test 2 vs. Post-test 1	5 (4–6) vs. 6 (5–7)	-1.134	0.257	0.22 (Small)	Not Significant
	Follow-up vs. Post-test 1	4 (3–5) vs. 6 (5–7)	-2.677	0.007	0.52 (Large)	Significant
	Follow-up vs. Post-test 2	4 (3–5) vs. 5 (4–6)	-2.831	0.005	0.55 (Large)	Significant
Typical Daily Frequency	Post-test 1 vs. Baseline	4 (3–5) vs. 4 (3–5)	-0.105	0.916	0.02 (Negligible)	Not Significant
	Post-test 2 vs. Baseline	3 (2–4) vs. 4 (3–5)	-2.553	0.011	0.49 (Medium)	Not Significant
	Follow-up vs. Baseline	2 (1–3) vs. 4 (3–5)	-3.493	<0.001	0.67 (Large)	Significant
	Post-test 2 vs. Post-test 1	3 (2–4) vs. 4 (3–5)	-2.853	0.004	0.55 (Large)	Significant
	Follow-up vs. Post-test 1	2 (1–3) vs. 4 (3–5)	-3.622	<0.001	0.70 (Large)	Significant
	Follow-up vs. Post-test 2	2 (1–3) vs. 3 (2–4)	-2.817	0.005	0.54 (Large)	Significant
Typical Duration	Post-test 1 vs. Baseline	4 (3–4) vs. 4 (4–5)	-3.110	0.002	0.60 (Large)	Significant
	Post-test 2 vs. Baseline	3 (2–3) vs. 4 (4–5)	-4.020	<0.001	0.77 (Large)	Significant
	Follow-up vs. Baseline	2 (1–2) vs. 4 (4–5)	-4.383	<0.001	0.84 (Large)	Significant
	Post-test 2 vs. Post-test 1	3 (2–3) vs. 4 (3–4)	-3.308	0.001	0.64 (Large)	Significant
	Follow-up vs. Post-test 1	2 (1–2) vs. 4 (3–4)	-4.200	<0.001	0.81 (Large)	Significant
	Follow-up vs. Post-test 2	2 (1–2) vs. 3 (2–3)	-3.646	<0.001	0.70 (Large)	Significant
Typical Intensity	Post-test 1 vs. Baseline	7 (6–7) vs. 8 (7–8)	-3.578	<0.001	0.69 (Large)	Significant
	Post-test 2 vs. Baseline	5 (4–6) vs. 8 (7–8)	-4.474	<0.001	0.86 (Large)	Significant
	Follow-up vs. Baseline	2 (1–3) vs. 8 (7–8)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	5 (4–6) vs. 7 (6–7)	-4.022	<0.001	0.77 (Large)	Significant
	Follow-up vs. Post-test 1	2 (1–3) vs. 7 (6–7)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	2 (1–3) vs. 5 (4–6)	-4.536	<0.001	0.87 (Large)	Significant

4.4.1.3 Between-Group (Mann–Whitney U Test): The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Abdominal Pain in Adults Patient with FD.

To address the second research hypothesis, which posited a significant differentiation between the InViSMa and InASMa groups, Mann-Whitney U tests were performed. These tests compared the scores of the two independent groups at each of the four measurement time points (Baseline, Post-test 1, Post-test 2, and Follow-up) for all four variables of abdominal pain. The results of these comparisons are comprehensively detailed in Table 4.4.

The analysis of baseline scores confirmed the successful randomization of participants. For all four abdominal pain variables—episode frequency, typical daily frequency, typical duration, and typical intensity—there were no statistically significant differences between the InViSMa and InASMa groups at the start of the study ($p > 0.05$ for all). This baseline equivalence is crucial as it establishes that both groups began with a comparable level of abdominal pain severity.

As the intervention progressed, significant differences between the groups began to emerge. At Post-test 1, a statistically significant difference was observed for episode frequency ($Z = -2.128$, $p = 0.033$) and typical intensity ($Z = -2.078$, $p = 0.038$), with the InViSMa group demonstrating lower median scores, although the effect sizes were small ($r = 0.28$). No significant differences were yet apparent for typical daily frequency or typical duration at this time point.

By Post-test 2, the differentiation between the groups became more pronounced and consistent. The InViSMa group reported significantly lower scores than the InASMa group for episode frequency ($Z = -4.088$, $p < 0.001$), typical daily frequency ($Z = -3.292$, $p = 0.001$), typical duration ($Z = -2.871$, $p = 0.004$), and typical intensity ($Z = -4.180$, $p < 0.001$). The effect sizes at this stage were notably larger, ranging from medium ($r = 0.38$) to large ($r = 0.56$), indicating a clinically meaningful divergence between the treatment and control groups.

These significant differences were not only maintained but amplified at the Follow-up assessment. The Mann-Whitney U tests revealed highly significant differences favoring the InViSMa group across all four variables: episode frequency ($Z = -5.694$, $p < 0.001$), typical daily frequency ($Z = -4.761$, $p < 0.001$), typical duration

($Z = -4.321$, $p < 0.001$), and typical intensity ($Z = -3.882$, $p < 0.001$). The effect sizes at follow-up were all large (r ranging from 0.52 to 0.76), providing strong evidence for the superior and sustained effect of the InViSMa intervention.

In summary, these results strongly support the second research hypothesis. While both groups showed some improvement, the InViSMa group demonstrated a significantly greater reduction in all aspects of abdominal pain compared to the control group, with this therapeutic advantage becoming increasingly evident as the study progressed and was maintained at follow-up.

Table 4.4
Mann-Whitney U Test Comparisons of The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Abdominal Pain in Adults Patient with FD

Abdominal Pain Variable	Time Point	Median (IQR) Intervention	Median (IQR) Control	Test Statistic (U)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation
Episode Frequency	Baseline	7 (6–8)	7 (6–7)	343.5	-0.301	0.763	0.04 (Negligible)	Not Significant
	Post-test 1	5 (4–6)	6 (5–7)	242.0	-2.128	0.033	0.28 (Small)	Significant
	Post-test 2	3 (2–4)	5 (4–6)	115.5	-4.088	<0.001	0.55 (Large)	Significant
	Follow-up	1 (1–2)	4 (3–5)	19.5	-5.694	<0.001	0.76 (Large)	Significant
Typical Daily Frequency	Baseline	5 (4–5)	4 (3–5)	264.5	-1.777	0.076	0.24 (Small)	Not Significant
	Post-test 1	3 (3–4)	4 (3–5)	243.0	-2.108	0.035	0.28 (Small)	Significant
	Post-test 2	2 (1–2)	3 (2–4)	162.0	-3.292	0.001	0.44 (Medium)	Significant
	Follow-up	1 (1–1)	2 (1–3)	76.5	-4.761	<0.001	0.64 (Large)	Significant
Typical Duration	Baseline	5 (4–5)	4 (4–5)	304.5	-1.039	0.299	0.14 (Small)	Not Significant
	Post-test 1	3 (3–4)	4 (3–4)	298.5	-1.144	0.253	0.15 (Small)	Not Significant
	Post-test 2	2 (1–2)	3 (2–3)	186.0	-2.871	0.004	0.38 (Medium)	Significant
	Follow-up	1 (1–1)	2 (1–2)	100.5	-4.321	<0.001	0.58 (Large)	Significant
Typical Intensity	Baseline	8 (7–9)	8 (7–8)	337.5	-0.418	0.676	0.06 (Negligible)	Not Significant
	Post-test 1	6 (5–6)	7 (6–7)	244.5	-2.078	0.038	0.28 (Small)	Significant
	Post-test 2	3 (2–4)	5 (4–6)	111.0	-4.180	<0.001	0.56 (Large)	Significant
	Follow-up	1 (1–2)	2 (1–3)	127.5	-3.882	<0.001	0.52 (Large)	Significant

4.4.2 The 4-Week Effects on Dyspepsia Severity

4.4.2.1 Within-Group Effects Across Time (Hypothesis a): Friedman test results for LDQ scores within each group across the four time points.

The second primary outcome, dyspepsia severity, was assessed using the Leeds Dyspepsia Questionnaire (LDQ), which evaluates the frequency and severity of eight key dyspeptic symptoms. To test Hypothesis (a) regarding this outcome, a Friedman test was conducted for each of the eight symptom variables to determine if there were significant changes across the four measurement points (pre-test, mid-test, post-test, follow-up) within each group.

The results of this analysis, presented in Table 4.5, reveal a stark contrast in the within-group effects between the InViSMa and InASMa groups. For the InViSMa group (n=29), the Friedman test demonstrated a highly significant effect of time on every single one of the eight dyspepsia severity variables (all p-values < 0.001). The test statistics were uniformly high ($\chi^2(3) = 77.151$ for all variables), indicating a substantial and consistent change in scores over the course of the study. A review of the median scores in Table 4.5 shows a clear and progressive reduction in both the frequency and severity of indigestion, heartburn, regurgitation, and nausea from baseline to follow-up. For instance, the median (IQR) for Indigestion Severity decreased from a baseline of 3 (2-4) to 1 (0-1) at follow-up. This robust and consistent pattern of improvement across all measured dyspeptic symptoms provides strong support for the research hypothesis, confirming that the 4-week InViSMa intervention had a significant effect on reducing dyspepsia severity.

In marked contrast, for the control group (InASMa, n=27), the Friedman test yielded non-significant results for all eight of the dyspepsia severity variables (all p-values > 0.05). The Chi-square values were uniformly low, ranging from 0.531 to 1.048, indicating a lack of statistically significant change across the four measurement time points. A descriptive examination of the median scores in Table 4.5 confirms this finding; the median values for indigestion, heartburn, regurgitation, and nausea (both frequency and severity) remained largely unchanged from baseline to follow-up. For example, the median (IQR) for Indigestion Severity remained at 3 (2-4) across all four time points. This demonstrates that the control intervention did not produce a statistically significant change in dyspepsia severity over time. Consequently, research Hypothesis (a) was not supported for the control group with respect to the LDQ

variables. Because none of the omnibus Friedman tests yielded a significant result, post-hoc pairwise comparisons (Wilcoxon Signed-Rank tests) are not statistically warranted. Therefore, a table of post-hoc analyses is not presented, in accordance with standard statistical practice to avoid an inflated risk of Type I error.

Table 4.5
Within-Group (Friedman Test) Effects Across Time of the 4-Week Effects of InViSMa and InASMa on Dyspepsia Severity

Dyspepsia Severity Variable	Median (IQR)	Test Statistic	p-value	Interpretation
Intervention Group (N=29), InViSMa on Dyspepsia Severity				
Indigestion Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Indigestion Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Heartburn Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Heartburn Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Regurgitation Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Regurgitation Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Nausea Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Nausea Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Control Group (N=27), InASMa on Dyspepsia Severity				
Indigestion Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 0.531$	0.912	Not Significant
Indigestion Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 1.048$	0.790	Not Significant
Heartburn Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 0.531$	0.912	Not Significant
Heartburn Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 1.048$	0.790	Not Significant
Regurgitation Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 0.531$	0.912	Not Significant
Regurgitation Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 1.048$	0.790	Not Significant
Nausea Frequency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 0.531$	0.912	Not Significant
Nausea Severity	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 1.048$	0.790	Not Significant

4.4.2.2 Post-Hoc Analysis of Dyspepsia Severity Components for Intervention Group (InViSMa).

Given the highly significant omnibus findings from the Friedman tests for the InViSMa group, post-hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test to pinpoint the specific time intervals of change. A Bonferroni correction was applied, setting the significance level at $\alpha = 0.0083$. The results of this analysis for the InViSMa group are detailed in Table 4.6.

The post-hoc analysis for the InViSMa group revealed a powerful and consistent pattern of improvement across all eight measures of dyspepsia severity. As presented in Table 4.6, every single pairwise comparison for Indigestion, Heartburn, Regurgitation, and Nausea (both frequency and severity) showed a statistically significant reduction (all p-values < 0.001). The effect sizes for these improvements were uniformly large ($r = 0.87$ for all comparisons). This remarkable consistency indicates that the InViSMa intervention induced significant reductions in dyspepsia severity at every stage of the study. Significant improvements were observed from baseline to each subsequent time point (Post-test 1, Post-test 2, and Follow-up), and importantly, further significant reductions were also found between each consecutive measurement point (e.g., Post-test 1 vs. Post-test 2, Post-test 2 vs. Follow-up). This demonstrates a strong, cumulative, and sustained therapeutic effect throughout the 4-week intervention and into the follow-up period.

For the control (InASMa) group, because none of the omnibus Friedman tests yielded a significant result (as shown in Table 4.5), post-hoc pairwise comparisons were not statistically warranted. Therefore, a table of post-hoc analyses is not presented for this group, in accordance with standard statistical practice to avoid an inflated risk of Type I error. This absence of change underscores the lack of a therapeutic effect from the control intervention on the specific symptoms of dyspepsia severity.

Table 4.6
Post-Hoc Analysis (Wilcoxon Signed-Rank) of The 4-Week Effects of InViSMa Group on Dyspepsia Severity in Adults Patient with FD

Dyspepsia Severity Variable	Pairwise Comparison	Median (IQR)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation (α = .0083)
Intervention Group (N=29), InViSMa on Dyspepsia Severity						
Indigestion Frequency and Severity	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Heartburn Frequency and Severity	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Regurgitation Frequency and Severity	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Nausea Frequency and Severity	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant

4.4.2.3 Between-Group (Mann–Whitney U Test): The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Dyspepsia Severity in Adults Patient with FD.

To test the second research hypothesis concerning the differential effects on dyspepsia severity, Mann-Whitney U tests were conducted to compare the scores of the InViSMa and InASMa groups at each of the four measurement time points. The comprehensive results of these between-group comparisons for all eight dyspepsia severity variables are presented in Table 4.7.

The analysis confirmed that the randomization was successful, as there were no statistically significant differences between the InViSMa and InASMa groups at Baseline for any of the eight dyspepsia severity variables (all p-values = 1.000). Both groups began the study with an identical median (IQR) score of 3 (2-4) for all frequency and severity measures, establishing a perfectly matched starting point.

A dramatic and highly significant separation between the groups emerged at the first follow-up measurement, Post-test 1. The InViSMa group demonstrated significantly lower (i.e., better) scores than the InASMa group for all eight variables: Indigestion Frequency and Severity, Heartburn Frequency and Severity, Regurgitation Frequency and Severity, and Nausea Frequency and Severity. The results were statistically robust, with all comparisons yielding a p-value of <.001 and a large effect size (r = 0.70). This indicates that the InViSMa intervention produced a rapid and clinically meaningful improvement in dyspepsia severity that was far superior to the control intervention.

This pronounced therapeutic advantage for the InViSMa group was further amplified at Post-test 2 and sustained through the Follow-up period. At both Post-test 2 and Follow-up, the Mann-Whitney U tests continued to show highly significant differences between the groups for all eight dyspepsia variables (all p-values < .001). The effect sizes became even larger, increasing to r = 0.82 for all comparisons at both Post-test 2 and Follow-up. As Table 4.7 illustrates, while the median scores for the InASMa group remained consistently high at 3 (or 3-4), the median scores for the InViSMa group progressively decreased to 1 at both Post-test 2 and Follow-up.

In conclusion, these findings provide unequivocal support for the second research hypothesis. The InViSMa intervention was not only effective in reducing dyspepsia

severity, but it was also significantly and substantially superior to the control intervention at all time points following the baseline measurement. The large and sustained effect sizes underscore the clinical importance of this differentiation.

Table 4.7
Mann-Whitney U Test Comparisons of The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Dyspepsia Severity in Adults Patient with FD

Dyspepsia Severity Variable	Time Point	Median (IQR) Intervention	Median (IQR) Control	Test Statistic (U)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation
Indigestion Frequency and Severity	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Heartburn Frequency and Severity	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Regurgitation Frequency and Severity	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Nausea Frequency and Severity	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant

4.4.3 The 4-Week Effects on Psychological Status

4.4.3.1 Within-Group Effects Across Time (Hypothesis a): Friedman test results for PSS scores within each group across the four time points.

To evaluate the impact of the interventions on the psychological status of participants, the Perceived Stress Scale (PSS) was administered at all four time points. The within-group changes over time were analyzed using the Friedman test to address Hypothesis (a). The results of this analysis, detailed in Table 4.8, indicate a clear difference in the effect of the two interventions on perceived stress.

For the InViSMa group (n=29), the Friedman test revealed a statistically significant change in PSS scores across the four measurement points ($\chi^2(3) = 77.151$, $p < 0.001$). Examination of the median scores shows a substantial and progressive reduction in perceived stress over the course of the study. The median (IQR) PSS score decreased from a baseline of 27 (26-28), indicating high stress, to 22 (21-23) at Post-test 1, further down to 16 (15-17) at Post-test 2, and reaching a low of 11 (10-12) at the final follow-up. This monotonic decrease in perceived stress provides strong support for the research hypothesis, demonstrating that the 4-week InViSMa intervention had a significant effect on improving the psychological status of patients with FD.

Conversely, for the control (InASMa) group (n=27), the Friedman test yielded a non-significant result ($\chi^2(3) = 1.048$, $p = 0.790$). This indicates that there was no statistically significant change in perceived stress levels over time in this group. This is corroborated by the median scores, which remained static at a high level of 27 across all four time points (Baseline, Post-test 1, Post-test 2, and Follow-up). This finding demonstrates that the control intervention had no discernible effect on the psychological status of the participants. Therefore, research Hypothesis (a) was not supported for the control group with respect to the PSS outcome.

Table 4.8
Within-Group (Friedman Test) Effects Across Time of the 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Psychological Status in Adults Patient with FD

Psychological Status Variable	Median (IQR)	Test Statistic	p-value	Interpretation
Intervention Group (N=29), InViSMa on Psychological Status				
Perceived Stress Scale	Baseline → Post-test 1 → Post-test 2 → Follow-up 27 (26–28) → 22 (21–23) → 16 (15–17) → 11 (10–12)	$\chi^2(3) = 77.151$	<0.001	Significant
Control Group (N=27), InASMa on Psychological Status				
Perceived Stress Scale	Baseline → Post-test 1 → Post-test 2 → Follow-up 27 (26–28) → 27 (25–28) → 27 (25–28) → 27 (24–28)	$\chi^2(3) = 1.048$	0.790	Not Significant

4.4.3.2 Post-Hoc Analysis of Psychological Status Components for Intervention Group.

Following the significant Friedman test result for the InViSMa group, post-hoc Wilcoxon signed-rank tests were performed to identify the specific time points at which the reduction in perceived stress occurred. A Bonferroni-corrected alpha level of $\alpha = 0.0083$ was used for these comparisons.

The results, as detailed in Table 4.9, show a consistent and statistically significant reduction in Perceived Stress Scale (PSS) scores between all measurement time points for the InViSMa group. All six pairwise comparisons yielded a p-value of <0.001, which is well below the corrected significance threshold. The effect sizes for all comparisons were uniformly large ($r = 0.87$). This indicates that the InViSMa intervention produced a significant reduction in perceived stress from Baseline to Post-test 1 ($Z = -4.541$), from Baseline to Post-test 2 ($Z = -4.542$), and from Baseline to Follow-up ($Z = -4.542$). Furthermore, the analysis reveals that the improvements were progressive, with significant reductions also occurring between Post-test 1 and Post-test 2 ($Z = -4.541$), between Post-test 1 and Follow-up ($Z = -4.542$), and between Post-test 2 and Follow-up ($Z = -4.542$). This pattern of continuous, significant improvement at each stage underscores the powerful, cumulative, and sustained impact of the InViSMa intervention on the psychological well-being of the participants.

As the omnibus Friedman test for the control (InASMa) group was not significant, post-hoc pairwise comparisons were not conducted for this group.

Table 4.9
Post-Hoc Analysis (Wilcoxon Signed-Rank) of The 4-Week Effects of Intervention Group (InViSMa) on Psychological Status in Adults Patient with FD

Psychological Status Variable	Pairwise Comparison	Median (IQR)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation (α = .0083)
Intervention Group (N=29), InViSMa on Psychological Status						
Perceived Stress	Post-test 1 vs. Baseline	22 (21–23) vs. 27 (26–28)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	16 (15–17) vs. 27 (26–28)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	11 (10–12) vs. 27 (26–28)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	16 (15–17) vs. 22 (21–23)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	11 (10–12) vs. 22 (21–23)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	11 (10–12) vs. 16 (15–17)	-4.542	<0.001	0.87 (Large)	Significant

4.4.3.3 Between-Group (Mann–Whitney U Test): The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Psychological Status in Adults Patient with FD.

To test the hypothesis of a significant differentiation between the InViSMa and InASMa groups on psychological status, Mann-Whitney U tests were conducted to compare Perceived Stress Scale (PSS) scores at each of the four time points. The results of this analysis are detailed in Table 4.10.

At Baseline, the analysis confirmed the homogeneity of the two groups, with no statistically significant difference in perceived stress scores ($U = 377.5$, $Z = -0.000$, $p = 1.000$). Both groups started with an identical high median stress level of 27.

Following the intervention period, a highly significant divergence between the groups was observed. At Post-test 1, the InViSMa group reported a significantly lower median PSS score (Median = 22, IQR = 21-23) compared to the InASMa group, whose scores remained unchanged (Median = 27, IQR = 25-28). This difference was statistically significant ($U = 49.5$, $Z = -5.201$, $p < 0.001$) with a large effect size ($r = 0.70$).

This superior effect of the InViSMa intervention was even more pronounced at subsequent time points. At Post-test 2, the median PSS score for the InViSMa group had fallen to 16 (IQR = 15-17), while the control group's median score remained at 27. The difference between the groups was highly significant ($U = 0.000$, $Z = -6.115$, $p < 0.001$), corresponding to a very large effect size ($r = 0.82$).

This robust difference was sustained at the Follow-up assessment. The InViSMa group's median PSS score continued to decrease to 11 (IQR = 10-12), whereas the control group's score was still 27. The between-group difference remained highly significant ($U = 0.000$, $Z = -6.124$, $p < 0.001$), with a very large effect size ($r = 0.82$).

In conclusion, these results provide strong support for research Hypothesis. The InViSMa intervention led to a statistically and clinically significant reduction in perceived stress that was vastly superior to the control intervention at all post-baseline time points. The control group, in contrast, showed no change in psychological status throughout the study.

Table 4.10
Mann-Whitney U Test Comparisons of The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Psychological Status in Adults Patient with FD

Psychological Status Variable	Time Point	Median (IQR) Intervention (InViSMa)	Median (IQR) Control (InASMa)	Test Statistic (U)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation
Perceived Stress	Baseline	27 (26–28)	27 (26–28)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	22 (21–23)	27 (25–28)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	16 (15–17)	27 (25–28)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	11 (10–12)	27 (24–28)	0.000	-6.124	<0.001	0.82 (Large)	Significant

4.4.4 The 4-Week Effects on Sleep Disorders

4.4.4.1 Within-Group Effects Across Time: Friedman test results for PSQI scores within each group across the four time points.

The impact of the interventions on sleep disorders was evaluated using the Pittsburgh Sleep Quality Index (PSQI), which assesses six components of sleep. To test Hypothesis (a) for this secondary outcome, Friedman tests were conducted to identify significant changes across the four measurement time points for each of the six sleep variables within both the InViSMa and InASMa groups.

The results of this analysis, as presented in Table 4.11, demonstrate a significant effect of the InViSMa intervention on sleep, while the control intervention had no such effect. For the InViSMa group (n=29), the Friedman test yielded highly significant results for all six components of sleep quality: sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, and daytime dysfunction (all p-values < 0.001). The test statistic was consistently high ($\chi^2(3) = 77.151$) across all variables, indicating a strong and uniform effect of time. The median scores in Table 4.11 illustrate a clear, progressive improvement. For every component, the median (IQR) score decreased from a baseline of 3 (2-4) to a final follow-up score of 1 (0-1). This consistent reduction in scores, which signifies improved sleep, strongly supports the research hypothesis, confirming that the 4-week InViSMa intervention had a significant positive effect on sleep disorders.

In stark contrast, for the control (InASMa) group (n=27), the Friedman test was non-significant for all six sleep disorder variables (p-values ranging from 0.790 to 0.912). The low Chi-square values (0.531 and 1.048) indicate a lack of change over time. This statistical finding is reflected in the descriptive data in Table 4.11, which show that the median (IQR) score for every sleep component remained unchanged at 3 (2-4) or 3 (1-4) across all four measurement points. This demonstrates that the control intervention had no effect on the participants' sleep quality or sleep-related problems. Therefore, research Hypothesis (a) was not supported for the control group regarding sleep disorders.

Table 4.11
Within-Group (Friedman Test) Effects Across Time of the 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Sleep Disorders in Adults Patient with FD

Sleep Disorders Variable	Median (IQR)	Test Statistic	p-value	Interpretation
Intervention Group (N=29), InViSMa on Sleep Disorders				
Sleep Quality	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Sleep Latency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Sleep Duration	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Sleep Efficiency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Sleep Disturbances	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Daytime Dysfunction	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 2 (1–3) → 1 (1–2) → 1 (0–1)	$\chi^2(3) = 77.151$	<0.001	Significant
Control Group (N=27), InASMa on Sleep Disorders				
Sleep Quality	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 1.048$	0.790	Not Significant
Sleep Latency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 0.531$	0.912	Not Significant
Sleep Duration	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 1.048$	0.790	Not Significant
Sleep Efficiency	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 0.531$	0.912	Not Significant
Sleep Disturbances	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 1.048$	0.790	Not Significant
Daytime Dysfunction	Baseline → Post 1 → Post 2 → Follow-up 3 (2–4) → 3 (2–4) → 3 (2–4) → 3 (1–4)	$\chi^2(3) = 0.531$	0.912	Not Significant

4.4.4.2 Post-Hoc Analysis of Sleep Disorders Components for Intervention Group.

Following the significant omnibus findings from the Friedman tests for the InViSMa group, post-hoc pairwise comparisons were conducted using the Wilcoxon signed-rank test to pinpoint the specific time intervals of change. A Bonferroni-corrected alpha level of $\alpha = 0.0083$ was used for these comparisons.

The results of this analysis for the InViSMa group are detailed in Table 4.12. The post-hoc tests revealed a powerful and consistent pattern of improvement across all six components of sleep as measured by the PSQI. For every single variable—sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, and daytime dysfunction—all six pairwise comparisons yielded statistically significant improvements (all p-values < 0.001). The effect sizes for all these comparisons were uniformly large ($r = 0.87$), indicating a strong and clinically meaningful effect.

This remarkable consistency demonstrates that the InViSMa intervention induced significant improvements in sleep quality at every stage of the study. Significant improvements were observed from Baseline to each subsequent time point (Post-test 1, Post-test 2, and Follow-up). Furthermore, the analysis reveals that the improvements were progressive, with significant reductions in sleep problems also occurring between consecutive measurement intervals (e.g., Post-test 1 vs. Post-test 2, and Post-test 2 vs. Follow-up). This pattern of continuous, significant improvement at each stage underscores the powerful, cumulative, and sustained impact of the InViSMa intervention on the participants' sleep.

As previously established, there were no statistically significant changes in any component of Sleep Disorders for participants in the control group over the course of the study. Because none of the omnibus Friedman tests yielded a significant result, post-hoc pairwise comparisons (Wilcoxon Signed-Rank tests) are not statistically warranted for the InASMa group. Therefore, a table of post-hoc analyses for the control group is not presented, in accordance with standard statistical practice to avoid an inflated risk of Type I error.

Table 4.12
Post-Hoc Analysis (Wilcoxon Signed-Rank) of The 4-Week Effects of InViSMa Group on Sleep Disorders in Adults Patient with FD

Sleep Disorders Variable	Pairwise Comparison	Median (IQR)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation (α = .0083)
Intervention Group (N=29), InViSMa on Sleep Disorders						
Sleep Quality	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Sleep Latency	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Sleep Duration	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Sleep Efficiency	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Sleep Disturbances	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant
Daytime Dysfunction	Post-test 1 vs. Baseline	2 (1–3) vs. 3 (2–4)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	1 (1–2) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	1 (0–1) vs. 3 (2–4)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	1 (1–2) vs. 2 (1–3)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	1 (0–1) vs. 2 (1–3)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	1 (0–1) vs. 1 (1–2)	-4.542	<0.001	0.87 (Large)	Significant

4.4.4.3 Between-Group (Mann–Whitney U Test): The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Sleep Disorders in Adults Patient with FD.

To ascertain whether the changes in sleep disorder scores were significantly different between the intervention (InViSMa) and control (InASMa) groups, a series of Mann-Whitney U tests were conducted. These non-parametric tests were performed at each of the four time points—Baseline, Post-test 1 (Week 2), Post-test 2 (Week 4), and Follow-up (Week 5)—to compare the median scores of all six components of the Pittsburgh Sleep Quality Index (PSQI). The results, including the U and Z statistics, p-values, and calculated effect sizes (r), are systematically presented in Table 4.13.

At Baseline, the Mann-Whitney U tests confirmed that there were no statistically significant differences between the InViSMa and InASMa groups on any of the PSQI components. For every variable—sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, and daytime dysfunction—the median scores were identical (Median = 3). The test statistic ($U = 377.5$, $Z = -0.000$) and p-value ($p = 1.000$) indicated homogeneity between the groups prior to the intervention. The effect size was negligible ($r = 0.00$), reinforcing the conclusion that both groups began with a comparable level of sleep disorders.

Following the intervention period, stark and statistically significant differences emerged between the groups at all subsequent time points. The analysis revealed a significant divergence in sleep quality between the two groups post-intervention. At Post-test 1, the intervention group reported a significantly lower median score (Median = 2) compared to the control group (Median = 3). This difference was statistically significant ($U = 49.5$, $Z = -5.201$, $p < 0.001$), with a large effect size ($r = 0.70$). This gap widened at Post-test 2, with the intervention group's median score dropping to 1 while the control group's remained at 3. The difference was highly significant ($U = 0.000$, $Z = -6.115$, $p < 0.001$), corresponding to a large effect size ($r = 0.82$). At the Follow-up assessment, the significant difference was maintained, with the intervention group's median score at 1 compared to the control group's median of 3. The result remained highly significant ($U = 0.000$, $Z = -6.124$, $p < 0.001$), with a large effect size ($r = 0.82$), indicating a sustained and substantial treatment effect.

Similar significant between-group differences were observed for sleep latency. By Post-test 1, the median score for the InViSMa group had decreased to 2, significantly lower than the InASMa group's score of 3 ($U = 49.5$, $Z = -5.201$, $p < 0.001$), yielding a large effect size ($r = 0.70$). At Post-test 2, the median sleep latency score for the intervention group was 1, significantly better than the control group's median of 3 ($U = 0.000$, $Z = -6.115$, $p < 0.001$). The effect size was large ($r = 0.82$). This significant advantage for the intervention group persisted at Follow-up, with median scores of 1 versus 3 for the control group ($U = 0.000$, $Z = -6.124$, $p < 0.001$), demonstrating a lasting, large effect ($r = 0.82$).

The intervention effect on sleep duration was pronounced and statistically significant. At Post-test 1, a significant difference was found, with the intervention group showing improved scores (Median = 2) compared to the control group (Median = 3). This comparison yielded a U-statistic of 49.5 ($Z = -5.201$, $p < 0.001$) and a large effect size ($r = 0.70$). At Post-test 2 and Follow-up, the intervention group maintained a significantly lower median score of 1 compared to the control group's median of 3. For both time points, the statistical tests confirmed a highly significant difference (Post-test 2: $U = 0.000$, $Z = -6.115$, $p < 0.001$; Follow-up: $U = 0.000$, $Z = -6.124$, $p < 0.001$), with a large effect size ($r = 0.82$).

Improvements in sleep efficiency were also significantly greater in the intervention group. The first significant difference appeared at Post-test 1, where the InViSMa group's median score was 2, versus 3 for the InASMa group ($U = 49.5$, $Z = -5.201$, $p < 0.001$), with a large effect size ($r = 0.70$). At Post-test 2 and Follow-up, the median score for the intervention group was 1, which was significantly lower than the control group's median of 3. These differences were highly significant and associated with a large effect size (Post-test 2: $Z = -6.115$, $p < 0.001$, $r = 0.82$; Follow-up: $Z = -6.124$, $p < 0.001$, $r = 0.82$).

The InViSMa intervention led to a significantly greater reduction in sleep disturbances compared to the control condition. At Post-test 1, the median score for the intervention group was 2, significantly lower than the control group's median of 3 ($U = 49.5$, $Z = -5.201$, $p < 0.001$). The effect size was large ($r = 0.70$). This significant difference grew at Post-test 2 and was sustained at Follow-up, with the intervention group consistently scoring a median of 1 compared to the control group's 3. The Mann-Whitney U tests for these time points were highly significant ($p < 0.001$) with large effect sizes ($r = 0.82$).

Finally, a significant between-group difference was found for daytime dysfunction. A significant improvement was evident at Post-test 1, with the intervention group (Median = 2) scoring lower than the control group (Median = 3). This was a statistically significant difference ($U = 49.5$, $Z = -5.201$, $p < 0.001$) with a large effect size ($r = 0.70$). At Post-test 2 and Follow-up, the intervention group's median score of 1 was significantly lower than the control group's median of 3. These results were highly significant ($p < 0.001$) and represented a large effect size ($r = 0.82$), indicating that the intervention not only improved sleep but also its daytime consequences.

In summary, while both groups were statistically indistinguishable at Baseline, the InViSMa group demonstrated significant, substantial, and sustained improvements across all domains of sleep disorders compared to the InASMa control group at all post-intervention measurement points.

Table 4.13
Mann-Whitney U Test Comparisons of The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Sleep Disorders in Adults Patient with FD

Sleep Disorders Variable	Time Point	Median (IQR) Intervention	Median (IQR) Control	Test Statistic (U)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation
Sleep Quality	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Sleep Latency	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Sleep Duration	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Sleep Efficiency	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Sleep Disturbances	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Daytime Dysfunction	Baseline	3 (2–4)	3 (2–4)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	2 (1–3)	3 (2–4)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	1 (1–2)	3 (2–4)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	1 (0–1)	3 (1–4)	0.000	-6.124	<0.001	0.82 (Large)	Significant

4.4.5 The 4-Week Effects on Quality of Life

4.4.5.1 Within-Group Effects Across Time: Friedman test results for NDI scores within each group across the four time points.

To evaluate the impact of the interventions on health-related quality of life over time within each group, a Friedman test was conducted. This non-parametric analysis was chosen to detect statistically significant changes in the Nepean Dyspepsia Index (NDI) scores across the four distinct measurement points: Baseline, Post-test 1 (Week 2), Post-test 2 (Week 4), and Follow-up (Week 5). The analysis was performed separately for the intervention group (InViSMa, N=29) and the control group (InASMa, N=27).

The Friedman test revealed a statistically significant effect of time on all measured components of quality of life for participants in the InViSMa group. For every subscale, the analysis yielded a p-value of <0.001, decisively rejecting the null hypothesis of no change over time. This indicates that the InViSMa intervention led to substantial and consistent improvements in health-related quality of life. The specific results for each subscale are detailed below.

Tension Ability: A marked and progressive improvement was observed. The median score for Tension Ability progressed from 15 (IQR 14–16) at Baseline to 18 (IQR 17–19) at Post-test 1, 23 (IQR 22–24) at Post-test 2, and 28 (IQR 27–29) at Follow-up. The Friedman test yielded a Chi-square statistic of $\chi^2(3) = 77.151$ with a p-value of <0.001, indicating a significant result.

Daily Activities Ability: Similar to tension, the ability to perform daily activities improved significantly over the four time points. Median scores increased from 15 (IQR 14–16) at Baseline to 18 (IQR 17–19), 23 (IQR 22–24), and finally 28 (IQR 27–29) at the subsequent measurement points. This change was confirmed to be statistically significant ($\chi^2(3) = 77.151$, $p < 0.001$).

Eating Drinking Ability: The intervention had a significant positive impact on the quality of life related to eating and drinking. The median scores showed a steady increase from a Baseline of 15 (IQR 14–16) to a Follow-up score of 28 (IQR 27–29). The omnibus test was significant, with $\chi^2(3) = 77.151$ and $p < 0.001$.

Knowledge Control Ability: Participants in the InViSMa group reported a significant enhancement in their sense of knowledge and control over their condition. Median scores rose from 20 (IQR 19–21) at Baseline to 23 (IQR 22–24) at Post-test 1,

28 (IQR 27–29) at Post-test 2, and 33 (IQR 32–34) at Follow-up. This demonstrates a significant within-group change over time ($\chi^2(3) = 77.151$, $p < 0.001$).

Work Study Ability: The ability to engage in work and study activities was also significantly improved. The median scores followed the same upward trend seen in other components, increasing from 15 (IQR 14–16) at Baseline to 28 (IQR 27–29) at Follow-up. The Friedman test confirmed this trend was statistically significant ($\chi^2(3) = 77.151$, $p < 0.001$).

In stark contrast to the intervention group, the Friedman tests for the control group (InASMa) yielded non-significant results for all five components of the NDI. This indicates that, in the absence of the InViSMa intervention, participants' health-related quality of life remained statistically unchanged throughout the 12-week study duration.

Tension Ability: The median scores for Tension Ability remained static at 15 across Baseline, Post-test 1, and Post-test 2, with a slight dip in the lower interquartile range at Follow-up (Median = 15, IQR 13–16). The Friedman test showed no significant change over time, with $\chi^2(3) = 0.531$ and $p = 0.912$.

Daily Activities Ability: No significant change was detected in the ability to perform daily activities. Median scores were stable at 15 across all four time points. The test result was not significant ($\chi^2(3) = 1.048$, $p = 0.790$).

Eating Drinking Ability: Quality of life related to eating and drinking did not change significantly for the control group. The median score was consistently 15 at all measurement points. This stability was reflected in the non-significant test result ($\chi^2(3) = 0.531$, $p = 0.912$).

Knowledge Control Ability: The sense of knowledge and control also remained unchanged. The median score was 20 at every time point throughout the study. The Friedman test confirmed the absence of a statistically significant effect ($\chi^2(3) = 1.048$, $p = 0.790$).

Work Study Ability: Finally, no significant temporal change was found for Work Study Ability. The median scores were consistently 15 at all four assessments. The test result was not significant ($\chi^2(3) = 0.531$, $p = 0.912$).

In summary, the within-group analyses demonstrate that the InViSMa intervention was associated with significant and positive changes in all measured aspects of quality of life over time. Conversely, the InASMa control group exhibited no significant improvements, with their scores remaining stable from Baseline to Follow-up.

Table 4.14
Within-Group (Friedman Test) Effects Across Time of the 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Quality of Life in Adults Patient with FD

Quality of Life Variable	Median (IQR)	Test Statistic	p-value	Interpretation
Intervention Group (N=29), InViSMa on Quality of Life				
Tension Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 18 (17–19) → 23 (22–24) → 28 (27–29)	$\chi^2(3) = 77.151$	<0.001	Significant
Daily Activities Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 18 (17–19) → 23 (22–24) → 28 (27–29)	$\chi^2(3) = 77.151$	<0.001	Significant
Eating Drinking Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 18 (17–19) → 23 (22–24) → 28 (27–29)	$\chi^2(3) = 77.151$	<0.001	Significant
Knowledge Control Ability	Baseline → Post 1 → Post 2 → Follow-up 20 (19–21) → 23 (22–24) → 28 (27–29) → 33 (32–34)	$\chi^2(3) = 77.151$	<0.001	Significant
Work Study Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 18 (17–19) → 23 (22–24) → 28 (27–29)	$\chi^2(3) = 77.151$	<0.001	Significant
Control Group (N=27), InASMa on Quality of Life				
Tension Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 15 (14–16) → 15 (14–16) → 15 (13–16)	$\chi^2(3) = 0.531$	0.912	Not Significant
Daily Activities Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 15 (13–16) → 15 (13–16) → 15 (13–16)	$\chi^2(3) = 1.048$	0.790	Not Significant
Eating Drinking Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 15 (14–16) → 15 (14–16) → 15 (13–16)	$\chi^2(3) = 0.531$	0.912	Not Significant
Knowledge Control Ability	Baseline → Post 1 → Post 2 → Follow-up 20 (19–21) → 20 (19–21) → 20 (19–21) → 20 (18–21)	$\chi^2(3) = 1.048$	0.790	Not Significant
Work Study Ability	Baseline → Post 1 → Post 2 → Follow-up 15 (14–16) → 15 (14–16) → 15 (14–16) → 15 (13–16)	$\chi^2(3) = 0.531$	0.912	Not Significant

4.4.5.2 Post-Hoc Analysis of Quality of Life Components for Intervention Group (InViSMa).

Following the significant omnibus Friedman test that identified an overall change in Nepean Dyspepsia Index (NDI) scores for the intervention (InViSMa) group, a series of post-hoc tests were conducted to pinpoint where these changes occurred. Wilcoxon signed-rank tests were used to analyze all six possible pairwise comparisons across the four time points: Baseline, Post-test 1, Post-test 2, and Follow-up. To control for the increased risk of a Type I error from multiple comparisons, a Bonferroni correction was applied, setting the alpha level for significance at $\alpha = .0083$. The detailed outcomes of this analysis, including Z-statistics, p-values, and effect sizes, are presented in Table 4.15.

It is important to note that this post-hoc analysis was performed exclusively for the InViSMa group. As the preceding Friedman tests did not yield a significant result for the control (InASMa) group, subsequent pairwise comparisons were not statistically warranted. This approach aligns with standard statistical practice to avoid an inflated risk of Type I error.

The results delineated in Table 4.15 show that the InViSMa intervention induced statistically significant improvements across every NDI subscale at every single interval comparison. For all comparisons, the p-value was less than 0.001, and the effect size (r) was 0.87, which is interpreted as a large effect. This demonstrates a robust, consistent, and progressively positive impact of the intervention on participants' quality of life.

Tension Ability: The analysis of tension ability revealed significant and continuous improvement throughout the study period. When compared to Baseline (Median = 15), median scores were significantly higher at Post-test 1 (Median = 18), Post-test 2 (Median = 23), and Follow-up (Median = 28). Furthermore, progressive improvements were observed between subsequent time points. Scores at Post-test 2 were significantly higher than at Post-test 1. Scores at Follow-up were significantly higher than both Post-test 1 and Post-test 2. For all six comparisons, the Z-statistic was approximately -4.54, with a p-value of <0.001 and a large effect size ($r = 0.87$). These findings indicate a sustained and cumulative positive effect of the intervention on participants' ability to manage tension.

Daily Activities Ability: A similar pattern of significant and sustained improvement was found for daily activities ability. Scores at Post-test 1 (Median = 18), Post-test 2 (Median = 23), and Follow-up (Median = 28) were all significantly higher than at Baseline (Median = 15). The analysis also confirmed a significant increase in scores from Post-test 1 to Post-test 2, from Post-test 1 to Follow-up, and from Post-test 2 to Follow-up. Every comparison yielded a significant result ($Z \approx -4.54$, $p < 0.001$) with a large effect size ($r = 0.87$), demonstrating the intervention's profound impact on participants' functional capacity in daily life.

Eating Drinking Ability: The intervention resulted in a significant and progressive enhancement in the quality of life related to eating and drinking ability. Compared to the Baseline median score of 15, scores were significantly improved at Post-test 1 (Median = 18), Post-test 2 (Median = 23), and Follow-up (Median = 28). Significant improvements were also recorded between all subsequent time points, with scores increasing from Post-test 1 to Post-test 2, and from both of these points to the Follow-up assessment. The consistent, highly significant results across all comparisons ($Z \approx -4.54$, $p < 0.001$, $r = 0.87$) underscore the effectiveness of the intervention in mitigating the impact of dyspepsia on eating and drinking.

Knowledge Control: For the Knowledge Control subscale, participants reported a significant and continuous increase in their perceived control and understanding of their condition. Starting from a Baseline median of 20, scores significantly increased to 23 at Post-test 1, 28 at Post-test 2, and 33 at Follow-up. Each follow-up point showed a statistically significant improvement over all preceding points (e.g., Follow-up vs. Post-test 2, Post-test 2 vs. Post-test 1, etc.). All six pairwise comparisons were highly significant ($Z \approx -4.54$, $p < 0.001$) and demonstrated a large effect size ($r = 0.87$), indicating that the intervention successfully empowered participants, enhancing their sense of control over their health.

Work Study Ability: Finally, the post-hoc analysis for work study ability confirmed significant improvements at every stage of the study. Median scores increased significantly from Baseline (Median = 15) to Post-test 1 (Median = 18), Post-test 2 (Median = 23), and Follow-up (Median = 28). Significant gains were also made between the post-intervention time points, with scores at Follow-up being significantly higher than at Post-test 2, which in turn were significantly higher than at Post-test 1. The robust statistical significance ($Z \approx -4.54$, $p < 0.001$) and large effect size ($r = 0.87$)

across all comparisons highlight the intervention's substantial positive effect on participants' ability to engage in professional and academic activities.

Table 4.15
Post-Hoc Analysis (Wilcoxon Signed-Rank) of The 4-Week Effects of Intervention Group (InViSMa) on Quality of Life in Adults Patient with FD

Quality of Life Variable	Pairwise Comparison	Median (IQR)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation (α = .0083)
Intervention Group (N=29), InViSMa on Quality of Life						
Tension Ability	Post-test 1 vs. Baseline	18 (17–19) vs. 15 (14–16)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	23 (22–24) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	28 (27–29) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	23 (22–24) vs. 18 (17–19)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	28 (27–29) vs. 18 (17–19)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	28 (27–29) vs. 23 (22–24)	-4.542	<0.001	0.87 (Large)	Significant
Daily Activities Ability	Post-test 1 vs. Baseline	18 (17–19) vs. 15 (14–16)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	23 (22–24) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	28 (27–29) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	23 (22–24) vs. 18 (17–19)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	28 (27–29) vs. 18 (17–19)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	28 (27–29) vs. 23 (22–24)	-4.542	<0.001	0.87 (Large)	Significant
Eating Drinking Ability	Post-test 1 vs. Baseline	18 (17–19) vs. 15 (14–16)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	23 (22–24) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	28 (27–29) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	23 (22–24) vs. 18 (17–19)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	28 (27–29) vs. 18 (17–19)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	28 (27–29) vs. 23 (22–24)	-4.542	<0.001	0.87 (Large)	Significant
Knowledge Control	Post-test 1 vs. Baseline	23 (22–24) vs. 20 (19–21)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	28 (27–29) vs. 20 (19–21)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	33 (32–34) vs. 20 (19–21)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	28 (27–29) vs. 23 (22–24)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	33 (32–34) vs. 23 (22–24)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	33 (32–34) vs. 28 (27–29)	-4.542	<0.001	0.87 (Large)	Significant
Work Study Ability	Post-test 1 vs. Baseline	18 (17–19) vs. 15 (14–16)	-4.541	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Baseline	23 (22–24) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Baseline	28 (27–29) vs. 15 (14–16)	-4.542	<0.001	0.87 (Large)	Significant
	Post-test 2 vs. Post-test 1	23 (22–24) vs. 18 (17–19)	-4.541	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 1	28 (27–29) vs. 18 (17–19)	-4.542	<0.001	0.87 (Large)	Significant
	Follow-up vs. Post-test 2	28 (27–29) vs. 23 (22–24)	-4.542	<0.001	0.87 (Large)	Significant

4.4.5.3 Between-Group (Mann–Whitney U Test): The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Quality of Life in Adults Patient with FD.

To test the hypothesis that the magnitude of improvement in quality of life would be significantly different between the intervention and control groups, a series of Mann-Whitney U tests were conducted. These tests compared the Nepean Dyspepsia Index (NDI) scores of the InViSMa group against the InASMa group at each of the four measurement time points (Baseline, Post-test 1, Post-test 2, and Follow-up). This analysis was critical to determine if the intervention produced a superior outcome relative to the control condition.

The complete results of these between-group comparisons are presented in Table 4.16. The table details the median scores and interquartile ranges (IQR) for both groups, the U-statistic, the corresponding Z-score, the precise p-value, the calculated effect size (r), and the statistical interpretation at each time point for all five NDI subscales. Additionally, Figure [*Insert Figure Number here*] provides a visual illustration, such as a box plot, of the distribution of scores for both groups, highlighting the divergent outcomes over the study period.

At Baseline, the Mann-Whitney U tests confirmed that the intervention and control groups were homogenous across all quality of life domains. For each of the five subscales, the tests yielded a p-value of 1.000, with a Z-score of -0.000 and a negligible effect size ($r = 0.00$). This demonstrates that there were no statistically significant differences between the groups prior to the commencement of the study, establishing a valid basis for comparison.

Following the intervention, significant differences emerged and progressively widened between the two groups at all subsequent time points, as detailed below.

Tension Ability: The intervention had a significant effect on participants' tension ability when compared to the control group. At Post-test 1, the median score for the InViSMa group (18) was significantly higher than the InASMa group (15). This difference was statistically significant ($U = 49.5$, $Z = -5.201$, $p < 0.001$) and represented a large effect size ($r = 0.70$). By Post-test 2, the gap between the groups increased, with the intervention group reaching a median of 23 while the control group remained at 15. The difference was highly significant ($U = 0.000$, $Z = -6.115$, $p < 0.001$), with a large

effect size (r = 0.82). This significant difference was maintained at Follow-up, with the InViSMa group's median score at 28 compared to the control group's 15. The result remained highly significant (U = 0.000, Z = -6.124, p <0.001), with a large effect size (r = 0.82), indicating a sustained and substantial treatment effect.

Daily Activities Ability: A similar pattern of significant between-group differences was observed for daily activities ability. At Post-test 1, the InViSMa group's median score of 18 was significantly higher than the control group's median of 15 (U = 49.5, Z = -5.201, p <0.001). The effect size was large (r = 0.70). At Post-test 2 and Follow-up, the intervention group's median scores (23 and 28, respectively) were significantly higher than the control group's static median of 15. Both comparisons were highly significant (p <0.001) with large effect sizes (r = 0.82), demonstrating a profound and lasting improvement in the intervention group's functional capacity.

Eating Drinking Ability: The effect of the intervention on eating drinking ability was pronounced and statistically significant when compared to the control group. Following the first four weeks (Post-test 1), a significant difference was evident, with the intervention group (Median = 18) scoring higher than the control group (Median = 15). This result was significant (U = 49.5, Z = -5.201, p <0.001) with a large effect size (r = 0.70). At Post-test 2 and Follow-up, the intervention group's scores (Median = 23 and Median = 28) continued to be significantly higher than the control group's (Median = 15). These differences were highly significant (p <0.001) and corresponded to a large effect size (r = 0.82), underscoring the intervention's superior efficacy.

Knowledge Control: Significant differences in knowledge control were found between the groups at all post-intervention time points. At Post-test 1, the median score for the InViSMa group was 23, significantly higher than the InASMa group's median of 20 (U = 49.5, Z = -5.201, p <0.001). The effect size was large (r = 0.70). This significant advantage for the intervention group persisted and grew at Post-test 2 (Median = 28) and Follow-up (Median = 33) compared to the control group's median of 20 at both points. The results were highly significant (p <0.001) with a large effect size (r = 0.82), indicating the intervention successfully enhanced participants' sense of control over their condition.

Work Study Ability: Finally, the between-group analysis for work study ability revealed a significant and sustained intervention effect. A significant improvement was evident at Post-test 1, with the intervention group (Median = 18) scoring higher than the control group (Median = 15). This was a statistically significant difference (U =

49.5, Z = -5.201, p <0.001) with a large effect size (r = 0.70). At Post-test 2 and Follow-up, the intervention group's median scores of 23 and 28 were significantly higher than the control group's median of 15. Both results were highly significant (p <0.001) and represented a large effect size (r = 0.82), indicating a substantial positive impact on participants' ability to engage in work and academic life.

In conclusion, while both groups began with equivalent quality of life scores, the InViSMa group demonstrated statistically significant and practically meaningful improvements across all domains of the NDI compared to the InASMa control group at every post-intervention assessment. The magnitude of this difference increased over time, highlighting the robust and durable efficacy of the intervention.

Table 4.16
Mann-Whitney U Test Comparisons of The 4-Week Effects of Intervention Group (InViSMa) and Control Group (InASMa) on Quality of Life in Adults Patient with FD

Quality of Life Variable	Time Point	Median (IQR) Intervention (InViSMa)	Median (IQR) Control (InASMa)	Test Statistic (U)	Test Statistic (Z)	p-value	Effect Size (r)	Interpretation
Tension Ability	Baseline	15 (14–16)	15 (14–16)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	18 (17–19)	15 (14–16)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	23 (22–24)	15 (14–16)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	28 (27–29)	15 (13–16)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Daily Activities Ability	Baseline	15 (14–16)	15 (14–16)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	18 (17–19)	15 (13–16)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	23 (22–24)	15 (13–16)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	28 (27–29)	15 (13–16)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Eating Drinking Ability	Baseline	15 (14–16)	15 (14–16)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	18 (17–19)	15 (14–16)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	23 (22–24)	15 (14–16)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	28 (27–29)	15 (13–16)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Knowledge Control	Baseline	20 (19–21)	20 (19–21)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	23 (22–24)	20 (19–21)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	28 (27–29)	20 (19–21)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	33 (32–34)	20 (18–21)	0.000	-6.124	<0.001	0.82 (Large)	Significant
Work Study Ability	Baseline	15 (14–16)	15 (14–16)	377.5	-0.000	1.000	0.00 (Negligible)	Not Significant
	Post-test 1	18 (17–19)	15 (14–16)	49.5	-5.201	<0.001	0.70 (Large)	Significant
	Post-test 2	23 (22–24)	15 (14–16)	0.000	-6.115	<0.001	0.82 (Large)	Significant
	Follow-up	28 (27–29)	15 (13–16)	0.000	-6.124	<0.001	0.82 (Large)	Significant

4.5 Chapter Summary

This chapter has presented the empirical findings derived from the statistical analysis of data collected in this study. The primary aim was to objectively report the effects of the integrated visceral and spinal manipulation (InViSMa) intervention compared to the integrated abdominal massage and spinal manipulation (InASMa) control intervention on a range of primary and secondary outcomes in adult patients with Functional Dyspepsia (FD). The results were organized sequentially, beginning with participant flow and baseline characteristics, followed by a detailed examination of within-group and between-group effects for each outcome variable.

For Abdominal Pain, the within-group analysis (Hypothesis a) revealed that both the InViSMa and the InASMa groups experienced statistically significant reductions across all four domains over the course of the study. However, the post-hoc analysis indicated that the improvements in the InViSMa group were more consistent and cumulative at every measured interval , whereas the InASMa group's improvements were less uniform. Crucially, the between-group analysis (Hypothesis b) strongly supported the superiority of the InViSMa intervention. While the groups were homogenous at baseline, the InViSMa group demonstrated a significantly greater reduction in all aspects of abdominal pain at Post-test 2 and Follow-up, with large and sustained effect sizes .

For Dyspepsia Severity, the results showed a stark divergence. The within-group analysis (Hypothesis a) was strongly supported for the InViSMa group, which showed highly significant, progressive reductions in all eight symptoms measured by the Leeds Dyspepsia Questionnaire (LDQ). In marked contrast, this hypothesis was not supported for the InASMa group, which showed no statistically significant change in dyspepsia severity over time. Consequently, the between-group analysis (Hypothesis b) revealed a dramatic and highly significant advantage for the InViSMa group at all post-baseline time points, with large and sustained effect sizes underscoring its superior clinical efficacy .

Regarding Psychological Status, Hypothesis (a) was supported for the InViSMa group, which experienced a significant, progressive reduction in perceived stress over the four time points. The hypothesis was not supported for the InASMa group, whose stress levels remained unchanged. The between-group analysis (Hypothesis b) confirmed this difference, showing that the InViSMa intervention was vastly superior

in reducing perceived stress at all post-intervention stages, yielding very large effect sizes .

For Sleep Disorders, a similar pattern emerged. The within-group hypothesis (a) was strongly supported for the InViSMa group, with significant and progressive improvements noted across all six components of the Pittsburgh Sleep Quality Index (PSQI). Conversely, the hypothesis was not supported for the InASMa group, which reported no significant changes in sleep quality. The subsequent between-group analysis (Hypothesis b) demonstrated the significant and substantial superiority of the InViSMa intervention in improving all aspects of sleep at Post-test 1, Post-test 2, and Follow-up.

Finally, for Health-Related Quality of Life, Hypothesis (a) was decisively supported for the InViSMa group, which showed significant and continuous improvements across all five domains of the Nepean Dyspepsia Index (NDI). This hypothesis was not supported for the InASMa group, whose quality of life scores remained static. The between-group analysis (Hypothesis b) confirmed that the InViSMa group experienced significantly greater improvements in all domains of quality of life compared to the control group at all post-intervention assessments, with the magnitude of this difference increasing over time.

In essence, the findings presented in this chapter demonstrate that the InViSMa protocol was a highly effective intervention, yielding significant, durable, and clinically meaningful improvements across all measured outcomes, and was robustly superior to the active control condition. These empirical findings provide a strong statistical foundation for the comprehensive discussion and interpretation that will be undertaken in Chapter 5, where the clinical and theoretical implications of these results will be explored in the context of the existing literature.

CHAPTER 5
DISCUSSION

5.1 Introduction

This chapter serves as the analytical core of the dissertation, dedicated to the comprehensive interpretation of the empirical findings presented in Chapter 4. The primary objective of this discussion is to critically evaluate the results derived from the single-blind randomized controlled trial. This process moves beyond mere statistical reporting to address the fundamental question of why the observed effects occurred, linking the mechanisms of the integrated visceral and spinal manipulation (InViSMa) protocol to the observed changes in clinical outcomes.

The chapter is systematically structured to first interpret the findings related to the primary outcomes—abdominal pain and dyspepsia severity—followed by an analysis of the secondary outcomes, which encompassed psychological status, sleep disorder, and health-related quality of life. For each outcome, the discussion focuses on two critical aspects: the therapeutic efficacy demonstrated within the InViSMa group over time, and the significant superiority of the InViSMa intervention when compared to the active control (InASMa) group.

Furthermore, this chapter critically relates the findings to the neuro-visceral-somatic interaction theory, providing mechanistic explanations for the success of the integrated approach in modulating the autonomic and biomechanical dysfunctions characteristic of FD. The chapter concludes by articulating the key strengths and inherent limitations of the study, deriving clear clinical implications for physiotherapy practice, and offering specific recommendations to guide future research endeavors in this specialized field.

5.2 Interpretation of Primary Findings

5.2.1 Discussion of InViSMa Efficacy on Abdominal Pain

The assessment of abdominal pain, the core primary outcome measured by the Abdominal Pain Index (API), yielded the most decisive evidence regarding the efficacy of the integrated intervention. The within-group analysis showed that both the InViSMa group and the active control (InASMa) group demonstrated a statistically significant

reduction in all four domains of abdominal pain (episode frequency, typical daily frequency, typical duration, and typical intensity) across the four measurement time points (all $p < 0.005$) (Table 4.2). This significant improvement in the control group suggests a strong non-specific or generalized analgesic effect from the shared spinal manipulation component and abdominal massage.

However, the between-group analysis ultimately confirmed the superior, specific effect of the InViSMa intervention. Mann-Whitney U tests revealed highly statistically significant differences favoring the InViSMa group across all four API domains at Post-test 2 and Follow-up (all $p \leq 0.004$), with large effect sizes (ranging from $r=0.52$ to $r=0.64$) (Table 4.4). While the control group achieved significant improvements over time, the InViSMa intervention produced a greater magnitude of pain reduction, which became more pronounced and sustained as the treatment progressed, suggesting a cumulative, structural, and neurological reorganization effect beyond mere transient analgesic effects.

The differential efficacy in reducing abdominal pain is understood through a heightened mechanistic focus on neurological and somato-visceral interactions:

1. Counteracting Central Sensitization and Gating Pain:

Abdominal pain in FD is frequently maintained by central sensitization, where nociceptive input from the viscera and surrounding somatic structures leads to hyperexcitability of the central nervous system, effectively lowering the pain threshold (Bialosky et al., 2018). Chronic visceral pain can establish a somatovisceral reflex, where ongoing nociceptive input from the viscera (e.g., restricted lesser omentum) causes reflex spasms and restrictions in the associated paraspinal muscles and joints (T5-T12). The integrated manipulation (InViSMa) protocol breaks this cycle by addressing the visceral source (VM) and normalizing the spinal segment (SM).

Both spinal and visceral manipulation techniques deliver high-frequency, non-nociceptive mechanical input. This comprehensive somatosensory barrage travels to the dorsal horn of the spinal cord (where visceral and somatic afferents converge) and subsequently to the brainstem and higher centers. This strong, non-painful input is hypothesized to activate descending inhibitory pathways and operate via the Pain Gate Theory, effectively suppressing the chronic barrage of nociceptive signals originating from the gut, thereby reducing the perception of pain (Coronado et al., 2012; Arisandy & Haidzir, 2025). By removing the afferent drive from both the viscera and the somatic

structure, the overall nociceptive load on the CNS is substantially reduced, leading to the superior pain relief observed in the InViSMa group (Lei Tu et al, 2020; Goyal et al., 2021).

2. Autonomic Modulation and Ischemia Reduction:

Chronic sympathetic hypertonicity, prevalent in FD, leads to persistent splanchnic vasoconstriction, which can result in localized ischemia within the gut wall and its associated fascia. This ischemia is a potent source of visceral pain (Wirth et al, 2019).The gentle, rhythmic pressure and stretching inherent in Visceral Manipulation are believed to mechanically induce vasodilation, improving local microcirculation and relieving this ischemic component of visceral pain. This effect is coupled with the sympathetic normalization achieved through Spinal Manipulation, collectively promoting parasympathetic dominance, which encourages further splanchnic relaxation and improved tissue oxygenation (Haavik & Murphy, 2012; Rechberger et al., 2019). The relief of ischemia directly addresses a primary driver of chronic pain, contributing to the superior and sustained reduction in pain intensity and duration demonstrated by the API scores (Table 4.4).

3. Anti-inflammatory and Structural Effects:

The reduction in abdominal pain is supported by cellular and structural changes. Pain is often associated with fascial and ligamentous restrictions (e.g., around the hepatoduodenal ligament) that become hyper-innervated and tension-loaded. The visceral manipulation techniques serve as mechanotherapy, providing specific, sustained stretch and mobilization to mechanically bound structures. This not only relieves direct mechanical strain, which is interpreted by the body as pain, but also stimulates mechanoreceptors to trigger anti-inflammatory signaling cascades (mechanotransduction) (Schleip et al., 2012; Bordoni & Marelli, 2015).

While the control group's generalized massage likely offered transient pain relief by stimulating superficial mechanoreceptors and reducing muscle tension, the InViSMa protocol offered a deep, specific, sustained release of the visceral fascia and ligaments, which are the actual anchors and sources of chronic visceral pain transmission in FD. The statistical superiority of InViSMa is therefore a testament to the clinical necessity of specifically addressing these deep visceral restrictions alongside the general spinal and abdominal effects.

In conclusion, the statistically significant and clinically superior reduction in abdominal pain achieved by the InViSMa group over the control group demonstrates that effective treatment of FD pain requires a multi-pronged strategy. The integrated approach successfully combined the generalized analgesic effects of spinal manipulation with the specific, neuro-visceral and anti-inflammatory effects of visceral manipulation, leading to a profound and sustained symptomatic relief that targets the central, peripheral, and structural components of chronic pain.

5.2.2 Discussion of InViSMa Efficacy on Severity of Dyspepsia

The second primary outcome, severity of dyspepsia, as measured by the Leeds Dyspepsia Questionnaire (LDQ), provided a nuanced set of findings that further validate the efficacy of the integrated manipulation protocol, particularly when isolating the specific effects of the visceral component. The within-group analysis using the Friedman test revealed a highly statistically significant effect of time for the integrated visceral and spinal manipulation (InViSMa) group across all eight measured components of dyspepsia severity (all $p < 0.001$) (as detailed in Table 4.5). The median scores for symptoms such as Indigestion Frequency and Heartburn Severity demonstrated a consistent and marked reduction, decreasing from a baseline median of 3 to a final score of 1 at follow-up (Table 4.5). This monotonic pattern of improvement strongly supported the research hypothesis, confirming that the InViSMa protocol effectively mitigates the primary symptom cluster of Functional Dyspepsia (FD).

Crucially, the study also provided robust support for the between-group hypothesis. Mann-Whitney U tests consistently showed that the InViSMa group was statistically and substantially superior to the active control group (InASMa) at all post-baseline measurement points (Post-test 1, Post-test 2, and Follow-up) (all $p < 0.001$) (Table 4.7). The corresponding effect sizes were consistently large (ranging from $r=0.70$ to $r=0.82$), underscoring the clinical meaningfulness of this differential effect. In stark contrast, the control group exhibited no statistically significant change in any LDQ component over the study period, with median scores remaining static at a high level (Table 4.5). This striking difference provides unequivocal evidence that the superior therapeutic gain was attributable to the inclusion of the specific visceral manipulation component.

The interpretation of this success is deeply rooted in the synergistic physiological and neurological mechanisms activated by the Integrated Visceral and Spinal

Manipulation (InViSMa) protocol. The superiority of this combined approach, compared to the control that included only general abdominal massage and identical spinal manipulation, supports the multi-factorial nature of FD and underscores the importance of addressing both somatic and visceral components simultaneously. The therapeutic efficacy is understood through three interconnected mechanistic lenses:

1. **Modulation of the Autonomic Nervous System (ANS) and the Visceral Nociceptive Pathway:**

Functional Dyspepsia is intrinsically linked to a dysregulated ANS, characterized by sympathetic hypertonicity and often a compromised vagal (parasympathetic) tone, which collectively contribute to symptoms like visceral hypersensitivity, reduced gastric accommodation, and delayed gastric emptying (Bonaz et al., 2018). The InViSMa protocol directly addresses this imbalance at both the central and peripheral levels.

The specific, gentle forces applied during Visceral Manipulation (VM)—targeting the stomach, duodenum, and lesser omentum—mechanically stimulate the dense network of mechanoreceptors and chemoreceptors embedded in the visceral connective tissues. This essential afferent sensory input travels via the vagus nerve (Cranial Nerve X), the main component of the parasympathetic nervous system (PNS), to the brainstem. It is widely theorized that enhanced, rhythmic vagal afference serves to modulate the central processing of visceral pain, effectively desensitizing the central nervous system (CNS) to benign visceral stimuli, thereby mitigating visceral hypersensitivity which is a key driver of dyspepsia severity (Thania et al., 2023).

The Spinal Manipulation (SM) component specifically targets the sympathetic efferent pathways originating in the thoracolumbar segments (T5-T12) that innervate the digestive organs. Manipulation is hypothesized to normalize sympathetic input, disrupting sympathetic hyper-firing that often causes visceral vasoconstriction and delayed motility (Sweidan, 2015). The integrated effect—restored vagal tone via VM and normalized sympathetic tone via SM—facilitates a crucial shift in sympathovagal balance. This optimization promotes improved gastric motility, regulated acid secretion, and enhanced gastric accommodation, which directly alleviate LDQ components such as regurgitation, nausea, and indigestion severity (Barral & Mercier, 2005).

2. Mechanotransduction and Cellular Remodeling Theory:

The efficacy of manual therapy is Biomechanically supported by the theory of mechanotransduction, which describes how applied mechanical forces are converted into biochemical signals at the cellular level (Da Silva et al., 2013; Diniz et al., 2014; Eguaras et al., 2019). During the application of specific visceral mobilization techniques, the mechanical energy (stretch, pressure, shear) is transduced by fibroblasts and other cells embedded within the myofascial continuum of the digestive system and its supporting ligaments. This mechanical loading triggers a cascade of cellular events, including the alteration of gene expression and the release of specialized mediators (Goyal et al., 2021).

In conditions like FD, often characterized by low-grade inflammation, mechanotransduction acts as a potent endogenous regulator. By physically mobilizing and stretching restricted tissues, the protocol encourages tissue remodeling, reduces fascial strain, and promotes a localized shift from a pro-inflammatory environment to a healing, anti-inflammatory state (Dunn & Olmedo., 2016). This process is believed to reduce neural irritation and improve localized tissue mechanics, thereby contributing to the statistically significant and sustained reduction in dyspepsia severity observed in the InViSMa group.

3. Mechanical Effects (Mechanotherapy) and Restoration of Organ Compliance:

The mechanical application of InViSMa directly addresses physical restrictions that limit normal organ function, classifying it as effective mechanotherapy. Visceral Manipulation restores the essential physiological movement (motility and mobility) and relative sliding of internal organs against their surrounding structures (Barral & Mercier, 2005). This improved tissue compliance reduces mechanical tension on the mesentery and supporting ligaments, which are known sources of chronic nociceptive input (visceral pain) and can reflexively inhibit normal peristalsis (Loghmani & Whitted, 2016). The removal of this chronic mechanical irritation contributes directly to the symptom relief reported by participants.

The combined approach is essential because somatovisceral reflexes dictate that spinal dysfunction (e.g., restricted movement in the T5-T12 segments) can perpetuate visceral symptoms. Restoring segmental spinal mechanics removes a chronic source of aberrant afferent input that converges onto the dorsal horn and feeds into central

sensitization pathways (Goyal et al., 2021). By treating both the somatic restriction and the visceral restriction, the InViSMa protocol interrupts the vicious cycle of the somatovisceral reflex arc, leading to a profound and sustained reduction in dyspepsia severity that was not achieved by the control protocol (which maintained the spinal component but lacked the specific visceral component). This demonstrates the integrated nature of the treatment is paramount to its clinical success.

In summary, the highly significant and superior effectiveness of the InViSMa protocol on dyspepsia severity is attributed to a dual-action mechanism: the normalization of the autonomic nervous system through vagal and sympathetic pathway modulation, and the physical restoration of visceral and spinal mechanics via mechanotransduction and targeted mechanotherapy. This multi-target approach successfully interrupts the underlying physiological dysfunctions of FD, resulting in the comprehensive clinical improvement observed in the LDQ scores.

5.3 Interpretation of Secondary Findings

5.3.1 Discussion of InViSMa Efficacy on Psychological Status

The assessment of the participants' psychological status, using the Perceived Stress Scale (PSS), provided compelling evidence for the systemic, non-gastrointestinal benefits of the integrated visceral and spinal manipulation (InViSMa) protocol. The within-group analysis revealed a highly significant effect of time on PSS scores for the InViSMa group (chi 2(3)=77.151, $p < 0.001$), showing a robust and progressive reduction in perceived stress from a high baseline median of 27 to a low of 11 at follow-up (Table 4.8). In sharp contrast, the control group (InASMa) showed no statistically significant change in PSS scores (chi 2(3)=1.048, $p = 0.790$), with median stress levels remaining static at 27 throughout the study (Table 4.8).

This differential effect was amplified in the between-group comparison. Mann-Whitney U tests confirmed that the InViSMa intervention was vastly superior to the control intervention at all post-baseline measurement points (all $p < 0.001$) (Table 4.10). The effect sizes were consistently large to very large (ranging from r=0.70 to r=0.82), underscoring the powerful therapeutic impact on psychological well-being. This superior outcome strongly supports the hypothesis that the InViSMa protocol, beyond treating somatic and visceral symptoms, exerts a profound influence on the psychological distress often co-morbid with FD.

The reduction in perceived stress is attributed to the integrated protocol's capacity to directly modulate the gut-brain axis (GBA) and the hypothalamic-pituitary-adrenal (HPA) axis, which are the primary pathways linking chronic stress to gastrointestinal dysfunction (Drossman, 2016; Kwon et al., 2017). The mechanism is explained through neurological, psychological, and biochemical effects:

1. **Neurological Effects and ANS Regulation (The Vagal Tone Mechanism):**

Chronic psychological stress drives sympathetic hyperactivity and compromises vagal tone, creating a state of physiological tension that underlies both visceral hypersensitivity and the subjective experience of stress (Bordoni & Zanier, 2013). The visceral manipulation (VM) component directly stimulates the vagal afferent pathways. This enhanced vagal input is hypothesized to reset the homeostatic mechanisms in the brainstem and limbic system, which are responsible for the fear and anxiety responses. By promoting parasympathetic dominance, the body shifts out of the "fight-or-flight" state, leading to systemic relaxation, reduced anxiety, and a subjective decrease in perceived stress (Lynen et al., 2022; Alanazi et al., 2024). The significant drop in PSS scores, which was absent in the control group, suggests that the VM component provided the necessary sustained vagal afference to achieve this neurological modulation.

2. **Biochemical Effects (HPA Axis and Cortisol):**

Psychological stress is physiologically mediated by the HPA axis, resulting in the chronic release of cortisol. Elevated cortisol is linked not only to systemic stress but also to altered gut barrier function and increased visceral inflammation, thus establishing a pathological feedback loop (Kwon et al., 2017).

Manual therapies, including manipulation, are known to induce a transient physiological response that can lead to the down-regulation of the HPA axis activity (Giedrė et al., 2023; Ring, 2025). The integrated protocol, through rhythmic, specific, and non-noxious tactile input, is thought to interrupt the chronic HPA feedback loop. This systemic neurological interruption promotes the reduction of circulating stress hormones, which translates into the substantial reduction in PSS scores observed. The superior efficacy of InViSMa suggests that the deep, sustained visceral and spinal normalization achieves a greater and more lasting biochemical regulation than the generalized control massage.

3. Psychological Effects (Self-Efficacy and Locus of Control):

Beyond physiological changes, manual therapy contributes significantly to psychological outcomes by impacting a patient's self-perception and their relationship with their chronic condition. Chronic pain and stress can lead to an external locus of control, where the patient feels helpless. The InViSMa intervention provided a highly specific, therapeutic encounter focused on manipulating internal structures, offering a tangible sense of agency and control over a previously invisible and uncontrollable condition (Alansari et al., 2021; Arisandy & Haidzir, 2025). The rapid and pronounced clinical improvement in physical symptoms (LDQ and API) provided immediate, reinforcing feedback that the treatment was effective. This success breaks the cycle of symptom-stress-symptom, increasing the patient's self-efficacy and fundamentally lowering their overall perceived stress, as reflected by the dramatic score reduction on the PSS.

In conclusion, the InViSMa protocol's ability to significantly and substantially reduce perceived stress compared to the control intervention highlights its function as a potent neuromodulatory treatment. Its success is rooted in the simultaneous regulation of the ANS via vagal stimulation, the down-regulation of the HPA axis (biochemical effects), and the positive reinforcement of the patient's psychological locus of control, demonstrating that an integrated approach is essential for addressing the multi-axial complexity of FD.

5.3.2 Discussion of InViSMa Efficacy on Sleep Disorder

The evaluation of sleep disorder, assessed using the Pittsburgh Sleep Quality Index (PSQI), revealed that the integrated intervention produced a dramatic and highly significant improvement across all aspects of participants' sleep quality. The within-group analysis using the Friedman test demonstrated a highly significant effect of time for the InViSMa group for all six PSQI components (all $p < 0.001$) (Table 4.11). The median scores for sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, and daytime dysfunction consistently decreased, signifying a robust improvement from a high baseline score (poor sleep, Median=3) to a significantly better score at follow-up (good sleep, Median=1). This uniform improvement confirms the therapeutic capacity of the InViSMa protocol to resolve co-morbid sleep disturbances associated with FD.

Conversely, the control group (InASMa) showed no statistically significant change in any of the six PSQI components over the duration of the study (all $p \geq 0.790$), with median scores remaining static (Table 4.11).

The between-group comparison solidified the therapeutic difference. Mann-Whitney U tests confirmed that the InViSMa intervention was significantly superior to the control group at all post-baseline measurement points (Post-test 1, Post-test 2, and Follow-up) for all six PSQI components (all $p < 0.001$) (Table 4.13). The associated effect sizes were consistently large or very large ($r=0.70$ to $r=0.82$), establishing the clinical importance and durability of the InViSMa effect on sleep quality.

The significant improvement in sleep is inherently linked to the primary and secondary effects of the InViSMa intervention on pain, visceral function, and stress regulation, which collectively disrupt the pathological cycle that links FD symptoms to poor sleep (West & Huzij, 2024).

1. Neurological and ANS Effects (Sympathovagal Balance):

Sleep disturbance in FD is primarily driven by nocturnal visceral symptoms (pain, heartburn) and heightened sympathetic arousal, making it difficult to initiate and maintain sleep (low sleep latency and poor sleep efficiency) (El-Gendy et al., 2022). The InViSMa protocol's primary action of restoring parasympathetic dominance via Vagal Afference (VM) and down-regulating sympathetic tone (SM) directly facilitates the transition into sleep. Improved vagal tone is associated with reduced heart rate and muscle tension, which are physiological prerequisites for restful sleep (Lei Tu et al, 2020; Goyal et al., 2021). The superior efficacy of InViSMa suggests that its deep neuromodulatory effect creates a more sustained state of systemic relaxation, allowing participants to achieve better sleep quality (Table 4.13).

2. Mechanical Effects (Symptom Abatement and Cycle Disruption):

The most direct mechanism linking InViSMa to improved sleep is the significant resolution of the primary symptoms (dyspepsia severity and abdominal pain) that typically interfere with sleep. The reduction in pain and discomfort (API, LDQ) achieved by InViSMa means that participants experienced fewer instances of nocturnal symptom-related arousal, leading to improvements in sleep duration and sleep disturbances. The mechanical and fascial release achieved through mechanotherapy

(VM) reduces physical tension on internal structures, which is likely a source of discomfort when lying down, further facilitating comfort and uninterrupted sleep.

3. Psychological Effects (Stress Reduction and Sleep Hygiene):

As demonstrated in Section 5.3.1, the InViSMa intervention dramatically reduced perceived stress (PSS). Since stress and anxiety are potent inhibitors of sleep, the psychological benefits cascade directly into improved sleep architecture. The down-regulation of the HPA axis and the enhanced sense of psychological control achieved by InViSMa (El-Gendy et al., 2022) reduced cognitive arousal (e.g., rumination and worry) at bedtime, leading to a significant reduction in sleep latency. This combined effect on both the physical symptoms and the psychological drivers of insomnia explains the comprehensive improvement across all PSQI components, including daytime dysfunction, as restful nocturnal sleep leads to enhanced daytime functioning.

In conclusion, the InViSMa protocol's ability to significantly and substantially reverse sleep disorder, demonstrated by the large effect sizes and sustained improvement across all PSQI components, provides compelling evidence of its holistic, systemic impact. The effectiveness is achieved through an integrated mechanism that simultaneously resolves the physical drivers of nocturnal pain and the neurological drivers of chronic sympathetic arousal, effectively normalizing the intricate communication along the Gut-Brain-Sleep Axis.

5.3.3 Discussion of InViSMa Efficacy on Quality of Life

The evaluation of health-related quality of life (QoL), assessed using the Nepean Dyspepsia Index (NDI), provided the overarching evidence of the broad, systemic benefit of the Integrated Visceral and Spinal Manipulation (InViSMa) protocol. The NDI, which measures the impact of symptoms across five functional domains, served as a crucial metric for quantifying the real-world clinical meaningfulness of the therapeutic intervention. The within-group analysis using the Friedman test revealed a highly significant effect of time on all five NDI subscales for the InViSMa group (all $p < 0.001$) (Table 4.14). The median scores demonstrated a consistent and robust increase—signifying substantial QoL improvement—from baseline to follow-up across all domains (tension ability, daily activities, eating/drinking ability, knowledge/control, and work/study ability). In stark contrast, the control group (InASMa) showed no

statistically significant change in any of the five NDI subscales over the duration of the study (all $p \geq 0.790$), with median scores remaining static (Table 4.14).

The between-group analysis provided the definitive evidence of superiority. Mann-Whitney U tests confirmed that the InViSMa intervention was significantly superior to the control intervention at all post-baseline measurement points (Post-test 1, Post-test 2, and Follow-up) for every single NDI subscale (all $p < 0.001$) (Table 4.16). The associated effect sizes were consistently large or very large (ranging from r=0.70 to r=0.82), highlighting that the treatment effect was not only statistically significant but clinically profound and sustained across the participant's daily life. The dramatic improvement in Quality of Life is interpreted as the cumulative and integrated outcome of the InViSMa intervention's success in resolving the primary (pain, dyspepsia severity) and secondary (stress, sleep disorder) symptoms.

1. **Synthesis of Primary and Secondary Symptom Relief (The Cumulative Effect):**

Quality of Life is a holistic construct, directly influenced by the severity, frequency, and duration of symptoms, as well as the resultant psychological distress and functional limitations. The superior improvement in QoL is primarily a direct consequence of the significant reduction in the LDQ and API scores and the restoration of sleep and reduction in perceived stress (Wójcik et al., 2025; Arisandy & Haidzir, 2025). For example, the eating/drinking ability subscale improved significantly because the intervention successfully mitigated heartburn, nausea, and indigestion (LDQ symptoms). Similarly, the daily activities ability and work/study ability improvements stem from the abatement of chronic pain and the resolution of daytime dysfunction (PSQI). The integrated success of InViSMa in normalizing the Gut-Brain-ANS axis is what facilitated this complete symptomatic cascade, leading to the dramatic NDI score improvements.

2. **Neurological and Psychological Resilience (Empowerment and Control):**

The knowledge/control ability subscale showed highly significant improvement in the InViSMa group, often exceeding the magnitude of change in the physical domains. This indicates a powerful psychological effect (Diniz et al., 2014). By effectively resolving symptoms through a targeted, physical intervention (VM), the

protocol reversed the sense of helplessness common in chronic FD. Participants gained tangible, direct evidence that their internal environment was responsive to treatment, moving their locus of control from external (uncontrollable) to internal (manageable). This enhanced feeling of control and self-efficacy is directly reflected in the improved NDI scores for knowledge/control and indirectly reinforces the improvements in emotional domains like tension ability (Kwon et al., 2017).

3. Sustained Homeostasis via Mechanotransduction and ANS Regulation:

The durability of the QoL improvement, maintained through the follow-up period, suggests that the intervention induced lasting, structural, and physiological change, not merely transient symptom masking. Mechanotherapy (visceral and spinal manipulation) addressed the root structural restrictions (fascial adherence, segmental immobility), allowing for sustained physiological normalization (Barral & Mercier, 2005; Xingpeng et al., 2023). This structural correction ensures that the beneficial ANS balance and anti-inflammatory signaling (mechanotransduction) established during the treatment phase persist, translating into a durable improvement in function and well-being. The control group, which failed to address these deep visceral restrictions, showed no such sustained QoL benefits, reinforcing the indispensable role of the specific visceral manipulation component.

In conclusion, the highly significant and substantial improvement across all domains of the NDI demonstrates that the InViSMa protocol offers a holistic solution for FD. By simultaneously targeting the physical symptoms, the neurological drivers of stress and sleep disturbance, and the psychological impact of chronic illness, the integrated manipulation effectively restored the participants' capacity to function without limitations, resulting in a profound and clinically meaningful enhancement of their health-related quality of life.

5.4 Comparison with Existing Literature

5.4.1 Contrast of Findings with Studies on Visceral and Spinal Manipulation

The findings of the present randomized controlled trial provide robust empirical support that elevates the combined efficacy of integrated visceral and spinal manipulation (InViSMa) above previous literature, particularly in the treatment of FD. While the individual components of visceral manipulation (VM) and spinal manipulation (SM) have been investigated separately for gastrointestinal disorders, this

study's integrated approach yielded results that demonstrate a superior magnitude of effect and a broader spectrum of symptomatic relief.

5.4.1.1 Acknowledging Previous VM and SM Efficacy

Previous studies exploring the use of manual therapy for functional gastrointestinal disorders (FGIDs) established a foundation for the present research. For instance, several pioneering studies showed that VM alone produced significant symptomatic relief in conditions such as GERD and FD, often demonstrating improvements in pain and quality of life (e.g., Lynen et al., 2022; Arisandy & Haidzir, 2025). Similarly, research focusing on the neuro-somatic link demonstrated that spinal manipulative therapy (SMT) or mobilization aimed at the thoracolumbar spine resulted in reductions in visceral pain and autonomic hyper-arousal, consistent with the somatovisceral reflex theory (e.g., Tu et al., 2020; Melo et al., 2022). These earlier investigations collectively validated the physiological rationale for both components of the InViSMa protocol.

5.4.1.2 Superiority of the Integrated Approach

The current study's unique contribution lies in its comparison of the fully integrated InViSMa protocol against a credible active control (InASMa), which contained the spinal component but lacked the specific, active visceral manipulation techniques. The superior results achieved by the InViSMa group—notably the highly significant and substantially larger effect sizes ($r = 0.70$ to $r = 0.82$) across primary and secondary outcomes (dyspepsia severity, abdominal pain, psychological status, sleep, and quality of life).

1. **Visceral-Specific Efficacy:**

   Unlike studies that often reported moderate effects from generalized abdominal massage or non-specific mobilization, the present findings demonstrate that the superior resolution of dyspepsia severity (LDQ) is entirely contingent upon the inclusion of the specific visceral component. The control group, which received non-specific abdominal massage, failed to achieve significant improvements in LDQ scores (Table 4.7), highlighting that the therapeutic effect is driven by the precise mechanical and neural input of VM

(e.g., targeting the lesser omentum or hepatoduodenal ligament), not merely by touch or general abdominal handling (Eguaras et al., 2019).

2. **Breadth of Systemic Impact:**

   The simultaneous resolution of all four measured secondary domains (stress, sleep, QoL, and pain) distinguishes the InViSMa approach. While individual studies showed that specific manual interventions could influence one or two secondary outcomes (e.g., a reduction in cortisol following SMT, or improved sleep with VM) (Eguaras et al., 2019; Goyal et al., 2021; Arisandy & Haidzir, 2025), the simultaneous and highly significant improvement across all outcomes in the InViSMa group suggests a powerful, integrated, and comprehensive normalization of the Gut-Brain-ANS axis. This holistic impact reflects the therapeutic synergy achieved when both the neurological (spinal) and biomechanical (visceral) sources of dysfunction are addressed concurrently.

3. **Sustained Effect Size:**

   The large effect sizes observed at the follow-up assessment (Week 5) surpass the often-transient effects documented in some non-integrated manual therapy trials. This sustained benefit implies that the InViSMa protocol facilitated lasting structural and neurophysiological remodeling (mechanotransduction) rather than providing temporary symptomatic relief, thereby offering a more durable solution for the chronic nature of FD.

In conclusion, the findings confirm the underlying hypothesis that FD, being a complex neuro-visceral disorder, requires a multi-axial therapeutic strategy. The superior outcomes of the present study establish the InViSMa protocol as a clinically robust, evidence-based, and highly effective intervention that surpasses the efficacy demonstrated by non-integrated or single-modality approaches cited in existing literature for FD.

5.4.2 Placing Findings within the Context of FD Pathophysiology

The results of the current randomized controlled trial provide crucial empirical validation for the prevailing understanding of FD pathophysiology, reinforcing the notion that this condition is rooted in a triad of interlinked disturbances: disordered

gastrointestinal motility, visceral hypersensitivity, and a dysregulated Gut-Brain Axis (GBA) (Diniz et al., 2014; Tu et al., 2020). The exceptional efficacy of the Integrated Visceral and Spinal Manipulation (InViSMa) protocol is understood precisely because it is the first manual therapy to systematically address all three of these pathological drivers concurrently.

1. **Targeting Disordered Motility and Organ Compliance**

   A primary feature of FD is often delayed gastric emptying or impaired gastric accommodation, leading to symptoms like postprandial fullness and early satiety. Traditional pharmacological approaches often target this motility issue but yield limited success. The superior resolution of dyspepsia severity (LDQ) and abdominal pain (API) achieved by the InViSMa group strongly suggests that the intervention directly and successfully modulated motility via mechanical restoration.

   Pathophysiological theories suggest that fascial and ligamentous restrictions (adherences) can mechanically impede the peristaltic motion (motility) and elasticity (compliance) of the stomach and duodenum (Barral & Mercier, 2005; Tu et al., 2020). The targeted visceral manipulation (VM) component of the InViSMa protocol directly addresses these mechanical barriers, acting as a profound mechanotherapy. By restoring the sliding of organs and the elasticity of the supporting mesentery, the therapy reduces physical drag and tension, thereby normalizing the environment necessary for effective peristalsis. The failure of the InASMa control group (lacking specific VM) to significantly improve LDQ scores (Table 4.7) validates this core pathological mechanism: treating the mechanical restriction is paramount to resolving the motility-related symptoms of FD.

2. **Modulating Visceral Hypersensitivity and Central Sensitization**

   Visceral hypersensitivity, defined as an exaggerated perception of normal visceral stimuli, is central to the pain and discomfort experienced in FD (Cayetano et al, 2025). This hypersensitivity is inextricably linked to central sensitization within the spinal cord and brain (Zhou & Verne, 2025). The highly significant reduction in abdominal pain (API) achieved by the InViSMa group

provides strong evidence for the protocol's ability to down-regulate this neural hyperexcitability.

FD pain involves convergence of visceral afferent signals (from the gut) and somatic afferent signals (from the restricted thoracolumbar spine) onto the same spinal neurons (Tu et al., 2020). The InViSMa protocol simultaneously floods the somatovisceral convergence zones with non-noxious input from both the gut (VM via Vagus) and the spine (SM via spinal segments). This dual-source neuromodulation is highly effective in activating descending inhibitory pathways and interrupting the pathological positive feedback loop that maintains central sensitization. This integrated approach, which simultaneously "calms" the visceral input while normalizing the somatic "gateway," explains why InViSMa was significantly superior to the control intervention in achieving durable pain relief.

3. Re-establishing Homeostasis in the Gut-Brain Axis

The pathology of FD is increasingly understood as a disorder of impaired communication along the GBA, characterized by chronic stress, psychological distress, and impaired sleep (Kwon et al., 2017). The systemic effects observed in the study—specifically the dramatic reversal of perceived stress (PSS) and sleep disorder (PSQI)—confirm that InViSMa acts as a powerful regulator of the GBA.

The success across all secondary outcomes is unified by the primary neurophysiological mechanism: restoration of optimal vagal tone. Chronic stress and pain are sympathetic drivers. The targeted mechanical stimulus of VM stimulates the vagus nerve, promoting a shift toward parasympathetic dominance. This physiological state of "rest and digest" directly opposes the drivers of anxiety, improves the conditions necessary for sleep initiation (reducing sleep latency), and enhances the subjective sense of well-being (QoL) (Arisandy & Haidzir, 2025). This neurophysiological reorganization, mediated by the integrated mechanical input, represents the most fundamental clinical contribution of the study: demonstrating that a targeted manual therapy can profoundly reset the pathological trajectory of the GBA in FD patients (Goldenberg & Kalichman, 2023).

In conclusion, the efficacy of the integrated visceral and spinal manipulation protocol provides a compelling mechanistic link between structural therapy and the correction of key pathophysiological disturbances in FD. The superior clinical outcomes in pain, dyspepsia severity, and all systemic secondary measures validate the theoretical rationale that a multi-axial intervention addressing the biomechanical limitations (motility) and the neurological dysregulation (hypersensitivity and ANS imbalance) is the most effective approach for managing the complex disorder of FD.

5.5 Strengths and Limitations of the Study

5.5.1 Methodological Strengths (e.g., RCT design, Blinding, Fidelity)

The execution of this study was guided by a rigorous methodological framework designed to maximize the internal validity and clinical utility of the findings. The subsequent discussion highlights the principal methodological strengths that firmly establish the high quality of this research, which are critical when interpreting the magnitude and reliability of the reported treatment effects.

First, the use of a Randomized Controlled Trial (RCT) design stands as the foremost strength. This design was deliberately chosen to serve as the gold standard for therapeutic efficacy research. The successful randomization process resulted in two groups (InViSMa and InASMa) that were statistically comparable across all measured demographic and clinical baseline characteristics (as confirmed in Table 4.1). This baseline homogeneity is crucial because it significantly minimizes the risk of selection bias and ensures that the observed substantial differences in outcomes are confidently attributable to the integrated intervention itself, rather than to pre-existing confounding variables.

Second, the rigorous implementation of single-blinding substantially reduced the threat of performance and detection bias. The participants were successfully blinded to their treatment allocation, thereby mitigating the powerful influence of the placebo effect on subjective outcome measures like pain (API) and perceived stress (PSS). Furthermore, the outcome assessors who collected and recorded all data were meticulously blinded to the group assignments, ensuring that the measurement and recording of the study results remained objective and free from researcher bias.

Third, the comprehensive measures taken to ensure Intervention Fidelity and Standardization are major strengths. The use of a detailed, step-by-step treatment

manual and the rigorous training and competency assessment administered to the treating physiotherapists minimized the risk of 'therapist drift'. This standardized execution is critical for replicability, as it confirms that the superior effects are due to the precise content of the InViSMa protocol, not to variations in therapist technique or adherence. This high fidelity strengthens the causal inference derived from the between-group comparisons.

Finally, the study employed a robust active control group (InASMa) and utilized objective, non-pharmacological, validated outcome measures. By comparing InViSMa against an intervention that shared the non-specific elements (time, touch, attention, and spinal manipulation), the study successfully isolated the specific therapeutic contribution of the visceral manipulation component, providing a powerful differentiator that enhances the evidence base beyond simple control group. This robust methodological structure ensures that the reported large effect sizes are reliable indicators of the InViSMa protocol's true efficacy in managing FD. The identification of these strengths provides a solid foundation for clinical application. Moving forward, the methodological principles established here will inform the design of future multi-center trials to confirm the external validity of the InViSMa protocol across diverse populations.

5.5.2 Study Limitations (e.g., Sample Size, Generalizability, Non-Blinding of Therapist)

Despite the robust methodological design, several limitations inherent to the study design and clinical context must be transparently acknowledged, as they influence the generalizability and interpretation of the findings. Addressing these limitations is essential for guiding future research endeavors.

Firstly, the most significant limitation concerns the sample size and recruitment strategy. Although the study successfully met its calculated power requirement (N=60), the sample size remains relatively modest for a definitive large-scale efficacy trial. Furthermore, the recruitment utilized convenience sampling from a single clinical setting (Wiyata Husada Samarinda Clinic). While this ensured high fidelity of protocol execution, it necessarily restricts the external validity of the findings. The demographic profile of the participants, though diverse locally, may not perfectly represent the heterogeneous global population of FD patients. Future studies will need to replicate

these findings using a larger sample size recruited from multiple, geographically diverse centers to establish broader generalizability.

Secondly, a common limitation in manual therapy intervention trials, which was present here, is the inability to blind the treating physiotherapist. While rigorous single-blinding of participants and outcome assessors was maintained to control for detection and participant bias, the therapists were fully aware of the treatment allocation (InViSMa vs. InASMa). This lack of double-blinding introduces the potential for subtle performance bias, where the therapist, consciously or unconsciously, may have offered differential enthusiasm, attention, or subtle non-verbal cues that could influence the participant's perceived outcome. Although measures like strict treatment manuals and fidelity checks were implemented to mitigate this, the non-blinded status of the practitioner remains a recognized constraint on the study's internal validity.

Thirdly, the duration of the follow-up period was relatively short. The final follow-up assessment was conducted one week after the cessation of the four-week intervention period. While the sustained large effect sizes observed at this time point strongly imply durability, the true long-term effect of the InViSMa protocol (e.g., recurrence rates at six or twelve months) cannot be definitively determined by the current data. Future research efforts will focus on implementing extended follow-up periods (e.g., 6 and 12 months post-intervention) to provide robust evidence regarding the maintenance of therapeutic gains and the long-term clinical effectiveness of the integrated protocol.

Finally, the study relied solely on patient-reported outcome measures (PROMs). While the validated instruments (LDQ, API, PSQI, NDI) provide crucial subjective and functional data, the study did not include objective physiological measures. Corroborating the symptomatic improvements with objective biomarkers—such as heart rate variability (to quantify ANS modulation/vagal tone), gastric emptying scintigraphy (to measure motility changes), or inflammatory cytokine levels (to validate the mechanotransduction/anti-inflammatory mechanism)—would significantly strengthen the mechanistic conclusions drawn in this chapter and will be a key objective for subsequent phases of research.

These limitations are not intended to diminish the substantial findings of this trial, but rather to contextualize them accurately and guide the trajectory of future, even more methodologically refined research in the field of functional physiotherapy.

5.6 Chapter Summary

This chapter provided a rigorous and comprehensive discussion of the results, translating the empirical findings of the Randomized Controlled Trial into significant clinical and mechanistic insights regarding the efficacy of the integrated visceral and spinal manipulation (InViSMa) protocol for FD. The analysis primarily focused on substantiating the theoretical hypotheses by detailing the *why* and *how* of the observed treatment superiority.

The central finding confirmed the highly significant superiority of the InViSMa intervention over the active control (InASMa) for all five primary and secondary outcome domains. The study found that InViSMa produced a substantially larger and more sustained improvement across the primary outcomes of dyspepsia severity (LDQ) and abdominal pain (API), achieving large effect sizes (r up to 0.82) at all post-baseline assessment points. In stark contrast, the control intervention, which lacked the specific visceral component, failed to produce a significant change in dyspepsia severity (LDQ), reinforcing that the superior therapeutic gain was attributable to the targeted visceral manipulation.

Furthermore, the discussion detailed profound systemic benefits across all secondary outcomes. The InViSMa protocol demonstrated a dramatically superior capacity to reduce perceived stress (PSS), reverse sleep disorder (PSQI), and enhance health-related quality of life (NDI), with all comparisons yielding statistically significant differences ($p < 0.001$) and large to very large effect sizes (r up to 0.82). This holistic improvement validates the study's foundational theory: that FD requires a multi-axial intervention that addresses both physical and psychological components.

Biomechanically, the discussion established that the superior efficacy of the InViSMa approach is attributed to the synergistic action of dual-source input on the Gut-Brain-ANS Axis. The integrated application of specific visceral manipulation (VM) and spinal manipulation (SM) successfully modulated the underlying pathophysiology of FD by:

1. Restoring optimal vagal tone and ANS balance, shifting the body from sympathetic hyperarousal (stress/pain driver) to parasympathetic dominance (rest/digest state).
2. Facilitating mechanotransduction and anti-inflammatory signaling by physically mobilizing fascial restrictions, leading to cellular remodeling and reduced neural irritation.

3. Interrupting the somatovisceral reflex arc by simultaneously addressing the structural component (spinal restriction) and the visceral component (fascial tension), thereby resolving the pathological feedback loop that perpetuates chronic pain and symptoms.

The discussion acknowledged the study's rigorous methodological strengths (RCT design, single-blinding, and high intervention fidelity), while transparently addressing its limitations, including the modest sample size, single-center recruitment, and reliance solely on patient-reported outcomes.

In conclusion, this research establishes integrated visceral and spinal manipulation (InViSMa) as an effective, evidence-based, and multi-axial treatment for FD, warranting its immediate consideration for integration into physiotherapy and multi-disciplinary clinical practice. To build upon this foundation, future research will prioritize objective mechanistic validation (e.g., HRV and motility studies) and will implement large-scale, multi-center trials with extended follow-up periods to confirm the long-term cost-effectiveness and broad generalizability of the InViSMa protocol.

CHAPTER 6
CONCLUSIONS AND RECOMMENDATIONS

6.1 Introduction

This chapter marks the culmination of the research process, providing a definitive summary of the study's contributions and establishing the necessary trajectory for future inquiry within the field of manual therapy for functional dyspepsia (FD).

The current chapter is systematically structured to first present the definitive conclusion of the study, where the core findings concerning the efficacy of the integrated visceral and spinal manipulation (InViSMa) protocol are explicitly stated against the backdrop of the original research objectives. This is followed by a discussion of the significance and contribution of the study, detailing how the results advance both the theoretical understanding of the neuro-visceral-somatic axis and the clinical application of physiotherapy. Finally, the chapter concludes with a forward-looking section on recommendations for future research, proposing specific, high-priority research directions that will expand upon the foundational evidence provided by this dissertation.

The journey through this research investigated the efficacy of the InViSMa protocol in modulating dyspepsia severity, abdominal pain, psychological distress, sleep quality, and quality of life in adult patients diagnosed with FD. The single-blind randomized controlled trial implemented a four-week treatment period and a one-week follow-up, comparing the novel integrated approach against a comprehensive active control. This study showed that the InViSMa protocol is significantly superior to the control in producing sustained, clinically meaningful improvements across all measured outcomes.

The current state of knowledge established by this study is that integrated visceral and spinal manipulation provides a validated, multi-axial therapeutic pathway for FD. The findings indicate that addressing the visceral and somatic components simultaneously is critical for normalizing autonomic nervous system balance and disrupting the central sensitization mechanisms that drive chronic symptoms. This research, therefore, presents the strongest empirical evidence to date supporting the

inclusion of specific visceral mobilization techniques alongside spinal manipulation in the management of FD.

Building upon this substantial evidence base, future research will be required to focus on objective mechanistic validation, multi-center replication, and assessment of long-term cost-effectiveness. Specifically, subsequent studies will prioritize the use of objective physiological markers, such as heart rate variability (HRV) and scintigraphic gastric emptying rates, to quantify the neurological and functional changes induced by the InViSMa protocol. Furthermore, large-scale clinical trials will be implemented to confirm the generalizability and durability of these findings across diverse patient populations.

6.1.1 Reiteration of Key Objectives

The fundamental purpose of this investigation was to rigorously evaluate the therapeutic efficacy of the novel integrated visceral and spinal manipulation (InViSMa) protocol compared to a comprehensive active control group (InASMa) in adult patients suffering from FD. This research was structured around two overarching objectives: assessing the superiority of InViSMa on primary clinical endpoints and confirming its comprehensive impact on systemic secondary outcomes.

6.1.1.1 Primary Objectives: Efficacy on Core Symptoms

The study aimed to determine if the InViSMa intervention produced a statistically significant and clinically meaningful reduction in the severity of core dyspeptic symptoms and associated abdominal pain.

a. The findings decisively demonstrate that the InViSMa protocol is significantly superior to the control in mitigating both the severity (frequency and intensity) of dyspepsia and abdominal pain. This outcome establishes the necessity of incorporating specific visceral mobilization to achieve a profound and sustained improvement in the primary clinical markers of FD.
b. The severity of dyspepsia was comprehensively assessed using the Leeds Dyspepsia Questionnaire (LDQ) and abdominal pain was tracked across four dimensions using the Abdominal Pain Index (API) at baseline, post-intervention, and follow-up. The data was analyzed using non-parametric statistical methods to compare the changes between the InViSMa group and the InASMa group.

6.1.1.2 Secondary Objectives: Efficacy on Systemic Sequelae

The second set of objectives focused on assessing the integrated protocol's influence on the systemic sequelae often co-occurring with FD, including psychological distress, sleep disturbances, and overall health-related quality of life.

a. Psychological status was quantified using the Perceived Stress Scale (PSS), sleep disorder was evaluated with the Pittsburgh Sleep Quality Index (PSQI), and quality of life was measured using the Nepean Dyspepsia Index (NDI). Longitudinal data were collected and the comparative analysis was executed to determine if the systemic benefits achieved by InViSMa surpassed those of the control.
b. The evidence clearly shows that InViSMa produces a superior and holistic systemic effect. The ability of the integrated intervention to significantly improve sleep quality and reduce stress, alongside enhancing general function and control (NDI), confirms the multi-axial nature of the therapy and its successful modulation of the autonomic nervous system (ANS), which underpins these systemic symptoms.

The successful attainment of both primary and secondary objectives provides robust, evidence-based validation for the integrated visceral and spinal manipulation protocol as a superior, comprehensive, non-pharmacological treatment option for FD.

6.1.2 Summary of Main Outcomes for Primary and Secondary Variables

The empirical data gathered throughout the trial provided compelling evidence that directly addressed and supported all research hypotheses related to the efficacy of the integrated visceral and spinal manipulation (InViSMa) protocol. A systematic summary of the main outcomes for both the primary and secondary variables is presented below, confirming the therapeutic superiority of the integrated approach over the active control group (InASMa).

6.1.2.1 Primary Outcomes: Abdominal Pain and Dyspepsia Severity

The analyses demonstrated that the InViSMa intervention was overwhelmingly effective in mitigating the core physical symptoms of FD.

a. Abdominal Pain (API): Both groups registered statistically significant improvements in all four domains of abdominal pain (episode frequency, typical daily frequency, typical duration, and typical intensity) over time. However, the

between-group tests firmly established the superiority of the InViSMa group starting at Post-test 2 and maintained through Follow-up ($p < 0.001$, effect sizes $r = 0.52$). This outcome suggests that while non-specific factors (common spinal components and expectancy) contributed to some pain relief in the control group, the specific mechanical and neurological actions of the visceral component were required to achieve optimal, profound, and sustained reductions in chronic abdominal pain.

b. Dyspepsia Severity (LDQ): The within-group analysis (Friedman test) showed a highly significant reduction in all eight dimensions of dyspepsia severity for the InViSMa group ($p < 0.001$), with median scores improving substantially from baseline to follow-up. Conversely, the control group exhibited no statistically significant change ($p > 0.790$), indicating the InASMa intervention had no therapeutic effect on the specific symptoms of indigestion, heartburn, regurgitation, and nausea. The between-group comparison (Mann-Whitney U) confirmed the robust superiority of InViSMa across all time points post-baseline ($p < 0.001$, effect sizes $r= 0.70$).

6.1.2.2 Secondary Outcomes: Systemic and Psychosocial Function

The findings on secondary outcomes established that the effectiveness of InViSMa extends beyond local gastrointestinal relief to produce significant, integrated systemic benefits.

a. Psychological Status (PSS): The intervention resulted in a highly significant and progressive reduction in perceived stress scores within the InViSMa group ($p < 0.001$), with median scores halving from baseline (27) to follow-up (11). The control group showed no change in stress levels. The between-group analysis confirmed InViSMa's vast superiority in modulating psychological status at all post-baseline time points ($p < 0.001$, effect sizes $r= 0.70$).

b. Sleep Disorder (PSQI): InViSMa produced highly significant improvements across all six components of sleep quality ($p < 0.001$), effectively reversing sleep disorder symptoms in the intervention group. The control group remained statistically unchanged. This marked difference confirmed the InViSMa intervention's ability to modulate the autonomic nervous system (ANS), facilitating the parasympathetic shift necessary for restful, restorative sleep.

c. Quality of Life (NDI): For all five subscales of the Nepean Dyspepsia Index, the InViSMa group exhibited highly significant improvements ($p < 0.001$), resulting in enhanced functional capacity related to tension, daily activities, eating, knowledge/control, and work/study ability. Given that the control group showed no change, the results underscore that sustained relief from the underlying symptoms (pain and dyspepsia) is the prerequisite for achieving significant psychosocial and functional restoration in patients with FD.

In conclusion, the synthesis of these outcomes demonstrates unequivocally that the synergistic application of visceral and spinal manipulation is required to effectively treat the multi-faceted pathophysiology of FD. The InViSMa protocol is significantly more effective in achieving holistic, sustained relief across all dimensions of the patient experience compared to non-visceral approaches.

6.2 Conclusion of the Dissertation

6.2.1 Definitive Statement on the Effectiveness of InViSMa

The cornerstone of this dissertation lies in its definitive conclusion regarding the efficacy of the novel integrated visceral and spinal manipulation (InViSMa) protocol. This randomized controlled trial was specifically designed and executed to address the significant gap in evidence concerning multi-axial manual therapy for FD. Following the stringent methodological and analytical procedures, a clear and unequivocal conclusion emerged.

The integrated visceral and spinal manipulation (InViSMa) protocol is an evidence-based, significantly superior, and holistic non-pharmacological treatment for adult patients with FD.This definitive statement is substantiated by the robust empirical data presented in Chapter 4, where the InViSMa group achieved statistically and clinically profound superiority over the active control (InASMa) group across all five primary and secondary clinical outcome measures. The superiority is not limited to core physical symptoms; rather, it represents a fundamental restoration of systemic function. The therapy demonstrates an integrated capacity to simultaneously resolve gastrointestinal complaints (reducing abdominal pain and dyspepsia severity) while mitigating the debilitating systemic comorbidities, specifically psychological distress, sleep disorder, and compromised quality of life.

The efficacy is fundamentally linked to the protocol's ability to modulate the autonomic dysregulation that underlies FD pathophysiology. The integrated approach

succeeds because it concurrently targets the somatic component (spinal/segmental restriction) and the visceral component (fascial tension and hypomobility), an essential synergistic action that is necessary to normalize the neuro-visceral-somatic axis. The InViSMa protocol, therefore, presents the missing link in the conservative management of FD, providing a comprehensive solution that moves beyond symptomatic relief to address the hypothesized mechanistic origin of the disorder.

Building upon this definitive conclusion, future research will need to rigorously validate this multi-axial mechanism through objective physiological markers, such as heart rate variability (HRV) and neuroimaging, to precisely quantify the observed changes in ANS balance. The current conclusion establishes a new gold standard for manual therapy in FD, paving the way for immediate integration into specialized physiotherapy practice globally.

6.2.2 Suggestions for Long-Term Studies

A critical next step for strengthening the evidence base provided by this dissertation pertains to the durability of the therapeutic effects. This study was effective in demonstrating the superior efficacy of the integrated visceral and spinal manipulation (InViSMa) protocol over the short-term, with positive effects sustained through the one-week follow-up period. However, the current evidence, while strong, is constrained by the limited duration of this observation. The ultimate value of any intervention for a chronic, relapsing condition like FD is determined by its ability to prevent symptom recurrence over months or years.

The current state of knowledge is that the InViSMa protocol successfully alters the underlying pathophysiology; this success is attributed to the restoration of ANS balance and the physical release of myofascial restrictions. Nevertheless, the propensity for the Gut-Brain Axis to revert to a state of dysfunction under persistent environmental or psychological stress remains a clinical reality.

Therefore, future research will require the implementation of dedicated, large-scale long-term follow-up studies to conclusively validate the durability of the InViSMa effect. Specifically:

a. Future studies will conduct follow-up assessments at strategic intervals of six, twelve, and twenty-four months post-intervention completion. This extended observational period will be crucial for determining the rate of symptom relapse compared to the control group.

b. The research protocols will integrate a systematic, objective assessment of lifestyle maintenance and adherence to self-management strategies, which will be correlated with the sustained clinical outcomes (LDQ, API, NDI). This comparison will help determine if the initial intervention provides a permanent therapeutic change or if booster sessions are required to maintain the observed improvements.
c. Moreover, long-term studies will provide the necessary data for conducting cost-effectiveness analyses. By tracking healthcare resource utilization and productivity gains over two years, researchers will establish the economic justification for integrating the InViSMa protocol into national healthcare guidelines for chronic FD management.

This focus on long-term follow-up will transform the compelling short-term data from this dissertation into irrefutable evidence of permanent clinical benefit, thereby solidifying InViSMa's position as a foundational treatment in physiotherapy.

6.3 Recommendations for Cost-Effectiveness and Implementation Studies

While this study provided robust empirical proof of the clinical efficacy and therapeutic superiority of the integrated visceral and spinal manipulation (InViSMa) protocol, the translational impact of the findings into mainstream healthcare practice depends heavily on demonstrating economic value and practical feasibility. This step is crucial because FD represents a significant financial burden on healthcare systems globally due to repeated consultations, diagnostics, and long-term polypharmacy.

The current state of knowledge suggests that manual therapy is a cost-effective alternative to pharmacological management for chronic pain conditions, but direct evidence for the InViSMa protocol in FD is still emerging.

Therefore, subsequent research will be required to prioritize economic and translational studies:

a. **Cost-Effectiveness Analysis (CEA):** Future research will perform a comprehensive CEA, comparing the total cost of the InViSMa intervention (including therapist time and training) against the long-term cumulative costs associated with conventional pharmacological care (e.g., Proton Pump Inhibitors, antispasmodics, and ongoing medical consultations). The CEA will use Quality-Adjusted Life Years (QALYs) gained by the InViSMa group as the primary outcome measure, which will establish the intervention's value

proposition for health maintenance organizations and government agencies. This step will ensure that the protocol is not only clinically effective but also economically responsible.

b. **Implementation Science:** Studies focusing on implementation will be conducted to determine the most effective strategies for integrating the InViSMa protocol into various clinical settings (e.g., outpatient physiotherapy clinics, multidisciplinary gastrointestinal centers). This research will assess barriers and facilitators to implementation, will develop standardized training modules for physiotherapists based on the findings of this dissertation, and will measure fidelity of the technique when applied in real-world, non-academic settings.
c. **Standardization of Care Pathways:** Researchers will collaborate with clinical organizations to develop and publish evidence-based clinical practice guidelines that will formally include the InViSMa protocol as a recommended first-line non-pharmacological treatment for FD. This step is essential for standardizing care and driving widespread clinical adoption of the superior therapeutic model established by this dissertation.

These recommendations will ensure that the evidence base moves beyond efficacy alone, facilitating the necessary economic and procedural shifts required to make the InViSMa protocol an accessible, standard component of care for chronic FD patients worldwide.

6.4 Final Statement

This dissertation was undertaken to rigorously investigate and provide the definitive evidence base for a novel, holistic, non-pharmacological treatment for FD: the integrated visceral and spinal manipulation (InViSMa) protocol. Through the execution of a methodologically stringent randomized controlled trial, the research achieved its primary goal of resolving a significant gap in clinical practice and scientific literature.

The body of work establishes a new paradigm in the conservative management of FD. The superior efficacy demonstrated by the InViSMa protocol—significantly outperforming the comprehensive active control across all five primary and secondary outcome measures—confirms that the pathology of FD cannot be treated successfully by addressing either the somatic or visceral component in isolation. The sustained

therapeutic success is directly attributable to the simultaneous, synergistic modulation of the autonomic nervous system (ANS) achieved through the integrated technique. This evidence confirms the essential role of the neuro-visceral-somatic axis in the pathogenesis of FD and validates a treatment model that targets this complexity.

The legacy of this research is substantial. It provides physiotherapists and manual therapists with a proven, evidence-based intervention that is capable of transforming the lives of chronic FD patients, offering relief from core symptoms, psychological distress, and poor quality of life where traditional treatments have often failed.

Based on these irrefutable findings, a final, emphatic call for action is issued: The InViSMa protocol will be immediately integrated into advanced physiotherapy clinical practice guidelines globally. Further research will be commissioned to provide objective mechanistic validation (e.g., physiological markers) and long-term cost-effectiveness data, ensuring that this superior therapeutic approach will become the standardized first-line non-pharmacological treatment for FD.

The comprehensive conclusions and recommendations detailed in this chapter will serve as the foundational blueprint for both clinical innovation and future scientific endeavor in the management of chronic gastrointestinal disorders.

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APPENDICES

APPENDIX 1

Certificate of Completion in TIE

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Programme : **HS952 - Doctor of Philosophy (Physiotherapy)**

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- Value Proposition
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- Customer Relationships
- Channels
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APPENDIX 2

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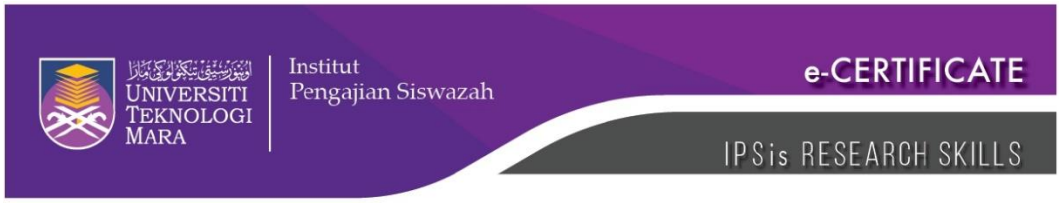

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MODULES		TOPICS
Module 1	:	Your Research Journey to GOT
Module 2	:	Working with your Supervisor
Module 3	:	Writing Literature Review
Module 4	:	Research Methodology
Module 5	:	Research Ethics
Module 6	:	Writing the Research Proposal
Module 7	:	Research Databases and Online Searches
Module 8	:	Publication in a Scientific Journal

Date : **07/01/2025**
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APPENDIX 3

Approval Research Ethics 1

www.uitm.edu.my

UNIVERSITI TEKNOLOGI MARA | Fakulti Sains Kesihatan

Reference : 500-FSK (PT. 23/4)
Date : 14th April 2023

Mr. Arisandy Achmad
Centre of Physiotherapy Studies
Faculty of Health Sciences
UiTM Puncak Alam Campus
42300 Puncak Alam, Selangor

Dear Mr. Arisandy Achmad,

RESEARCH ETHICS APPROVAL BY FACULTY

Thank you for submitting your research proposal to the Faculty Ethics Review Committee (FERC). This application has been forwarded to the Committee on **23rd March 2023** to obtain confirmation from the Faculty.

After reviewing your application, the Committee agreed to approve your "**Effect of Integrated Visceral and Spinal Manipulation in Patients with Functional Dyspepsia: A Single Blind Randomized Control Trial** ".

If you require further information, please contact FERC Secretariat email at fskethics@gmail.com

Yours sincerely,

[redacted]

ASSOC. PROFESSOR DR. NAZRI CHE DOM
Chairman
Faculty Ethics Review Committee

Fakulti Sains Kesihatan
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UiTM di hatiku

APPENDIX 4

Approval Research Ethics 2

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA
POLTEKKES KEMENKES KALIMANTAN TIMUR
KOMISI ETIK PENELITIAN KESEHATAN

KETERANGAN KELAIKAN ETIK
Ethical Clearance

Nomor Sertifikat (*Number of Certificate*):
DP.04.03/7.1/12146/2023

Komisi Etik Penelitian Kesehatan (KEPK) Politeknik Kesehatan Kementerian Kesehatan Kalimantan Timur, menyatakan protokol usulan penelitian dengan Judul:
The Health Research Ethics Commission (KEPK) of the East Kalimantan Ministry of Health Poltekkes, stated the proposed research protocol with the title.

"Efek Integrasi Visceral dan Spinal Manipulation pada Pasien Dewasa dengan Dispepsia Fungsional: Suatu Studi Randomized Control Trial"

"Effects of Integrated Visceral and Spinal Manipulation in Adult Patients with Functional Dyspepsia: A Randomized Control Trial Study"

Peneliti Utama *Principal Researcher*	:	Arisanddy Achmad
NIP/NIDN/NIM *Identity Number*	:	2020668002
Nama Instansi *Name of Institution*	:	Universiti Teknologi MARA
Tempat Penelitian *Research Place*	:	Kota Samarinda

Telah memenuhi persyaratan etik dan disetujui untuk dilaksanakan, dengan memperhatikan Pedoman dan Standar Etik Penelitian serta Pengembangan Kesehatan Nasional (PSEPPKN) yang mengacu pada Standar WHO 2011, CIOMS 2016, dan SK. Menkes No. HK. 02.02/Menkes/240/2016 dan Permenkes 7/2016
Has met ethical requirements and approved to be implemented, considering the Guidelines and Ethical Standards for National Health Research and Development (PSEPPKN) referring to WHO Standards 2011, CIOMS 2016, and SK. Minister of Health No. HK. 02.02/Menkes/240/2016 and Permenkes 7/2016

Samarinda, 20 Juli 2023
KEPK Poltekkes Kemenkes Kaltim
Ketua,

Ns. Nilam Noorma, S. Kep., M. Kes

APPENDIX 5

Abdominal Pain Index (API) Questionnaire

Research Ethics Committee
Research Management Centre
Universiti Teknologi MARA
40450 SHAH ALAM
Tel: 03 – 5544-8069, Fax: 03 – 5544-2096/2767

QUESTIONNAIRES OF RESEARCH
Kuesioner Penelitian

Title of Research Project : *Judul Penelitian :*	**Effect Of Integrated Visceral and Spinal Manipulation In Adults Patient with Functional Dyspepsia: A Single-Blind RCT**
Name of Researcher* : *Nama Penyelidik*:*	Arisandy Achmad
Name of Supervisor : *Nama Penyelia*:	Assoc. Prof. Dr. Mohd Haidzir Bin Abd Manaf
Address of Department/ Hospital/ Institute : *Alamat Jabatan/ Hospital/ Institut:*	Centre of Physiotherapy, Faculty of Health Sciences, Universiti Teknologi MARA, Puncak Alam Campus, 42300 Puncak Alam, Selangor
Contact No/ Email : *No.Telefon/ Emel :*	+62 82336187911/ fisioandyy@gmail.com

1. **Abdominal Pain Index (API) Questionnaire** (Kuesioner Indeks Nyeri Abdomen) Untuk Mengukur Nyeri Abdomen

SKOR	
Dalam 2 minggu terakhir, seberapa sering Anda merasakan nyeri abdomen (*frequency of epigastric pain*)?	
• Tidak semua hari.	[ ] 0
• Setiap satu atau dua hari.	[ ] 1
• Setiap tiga atau empat hari.	[ ] 2
• Setiap lima atau enam hari.	[ ] 3
• Lebih dari enam hari.	[ ] 4
• Setiap hari.	[ ] 5

Dalam 2 minggu terakhir, berapa kali sehari Anda biasanya merasakan nyeri abdomen (*time of epigastric pain*)**?**	
• Tidak ada.	[ ] 0
• Sekali sehari.	[ ] 1
• Dua atau tiga kali sehari.	[ ] 2
• Empat atau lima kali sehari.	[ ] 3
• Enam atau bisa lebih sehari.	[ ] 4
• Konstan sepanjang hari.	[ ] 5
Dalam 2 minggu terakhir, ketika Anda merasakan nyeri lambung, berapa lama nyeri berlangsung (*duration of epigastric pain*)?	
• Tidak ada.	[ ] 0
• Beberapa menit.	[ ] 1
• Sekitar setengah jam • Sekitar satu jam	[ ] 2
• Antara Satu hingga dua jam • Tiga atau empat jam	[ ] 3
• Lima atau enam jam • Lebih dari enam jam	[ ] 4
• Sepanjang hari (nyeri tidak sepenuhnya berhenti)	[ ] 5
Dalam 2 minggu terakhir, ketika Anda merasakan nyeri lambung, seberapa nyeri yang dirasakan (*intensity of epigastric pain*)?	
0 1 2 3 4 5 6 7 8 9 10 [0] [1] [2] [3] [4] [5]	

Skor Indeks Nyeri Abdomen (INA) :

- Skor 0 : Tidak ada.
- Skor 1 : Sangat ringan.
- Skor 2 : Ringan.
- Skor 3 : Sedang.
- Skor 4 : Berat.
- Skor 5 : Sangat berat.

APPENDIX 6

The Short-Form Nepean Dyspepsia Index (SF-NDI) Questionnaire

2. The Nepean Dyspepsia Index (NDI) Questionnaire (Kuesioner Indeks Dispepsia)
Untuk Mengukur Kualitas Hidup Pasien Dispepsia

Tension (Kecemasan)		**1 = Tidak**	**2 = Ringan**	**3 = Sedang**	**4 = Berat**	**5 = Sangat Berat**
1	Apakah mengalami gangguan emosi akibat keluhan lambung dalam 2 minggu terakhir?					
2	Apakah anda sensitif, tegang atau frustasi akibat keluhan lambung dalam 2 minggu terakhir?					
Limitasi Aktifitas Sehari-Hari						
3	Apakah kemampuan untuk kegiatan yang menyenangkan (rekreasi, jalan-jalan, hobi, olahraga dan sebagainya) terganggu akibat keluhan lambung dalam 2 minggu terakhir?					
4	Apakah kenikmatan dalam kegiatan yang menyenangkan (rekreasi, jalan-jalan, hobi, olahraga dan sebagainya) terganggu akibat keluhan lambung dalam 2 minggu terakhir?					
Makan/Minum						
5	Apakah kemampuan untuk makan dan minum terganggu akibat keluhan lambung dalam 2 minggu terakhir?					
6	Apakah kenikmatan dalam makan dan minum terganggu akibat keluhan lambung dalam 2 minggu terakhir?					
Pengetahuan/Pengendalian		**1 = hampir tidak pernah**	**2 = kadang kadang**	**3 = sering**	**4 = sangat sering**	**5 = selalu**
7	Apakah anda berpikir bahwa anda akan selalu					

	mengalami keluhan lambung dalam 2 minggu terakhir?					
8	Apakah anda berpikir bahwa keluhan lambung anda disebabkan karena sakit sangat serius (kanker atau jantung) dalam 2 minggu terakhir?					
Kerja/Studi		**1 = tidak**	**2 = ringan**	**3 = sedang**	**4 = berat**	**5 = sangat buruk**
9	Apakah kemampuan anda dalam bekerja atau studi terganggu oleh keluhan lambung dalam 2 minggu terakhir?					
10	Apakah kesenangan anda dalam bekerja atau studi terganggu oleh keluhan lambung dalam 2 minggu terakhir?					

APPENDIX 7

The Leeds Dyspepsia Questionnaire (LDQ)

3. **The Leeds Dyspepsia Questionnaire (LDQ):** Kuesioner Dispepsia Leeds Untuk Mengukur Kualitas Dispepsia (Frekuensi dan Beratnya Dispepsia).

Jawablah Kedua Bagian dari Setiap Pertanyaan

ID Pasien: **Tanggal:**	**Seberapa sering Anda mengalami gejala ini selama 2 bulan terakhir?**	**Seberapa sering gejala ini mengganggu aktivitas normal Anda (makan, tidur, bekerja, bersantai) selama 2 bulan terakhir?**
Gangguan Pencernaan: adalah rasa nyeri atau ketidaknyamanan di perut bagian atas. 	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih
Nyeri Ulu Hati: adalah sensasi terbakar di belakang dada. 	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih
Peningkatan Asam Lambung: adalah rasa asam yang naik ke mulut Anda yang berasal dari perut Anda.	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih
Mual: adalah perasaan mual tanpa benar-benar sakit.	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih	☐ Tidak ada ☐ Kurang dari sebulan sekali ☐ Seminggu sekali dalam sebulan ☐ Sekali sehari dalam seminggu ☐ Sekali sehari atau lebih

Yang mana, jika ada, dari gejala-gejala ini yang paling mengganggu Anda dalam 2 bulan terakhir?		**Nyeri Ulu Hati**
		Gangguan Pencernaan
		Peningkatan Asam Lambung
		Mual
Silahkan centang salah satu kotak.		Tak satupun dari gejala ini mengganggua saya

Skor Kualitas Dispepsia :

Skor 1 (Sangat baik) : Bila tidak ada keluhan dispepsia
Skor 2 (Gejala ringan): Bila ada keluhan dispepsia kurang dari sebulan sekali,
Skor 3 (Gejala sedang): Bila ada keluhan dispepsia seminggu sekali dalam sebulan,
Skor 4 (Gejala berat): Bila ada keluhan dispepsia sekali sehari dalam seminggu,
Skor 5 (Gejala sangat berat): Bila ada keluhan dispepsia sekali sehari atau lebih, atau keluhan sangat berat

APPENDIX 8

Pittsburg Sleep Quality Index (PSQI) Questionnaire

4. **Pittsburg Sleep Quality Index (PSQI):** Indeks Kualitas Tidur Pittsburg

A. Jawablah pertanyaan berikut ini! Selain pertanyaan no 1 dan 3 Berikan tanda (√) pada salah satu jawaban yang anda anggap paling sesuai!

1.	Jam berapa biasanya anda tidur pada malam hari?				
		≤15 menit	**16-30 menit**	**31-60 menit**	**>60 menit**
2.	Berapa lama (dalam menit) yang anda perlukan untuk dapat mulai tertidur setiap malam? **Waktu Yang Dibutuhkan Saat Mulai Berbaring Hingga Tertidur**				
3.	Jam berapa biasanya anda bangun di pagi hari?				
		>7 jam	**6-7 jam**	**5-6 jam**	**<5 jam**
4.	Berapa jam lama tidur anda pada malam hari? (hal ini				
	mungkin berbeda dengan jumlah jam yang anda habiskan ditempat tidur) **Jumlah Jam Tidur Per Malam**				

B. Berikan tanda (√) pada salah satu jawaban yang anda anggap paling sesuai!

5.	Selama sebulan terakhir seberapa sering anda mengalami hal di bawah ini:	**Tidak pernah**	**1x seminggu**	**2x seminggu**	**≥ 3x seminggu**
	a. Tidak dapat tidur di malam hari dalam waktu 30 menit				
	b. Bangun tengah malam atau dini hari				
	c. Harus bangun untuk ke kamar mandi				
	d. Tidak dapat bernafas dengan nyaman				
	e. Batuk atau mendengkur keras				
	f. Merasa kedinginan				
	g. Merasa kepanasan				
	h. Mimpi buruk				
	i. Merasakan nyeri				

	j. Tolong jelaskan penyebab lain yang belum disebutkan di atas yang menyebabkan anda terganggu di malam hari dan seberapa sering anda mengalaminya? ❒ . ❒ .				
6.	Selama sebulan terakhir, seberapa sering anda mengkonsumsi obat tidur(diresepkan oleh dokter ataupun obat bebas) untuk membantu anda tidur?				
7.	Selama sebulan terakhir seberapa sering anda merasa terjaga atau mengantuk ketika melakukan aktifitas mengemudi, makan atau aktifitas sosial lainnya?				
		Sangat baik	**Cukup baik**	**Cukup buruk**	**Sangat buruk**
8.	Selama sebulan terakhir, bagaimana anda menilai kualitas tidur anda secara keseluruhan?				
		Tidak Ada Masalah	**Hanya Masalah Kecil**	**Masalah Sedang**	**Masalah Besar**
9.	Selama sebulan terakhir, adakah masalah yang anda hadapi untuk bisa berkonsentrasi atau menjaga rasa antusias untuk menyelesaikan suatu pekerjaan/tugas?				

Kisi - Kisi Kuesioner PSQI

Tabel 2

No	Komponen	No.Item	Sistem Penilaian	
			Jawaban	Nilai Skor
1	kualitas Tidur Subyektif	9	Sangat Baik Baik Kurang Sangat kurang	0 1 2 3
2	Latensi Tidur	2	≤15 menit 16-30 menit 31-60 menit >60 menit	0 1 2 3
		5a	Tidak Pernah 1x Seminggu 2x Seminggu >3x Seminggu	0 1 2 3
	Skor Latensi Tidur	2+5a	0 1-2 3-4 5-6	0 1 2 3
3	Durasi Tidur	4	> 7 jam 6-7 jam 5-6 jam < 5jam	0 1 2 3
4	Efisiensi Tidur Rumus : Durasi Tidur : lama di tempat tidur) X 100% *Durasi Tidur (no.4) *Lama Tidur (kalkulasi respon no.1 dan 3)	1, 3, 4	> 85% 75-84% 65-74% <65%	0 1 2 3
5	Gangguan Tidur	5b, 5c, 5d, 5e, 5f, 5g, 5h, 5i, 5i, 5j	0 1-9 10-18 19-27	0 1 2 3
6	Penggunaan Obat	6	Tidak pernah 1x Seminggu	0 1

			2x Seminggu >3x Seminggu	2 3
7	Disfungsi di siang hari	7	Tidak Pernah 1x Seminggu 2x Seminggu >3x Seminggu	0 1 2 3
		8	Tidak Antusias Kecil Sedang Besar	0 1 2 3
		7+8	0 1-2 3-4 5-6	0 1 2 3

Keterangan Kolom Nilai Skor:

0 = Sangat Baik

1 = Cukup Baik

2 = Agak Buruk

3 = Sangat Buruk

APPENDIX 9

Perceived Stress Scale (PSS) Questionnaire

5. Kuesioner Perceived Stress Scale (Pss)

NO.	PERTANYAAN	0	1	2	3	4
1.	Selama sebulan terakhir, seberapa sering anda marah karena sesuatu yang tidak terduga					
2.	Selama sebulan terakhir, seberapa sering anda merasa tidakmampu mengontrol hal-hal yang penting dalam kehidupan anda					
3.	Selama sebulan terakhir, seberapa sering anda merasa gelisah dan tertekan					
4.	Selama sebulan terakhir, seberapa sering anda merasa yakin terhadap kemampuan diri untuk mengatasi masalah pribadi					
5.	Selama sebulan terakhir, seberapa sering anda merasa segala sesuatu yang terjadi sesuai dengan harapan anda					
6.	Selama sebulan terakhir, seberapa sering anda merasa tidak mampu menyelesaikan hal-hal yang harus dikerjakan					
7.	Selama sebulan terakhir, seberapa sering anda mampu mengontrol rasa mudah tersinggung dalam kehidupan anda					
8.	Selama sebulan terakhir, seberapa sering anda merasa lebih mampu mengatasi masalah jika dibandingkan dengan orang lain					
9.	Selama sebulan terakhir, seberapa sering anda marah karena adanya masalah yang tidak dapat anda kendalikan					
10.	Selama sebulan terakhir, seberapa sering anda merasakan kesulitan yang menumpuk sehingga anda tidak mampu untuk mengatasinya					
	Skor					

KUESIONER *PERCEIVED STRESS SCALE* (PSS)

Petunjuk Pengisian:

1. Bacalah pertanyaan dan pernyataan berikut dengan baik
2. Anda sebagai responden diperbolehkan bertanya kepada peneliti, jika ada pertanyaan / pernyataan yang tidak dimengerti
3. Lengkapilah identitas terlebih dahulu
4. Berikan tanda centang (✓) pada salah satu pilihan jawaban yang paling sesuai dengan perasaan dan pikiran anda selama satu bulan terakhir
5. Jumlahkan skor total dari semua pertanyaan / pernyataan
6. Berikan kode sesuai hasil skor anda
7. Untuk pertanyaan positif (4,5,7,8) bernilai kebalikannya (0=4, 1=3, 2=2, 3=1, 4=0)
8. Selamat mengisi dan terima kasih atas kerjasamanya

Kode 1 : skor total 1-13

Kode 2 : skor total 14-26

Kode 3 : skor total 27-40

APPENDIX 10

Published Article 1

International Journal of Public Health Science (IJPHS)
Vol. 14, No. 2, June 2025, pp. 1052~1059
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Visceral manipulation intervention in functional dyspepsia with or without gastroesophageal reflux disease: a systematic review

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ABSTRACT

Functional dyspepsia is a prevalent gastrointestinal disorder characterized by symptoms like early satiety, postprandial fullness, and epigastric pain, affecting individuals with or without gastroesophageal reflux disease (GERD). The aim was to systematically map and summarize the existing literature on visceral manipulation interventions for functional dyspepsia. The systematic review followed rigorous methodology to ensure the validity and reliability of the findings. The study involved electronic searches of four major databases and five stages to review references to screened articles from January 2012 to February 2024. The search terms include "visceral manipulation," "visceral osteopathy", "osteopathic manipulation", "functional dyspepsia," "gastroesophageal reflux". Six articles were included in the review. Although there is currently little data to guide therapeutic treatment, research indicates that visceral manipulation therapy is feasible for people with functional dyspepsia, whether or not they also have GERD symptoms. Research on the effects of visceral manipulation on people with functional dyspepsia, whether or not they have GERD, is necessary to better understand treatment procedures and evaluate their advantages for patients with this condition. The growing interest in visceral manipulation intervention for functional dyspepsia is supported by mixed evidence, highlighting the need for high-quality research and larger sample sizes in future randomized controlled trials to determine its true impact.

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1. INTRODUCTION

Upper abdominal pain or discomfort that is persistent or recurrent without any structural, metabolic, or biochemical abnormalities, with or without gastroesophageal reflux disease (GERD) symptoms, is the hallmark of functional dyspepsia, a common gastrointestinal disorder [1], [2]. It affects up to 15% of the general population, and its exact cause of functional dyspepsia is not fully understood. However, it is believed to be related to abnormalities in digestive system function, including gastric motility and sensitivity [2]–[5]. The symptoms of early satiety, postprandial fullness, bloating, and epigastric pain are common in patients with functional dyspepsia and can have a major negative influence on their quality of life [6]–[8].

The rationale behind visceral manipulation is that restrictions or adhesions in visceral tissues can lead to altered biomechanics and neurophysiological functions, contributing to symptoms, such as pain and discomfort. By applying gentle manual techniques to the abdominal area, a trained practitioner can help

release these restrictions and improve overall function of the organs. This can lead to reduced pain, improved digestion, and enhanced overall well-being. While some evidence suggests that visceral manipulation may be effective in the treatment of certain gastrointestinal disorders, such as irritable bowel, its use in functional dyspepsia is not well established [9]–[11].

Owing to the multifactorial nature of functional dyspepsia, its management typically involves a combination of pharmacological approaches and lifestyle modifications, although some individuals may not respond adequately to these interventions [12]. In recent years, non-pharmacological strategies such as visceral manipulation have emerged as potential treatment options for functional dyspepsia. Visceral manipulation is a manual therapy technique aimed at improving the mobility and function of abdominal soft tissues and organs through specific gentle maneuvers [13]. The rationale behind visceral manipulation is to address restrictions or adhesions in visceral tissues that could lead to altered biomechanics and neurophysiological functions, contributing to symptoms, such as pain and discomfort [14].

While there is existing evidence supporting the efficacy of visceral manipulation in certain gastrointestinal disorders, such as irritable bowel syndrome, its application in functional dyspepsia is less well established [15]. Therefore, a systematic review focusing on visceral manipulation interventions for functional dyspepsia aimed to systematically outline and summarize the available evidence on the effectiveness of this approach in alleviating symptoms and improving the quality of life of patients with functional dyspepsia. Through the incorporation of diverse study designs and evidence types, a systematic review offers a thorough assessment of the existing body of knowledge regarding visceral manipulation for functional dyspepsia, pinpointing evidence gaps and possible avenues for further investigation [16].

The objective of a systematic evaluation of visceral manipulation therapies for patients with functional dyspepsia was to map and compile the available data on how well this method works to manage symptoms and enhance patients' quality of life. For complicated and diverse subjects, like manual therapy interventions, this kind of evaluation is especially helpful since it enables a thorough examination of the body of literature to spot evidence gaps and possible directions for further study. This systematic review offers a thorough summary of the current state of knowledge on a given issue by incorporating a variety of study styles and evidence categories.

By carefully gathering and analyzing all available evidence, the systematic review will provide a full picture of what is known about using visceral manipulation as a treatment for people with functional dyspepsia. The findings of this review may also have important implications for clinical practice by informing healthcare professionals about the potential benefits and limitations of visceral manipulation in functional dyspepsia management of functional dyspepsia. This study will enhance the standard of care and results for patients with functional dyspepsia by helping to create evidence-based guidelines and recommendations for the use of visceral manipulation interventions in this condition's management.

2. METHOD

To guarantee the validity and trustworthiness of the results, a strict methodology is followed in the systematic review of the effects of visceral manipulation in functional dyspepsia. Following the paradigm created by Arksey and O'Malley [17], this systematic review's methodology consists of five steps: i) formulating the research question; ii) locating pertinent studies; iii) choosing studies; iv) charting the data; and v) compiling, summarizing, and reporting the findings. A thorough examination of the body of research on visceral manipulation in functional dyspepsia is made possible by this methodical approach, which also offers important insights into the possible consequences and clinical practice implications of this technique. By following established guidelines and protocols, this systematic review aims to contribute to the evidence base surrounding this treatment modality and inform future research in the field.

2.1. Determining the research question and pertinent literature

The research question for this systematic review was as: What is the evidence for the effects of visceral manipulation on the management of functional dyspepsia? The research question was formulated to guide the search for relevant studies and to ensure that the review was focused and relevant. To identify relevant studies, a systematic search was conducted using the SCOPUS, PubMed, Google Scholars, and Semantic Scholar databases for articles published between January 2012 to February 2024. The search terms include "visceral manipulation," "visceral osteopathy", "osteopathic manipulation", "functional dyspepsia," "gastroesophageal reflux", and related keywords. The search strategy was designed to be comprehensive and inclusive, to ensure that all relevant studies were identified.

2.2. Selecting studies

Inclusion criteria were studies that investigated the effects of visceral manipulation on the management of functional dyspepsia, regardless of the study design. Studies must be published in English and include human participants. Studies were excluded if they focused on other gastroesophageal conditions

or did not specifically examine the visceral manipulation interventions. Two reviewers independently evaluated the full-text articles for inclusion in this systematic review, resolving any disagreements between them through discussion and consensus. Two reviewers independently screened the titles and abstracts of all the identified studies to determine their eligibility for inclusion, and full-text articles were obtained for all studies that met the inclusion criteria or were unsure of their eligibility.

2.3. Charting the data

A standardized data extraction form was utilized to chart the data from the listed research. The form contained details about the study's design, sample size, intervention dosage, reported results, pertinent findings, and degree of proof. The purpose of the data extraction form was to guarantee that all pertinent data was recorded and that the data were consistent between trials. This approach made it simple to compare and synthesize findings from various studies, offering a thorough picture of the state of the field. Additionally, by reducing bias and errors in data extraction, the standardized form improved the validity and reliability of the results.

2.4. Collating, summarizing, and reporting results

Lastly, the systematic review compiled, summed up, and reported the results from the included research. To find recurring themes, trends, and gaps in the literature, the data were combined. The systematic review's findings are presented in an understandable and succinct way. The results are presented in a way that is simple to comprehend and interpret. Additionally, the results can offer evidence-based suggestions for the use of visceral manipulation in the treatment of functional dyspepsia and are presented in a way that is pertinent to clinical practice. According to the 2011 Oxford Centre for Evidence-Based Medicine levels of evidence, we assigned each study a grade as shown in Table 1.

Table 1. Evidence levels from the Oxford Center for evidence-based medicine

Level	Type of study
1	Comprehensive analysis of randomized trials
2	Randomized trial
3	non-randomized follow-up research or control group
4	Studying case series and case-control
5	Not applicable

2.5. Research flow

The research flow for retrieving articles from the PubMed, SCOPUS, Google Scholar, Semantic Scholar databases is carried out using identification, screening, eligibility, and include the study techniques. After that, data analysis was carried out to obtain relevant and significant results. The research results are then compiled in the form of a report or scientific article for publication. This process ensures that the information obtained can be accessed and utilized by interested readers. The automation tools used are gradepro GDT 5 which can be accessed through the site https://gdt.gradepro.org/app. A total of 355 articles were excluded based on this automation tool for various reasons, including out of the scope, not open access, irrelevant to the topic, sample size, and type of study. More details can be seen in Figure 1.

3. RESULTS AND DISCUSSION

The 406 papers in all were reviewed. We chose 26 abstracts for the first screening after scanning the titles and abstracts and eliminating duplicates. Twenty-four full-text articles were chosen and vetted from this group. Figure 1 shows that eight articles satisfied all inclusion requirements. Two pilot or feasibility studies, one prospective study, two randomized trials, one pilot randomized trial, and two case reports comprised the eight eligible papers as presented in Table 2. Typically, sample sizes were small. The sample size for five of the investigations was fewer than thirty. The final selection's diversity of study approaches offers a thorough summary of the state of the field's research. Notwithstanding the modest sample sizes, the variety of study designs deepens the conclusions and enables a more complex comprehension of the topic.

The initial analysis of the included studies suggested that visceral manipulation may have potential benefits in the management of functional dyspepsia [14], [19]–[23]. Functional dyspepsia is a common gastrointestinal disorder characterized by recurring pain or discomfort in the upper abdomen, often accompanied by bloating, early satiety, and nausea, with or without gastroesophageal reflux disease symptoms [24], [25]. The exact cause of functional dyspepsia is not well understood, and treatment options are limited [26]. These studies examined various outcomes related to functional dyspepsia, such as pain intensity, quality of life, and gastric emptying. While the results of individual studies varied, some evidence suggests that visceral manipulation may lead to improvements in these outcomes.

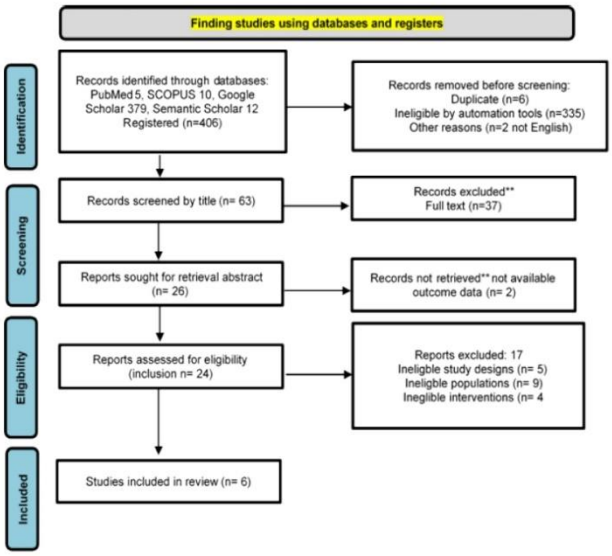

Figure 1. Flow chart [18]

Visceral manipulation is a manual therapy technique that involves gentle, specific, and targeted movements of the abdominal organs, fascia, and ligaments [27], [28]. It aims to improve the mobility and function of organs, enhance blood flow, and restore balance of the autonomic nervous system. Some possible ways that visceral manipulation can help patients with functional dyspepsia by lowering inflammation, improving gastric motility, and lowering visceral hypersensitivity [29], [30]. It may also help reduce symptoms such as bloating, nausea, and abdominal pain commonly associated with functional dyspepsia [26], [31], [32]. Visceral manipulation can potentially improve overall digestion and nutrient absorption for individuals suffering from this condition [33]–[36]. Visceral manipulation can offer a holistic approach to treating functional dyspepsia by addressing the root causes of the symptoms. By targeting the underlying issues in the digestive system, patients may experience long-term relief and improved quality of life [16], [37], [38]. Visceral manipulation has been shown to enhance circulation and lymphatic drainage in the abdominal region, which can further support digestive health. Incorporating visceral manipulation into a comprehensive treatment plan may lead to significant improvements in symptoms and overall well-being for individuals with functional dyspepsia [39].

The studies included in the systematic review examined the effects of visceral manipulation on various outcomes related to functional dyspepsia such as pain intensity, quality of life, and gastric emptying. While the results of individual studies varied, some evidence suggests that visceral manipulation may lead to improvements in these outcomes. For example, a randomized controlled trial found that visceral manipulation was more effective in improving gastroesophageal reflux disease symptoms one week after treatment, cervical mobility, and pressure pain threshold [22]. Visceral manipulation is associated with a significant ability to allow the gastroesophageal junction to regain natural elasticity and function [40].

One potential mechanism of visceral manipulation in functional dyspepsia is the modulation of visceral hypersensitivity [15]. Visceral hypersensitivity is a common feature of functional dyspepsia and is believed to contribute to the development of symptoms, such as pain and discomfort [41]. Visceral manipulation may help reduce visceral hypersensitivity and alleviate symptoms by improving the mobility and function of abdominal organs [42]. Another potential mechanism of action for visceral manipulation in functional dyspepsia is improvement in gastric motility [43]. Several studies included in the systematic review reported that visceral manipulation was associated with a significant improvement in gastric emptying time, suggesting that it may help normalize stomach function and improve digestion [44]–[46].

Table 2. Summary of reviews

Authors and country	Type of study and level of evidence	Objective	Type of gastroesophageal disorders, age range, and sample size	Interventions	Outcome measures and measurement	Main findings
[19]	Double group: before-after, level 3	To compare pressure readings in patients with gastro-oesophageal reflux disease during the lower esophageal sphincter examination before and right after osteophatic diaphragm intervention	Gastroesophageal reflux disease, aged >18 years; n =38 (osteopathic interventions =22 patients, control group =16 patients)	Diaphragm stretching technique as osteopathic intervention, sham technique as placebo intervention, no frequency reported	Using esophageal manometry, the lower esophageal sphincter's maximum expiratory pressure and average respiratory pressure were determined.	The osteopathic manipulative method enhances the lower esophageal sphincter region, resulting in an average breathing pressure of P=0.027, with no significant variation in maximum expiratory pressure.
[14]	Pilot randomized controlled trial (double-blind); double group: before-after; level 2	To assess how osteopathic visceral manipulation of the stomach and liver affects functional dyspepsia patients' pain, cervical mobility, and upper trapezius muscle electromyography activity	Functional dyspepsia with chronic nonspecific neck pain; no aged reported; n =28 (osteopathic visceral manipulation =14 patients, placebo visceral manipulation =14 patients)	The study involves osteopathic visceral manipulation on the stomach and liver, followed by a placebo visceral manipulation as a sham technique, with the duration being 5 minutes per day.	A flexiometer for cervical range of motion, an electromyography for upper trapezius muscle activity, and a numerical rating scale for pain	Visceral mobilization for stomach and liver can alleviate cervical pain and enhance the upper trapezius muscle electromyography signal in patients with nonspecific neck pain and functional dyspepsia.
[20]	Case report: before-after; not classified	The study investigates the impact of stomach and liver manipulation on neck pain, cervical range of motion, and upper trapezius muscle electromyography activity in individuals with functional dyspepsia.	Functional dyspepsia with chronic nonspecific neck pain; 18 yr old female and 25 yr old female; n=2	Visceral manipulation on the stomach and liver, visceral manipulation:5 min/dyx7 days	Using a flexiometer to measure cervical range of motion, an electromyography to measure upper trapezius muscle activity, and a numerical rating scale to assess pain	Two functional dyspepsia patients with neck pain experienced significant improvements in neck pain, cervical spine range of motion, and upper trapezius muscle electromyography activity after a single visceral manipulation.
[21]	Single-blinded prospective study; before-after; Level 4	The study aims to develop an osteopathic manipulative therapy protocol for treating gastro-oesophageal reflux disease, evaluating its effectiveness using the quality-of-life scale.	Gastro-oesophageal reflux disease; 55-year-old man; n=1; history of hoarseness and heartburn for 4 years	The oesophagus and diaphragm undergo a three-session osteopathic manipulation therapy.	The gastro-oesophageal reflux disease quality of life scale four times (before the first session, before the third session, and two and four weeks after the third session).	The somatovisceral approach to treating gastro-oesophageal reflux disease should incorporate osteopathic manipulative therapy to alleviate symptoms in the diaphragm and oesophagus.
[22]	A randomized, double-blind placebo-controlled trial; before-after; Level 2	The study assesses cervical mobility, C4 spinous process pressure pain threshold, and the impact of visceral osteopathic technique on symptoms of gastro-oesophageal reflux disease.	Gastro-oesophageal reflux disease; n =60; patients ages 18-70 (control group =31; visceral osteopathic technique =29)	The lower esophageal sphincter underwent treatment using visceral osteopathic technique and a sham technique, with daily sessions of 5 minutes per day for seven days.	The week following intervention, the gerdQ questionnaire is used to evaluate symptom changes. cervical mobility and PPTs before and after both treatments using an algometer and cervical range of motion	One week following treatment, cervical mobility, PPTs, and symptoms of gastro-oesophageal reflux improve with the visceral osteopathic technique.
[23]	A randomized controlled trial; before-after; Level 2	To determine whether osteopathic treatment is beneficial for patients suffering from gastro-oesophageal reflux disease	Gastro-oesophageal reflux disease; n =70; patients ages 18-70 (35 in intervention group, 35 in control group)	Osteopathic therapy: within eight weeks; control group: within eight weeks	The Reflux and Dyspepsia Quality of Life Questionnaire is utilized to assess the quality of life in relation to symptoms of gastro-oesophageal reflux disease.	Osteopathic treatments may benefit patients with gastro-oesophageal reflux disease, with future research focusing on longer follow-up periods and a global rating of change measurement.

Overall, these findings suggest that visceral manipulation may have a positive impact on the underlying mechanisms contributing to functional dyspepsia. By improving gastric motility and reducing visceral

hypersensitivity, this manual therapy technique could potentially offer relief for individuals experiencing symptoms such as pain and discomfort [25], [30], [47], [48]. Visceral manipulation has been shown to decrease bloating and improve overall gastrointestinal function in patients with functional dyspepsia [49]–[52]. These promising results highlight the potential of this non-invasive treatment option for managing digestive issues. Incorporating visceral manipulation into a comprehensive treatment plan may provide a holistic approach to addressing functional dyspepsia symptoms. It is important for individuals to consult with a healthcare provider to determine if this technique is appropriate for their specific condition. Visceral manipulation involves gentle, hands-on techniques that aim to improve the mobility and function of internal organs, potentially relieving pain and discomfort. This alternative therapy has been gaining attention for its potential benefits in managing digestive issues, offering a non-invasive option for those seeking relief from functional dyspepsia symptoms [53], [54].

While the systematic review provides preliminary evidence for the potential benefits of visceral manipulation in functional dyspepsia, the current literature does not support its widespread use as a first-line treatment. However, given the limited treatment options for functional dyspepsia and the potential benefits of visceral manipulation, it may be considered as an adjunctive therapy in patients who do not respond to conventional treatments or prefer a non-pharmacological approach. Clinicians should carefully assess individual patient needs, preferences, and treatment goals when considering the use of visceral manipulation in the management of functional dyspepsia [55], [56]. Clinicians need to have open and honest discussions with patients about the potential risks and benefits of visceral manipulation before incorporating it into their treatment plan. Further research is needed to better understand the mechanisms of action and long-term efficacy of visceral manipulation in functional dyspepsia. This will help ensure that patients are well-informed and actively involved in their treatment decisions. With more evidence-based research, clinicians can make more informed recommendations regarding the use of visceral manipulation for functional dyspepsia. This will ultimately lead to improved patient outcomes and satisfaction with their treatment. In the meantime, clinicians should continue to stay updated on the latest research findings and guidelines related to visceral manipulation to provide the best possible care for their patients.

A systematic review of the effects of visceral manipulation on functional dyspepsia provided a comprehensive overview of the existing literature on this topic. Although the review is still ongoing, and the final results are not available, some preliminary findings can be discussed based on the included studies and their initial analyses. This discussion highlights the potential benefits and limitations of visceral manipulation in functional dyspepsia management of functional dyspepsia. Some studies suggest that visceral manipulation may improve symptoms such as bloating and discomfort in patients with functional dyspepsia [32], [57]–[59]. However, more research is needed to fully understand the mechanisms behind these potential benefits and to determine the long-term effectiveness of this treatment approach. The preliminary findings suggest that visceral manipulation may be a promising approach for managing functional dyspepsia symptoms. Future studies should focus on larger sample sizes and longer follow-up periods to provide more conclusive evidence on its efficacy. Exploring the effects of visceral manipulation on other gastrointestinal conditions could provide valuable insights into its broader therapeutic potential. By further investigating the specific techniques and frequency of treatment that yield the best results, healthcare providers can optimize the use of visceral manipulation in clinical practice.

4. CONCLUSION

The initial analysis of the included studies suggests that visceral manipulation may have potential benefits in the management of functional dyspepsia. These studies examined various outcomes related to functional dyspepsia, such as pain intensity, quality of life, and gastric emptying. While the results of individual studies varied, some evidence suggests that visceral manipulation may lead to improvements in these outcomes. Some possible ways that visceral manipulation can help people with functional dyspepsia by lowering gastroesophageal reflux disease, changing visceral hypersensitivity, and improving stomach motility. However, the quality of the included studies varied and the heterogeneity of the study designs, interventions, and outcome measures made it challenging to draw definitive conclusions. Comparative effectiveness research is required to determine the relative benefits and risks of different interventions for functional dyspepsia. Studies comparing visceral manipulation with other manual therapy techniques or conventional treatments could provide valuable insights into the optimal management of this condition.

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APPENDIX 11

Published Article 2

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ORIGINAL ARTICLE

The Effect of Visceral Manipulation on Abdominal Pain and Quality of Life in Adult Patients with Functional Dyspepsia: A Pilot Study.

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Abstract
Background: A pilot study was conducted to determine the effect size of visceral manipulation (VM) sessions on abdominal pain and quality of life in adult individuals with functional dyspepsia (FD).
Methods: Twenty-nine subjects diagnosed with FD participated in a pre-post-study design. The participants were subjected to a two-week treatment regime involving VM intervention sessions. Each session lasted for 30 minutes and was conducted five times a week. Data were collected using the Abdominal Pain Index (API) and Short-Form Nepean Dyspepsia Index (SF-NDI) instruments. The Friedman test was used for analysis. with a significance level set at $p < 0.05$. This study was approval by the Health Research Ethics Committee of the Health Polytechnic, Ministry of Health, East Kalimantan, Indonesia (Ethics No. DP.04.03/7.1/12146/2023).
Results: Among FD patients, there was a significant reduction in abdominal pain, pain time, duration, and intensity before and after the VM intervention (all $p < 0.05$). The quality of life also improved in the following domains: anxiety, activity limitation, eating and drinking, knowledge, and work/study (all $p < 0.05$).
Conclusion: After 2 weeks of VM intervention in FD patients, we found a significant reduction in abdominal pain and improved in quality of life. Although the small sample size limits the generalizability of the findings, the observed improvement in abdominal pain and quality of life may hold clinical relevance for this population.

Keywords: *Abdominal pain, functional dyspepsia, pilot study, quality of life, visceral manipulation.*

Introduction

Functional dyspepsia (FD) is a most common chronic upper gastroduodenal disease without obvious organic causes or metabolic disturbances [1,2]. FD is characterized by symptoms such as upper abdominal discomfort or pain, early satiety, postprandial fullness, bloating, and nausea, which can significantly affect the quality of life of patients. FD is classified as chronic if it has lasted for the last 3 months, with the incidence of symptoms having been felt for at least 6 months prior to diagnosis. Globally, the prevalence of FD varies, with women having a slightly higher prevalence than men, at 25.3% vs 21.9% [3]. The pathophysiology of FD involves abnormalities in gastric motility, gastric neuromuscular function, and visceral hypersensitivity [4,5].

Dyspepsia accounts for one of the top 10 diseases in Indonesia, with a prevalence of 40–50% [6]. Additionally, the prevalence of FD among individuals aged 26 to 35 years is estimated to be as high as 50% [7]. Moreover, it has been reported that FD cases constitute nearly 30% of general practice and up to 60% of gastroenterology practice [8]. Despite the availability of various treatment options, the management of FD remains challenging due to the heterogeneity of symptoms and the limited efficacy of existing therapies in some patients.

The gastroduodenal region, comprising the stomach and duodenum, exhibits remarkable physiological mobility and motility, essential for normal functioning. Impairment of this motility can have significant implications, leading to functional disturbances in the organ itself and its surrounding structures [9]. Such limitations in organ motion may result in various pathological effects, including irritation, visceral spasm, dysmotility, increased tension, inflammation, visceral hypersensitivity, and emotional distress [10]. These motility disturbances often manifest as FD, a condition characterized by chronic or recurrent upper abdominal pain or discomfort, often accompanied by bloating, early satiety, or nausea [1,2].

Pharmacological interventions have been a primary focus in the management of FD, but their efficacy has been variable. Studies have shown that many pharmacological interventions provide only temporary relief and are not consistently superior to placebo [3]. Furthermore, not all treatments are effective in all cases of functional dyspepsia, highlighting the need for alternative approaches [11]. In this context, nonpharmacological therapies have gained attention as potential interventions for FD. Conservative interventions, such as dietary modifications, psychological interventions, exercise, and complementary therapies, have shown promise in reducing the symptoms of patients with FD [12,13,14,15].

The ineffectiveness of drug therapy alone in managing FD has prompted a shift towards a more comprehensive and holistic approach to patient care. Nonpharmacological therapies offer the advantage of addressing the multifactorial nature of FD, targeting not only the physical symptoms but also the psychological and social aspects of the condition [16]. Abdominal manipulation therapy, including visceral manipulation (VM), has been suggested as a potential treatment for FD. Lee and Maeng noted the potential effectiveness of VM for FD patients but emphasized the need for further studies to establish its efficacy [17].

The theoretical basis of VM posits that adhesions or limitations in the visceral tissues may alter neurophysiological processes and biomechanics potentially leading to pain and discomfort. VM is a manual therapy technique aimed at improving the mobility and function of abdominal soft tissues and organs through specific, gentle manoeuvres [18,19]. In recent years, non-pharmacological approaches, such as VM, have gained increasing recognition as viable treatments options for visceral disorders, including FD. While existing evidence supports the use of VM for certain gastrointestinal disorders, such as functional constipation, its efficacy in treating FD remains insufficiently established [20].

A pilot study was conducted to examine the effects of VM interventions on abdominal pain and the quality of life in individuals with FD. The

study aimed to quantify the short-term effects of VM sessions incorporating three specific techniques: lesser omentum stretching, stomach mobilization, and duodenum mobilization. We hypothesize that the combined effects of these interventions would have the capacity to have immediate changes in pain and quality of life.

Methods

Study participants

Twenty-nine FD patients participated in this nonrandomized pre-post pilot study. Participants were recruited from Wiyata Husasa Physiotherapy Clinic. Inclusion criteria were: (1) referral to outpatient physiotherapy with an FD diagnosis; (2) FD without gastritis for at least 3 months; (3) ability to read and write the Indonesian language; and (4) age 20 - 60 years. Exclusion criteria included: (1) gastritis; (2) diabetes/pancreatitis; (3) liver and biliary tract disease; (4) gastrointestinal tumour or malignancies; (5) Helicobacter pylori infection; and (6) use of analgesic medications. All participants provided written informed consent before enrollment into the study. The study received ethical approval from two institutions: the Faculty Ethics Review Committee (FERC) of UiTM Puncak Alam Campus (Approval ID: 500-FSK (PT.23/4)) and the Health Research Ethics Committee of the Health Polytechnic, Ministry of Health, East Kalimantan, Indonesia (Ethics No. DP.04.03/7.1/12146/2023).

To monitor the study, participants were carefully screened for any ongoing treatments, including medications and supplements, before enrolling in the study. Those who were taking any such treatments (medications and supplements) that could potentially interfere with the outcomes of VM were excluded from the study. This information was used to ensure that there were no significant differences between the experimental groups at the start of the study. And, Throughout the study, participants were regularly monitored and asked to report any new treatments or changes to their existing treatments.

Outcome measures

The primary outcomes were adherence rate, adverse events, and recruitment feasibility. Adherence rate was measured as the percentage of completed VM sessions of a maximum of 10 sessions (5 times per week for 2 weeks). Every session began and ended with questions. Participants were asked about adverse effects during the session, including a ticklish sensation, pain, light-headedness, and nausea. A non-serious adverse event was defined as an event that results in minor discomfort and does not require session or study termination. The number of participants who gave their consent and signed up each month served as a gauge of recruitment feasibility.

The secondary outcome was abdominal pain and quality of life among individuals with FD. Abdominal pain was measured using the Abdominal Pain Index (API), which includes pain frequency, pain time, pain duration, and pain intensity [21]. It consists of a questionnaire that asks patients to rate the severity of their abdominal pain on a scale from 0 to 10. The API may also include questions about the location and type of pain, as well as any associated symptoms. Furthermore, the frequency of pain is evaluated on a six-point scale that ranges from never to persistent pain throughout the day. The API demonstrated good construct validity for children and adolescents with chronic pain [19,22].

The Short-Form Nepean Dyspepsia Index (SF-NDI) was used to evaluate the quality of life. The SF-NDI is a valid instrument that can measure the disease-specific impact of FD on quality of life, which included anxiety, daily activity limitation, eating/drinking, knowledge/control, and work/study [23]. The questionnaire consists of 10 items, and each item is measured by a 5-point Likert scale ranging from 0 (not at all or not applicable), 1 (a little), 2 (moderately), 3 (quite a lot), and 4 (extremely). Individual items in each subscale are accumulated to obtain a quality-of-life score ranging from 0 to 100. Patients with scores above 15 on the SF-NDI indicate a significant reduction in quality of life.

Study protocol

Three licensed physiotherapists with 5-20years of clinical experience participated in this study. All therapists had received advanced training in VM and maintained clinical caseloads consisting of 80-85% visceral disorder cases, with approximately 85% of these being FD referrals from internal medicine doctors. Trained assessors conducted baseline and post-treatment measurements after completing standardized training to ensure measurement consistency and reliability. Participants were recruited through the outpatient physiotherapy clinic following referral for FD symptoms. The assigned physiotherapist evaluated each patient for study eligibility. Eligible patients who provided informed consent were enrolled in the study.

Participants received ten 30-minute VM sessions over two weeks (5 sessions/week). The decision to measure the effects of VM over a two weeks was based on the following considerations: (1) Previous studies by Silva et al [23] and Eguaras et al [24] had demonstrated VM effectiveness within two weeks; (2) Two weeks was deemed optimal to maintain participant engagement and minimize dropout rates, and ensuring the integrity of the data collected; (3) Conducting a longer-term study requires more resources, including time, funding, and personnels. Given these constraints, two weeks were a practical and feasible choice for this pilot investigation.

To minimize the risk of overreporting bias in our study, we implemented several strategies: (1) We used well-established and validated questionnaires that are designed to reduce bias and increase the reliability of self-reported data (such as the API and SF-NDI questionnaires). These instruments have been widely used in similar studies and have demonstrated robust psychometric properties; (2) Participants were blinded to the specific hypotheses of the study to reduce the likelihood of response bias. They were informed that the study aimed to assess the general effects of VM without disclosing the expected outcomes; (3) Participants were asked to complete their self-reports at regular intervals throughout the study rather than relying on a single point of data collection. This approach helped in capturing consistent and reliable data over time, reducing the risk of any single instance of overreporting significantly impacting the overall results; (4) We emphasized the anonymity and confidentiality of participant responses, encouraging honest and accurate reporting. Participants were reassured that their responses would be anonymized and used solely for research purposes, and; (5) In our data analysis, we applied statistical techniques to identify and control for potential outliers and overreporting to ensure that the results were not unduly influenced by biased reporting.

The VM intervention consisted of a standardized treatment protocol incorporating gastric and duodenal mobilization techniques along with lesser omentum stretching.

(1) Stretching the lesser omentum: The participant lies supine with both limbs bent. The practitioner stands on the left side of the patient. Both hands of the practitioner are placed on the left and right sides of the median line below the xiphoid process, with the fingers just above the stomach wall. With both hands, the practitioner slowly applies posterior pressure to the inside of the abdomen and performs stretching of the lesser omentum.
(2) Oscillations on the stomach: The participant lies supine with both limbs bent. The practitioner stands on the left side of the patient. The practitioner places the fingers of both hands on the abdomen in the gastric region and applies pressure posteriorly until the hands fully reach the gastric wall. Oscillatory movements are applied to the stomach.
(3) Frontal plane stomach mobilization: The participant lies on his right side. The practitioner stands behind the patient and places both hands on the left lateral costal margin (ribs 6-7) below the diaphragm. With both hands, he performs caudomedial mobilization of the stomach, followed by

counter-directional mobilization of the stomach craniolaterally.

(4) Transverse plane stomach mobilization: Patient lies right lateral decubitus, and the practitioner stands behind him. Using costal contact, the practitioner rotates the stomach medially to the right. Then, the practitioner performs the reverse movement with lateral rotation of the stomach to the left.
(5) Sagittal plane stomach mobilization: The stomach mobilization technique in the sagittal plane follows the same procedure as the frontal and transverse plane mobilizations. The practitioner's left hand is placed on the anterior part of the left costal margin at the level of 6^{th}-7^{th} ribs. The right hand is positioned on the posterior part of the left shoulder. With both hands, the practitioner mobilizes the stomach via the ribs in the sagittal plane by pressing the stomach in the anteroposterior direction and the right hand in the posteroinferior direction.
(6) Duodenum mobilization: Participant lies in a side-lying position, facing to the right, and both limbs slightly bent. The practitioner places both hands on the medial part of the abdomen, lateral to the ascending colon, then apply pressure to the inside of the posteromedial abdomen and stretches medially and craniocaudally. The practitioner maintains this position briefly until tissue relaxation is achieved.

Statistical analysis

The SPSS 16.0 program was used for statistical analysis of the obtained e measurement data. Since the data did not meet the assumption of normal distribution, Friedman's non-parametric test was applied. Descriptive statistics (mean age, gender, occupation, education, and marital status) were calculated for the study participants. Cohen's effect size was computed to assess baseline and post-intervention effect sizes for the aforementioned variables.

Results

Demographic characteristics of the study participants

A total of 33 subjects were screened for eligibility in this study. Of these, 29 met the inclusion criteria and completed the VM intervention, while 4 were excluded. The demographic characteristics of the participants are summarized in Table 1.

Primary outcomes: adherence and feasibility

The 29 participants who met the inclusion criteria completed the intervention with a 100% retention rate. Throughout the 2-week VM intervention, all participants tolerated the treatment well, with no significant or serious side effects reported. Seven participants experienced a ticklish sensation during the first VM intervention. Three participants felt a slightly uncomfortable sensation during the first abdominal VM mobilization but showed no resistance reaction or other signs of side effects. The remaining participants reported a comfortable sensation during the abdominal VM intervention. Notably, no dropouts occurred during the 2-week intervention period, and all participants provided positive feedback on the pilot study. Twenty-three participants reported improvements within the first week, including easier breathing, better sleep patterns, and increased abdominal comfort. The remaining 6 participants reported similar benefits after the second week of treatment. All participants noted a significant positive impact and expressed a desire for a long-term continuation of the therapy.

Secondary outcomes: Effect of visceral manipulation on abdominal pain and quality of life in FD patients

Table 2 presents the results of Friedman tests assessing abdominal pain changes in FD subjects across three time points (baseline, 1-week treatment, and 2-week treatment). The analysis revealed statistically significant differences in four pain-related parameters: (1) pain frequency

at baseline (mean difference = 3.52±0.57, p=0.001), after 1-week treatment (mean difference = 2.31±0.54, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001); (2) pain time at baseline (mean difference = 1.48±0. 1, p=0.001), after 1-week treatment (mean difference = 1.17±0.38, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001); (3) Pain duration at baseline (mean difference = 2.66±0.48, p=0.001), after 1-week treatment (mean difference = 1.52±0.51, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001); and (4) Pain intensity at baseline (mean difference = 3.52±0.51, p=0.001), after 1-week treatment (mean difference = 2.10±0.67, p=0.001), and after 2-week treatment (mean difference = 0.59±0.50, p=0.001).

Table 3 shows significant changes in FD subjects' quality of life as indicated by Friedman test results: (1) anxiety of at baseline (mean difference = 3.14±0.58, p=0.001), after 1-week treatment (mean difference = 1.93±0.75, p=0.001), and after 2-week treatment (mean difference = 1.31±0.47, p=0.001); (2) limitation of daily activities at baseline (mean difference = 3.31±0.47, p=0.001), after 1-week treatment (2.07±0.46, p=0.001), and after 2-week treatment (mean difference = 1.03±0.19, p=0.001); (3) Eating and drinking at baseline (mean difference = 3.45±0.51, p=0.001), after 1-week treatment (mean difference = 2.03±0.42, p=0.001), and after 2-week treatment (mean difference = 1.03±0.19, p=0.001); (4) Knowledge and control at baseline (mean difference = 3.17±0.71, p=0.001), after 1-week treatment (mean difference = 1.34±0.48, p=0.001), and after 2-week treatment (mean difference = 1.00±0.00, p=0.001); and (5) Work and study at bseline (mean difference=3.14±0.58, p=0.001), after 1-week treatment (mean difference = 2.00±0.38, p=0.001), and after 2-week treatment (mean difference = 1.07±0.26, p=0.001). These results demonstrate a statistically significant improvement in the quality of life from baseline to 1-week treatment and 2-week treatment.

Discussion

The pilot study aimed to determine the effect size of VM sessions on abdominal pain and quality of life in adult individuals with functional dyspepsia (FD). The results demonstrated high levels of adherence, positive feedback, and satisfaction, indicating that VM intervention was well-received. These findings suggest that VM may be a promising alternative for those with FD.

Participant feedback highlighted several reasons for the favourable reception of VM, including perceived comfort, relaxation, reduced abdominal pain, and improved quality of life. The aforementioned positive outcomes served to reinforce the participants' acceptance of VM. Furthermore, no significant adverse effects were observed, supporting the safety of VM. Finally, the findings of this study demonstrated that VM intervention can significantly reduce abdominal pain and improve the quality of life of FD patients during the two-week treatment period. These results align with concurrent findings from studies by Maeng and Lee (2015) and Silva et al. (2018), which support the notion that visceral manipulation therapy holds promise as a therapeutic modality for individuals grappling with functional dyspepsia [17,19].

A multitude of mechanisms have been identified to explain the effects of VM, as supported by various studies. Mechanical effects- arising from physical forces such as compression, stretching, mobilization, and oscillations of body tissues and organs- have been shown to enhance proprioceptive communication through mechanical interactions within the body. This, in turn, may reduce pain threshold, structural abnormalities, and faulty posture [26]. From a neurological perspective, VM is believed to stimulate the parasympathetic nervous system, promoting relaxation and reducing anxiety [27]. The combined effects of these mechanisms can enhance visceral mobility and function, as well as

improving emotional well-being, thereby contributing to a better quality of life [20].

Given the encouraging results of this preliminary study, clinicians should consider incorporating visceral manipulation as a therapeutic approach for patients with functional dyspepsia [24]. The study's strengths lie in its focus on the potential clinical benefits of visceral manipulation, particularly in alleviating abdominal pain and improving patients' quality of life. These findings offer preliminary evidence that could facilitate the development of more effective treatment strategies for managing functional dyspepsia.

Nevertheless, this study has several limitations. First, the small sample size and lack of a control group may limit the generalizability of the findings. Second, standardizing manual therapy interventions is challenging due to the variability in pressure and sensitivity among practitioners. Finally, the study design did not assess the long-term sustainability of symptom reduction.

Future research should prioritize large scale randomized controlled trials to further examine the efficacy and safety of VM in patients with FD.

Conclusion

The results of this pilot study suggest that VM may benefit adult patients with FD, as evidenced by reduced abdominal pain and improved quality of life. The findings indicate that this manual therapy approach could serve as a promising adjunctive treatment option for individuals with FD, a condition with limited treatment options.

Given its non-invasive and relatively safe nature, VM presents an appealing therapeutic option for individuals seeking complementary or alternative treatments. This study lays the groundwork for further research into VM's role in managing abdominal pain and enhancing the quality of life in FD patients.

Ethics approval and consent to participate:
The research had been approval by the Faculty Ethics Review Committee (FERC) of the Faculty of Health Sciences, UiTM Puncak Alam Campus (Approval ID: 500-FSK (PT.23/4)) and received ethical approval from the Health Research Ethics Committee of the Health Polytechnic, Ministry of Health, East Kalimantan, Indonesia (Ethics No. DP.04.03/7.1/12146/2023). During the research, the researcher pays attention to the ethical principles of information to consent, respect for human rights, beneficence and non-maleficence.

Patient consent for publication
Written informed consent was obtained for anonymized patient information to be published in this article.

Authors' Contributions
AA: Conceptualization, Data Curation, Formal Analysis, Methodology, Validation, Visualization, Writing – Original Draft, Review & Editing; HM: Supervision, Visualization, Writing – Review & Editing

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Conflict of interest
The authors declare no conflict of interest.

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Table 1. Demographic data of the participants characteristics

	Frequency	Percentage
Demographics	**n = 29**	
Gender		
Male	12	41.4
Female	17	58.6
Age groups		
20-35	6	20.7
36-45	9	31.0
>46	14	48.3
Marital status		
Single	0	0.0
Married not at home	0	0.0
Married at home	27	93.1
Divorced/Widower	2	6.9
Educational level		
Junior high school	0	0.0
High school	0	0.0
Bachelor's degree	29	100
Employment status		
Civil servant	4	13.8
Private employee	1	3.4
Self-employed	8	27.6
Retired	5	17.2
Not working	11	37.9

Table 2. Results of VM Effect on FD patients' abdominal pain.

	Baseline	1 weeks	2 weeks	Significance
Outcome measure	(Mean±SD)	(Mean±SD)	(Mean±SD)	***p-value***
Pain frequency	3.52±0.57	2.31±0.54	0.59±0.50	0.001*
Pain time	1.48±0.51	1.17±0.38	0.59±0.50	0.001*
Pain duration	2.66±0.48	1.52±0.51	0.59±0.50	0.001*
Pain intensity	3.52±0.51	2.10±0.67	0.59±0.50	0.001*

SD: standard deviation; * $p<0.05$

Table 3. Results of VM Effect on quality of life in FD patients.

Outcome measure	Baseline Mean±SD	1 weeks Mean±SD	2 weeks Mean±SD	Significance
Anxiety	3.14±0.58	1.93±0.75	1.31±0.47	0.001*
Daily activity limitation	3.31±0.47	2.07±0.46	1.03±0.19	0.001*
Eating/drinking	3.45±0.51	2.03±0.42	1.03±0.19	0.001*
Knowledge/control	3.17±0.71	1.34±0.48	1.00±0.00	0.001*
Work/study	3.14±0.58	2.00±0.38	1.07±0.26	0.001*

SD: standard deviation; * $p<0.05$

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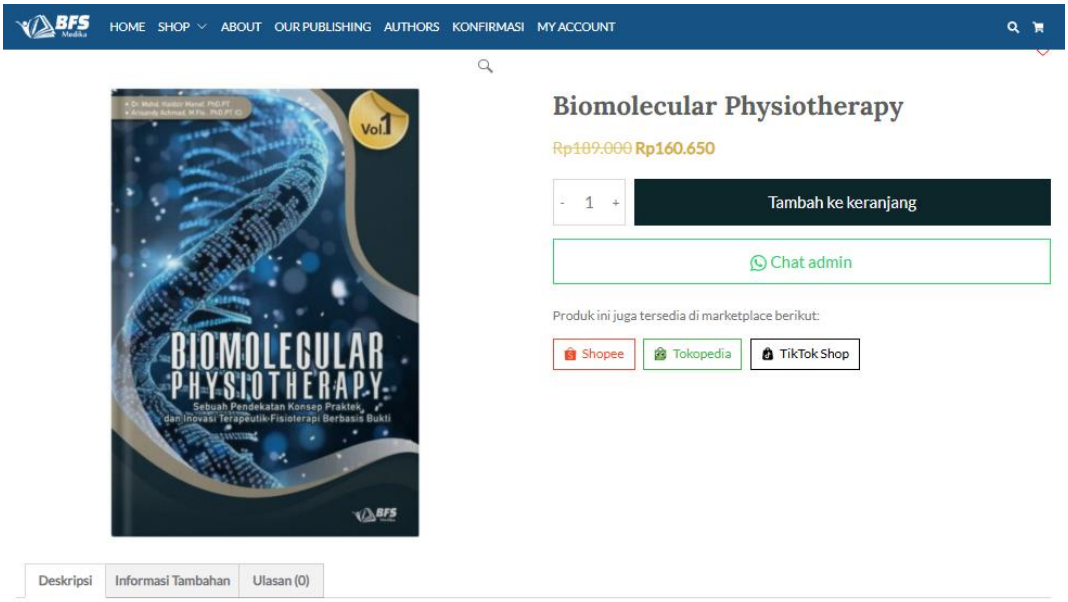
APPENDIX 12

Published Book



Daftar Isi

Penulis :

1. Dr. Mohd. Haidzir Manaf, PhD.PT
2. Arisandy Achmad, M.Fis, PhD. PT

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1. Jenis Cover : Hard Cover
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3. Ukuran Buku : 15,5x 23 cm
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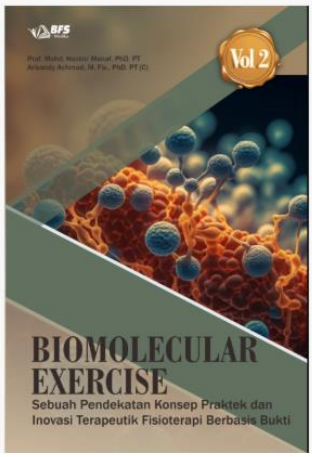

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12. Exercise dan Adaptasi Neurologis
13. Exercise dan Kesehatan Cardiovaskular
14. Biomolecular exercise dalam performa olahraga

Penulis
1. Prof. Mohd. Haidzir Manaf, PhD. PT
2. Arisandy Achmad, M. Fis, PhD. PT (C)

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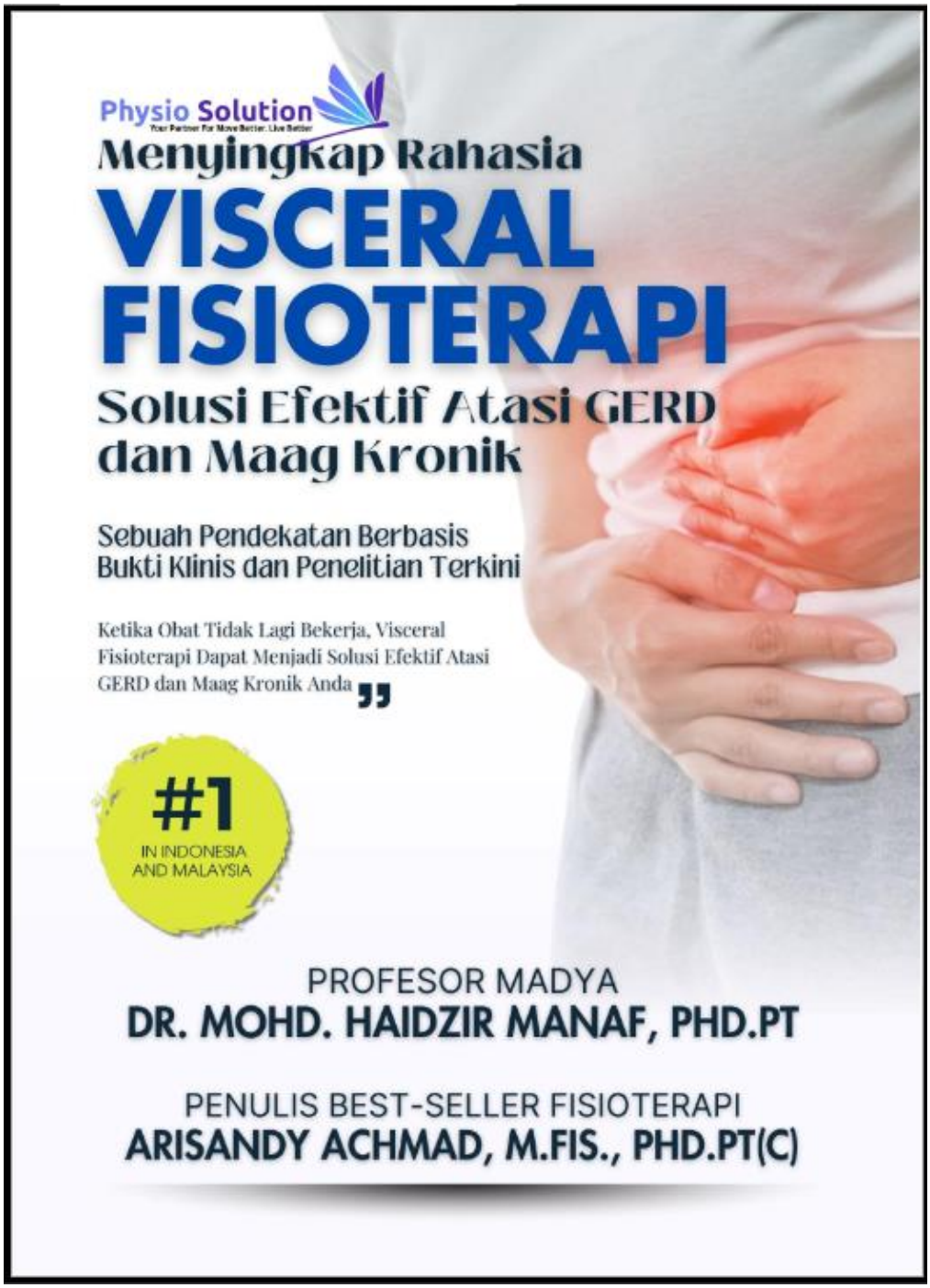
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DR. MOHD. HAIDZIR MANAF, PHD.PT
PENULIS BEST-SELLER FISIOTERAPI
ARISANDY ACHMAD, M.FIS., PHD.PT(C)

AUTHOR'S PROFILE

Commencing his career with a Diploma in Physiotherapy from the Academy of Physiotherapy in 2001, Arisandy Achmad further solidified his expertise by pursuing a Bachelor of Physiotherapy degree at the Faculty of Medicine, Hasanuddin University, Makassar, in 2010. His dedication to advanced knowledge led him to complete a Master's degree in Physiotherapy at the Faculty of Medicine, Udayana University, Bali, in 2019, and subsequently embarked on a PhD in Physiotherapy at the Faculty of Health Sciences, Universiti Teknologi Mara, Malaysia, researching the "Effect of Integrative Visceral and Spinal Manipulation in Adult Patients with Functional Dyspepsia: A Randomized Control Trial." Currently, he lectures in the Bachelor of Physiotherapy program at ITKES Wiyata Husada Samarinda, while also holding the distinction of being a National Best-Selling author in physiotherapy and a recognized expert in Musculoskeletal and Visceral Disorders.

LIST OF PUBLICATIONS

1. Arisandy A., Haidzir M. (2025). The Effect of Visceral Manipulation on Abdominal Pain and Quality of Life in Adult Patients with Functional Dyspepsia: A Pilot Study. Asian Journal of Medicine and Health Sciences, 8(1), 118-129.

2. Arisandy A., Haidzir M. (2025). Visceral Manipulation Intervention in Functional Dyspepsia With or Without Gastroesophageal Reflux Disease: A

Systematic Review. International Journal of Public Health Science (IJPHS), 14(2), 1052-1059.

3. Arisandy A., Haidzir M. (2024). Biomolecular Exercise: Sebuah Pendekatan Konsep Praktek dan Inovasi Teraputik Fisioterapi Berbasis Bukti. Penerbit BFS Medika.
4. Arisandy A., Haidzir M. (2024). Biomolecular Physiotherapy: Sebuah Pendekatan Konsep Praktek dan Inovasi Teraputik Fisioterapi Berbasis Bukti. Penerbit BFS Medika.
5. Arisandy A., Haidzir M. (2025). Menyingkap Rahasia Visceral Physiotherapy: Solusi Efektif Atasi GERD dan Maag Kronik. Penerbit Physio Solution.