Hualien Tzu Chi Hospital
The Application for In-Hospital Medical Technology Research Project

1.Basic Information

Application Number：_____

Project Category (Select one)	■Individual Research Project: The project leader is a senior staff member of the hospital. ■Experimental Research (Up to 800,000 NTD □Non-Experimental Research (Up to 400,000 NTD) □Holistic Care Departmental Project (Up to 800,000 NTD) (Only department heads are eligible to apply) □New Staff Research Project (Up to 200,000 NTD) □University-Hospital Collaborative Research Project (Up to 400,000 NTD) □Ministry of Science and Technology Transfer to Hospital Project (Up to 800,000 NTD) □Medical Education Research Project (Up to 400,000 NTD)				
Personnel Category (Select one)	■Physician □Non-Physician				
Project Title	Comprehensive management strategies for gastroesophageal reflux disease: A study of multidimensional interventions and health impacts				
Name of the Project Leader	Wei-Yi Lei	**Title/Position**	Attending Physician	**Applying Department/Division**	Gastroenterology Department
Project Execution Period	From January 1, 2025 to December 31, 2026				
Research Nature and Classification	□Basic Research ■Applied Research □Technology Development (Note: Those who select Applied Research and Technology Development must also select the category of Innovation R&D.) Innovation R&D Classification：■(1) Clinical Research □(2) Translational Research □(3) Medical Engineering and Materials □(4) Informatio □(5) Medical Assistance Operations □(6) Others, please specify _____。				
Holistic Care (Please refer to the term description, multiple selections are allowed)	Holistic Care Classification： (1) Patient-Centered (■ Physical, ■ Psychological, ■ Environmental, ■ Spiritual) (2) Health Education (■ Behavior Change, ■ Health Promotion, ■ Disease Prevention, ■ Early Diagnosis, □ Early Treatment) (3) Others, please specify _____。				

Has this in-house project applied for the 2023 Ministry of Science and Technology's Special Research Program?

■ No □ Yes.

Has any government agency subsidy for research projects been applied for this year?

■ No □ Yes, a total of____ projects.

A total of__1__ in-house research projects have been applied for this year as the principal investigator (jointly hosted projects are not included).

The priority of this project is__1__.

Has this project applied for:

□ No need

■ Human Experiments / Human Samples (including human embryos/human embryonic stem cells)

□ Animal Experiments

□ Biosafety (including recombinant DNA experiments/genetically modified organism field trials/Level 2 or higher infectious biological materials)

【Please check the applicable items】

Project Contact Person	Name: Lei Wei-Yi Phone: (Office) (03) 8561825-13224 (Home) 0970-339629 E-Mail: aquarious@seed.net.tw

2. **Application for Subsidy Funding** (The budget allocation will be included in the review and evaluation criteria, please do not inflate the figures.)

Based on the actual needs of the research project, the following items can be applied for subsidy funding:

- For individual research projects:
  - Experimental research: Maximum of 800,000 NTD
  - Non-experimental research: Maximum of 400,000 NTD
- For new personnel research projects: The total research funding is limited to 200,000 NTD.
- For collaborative research projects between schools and institutions: The total research funding is limited to 400,000 NTD.
- For holistic care department projects: The maximum funding is 800,000 NTD.
- For Ministry of Science and Technology transferred in-house projects: The maximum funding is 800,000 NTD.

Subsidy Items		Requested Amount
Administrative Expenses	1. Research Personnel Costs	376,248 NTD
	2. Experimental Animal Costs	0 NTD
	3. Consumables, Materials, Books, and Miscellaneous Expenses	423,752 NTD
Research Equipment Costs		0 NTD
Total Amount		800,000 NTD

3. Equipment Configuration

4. The names of the main instruments required for this project, their placement locations, and the signature of the responsible person consenting to their use.

Instrument Name	Installation Location (Department)	Signature and Seal of the Department Head Approving the Use of the Instrument

4. Personnel Involved in the Project

(1) Principal Research Personnel

Category (Principal Investigator, Co-Principal Investigator, Collaborating Principal Investigator, Research Assistant, etc.)	Name	Current Position	Specific Job Role, Tasks, and Scope of Work in this Research Project
Principal Investigator	Lei Wei-Yi	Attending Physician, Gastroenterology	Research project planning and participant recruitment, progress monitoring, data statistical analysis, and report writing.
Co-Principal Investigator	Chen Jian-Lin	Director of Gastroenterology Department	Project progress supervision, project planning discussions, participant recruitment, and data analysis.
Co-Principal Investigator	Weng Ming-Wen	Attending Physician, Gastroenterology	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Yi Zhi-Xun	Attending Physician, Gastroenterology	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Liu Zuo-Cai	Director of the Digestive Function Testing Department	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Hong Rui-Sheng	Attending Physician, Gastroenterology	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Wang Wen-Hui	Director of Gastroenterology Department, E-Da Hospital	Research project participant recruitment and actual case handling.
Co-Principal Investigator	Lin Hui-Min	Director, Department of Nutrition / Chief, Clinical Nutrition Division	Conduct nutrition counseling and patient education.
Research Assistant	Huang Chun-Hsiang	Research Assistant	Survey administration, data collection, organization and analysis, and handling administrative tasks.
Research Assistant	Li Yan-Jia	Research Assistant	Survey administration, data collection, organization and analysis, and handling administrative tasks.

※If there are insufficient fields, please copy them as needed.

(2) Research projects that the principal investigator, co-principal investigator, and co-researchers have participated in during the past three years.

Name	Project Name	Role and Responsibilities in the Project	Start and End Date	Funding Agency
Lei Wei-Yi	Esophageal visceral hypersensitivity and hypervigilance in disorders of gut-brain interaction: the roles of neuromodulators and cognitive-behavioral therapy	Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Application of diaphragmatic breathing in patients with disorders of gut-brain interaction: impact on gastrointestinal and psychological symptoms as well as autonomic nervous system interaction: impact on gastrointestinal and psychological symptoms as well as autonomic nervous system	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Identify pathophysiological mechanisms using postprandial HRIM in patients with GERD and belching disorders: implications for symptom generation and the role of speech therapy	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden in patients with functional dyspepsia--a double-blind, randomized, placebo-controlled study patients with functional dyspepsia--a double-blind, randomized, placebo-controlled study	Co-Principal Investigator	2024/01/01~ 2025/12/31	Buddhist Tzu Chi Medical Foundation
Lei Wei-Yi	Relevance of esophageal hypervigilance, functional gastrointestinal disorders, and psychological distress as pathophysiological mechanisms to esophageal symptoms	Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Efficacy of Jing Si Herbal Tea Liquid Packet for Psychophysiological Symptoms Associated with Gut–Brain Axis Dysfunction in Patients with Long COVID: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial	Co-Principal Investigator	2023/01/01~ 2023/12/31	Buddhist Tzu Chi Medical Foundation
Lei Wei-Yi	Interaction among supragastric belching, psychologic distress and esophageal acid reflux: Implications for optimal management of GERD	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
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Lei Wei-Yi	Antireflux mucosal ablation for the treatment of PPI-dependent gastroesophageal reflux disease: treatment efficacy and physiological alteration	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Exploring capsaicin sensitization, sensorimotor function, psychophyiological reflux characteristics in human esophagus: therapeutic implications for esophageal dysfunction and gastroesophageal reflux disease	Co-Principal Investigator	2023/8/1~ 2026/07/31	National Science and Technology Council
Lei Wei-Yi	Investigating the Pathophysiological Mechanisms of Gastroesophageal Reflux	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital

	Disease Through Esophageal Reflux Clearance, Mucosal Integrity, and Psychophysiological Characteristics: Toward Precision Diagnosis and Treatment			
Lei Wei-Yi	Clinical Application of High-Resolution Impedance Pharyngeal Function Testing and the Sydney Swallow Questionnaire in Oropharyngeal Dysphagia and Dysphonia	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Artificial intelligence in high resolution manometry: studies with deep-learningbased unsupervised model using variational autoencoder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Development and Clinical Validation of a Supervised Machine Learning Model for the Analysis of 24-Hour Esophageal pH-Impedance Monitoring in the Diagnosis of Gastroesophageal Reflux Disease	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Lei Wei-Yi	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
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Chen Jian-Lin	Relationships among mucosal afferent innervation, esophageal peristalsis and pharmacological modulation in the human esophagus: implications for pathophysiology and management in patients with GERD	Co-Principal Investigator	2022/8/1~ 2025/07/31	National Science and Technology Council
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	Monitoring in the Diagnosis of Gastroesophageal Reflux Disease			
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Yi Zhi-Xun	Esophageal acid sensitivity and secondary peristalsis: implication for gastroesophageal reflux disease and relevant disease phenotypes	Principal Investigator	2021/1/1~ 2021/12/31	Hualien Tzu Chi Hospital
Yi Zhi-Xun	Investigating the Role of the Esophageal Microbiome in Novel Impedance Metrics, Clinical Phenotypes, and Esophageal Hypersensitivity in Gastroesophageal Reflux Disease	Co-Principal Investigator	2021/1/1~ 2021/12/31	Hualien Tzu Chi Hospital
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Liu Zuo-Cai	Artificial intelligence in high resolution manometry: studies with deep-learningbased unsupervised model using variational autoencoder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
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Liu Zuo-Cai	Evaluation of esophageal peristalsis, mucosa integrity, and acid sensitivity: implications for pathophysiology and therapeutic strategies in gastroesophageal reflux disease	Co-Principal Investigator	2020/8/1~ 2023/07/31	National Science and Technology Council
Hong Rui-Sheng	Identify pathophysiological mechanisms using postprandial HRIM in patients with GERD and belching disorders: implications for symptom generation and the role of speech therapy	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital

Hong Rui-Sheng	Esophageal visceral hypersensitivity and hypervigilance in disorders of gut-brain interaction: the roles of neuromodulators and cognitive-behavioral therapy	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Application of diaphragmatic breathing in patients with disorders of gut-brain interaction: impact on gastrointestinal and psychological symptoms as well as autonomic nervous system	Co-Principal Investigator	2024/01/01~ 2024/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden in patients with functional dyspepsia--a double-blind, randomized, placebo-controlled study	Co-Principal Investigator	2024/01/01~ 2025/12/31	Buddhist Tzu Chi Medical Foundation
Hong Rui-Sheng	Oropharyngeal swallowing physiology in patients with esophageal hypomotility: Studies with HRPM	Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Clinical Application of High-Resolution Impedance Pharyngeal Function Testing and the Sydney Swallow Questionnaire in Oropharyngeal Dysphagia and Dysphonia	Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Efficacy of Jing Si Herbal Tea Liquid Packet for Psychophysiological Symptoms Associated with Gut–Brain Axis Dysfunction in Patients with Long COVID: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial	Co-Principal Investigator	2023/01/01~ 2023/12/31	Buddhist Tzu Chi Medical Foundation
Hong Rui-Sheng	Interaction among supragastric belching, psychologic distress and esophageal acid reflux: Implications for optimal management of GERD	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Relevance of esophageal hypervigilance, functional gastrointestinal disorders, and psychological distress as pathophysiological mechanisms to esophageal symptoms	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Antireflux mucosal ablation for the treatment of PPI-dependent gastroesophageal reflux disease: treatment efficacy and physiological alteration	Co-Principal Investigator	2023/01/01~ 2023/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Exploring capsaicin sensitization, sensorimotor function, psychophyiological reflux characteristics in human esophagus: therapeutic implications for esophageal dysfunction and gastroesophageal reflux disease	Co-Principal Investigator	2023/8/1~ 2026/07/31	National Science and Technology Council
Hong Rui-Sheng	Investigating the Pathophysiological Mechanisms of Gastroesophageal Reflux Disease Through Esophageal Reflux Clearance, Mucosal Integrity, and Psychophysiological Characteristics: Toward Precision Diagnosis and Treatment	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Impact of opioids on esophageal peristalsis and acid reflux characteristics: relevance for esophageal pathophysiology and therapeutic implications	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Development and Clinical Validation of a Supervised Machine Learning Model for the Analysis of 24-Hour Esophageal pH-Impedance Monitoring in the Diagnosis of Gastroesophageal Reflux Disease	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital

Hong Rui-Sheng	Artificial intelligence in high resolution manometry: studies with deep-learningbased unsupervised model using variational autoencoder	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Impact of regulating diet and exercise on clinical characteristics and intestinal microbiota in patients with metabolic-related fatty liver	Co-Principal Investigator	2022/1/1~ 2022/12/31	Hualien Tzu Chi Hospital
Hong Rui-Sheng	Jing Si Herbal Tea in the treatment of dyspeptic symptoms and psychophysical burden in patients with functional dyspepsia--a double-blind, randomized, placebo-controlled study	Co-Principal Investigator	2022/1/1~ 2022/12/31	Buddhist Tzu Chi Medical Foundation
Hong Rui-Sheng	Evaluation of esophageal peristalsis, mucosa integrity, and acid sensitivity: implications for pathophysiology and therapeutic strategies in gastroesophageal reflux disease	Co-Principal Investigator	2020/8/1~ 2023/07/31	National Science and Technology Council

5. Research Related to Costs

Project Name		Description	Unit Price (NTW)	Quantity	Total Price (NTW)	Remarks
1. Operational Expenses	1.Research Personnel Costs (For related insurance premiums, please consult the Human Resources Department)	**(1) Full-time Personnel (for individual project applications only):** • Work remuneration (including year-end bonus reserve) • Employer contribution to labor and health insurance • Employer contribution to labor pension (6% of insured salary)				
		(2) Part-time Personnel (must be enrolled students): • Work remuneration □ Undergraduate student □ Master's student □ Other: _____ • Employer contribution to labor and health insurance • Employer contribution to labor pension (6% of insured salary)				
		(3) Temporary Workers: • Work remuneration • Employer contribution to labor and health insurance • Employer contribution to labor pension (6% of insured salary)	26,352 2,533 33 1,818 618	12 12 12 12 12	316,224 30,396 396 21,816 7,416	hourly pay NT$183 per month 144hrs
				Subtotal:	NT$376,248	
	2.Animal Experimentation Fees					
				Subtotal:	0	
	3.Consumables, Equipment, Books, and Miscellaneous Expenses	Participant stipend (Study 1) wedge pillow Participant stipend (Study 2)	300 1,000 300 600	120 120 220 220	36,000 120,000 66,000 132,000	

		nutritional counseling	200	250	50,000	
		Participant stipend (Study 3)	9,752	1	9,752	
		Computer peripheral consumables expenses：toner cartridges, ink cartridges, printer drums/photoconductor units, specialty printer paper, etc.	10,000	1	10,000	
		Miscellaneous：postage and telecommunications fees, printing costs, photocopy paper, photocopying fees, binding costs, stationery expenses, poster production costs, data processing/statistical analysis fees, data analysis fees, manuscript submission fees, publication fees.				
				Subtotal:	423,752	
2. Research Equipment Costs (According to regulations, books, computers, and peripheral equipment are not included in the subsidy. Medium and large instruments will be applied for collectively by the research department, based on necessity, for shared use.)						
				Subtotal:	0	
Total					800,000	

6. Project Abstract

（Please provide a summary of the key points of this project within 500 words, and create customized keywords based on the nature of the project.）

Gastroesophageal reflux disease (GERD) is a common gastrointestinal disorder, with around 80% of patients experiencing nighttime symptoms. The prolonged nighttime reflux increases esophageal acid exposure, leading to complications like erosive esophagitis and extra-esophageal symptoms such as asthma and chronic cough. These symptoms disrupt sleep and affect daytime work and quality of life. Diet significantly influences GERD; high-fat foods, spicy foods, caffeine, carbonated beverages, and fermentable oligosaccharides disaccharides monosaccharides and polyols (FODMAPs) can worsen symptoms by lowering the pressure of the lower esophageal sphincter or delaying gastric emptying. Eating before bed or lying down immediately after meals can also aggravate symptoms. Treatment typically includes weight loss, bed elevation, smoking and alcohol cessation, avoiding meals before bedtime, and certain food restrictions. However, most dietary studies are observational, and there is limited evidence from randomized controlled trials. Proton pump inhibitors are standard treatments, but about 40% of patients do not achieve satisfactory symptom relief after treatment. Many of these patients suffer from disorders of gut-brain axis interaction (DGBI), characterized by visceral hypersensitivity and heightened esophageal vigilance. Additionally, these patients often have comorbid functional gastrointestinal disorders, increasing diagnostic complexity and leading to poor treatment outcomes. The interaction between visceral hypersensitivity, psychological distress, and central sensitization in GERD patients with functional gastrointestinal disorders remains unclear. This study aims to explore GERD symptoms and their influencing factors from multiple perspectives and propose non-pharmacological treatment strategies. The research focuses on nighttime reflux symptoms, dietary interventions, and the interaction between functional gastrointestinal disorders and GERD, providing empirical support to improve patients' symptoms and quality of life. The results of this study will help clarify the pathophysiological mechanisms related to GERD, esophageal DGBI, and functional gastrointestinal disorders. Additionally, the research findings will provide effective treatment strategies for patients with refractory reflux and DGBI in clinical settings.

Key words: gastroesophageal reflux disease, lifestyle and dietary interventions, disorders of gut-brain interaction

7. Background and Objectives of the Research Project

（Please provide a detailed description of the background, objectives, significance of this research project, as well as the research status both domestically and internationally related to this project. Also, include a review of important references and literature.）

Research Background

◆Clinical significance of gastroesophageal reflux disease and nocturnal gastroesophageal reflux

Gastroesophageal reflux disease (GERD) is defined as the reflux of gastric contents into the esophagus, resulting in symptoms and/or mucosal injury, and is a common chronic disease in clinical practice. The prevalence of GERD can be as high as 30% in Western countries,[1] while it is relatively lower in East Asia,[2] although an increasing trend has been observed in recent years. Typical symptoms include heartburn and acid regurgitation, which often impair patients' quality of life and may lead to insomnia, depression, or anxiety.[3] Chronic acid exposure to the distal esophagus not only causes mucosal injury but may also result in serious complications such as esophageal stricture, Barrett's esophagus, and esophageal adenocarcinoma.[4] Frequent medical visits, diagnostic procedures, pharmacological treatments, and surgeries related to GERD contribute substantially to healthcare utilization. According to statistics, the annual medical and non-medical costs associated with GERD in the United States alone are estimated to approach 1 billion US dollars.[5] Therefore, GERD represents an important issue not only in clinical medicine but also in national public health policy.

Nocturnal symptoms of gastroesophageal reflux disease (GERD) often have a significant impact on sleep quality. Patients frequently report difficulty falling asleep, disrupted sleep patterns, or awakening during the night. Studies have shown that up to 80% of patients with GERD experience nocturnal symptoms, which not only interfere with daytime work and social activities but also negatively affect health-related quality of life.[6,7] Several pathogenic mechanisms contribute to GERD, including important esophageal clearance mechanisms such as primary peristalsis, salivary secretion, and secondary peristalsis, all of which are suppressed during sleep. These physiological changes during sleep render the esophagus more vulnerable to acid reflux injury at night.[8] Although reflux episodes occur less frequently during sleep than during wakefulness, nocturnal reflux episodes tend to last longer, thereby increasing distal esophageal acid exposure time and resulting in greater mucosal damage.[9,10] Studies have demonstrated that nocturnal acid reflux is associated with esophageal complications such as erosive esophagitis, esophageal stricture, Barrett's esophagus, and adenocarcinoma.[11] In addition, nocturnal reflux has also been linked to various extraesophageal manifestations of GERD, including asthma, dental erosion, and chronic cough.[12,13]

◆Association Between Diet and Gastroesophageal Reflux Symptoms

Diet is an important factor influencing gastroesophageal reflux disease (GERD) symptoms, and certain foods and eating habits may exacerbate reflux symptoms. Previous studies have shown that a

high-fat diet can delay gastric emptying and reduce lower esophageal sphincter (LES) pressure, thereby increasing the risk of acid reflux.[14,15,16] For example, in a randomized crossover study conducted by Fan et al., patients with erosive esophagitis who consumed a high-fat meal demonstrated a higher percentage of esophageal acid exposure over a 4-hour period compared with those who consumed a standard meal (5.2% vs. 4%).[17]

In addition, certain foods such as coffee, caffeine, spicy foods, and citrus fruits may have minimal effects on LES pressure but can exert irritative effects on the esophageal mucosa, potentially triggering reflux symptoms even without increasing reflux events.[16,18] Regarding carbohydrate intake, recent studies have confirmed that patients with GERD consuming a high-carbohydrate diet tend to experience more severe reflux symptoms, along with a greater number of reflux episodes and increased acid exposure on pH monitoring.[19,20]

With respect to diets containing fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs), a study by Plaidum et al. demonstrated that patients in the high-FODMAP diet group experienced more severe postprandial reflux symptoms within 2 hours after meals compared with those in the low-FODMAP diet group.[21] However, another study investigating low-FODMAP dietary intervention in patients with refractory GERD did not demonstrate significant benefits.[22]

In addition, the timing of food intake also affects gastroesophageal reflux symptoms. Studies have demonstrated that lying down or going to sleep within a short interval after eating (<3 hours) is associated with increased GERD symptoms and a greater need for medication.[23] Obesity has been confirmed in numerous studies as a risk factor for GERD. This may be attributable to frequent consumption of high-fat or other reflux-inducing foods, increased intra-abdominal fat leading to elevated intra-abdominal pressure and subsequent reflux, as well as physiological changes induced by visceral adipose tissue products.[24] Even among individuals with a normal body mass index (BMI), obesity or weight gain has been associated with the new onset of reflux symptoms.[25]

◆Effects of Dietary Intervention and Lifestyle Modification on Gastroesophageal Reflux Disease

Common recommendations for the management of gastroesophageal reflux disease (GERD) include weight reduction in overweight or obese patients, elevation of the head of the bed, smoking cessation, alcohol avoidance, avoidance of late-night meals and eating before bedtime, maintaining an upright posture during and after meals, and avoiding foods that may exacerbate reflux symptoms, such as coffee, chocolate, carbonated beverages, spicy foods, acidic foods, and high-fat foods.[26,27] However, the evidence supporting these recommendations remains limited, as most studies are small, uncontrolled, and lifestyle modification is rarely evaluated as the sole intervention.

Regarding nocturnal reflux, recent studies have demonstrated that elevating the head of the bed or sleeping on a wedge pillow can improve nocturnal reflux symptoms and reduce nocturnal esophageal acid exposure.[28–30] In addition, previous studies have shown that, compared with the left lateral decubitus position, the right lateral decubitus position significantly increases nocturnal and postprandial reflux.[31,32] More recent studies have further confirmed that the left lateral position, compared with the supine and right lateral positions, can significantly shorten esophageal acid exposure time and facilitate faster esophageal acid clearance.[33]

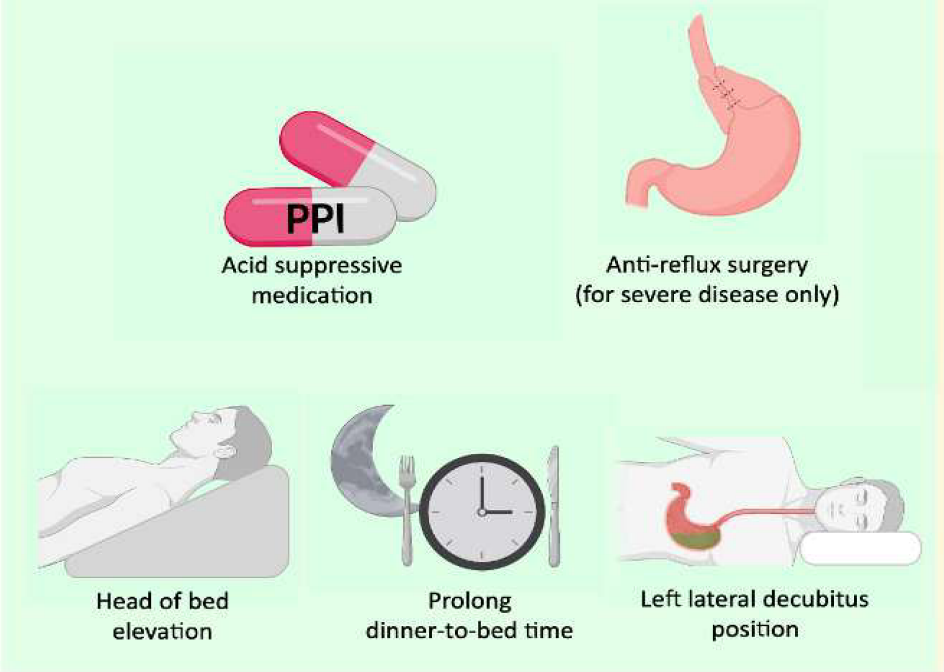


Figure 1. Potential Therapeutic Strategies for Nocturnal Reflux Symptoms

Regarding dietary interventions, in addition to recommending avoidance of food intake within 2–3 hours before bedtime for the treatment of nocturnal reflux symptoms, low-carbohydrate diets have shown certain benefits in reducing GERD symptoms and decreasing esophageal acid exposure time.[19,20,34] Although the underlying mechanism has not been fully elucidated, it is thought to be related to reduced gastric distension. Studies investigating low-fat dietary interventions have not yielded consistent results, and the fat content of the diet may be an important influencing factor. With regard to smoking cessation, a large cohort study demonstrated improvement in GERD symptoms following smoking cessation.[35] Another smoking cessation study using questionnaire assessments also found that individuals who successfully quit smoking for one year experienced significantly greater improvement in GERD symptoms compared with those who did not quit smoking (44% vs. 18%).[36] As for the effect of weight reduction on GERD, numerous studies have shown consistent findings indicating that reflux symptoms in overweight or obese patients with GERD improve significantly with weight loss.[27]

◆The Relationship Between Gastroesophageal Reflux Disease and Functional Gastrointestinal Disorders

Functional gastrointestinal disorders include functional dyspepsia (FD) and irritable bowel syndrome (IBS). In 2016, experts revised the diagnostic criteria for these two disorders based on the Rome IV criteria. Both of these functional disorders and gastroesophageal reflux disease (GERD) are common gastrointestinal diseases encountered in clinical practice and frequently coexist. Previous studies have confirmed that dyspepsia commonly occurs in association with GERD.

In a study conducted by Tack at a secondary referral center in Belgium involving 247 patients with dyspeptic symptoms but without typical reflux symptoms and with normal upper gastrointestinal endoscopy findings, 23% were found to have abnormal 24-hour pH monitoring results.[37] Epidemiological studies in Asia have shown that more than 30% of patients with GERD also experience dyspeptic symptoms.[38] Regarding GERD subtypes, studies have found that GERD patients with dyspeptic symptoms are more likely to have non-erosive reflux disease (NERD) rather than erosive esophagitis.[39,40]

In terms of symptom presentation, a study by Noh et al. on GERD patients with concomitant functional dyspepsia found that patients with NERD more commonly presented with epigastric pain syndrome (EPS), characterized predominantly by epigastric pain or burning sensation, whereas patients with erosive esophagitis more commonly exhibited symptoms of postprandial distress syndrome (PDS), characterized mainly by postprandial discomfort or early satiety.[41] GERD and IBS also frequently coexist and are closely associated. The reported prevalence of overlap between these two disorders ranges from 3% to 79%; when endoscopy-based diagnostic criteria are used, the prevalence ranges from 10% to 74%.[42]

In addition, these three disorders are frequently diagnosed concurrently. Our previous studies showed that approximately 40% of patients with gastroesophageal reflux disease (GERD) also have concomitant functional gastrointestinal disorders, with prevalence rates of 2.2% for GERD-FD, 0.9% for GERD-IBS, and 0.9% for GERD-FD-IBS, respectively.[43] The coexistence of these disorders may be attributed not only to their high prevalence, but also to shared pathophysiological mechanisms, such as visceral hypersensitivity, abnormal gastrointestinal motility, genetic factors, and dysfunction of the brain-gut axis. Furthermore, when multiple disorders occur simultaneously, the presentation and severity of esophageal and gastrointestinal symptoms may change or become more diverse, thereby increasing diagnostic difficulty and often leading to unsatisfactory treatment outcomes. Psychological factors, including comorbid anxiety and depression, may also play a significant role in these patients.

◆Disorders of gut-brain axis interaction in the esophagus and esophageal mucosal integrity

Disorders of gut-brain axis interaction in the esophagus (DGBI) refer to symptomatic gastrointestinal disorders without identifiable structural abnormalities. According to the Rome IV criteria,[44] there are five categories of esophageal DGBI: functional chest pain, reflux hypersensitivity (RH), functional heartburn (FH), globus, and functional dysphagia. By definition, patients must have chronic esophageal symptoms persisting for at least three months, with symptom onset occurring at least six months before diagnosis. In addition, structural, inflammatory, motility-related, and metabolic abnormalities of the esophagus must be excluded. Therefore, the diagnosis of esophageal DGBI requires upper gastrointestinal endoscopy, esophageal pH-impedance monitoring, and high-resolution esophageal manometry to exclude other possible esophageal diseases that may cause similar symptoms. Regarding the pathophysiology, esophageal visceral hypersensitivity and hypervigilance are currently considered possible underlying mechanisms; however, the exact mechanisms remain to be further elucidated.

From a diagnostic perspective, disorders of gut-brain axis interaction in the esophagus require normal endoscopic findings and normal acid exposure time (AET) on reflux monitoring. Because catheter-based esophageal pH monitoring can only detect reflux activity during the 24-hour testing period, patients may alter their daily activities or eating habits due to catheter-related discomfort, which may affect the diagnostic results to varying degrees. Therefore, in recent years, 24-hour esophageal pH-impedance monitoring has incorporated the calculation of mean nocturnal baseline impedance (MNBI) to improve the diagnostic accuracy for esophageal DGBI or to help exclude gastroesophageal reflux disease (GERD). Patients with esophageal DGBI (without GERD) generally demonstrate normal MNBI values.

MNBI is calculated by averaging impedance values obtained from three separate 10-minute nocturnal periods during sleep, each spaced one hour apart (for example, 1:00, 2:00, and 3:00 AM) during esophageal pH-impedance monitoring. Studies have shown that MNBI is highly correlated with mucosal integrity, acid exposure time, and reflux symptoms.[45,46]

Although proton pump inhibitor (PPI) are currently the mainstay treatment for gastroesophageal reflux disease (GERD), up to 50% of patients continue to experience persistent symptoms despite PPI therapy.[47] Studies have shown that among patients with heartburn symptoms refractory to PPI treatment, more than 90% are diagnosed with reflux hypersensitivity or functional heartburn.[48,49] Therefore, many patients with refractory GERD actually have disorders of gut-brain axis interaction in the esophagus.

The unsatisfactory treatment outcomes in these patients may be attributed to the complex pathophysiological mechanisms involved and the limited understanding of disturbances in brain-gut interaction. Recent consensus statements have suggested that non-reflux-related factors, such as

altered perception and visceral hypersensitivity, may contribute to refractory esophageal symptoms.[50] Furthermore, the Esophageal Hypervigilance and Anxiety Scale (EHAS) has been validated as an effective tool for assessing esophageal hypersensitivity,[51] and is therefore considered potentially useful in the diagnosis of esophageal disorders of gut-brain axis interaction.

Research Objectives

The objectives of this study：

To investigate the effects of dietary intervention on esophageal reflux symptoms.

Hypotheses:

1. Both dietitian-led dietary intervention and educational leaflet-based dietary intervention can improve esophageal symptoms in patients with gastroesophageal reflux disease through modifications of lifestyle and dietary habits.
2. Compared with educational leaflet-based dietary intervention, dietitian-led dietary intervention can achieve greater improvements in reflux symptoms and overall dietary adherence among patients.

8. Research Methods, Procedures, and Execution Progress

1. Please describe in detail the research methods adopted in this project and the reasons for choosing them.
2. Potential challenges and solutions expected during the project.
3. If this is a continuous project, please also attach the progress report from the previous year or primary data.

Research Method

Participant

This study is expected to be conducted over a period of two years, with the study duration extending through December 31, 2026. A total of 220 patients with chronic gastroesophageal reflux symptoms will be recruited from the Division of Gastroenterology at Hualien Tzu Chi Hospital.

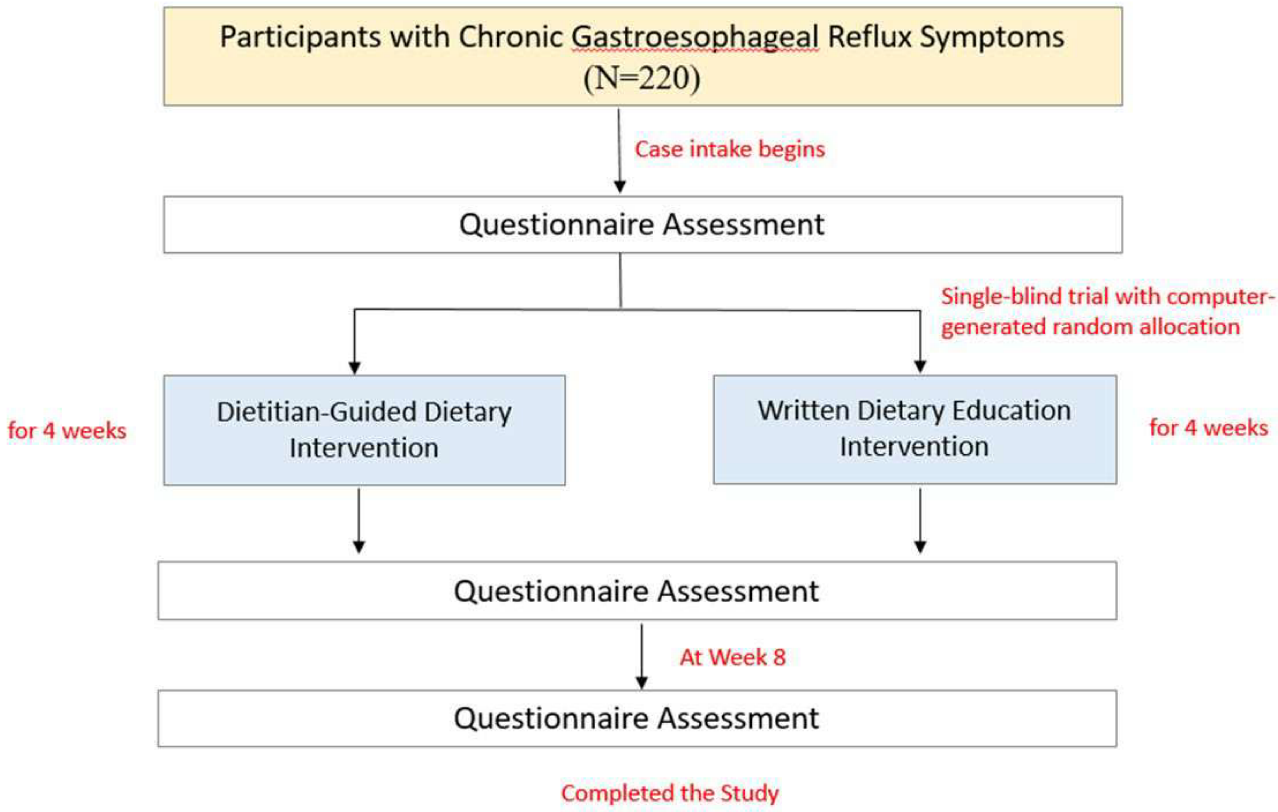
Inclusion criteria for participants：

1. Adults aged 18–79 years who are conscious, mentally competent, and willing to provide written informed consent.
2. Subjects with chronic gastroesophageal reflux symptoms (acid regurgitation, chest pain, or heartburn) who are willing to undergo dietary intervention.

Exclusion criteria for participants：

1. Patients with esophageal stricture, current or previous diagnosis of esophageal malignancy, or a history of esophageal, upper gastrointestinal, or pharyngeal surgery.
2. Patients with structural esophageal disorders (such as diverticula or esophageal rings), infectious esophagitis, or eosinophilic esophagitis.
3. Patients with major esophageal motility disorders.
4. Patients currently using medications that may affect esophageal motility (such as opioids, nitrates, calcium channel blockers, etc.).
5. Patients who have continuously used, within the past three months, or are currently taking antidepressants, selective serotonin reuptake inhibitors (SSRIs), or other psychiatric medications.
6. Pregnant women, or individuals unable to comply with lifestyle modification and dietary intervention for other reasons.

Research Design Flowchart



Steps to Follow

Subjects who meet the inclusion criteria will first provide written informed consent before completing the baseline questionnaires. Each subject will then be randomly assigned by computer to one of two study groups. One group will receive a diet intervention guided by a registered dietitian, while the other group will receive a written dietary education intervention. The intervention period for both groups will last 4 weeks.

Questionnaire assessments will be conducted at the end of the 4-week intervention period and again 8 weeks after the completion of the intervention, after which the study will be concluded.
The questionnaires used in this study include:

- Gastroesophageal Reflux Disease Questionnaires: Gastroesophageal Reflux Disease Questionnaire (GERDQ) and Reflux Symptom Index (RSI)
- Esophageal Hypervigilance and Anxiety Questionnaire: Esophageal Hypervigilance and Anxiety Scale (EHAS)

- Sleep and Psychological Well-being Questionnaires: Pittsburgh Sleep Quality Index (PSQI), Taiwanese Depression Questionnaire (TDQ), State-Trait Anxiety Inventory (STAI), and Visceral Sensitivity Index (VSI)
- Functional Gastrointestinal Disorders Questionnaires: Functional Dyspepsia (FD), Irritable Bowel Syndrome (IBS), and Gastrointestinal Symptom Rating Scale (GSRS)
- Quality of Life Questionnaires: Gastroesophageal Reflux Disease–Health-Related Quality of Life (GERD-HRQL) and 12-Item Short Form Health Survey (SF-12) Questionnaire.

Statistical Analysis

Data normality will be assessed using the Kolmogorov–Smirnov test. Continuous variables with a normal distribution will be presented as mean ± standard deviation (SD), whereas non-normally distributed variables will be expressed as median and interquartile range (IQR).

Categorical variables will be analyzed using the Chi-square test or Fisher's exact test, as appropriate. Continuous variables with a normal distribution will be compared using the unpaired t-test, while non-normally distributed continuous variables will be analyzed using the Mann–Whitney U test**.**

A P value **<** 0.05 will be considered statistically significant.

All statistical analyses will be performed using SPSS for Windows, Version 19.0 (SPSS Inc., Chicago, IL, USA).

Clinical Significance and Innovation of the Study

1. This study aims to investigate the effectiveness of individualized dietary counseling and intervention strategies provided by registered dietitians in controlling reflux symptoms. The findings of these non-pharmacological interventions may not only offer clinicians an alternative approach to symptom management through lifestyle modification but also provide evidence-based support for dietary interventions in patients with gastroesophageal reflux disease (GERD). Furthermore, the study may help elucidate the complex relationship between dietary factors and esophageal physiological function.

2. This study will utilize assessments of visceral sensitivity, psychological well-being, esophageal hypervigilance and anxiety, and functional gastrointestinal disorders to evaluate the impact of functional gastrointestinal disorders on patients with reflux symptoms. Specifically, it will examine whether these individuals experience more severe esophageal symptoms and possess a lower threshold for esophageal hypervigilance as a result of visceral hypersensitivity.

9.Expected Work Items and Specific Outcomes

(1) Please list the expected tasks to be completed within the execution period.
(2) Expected contributions to academic research and other applied areas.
(3) Expected training that participants will receive.

(1) Expected Work Items

1. This study aims to investigate the effects of lifestyle modification and dietary adjustments on symptom improvement, psychological well-being, and quality of life in patients with gastroesophageal reflux disease (GERD). In addition, we will compare the effectiveness of different dietary education interventions in improving reflux symptoms.

2. This study will also examine differences in esophageal hypervigilance and visceral hypersensitivity thresholds between GERD patients with and without concomitant functional gastrointestinal disorders (FGIDs).

(2) Expected Contributions to Academic Research, National Development, and Other Applications

1. The data generated from this study will enhance our understanding of the effects of lifestyle modification and professional dietary counseling on the physiological, psychological, and quality-of-life outcomes of patients with GERD. The findings may facilitate the development of personalized non-pharmacological treatment strategies in clinical practice.

2. This study will improve our understanding of the roles of visceral hypersensitivity, esophageal hypervigilance, and anxiety in disorders involving abnormal esophageal–brain–gut axis communication, as well as in refractory gastroesophageal reflux disease. The results may provide valuable guidance for the future management and treatment of these patient populations.

(3) Expected Training Benefits for Participating Personnel

In addition to receiving fundamental research training in study design and implementation, questionnaire development and administration, data analysis and statistics, figure and table preparation, oral presentation skills, manuscript writing, and publication procedures, participating personnel will gain experience in the design and data analysis of clinical research on esophageal pathophysiology. They will also become familiar with the role of cognitive behavioral therapy (CBT) and its practical implementation in clinical research and patient care.

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