THE EFFECT OF MAWANGDUI EXERCISE ON THE PULMONARY FUNCTION, PHYSICAL FITNESS AND QUALITY OF LIFE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS

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by

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LIST OF ABBREVIATIONS

6MWT	6-min walk test
BMI	Body mass index
Borg CR-10 score	Borg Category-Ratio-10 score
CAT	COPD assessment test
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
DALYs	Disability adjusted life years
ESWT	Endurance shuttle walk test
FEV_1	Forced expiratory volume in one second
FEV_1%pred	Forced expiratory volume in one second percentage of predicted value
FVC	Forced vital capacity
GBDS	Global Burden of Disease Study
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ISWT	Incremental shuttle walk test
LMICs	Low-and middle-income countries
METs	Metabolic equivalents
mMRC	Modified Medical Research Council dyspnoea
NO_2	Nitrogen dioxide
PM	Particulate matter
$PM_{2.5}$	Particulate matter with 2.5 microns
RM	Repetition maximum
SGRQ	St. George's Respiratory Questionnaire
SpO_2	Blood oxygen saturation
SO_2	Sulfur dioxide
WBC	White blood cells
HIIT	High-intensity interval training
MMP-9	Matrix metalloproteinase 9
EMT	Epithelial-mesenchymal transition

LIST OF APPENDICES

KESAN SENAMAN MAWANGDUI TERHADAP FUNGSI PARU-PARU, KECERGASAN FIZIKAL DAN KUALITI HIDUP DALAM KALANGAN PESAKIT BERPENYAKIT PARU-PARU OBSTRUKTIF KRONIK (COPD)

ABSTRAK

Senaman fizikal merupakan komponen penting dalam pemulihan rehabilitasi pulmonari bagi pesakit penyakit paru-paru obstruktif kronik (COPD). Walau bagaimanapun, terdapat senaman intervensi tertentu yang mungkin membataskan pesakit COPD, kerana ia menyebabkan keletihan dan sesak nafas, dan seterusnya mengurangkan kualiti hidup. Senaman Mawangdui merupakan satu senaman aerobik berintensiti rendah hingga sederhana yang semakin popular di China sebagai intervensi fizikal tambahan, terutamanya untuk pesakit yang mempunyai kontraindikasi terhadap senaman. Kajian ini bertujuan untuk: (1) memahami ciri-ciri dan faktor risiko pesakit COPD (umur, jantina, merokok, berhenti merokok, gred COPD, purata tempoh kemasukan wad hospital dan penyakit komorbiditi); (2) menyiasat kesan senaman Mawangdui terhadap fungsi paru-paru (FEV_1, FVC, FEV_1 %pred), keupayaan senaman (6MWT, Borg CR-10, SpO_2), kecergasan fizikal (kekuatan otot belakang-kaki-dada dan keanjalan duduk-rentangkan), gejala sesak nafas (CAT, mMRC), dan kualiti hidup (SGRQ) dalam kalangan pesakit COPD**.** Dua kajian dijalankan. Kajian 1 melibatkan penyiasatan rentas-mengufuk retrospektif terhadap rekod klinikal pesakit COPD di Hospital Perubatan Tradisional Cina Changde, China dan Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, Malaysia. Dalam Kajian 2, 45 pesakit COPD dalam peringkat stabil (purata umur 65.2 tahun) menjalani sesi intervensi selama 12 minggu di komuniti. Kumpulan intervensi (n=22) menjalankan latihan Mawangdui selama 60 minit setiap sesi, 5 kali

seminggu, manakala kumpulan kawalan (n=23) mengekalkan aktiviti harian tanpa senaman tambahan. Keputusan telah dinilai pada permulaan, 24 jam, 6 minggu, dan 12 minggu selepas intervensi. Analisis Kajian 1 mendapati bahawa COPD lebih lazim pada pesakit lelaki, di kedua-dua negara China dan Malaysia. Merokok adalah lazim dalam kalangan pesakit COPD, dengan lelaki merokok lebih banyak daripada wanita. Bilangan berhenti merokok dalam pesakit COPD adalah kurang daripada 50% di kedua-dua hospital. Pesakit COPD di Hospital Changde mempunyai tahap keparahan yang lebih tinggi dan tempoh kemasukan wad hospital yang lebih lama berbanding Hospital USM. Walau bagaimanapun, terdapat lebih banyak penyakit serentak COPD di Hospital USM Kota Bharu berbanding di Hospital Changde. Umur dan gred fungsi paru-paru berkait secara signifikan dengan purata tempoh penginapan hospital dalam kalangan pesakit COPD di kedua-dua hospital. Bagi Kajian 2, pada minggu ke-12 selepas intervensi, kumpulan intervensi senaman Mawangdui menunjukkan kesan positif ke atas gejala sesak nafas (CAT, mMRC), keupayaan senaman (6MWT, Borg CR-10, SpO_2), kekuatan otot belakang-kaki-dada, fleksibiliti duduk-capai, BMI, peratus lemak badan, jisim lemak dan kualiti kehidupan (skor SGRQ). Kesimpulannya, pesakit COPD yang tinggal dalam iklim yang berbeza mempunyai tabiat merokok dan penyakit seiringan yang serupa, dan mereka perlu meningkatkan gaya hidup sihat. Senaman Mawangdui dapat menghasilkan kesan positif ke atas gejala sesak nafas, kecergasan fizikal dan kualiti hidup pesakit COPD peringkat ringan dan sederhana yang stabil. Senaman Mawangdui boleh disyorkan sebagai sebahagian daripada pemulihan pulmonari untuk pesakit COPD dalam peringkat ringan dan sederhana penyakit ini.

Kata kunci COPD, Senaman Mawangdui, fungsi paru-paru, kecergasan fizikal, kualiti hidup

THE EFFECT OF MAWANGDUI EXERCISE ON THE PULMONARY FUNCTION, PHYSICAL FITNESS AND QUALITY OF LIFE IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) PATIENTS

ABSTRACT

Physical exercise is an important component of pulmonary rehabilitation for chronic obstructive pulmonary disease (COPD) patients. However, certain physical therapy may be restrictive to COPD patients, as it induces fatigue and shortness of breath, thus reducing quality of life. Mawangdui exercise, a type of low-to-medium-intensity aerobic exercise, has been gaining popularity in China as adjuvant physical therapy, particularly for patients with contraindications to exercise. This study aims to: (1) understand the characteristics and risk factors of patients with COPD (age, sex, cigarette smoking, smoking cessation, COPD grade, average length of hospital stay, and comorbidities); (2) investigate the effects of Mawangdui exercise on pulmonary function (FEV_1, FVC, FEV_1 %pred), exercise capacity (6MWT, Borg CR-10, and SpO_2), physical fitness (back-leg-chest muscle strength and sit-and-reach flexibility), dyspnoea symptoms (CAT, mMRC), and quality of life (SGRQ) in patients with COPD. Two studies were conducted. Study 1 is a retrospective, cross-sectional investigation of the COPD patients' clinical records conducted in Changde First Hospital of Traditional Chinese Medicine in China and Hospital Universiti Sains Malaysia (HUSM), Kota Bharu, in Malaysia; In study 2, 45 COPD patients in stable stage (mean age: 65.2 years) underwent 12 weeks sessions in communities. Intervention group (n=22) practised Mawangdui exercise for 60 minutes per session, 5 times per week, while the control group (n=23) maintained daily activities without

additional exercise. The outcomes were assessed at baseline, 24 hours, 6 weeks, and 12 weeks post-intervention. Analysis of study 1 revealed that COPD was prevalent in male patients, both in China and Malaysia. Cigarette smoking was prevalent in COPD patients, with men smoking more than women. The number of smoking cessation in COPD patients was less than 50% in both hospitals. COPD patients in Changde hospital have higher severity and longer hospital stays than HUSM. However, there are more comorbidities in COPD patients from HUSM than in Changde hospital. As for study 2, at 12 weeks post intervention, Mawangdui exercise showed improvement in dyspnoea symptoms (CAT, mMRC), exercise capacity (6MWT, Borg CR-10, and SpO_2), back-leg-chest muscle strength, sit-and-reach flexibility, BMI, body fat%, fat mass and quality of life (SGRQ). In conclusion, COPD patients living in different climates have similar smoking habits and comorbidities, and they should improve their healthy lifestyles. Mawangdui exercise improved exercise capacity, dyspnoea symptoms, physical fitness, and quality of life in stable mild and moderate COPD patients. Mawangdui exercise can be recommended as part of pulmonary rehabilitation for COPD patients in the mild and moderate stages of the disease.

Keywords COPD, Mawangdui exercise, pulmonary function, physical fitness, quality of life

CHAPTER 1

INTRODUCTION

1.1 Background of the study

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic respiratory diseases, caused by chronic respiratory symptoms due to airways and/or alveoli abnormalities that cause persistent, often progressive airflow obstruction (GOLD, 2023). The main symptoms of COPD are shortness of breath, chronic cough and sputum production. COPD remains a leading cause of mortality, placing a heavy burden on medical health services. (Chen et al., 2023； Li et al., 2023a).

According to the World Bank reports (2019), China and Malaysia are both upper-middle income countries with rapidly increasing development. In China, the prevalence rate of COPD among people over 20 years old is 8.6%, and it is estimated that the number of patients is close to 100 million. The prevalence rate of COPD among people over 40 years old is 13.6%, 65.9% higher than ten years ago. The number of COPD among people over 40 years old is estimated to be 77 million (Wang et al., 2018). In Malaysia, the number of estimated COPD cases is 2.017 million, accounting for 6.5%, affecting more men (8.5%) than women (4.5%) (Loh et al., 2016). The prevalence of COPD in Malaysia is expected to continue to increase as the number of people aged 60 years or over is projected to be 9.6 million in 2050, which is triple the current number (United Nations, 2017). The hospital admission rates for exacerbations due to COPD are quite high in Malaysia, and COPD is the fifth leading cause of disease burden, and this figure is projected to rise soon (Marzuki et al., 2020).

Environmental factors such as temperature and humidity significantly impact COPD. Current research includes limited cross-sectional studies examining the effects of varying environmental temperatures and humidity across different countries (Mekhuri et al., 2023). For instance, Changde, China, experiences four distinct seasons, including hot summers and cold winters. The adverse effects of cold weather on COPD have been well-documented, with evidence indicating that cold temperatures combined with increased air pollution can exacerbate COPD symptoms (Liu et al., 2021d; Bao et al., 2020; Ju et al., 2021). Conversely, extreme heat events and high humidity during summer are associated with an increased risk of COPD-related mortality (Deng et al., 2023). In Hunan, China, coal-fired power generation and heating in winter contribute to significant air pollution, impacting respiratory health (Changde City Government, 2023). In contrast, Malaysia experiences consistently hot and humid conditions throughout the year, resulting in minimal environmental impact for its residents. However, Malaysia experiences seasonal impact of forest and plantation burning from the neighbouring Sumatera regions that causes haze. Understanding the impact of these environmental variables and cultural differences on COPD is crucial for advancing management strategies and improving patient outcomes.

The treatment of COPD includes pharmacological therapeutic drugs, surgery, pulmonary rehabilitation, and physical exercise therapy. Drug therapy has always been essential for acute exacerbation and maintenance of COPD. However, Holland et al. (2014) reported that long-term use of glucocorticoids can slow COPD patients' exacerbation but not prevent pulmonary function decline. Therefore, for COPD patients to over-rely on drugs may not be appropriate in the long term.

Physical exercise therapy as the core intervention of pulmonary rehabilitation programme can maintain COPD patients' stable condition, improve functional status, reduce hospitalisation rate and enhance activity ability (Rochester et al., 2023; Tonga & Oliver, 2023; He et al., 2023). Liu et al. (2024) demonstrated that performing pulmonary rehabilitation training can improve exercise endurance, reduce the number of acute exacerbation episodes and delay the deterioration of pulmonary function in COPD patients.

Traditional Chinese exercises include breathing exercise, mind-body exercise and whole-body exercise. Breathing exercise encourages patients to slow down, inhale deeply, and incorporate deep abdominal breathing into their movements. This approach promotes thoracic expansion and allows more oxygen to enter the lungs, which is beneficial for the rehabilitation of pulmonary ventilation dysfunction (Hallisy, 2018). Traditional Chinese exercises are mind-body practices. There is evidence that mind-body interventions, such as Tai Chi, can reduce levels of cortisol, adrenaline, and norepinephrine (stress-related hormones), which is beneficial in reducing anxiety and tension (Moraes et al., 2018). Additionally, Traditional Chinese exercises are whole-body activities that emphasise coordinated movements of the limbs and trunk. They involve circular arm movements, leg flexions, and half squats, which help to strengthen the body's core muscles, such as the latissimus dorsi and rectus abdominis, and improve endurance and flexibility (Long & Liu, 2023). These characteristics show that traditional Chinese exercises seem more advantageous for COPD patients than conventional exercises.

A previous study by Liu et al. (2023) reported that a 30-minute Tai Chi performed three times per week for eight weeks elicited positive effects on

pulmonary function, exercise capacity and quality of life in COPD patients. Other than Tai Chi, similar exercises in movements and intensities were conducted to improve COPD conditions, such as *Liuzijue* and *Baduanjin* (Liu et al., 2023; Liu et al., 2021c; Yang et al., 2020). *Liuzijue* positively affected exercise capacity and quality of life in patients with COPD (Liu al., 2021). *Baduanjin* has the potential to forestall the decline in pulmonary function associated with COPD and offers a straightforward, cost-effective daily pulmonary rehabilitation option for individuals with mild COPD (Yang et al., 2020).

To date, one similar exercise therapy that is gaining much attention is Mawangdui exercise. Mawangdui exercise is an ancient Chinese form of physical movement for general health maintenance (The Chinese Health Qigong Association, 2013). A newer form of exercise based on this ancient physical form has been created by the Chinese Health Qigong Association (2013). Mawangdui exercise comprises 12 distinct physical movements. Each movement consists of several sub-movements, each lasting 1.5 minutes, performed consecutively at a slow pace. There are no rest periods between each movement; however, a 2-minute rest is provided after the completion of all 12 movements. The entire set takes approximately 20 minutes to complete.

Mawangdui exercise has been widely applied in hospitals and clinics across China (Li, 2023) and investigation on the effect of Mawangdui exercise for chronic diseases. However, through literature and database search of Pubmed, Scopus, China National Knowledge Infrastructure (CNKI), and Wanfang database (researched from January 2013 to December 2023), there were 89 of published data on Mawangdui exercise as a treatment for chronic diseases, such as type 2 diabetes and hypertension

(Chen et al., 2013; Liu & Liu, 2014; Wang et al., 2023; Yang et al., 2023; Zhao, 2014). Among the results synthesised, it was found that Mawangdui exercise may have the potential to improve pulmonary function, strength, endurance, mental health and quality of life (the results synthesised in Table 2.6). In addition, The Mawangdui exercise has 12 movements, making it simpler than Tai Chi, which has 24 movements. This simplicity is more conducive to long-term adherence for COPD patients. However, the researchers found no studies on pulmonary rehabilitation for COPD patients at Mawangdui exercise. In addition, although studies have reported that Mawangdui exercise improved strength and endurance of participants, no research detailing the muscles involved and mechanism of movements in Mawangdui to understand the therapeutic effects.

According to GOLD, it has been reported that recovery of patients with COPD would be difficult and restoring to normal pulmonary function will be a challenge after being diagnosed with COPD, therefore COPD disease state is not reversible completely (GOLD, 2024). As Mawangdui exercise includes body movements and mindful breathing, the movements of Mawangdui exercise are simpler than those of Tai Chi. It may have potential therapeutic benefits for COPD patients to relieve its symptoms. However, there is still lacked data to confirm the therapeutic effects of Mawangdui exercise for COPD. Therefore, it is hypothesised that Mawangdui exercise could improve the pulmonary function, physical fitness levels and quality of life of COPD patients, especially for COPD patients in the stable stage.

Early initiation of pulmonary rehabilitation following an acute exacerbation of COPD has been shown to result in more rapid improvements in physical

performance compared to rehabilitation commenced during the stable phase of the disease (Kjærgaard et al., 2020). Consequently, the current study focused on patients with mild to moderate stable stages of COPD as the target population.

1.2 Problem statement & study rationale

Randomised controlled trials have been conducted to examine how exercise training affects patients with COPD's ability to exercise (Zhang et al., 2016). Previous randomised controlled trials demonstrated that traditional Chinese exercises such as Tai Chi, *Liuzijue*, Qigong, *Yijinjing* and *Baduanji* were used as adjunct rehabilitation treatments for COPD. Several studies have shown Mawangdui's positive influence on patients with hypertension and diabetes (Liu & Liu, 2014; Chen et al., 2013). However, limited studies reported the effect of Mawangdui exercise on COPD patients. Mawangdui exercise seems to be suitable for pulmonary rehabilitation of COPD due to body movements and mindful breathing patterns. Exertional heat during exercise activities outdoors in hot and humid weather greatly impacts pulmonary circulation diseases (Almagro et al., 2015). In the high temperature season, the higher the humidity, the more serious the COPD patient's symptoms (Boutou et al., 2019). There were a few national cross-sectional studies on the different environmental temperatures and humidity between different countries in COPD (Boutou et al., 2019; Hang et al., 2018). Therefore, this study was proposed to investigate the differences in the characteristics and risk factors between COPD patients residing in the cold (Hunan, China) and hot-humid (Kelantan, Malaysia) climates, and Mawangdui exercise intervention on pulmonary function, physical fitness levels and quality of life in stable COPD patients.

1.3 Research questions

(1) What are the differences in the characteristics and risk factors between COPD patients residing in cold (Hunan, China) and hot-humid (Kelantan, Malaysia) climates?

(2) How does Mawangdui exercise intervention affect pulmonary functions, exercise capacity, body composition, back-leg-chest muscle strength, sit-and-reach flexibility, dyspnoea symptoms, and quality of life in COPD patients?

1.4 Objectives of the study

1.4.1 General objective

To investigate the differences in the characteristics and risk factors between COPD patients residing in the cold (Hunan, China) and hot-humid (Kelantan, Malaysia) climates, and the effect of Mawangdui exercise intervention on the pulmonary function, physical fitness levels and quality of life in stable COPD patients.

1.4.2 Specific objective

Study 1: To compare the different characteristics of COPD patients, including age, sex, cigarette smoking, smoking cessation, COPD grade, average length of hospital stays and comorbidities and risk factors residing in cold winter in China (November to February) and hot-humid climates in Malaysia (June to September).

Study 2: To determine the effect of Mawangdui exercise intervention on body composition (BMI, body fat %, fat-free mass, fat mass), pulmonary functions (FEV_1, FVC, FEV_1 %pred), exercise endurance (6MWT, Borg-CR10, SpO_2), physical fitness components (back-leg-chest muscle strength, sit-and-reach

flexibility), dyspnoea symptoms (CAT, mMRC), and quality of life (SGRQ) in patients with stable COPD.

1.5 Hypotheses of the study

(1) Age, sex, cigarette smoking, smoking cessation, COPD grade, average length of hospital stays, comorbidities, and risk factors are significantly different between COPD patients residing in cold winter in China (November to February) and hot-humid climates in Malaysia (June to September).

(2) Mawangdui exercise intervention significantly affects pulmonary functions (FEV_1, FVC, FEV_1 %pred), exercise capacity (6MWT, Borg-CR10, SpO_2), body composition (BMI, body fat %, fat-free mass, fat mass), back-leg-chest muscle strength, sit-and-reach flexibility, dyspnoea symptoms (CAT, mMRC), and quality of life (SGRQ) in stable COPD patients.

1.6 Conceptual framework of the study

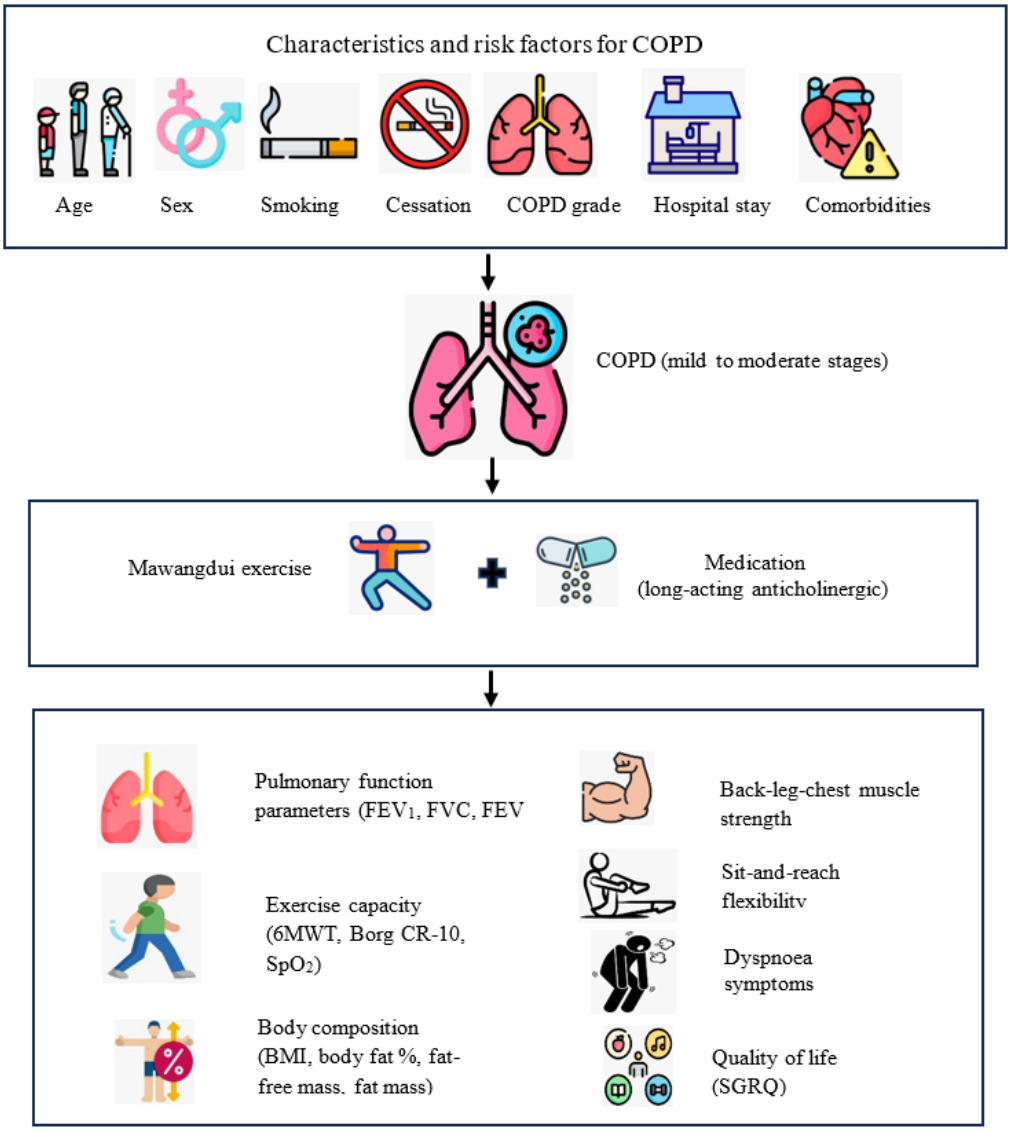

Figure 1.1 Conceptual framework of the study

COPD: Chronic obstructive pulmonary disease; FEV_1: Forced expiratory volume in one second, FVC: Forced vital capacity, FEV_1% pred: Forced expiratory volume in one second as percentage of predicted value, BMI: Body mass index, 6MWT: six-minute walk test, Borg Category-Ratio-10 score, SpO_2: oxygen saturation, CAT: COPD assessment test, mMRC: modified Medical Research Council dyspnoea scale, SGRQ: St. George's respiratory questionnaire. Figure icons were downloaded from the Noun Project (thenounproject.com).

1.7 The Justification for Study 1 Leading to Study 2

Study 1 was titled "A retrospective, cross-sectional study of COPD patients' clinical records: A case study of two hospitals in China and Malaysia". This study aimed to collect patients' clinical records on Chinese and Malaysian COPD patients to explore the differences in COPD characteristics as they normally reside in two respective climatic conditions. In addition, the study obtained first-hand data about COPD patients normally residing in two contrasting regions through cross-sectional investigation rather than from the literature, which provided detailed information of the characteristics and risk factors of COPD patients, such as age, sex, cigarette smoking, smoking cessation, COPD grade, average length of hospital stays and comorbidities. These data provided a comprehensive consideration for implementing the Mawangdui exercise for patients with COPD in **study 2**.

Study 2 was titled "Effect of Mawangdui exercise on pulmonary function, physical fitness, and quality of life in patients with stable COPD: A randomised controlled trial". The researcher implemented the Mawangdui exercise intervention for COPD patients based on the information obtained from **Study 1.** To ensure successful trial completion, the researcher developed a feasible intervention programme based on the reviewed literature and the data from **Study 1**. The severity of COPD patients will be used as a consideration to determine the exercise intensity in the Mawangdui exercise programme.

1.8 Operational definitions

COPD: Chronic obstructive pulmonary disease, a chronic disease of the respiratory system. The main symptoms are cough and shortness of breath. COPD is not totally reversible due to airway restriction, which results in major systemic symptoms such as shortness of breath (dyspnoea).

Mawangdui exercise: A form of exercise that originated in China, including mind, whole-body, and breathing exercises. It is a mild to medium-intensity aerobic exercise with 12 main movements. Each movement included several sub-movements. It is popular among the older community in China.

Pulmonary function: Pulmonary function was measured with the parameters (FEV_1, FVC, FEV_1%pred).

Physical fitness: Physical fitness includes body composition, exercise capacity, muscular strength, flexibility, and dyspnoea symptoms. The measures of exercise capacity via BMI, body fat %, fat-free mass, fat mass, 6MWT test, Borg CR-10, SpO_2, muscular strength via back-leg-chest muscle strength test, flexibility via sit-and-reach flexibility test, and dyspnoea symptoms via CAT, mMRC.

Quality of life: Measured through St. George's Respiratory Questionnaire (SGRQ).

Stable COPD: Symptoms of COPD, such as cough and shortness of breath, are well managed, and pulmonary decline is minimised.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction of COPD

2.1.1 Definition and classification of COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2023) defines chronic obstructive pulmonary disease (COPD) as a diverse respiratory ailment marked by persistent respiratory symptoms (such as dyspnoea, cough, and sputum production). These symptoms result from abnormalities in the airways (bronchitis, bronchiolitis) and/or alveoli (emphysema), leading to enduring and frequently advancing airflow obstruction. The limitation of the airflow is not fully reversible, causing shortness of breath and significant systemic effects, with a high disease rate, high disability rate, high mortality rate, and a long course of disease (Yan et al., 2021). The classification of COPD in Malaysia follows the GOLD guidelines, and the full guidelines for managing COPD were published in November 2009 (Ministry of Health Malaysia, 2009) (Table 2.1).

Table 2.1 Classification of COPD severity

COPD stage	Severity	Post-bronchodilator spirometric values	Symptoms that may be present

I	Mild	$FEV_1/FVC < 0.70$ $FEV_1 \geq 80\%$ predicted	Chronic cough and sputum production may be present. At this stage, the individual is usually unaware that his or her pulmonary function is abnormal.
II	Moderate	$FEV_1/FVC < 0.70$ $50\% \leq FEV_1 < 80\%$ predicted	Dyspnoea, typically on exertion, cough, and sputum production are sometimes also present. This is the stage at which patients usually seek medical attention because of chronic respiratory symptoms or an exacerbation of COPD.
III	Severe	$FEV_1/FVC < 0.70$ $30\% \leq FEV_1 < 50\%$ predicted	Greater dyspnoea, reduced exercise capacity, fatigue, and repeated exacerbations almost always impact the patient's quality of life.
IV	Very severe	$FEV_1/FVC < 0.70$ $FEV_1 < 30\%$ predicted or $FEV_1 < 50\%$ predicted plus chronic respiratory failure	Respiratory failure may lead to cor pulmonale with signs which include elevation of the jugular venous pressure and pitting ankle oedema. At this stage, quality of life is markedly impaired, and exacerbations may be life threatening.

Source: Ministry of Health Malaysia, 2009 and GOLD, 2023

2.1.2 Clinical presentation

Patients with COPD commonly report symptoms such as dyspnoea, limitations in physical activity, and/or cough, with or without sputum production. These patients may encounter acute episodes marked by heightened respiratory symptoms known as exacerbations, impacting overall health status and prognosis, and need targeted preventive and therapeutic interventions. Moreover, patients with COPD often have concurrent comorbidities that influence the clinical state and outlook, demanding specific treatments. These comorbid conditions can exacerbate an acute exacerbation (GOLD, 2023).

The pathophysiology of COPD involves a complex interplay of multiple factors (Figure 2.1). Key risk factors for COPD include smoking, infections, air pollution, and early life events such as preterm birth and childhood lung infections. These risk factors activate alveolar macrophages and respiratory epithelial cells,

resulting in oxidative stress and the release of various inflammatory mediators, which collectively trigger an inflammatory response. Activated alveolar macrophages and epithelial cells also secrete proteases, including neutrophil elastase and matrix metalloproteinase 9 (MMP-9), which contribute to the damage of lung parenchyma. This damage leads to pulmonary vascular remodelling, disruption of alveolar walls, and mucus hypersecretion. Furthermore, these activated cells release fibrotic mediators that induce epithelial-mesenchymal transition (EMT), resulting in small airway fibrosis and loss of elasticity. These pathological changes exacerbate COPD symptoms, such as wheezing and difficulty in breathing (Arezina et al., 2023).

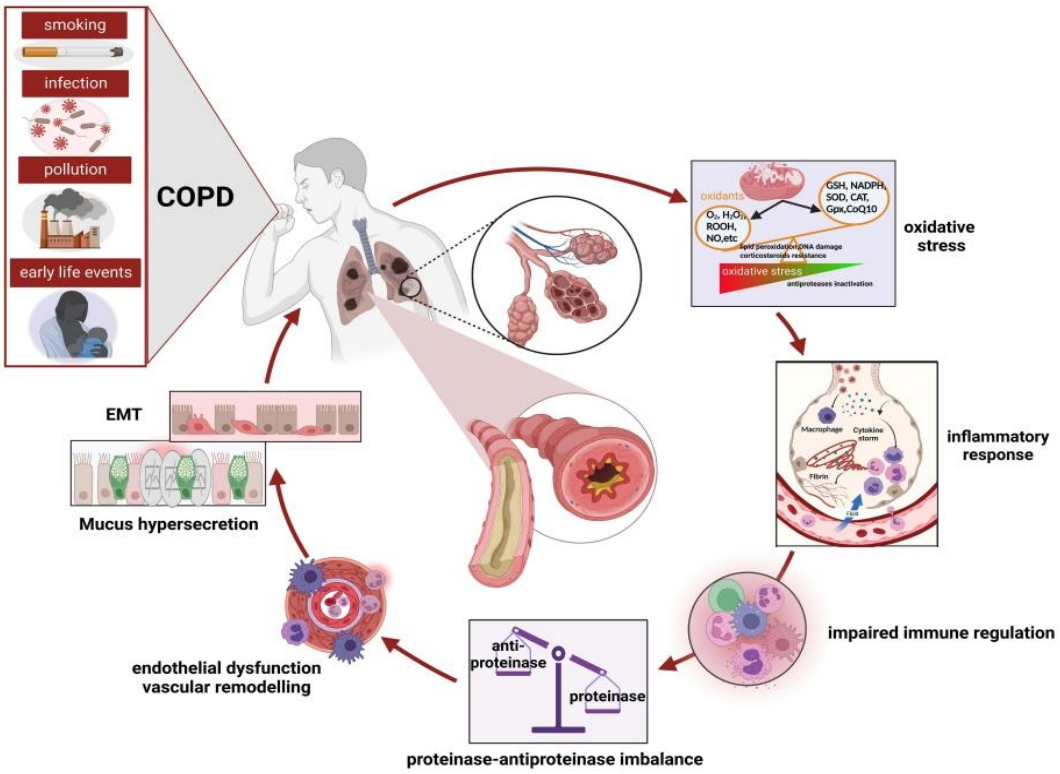

Figure 2.1 The pathophysiology of COPD (Source from Arezina et al., 2023)

2.1.3 Prevalence of COPD

The management and treatment of COPD continues to pose significant challenges for healthcare systems. It is projected that the number of COPD cases worldwide in individuals aged 25 and older will rise by 23% between 2020 and 2050,

nearing 600 million patients globally by 2050 (Boers et al., 2023). It is estimated to be the world's third leading cause of mortality by 2030, which poses a substantial socioeconomic burden, especially in Asia (Ayilya & Nazeer, 2023). In Malaysia, according to an available report, an estimated 448,000 Malaysians suffered from COPD in 2010, resulting in a projected financial burden of approximately 2.8 billion Malaysian ringgit (MYR) (Abu Hassan et al., 2014). The prevalence of COPD in Malaysia is anticipated to keep rising, with the population aged 60 and older projected to reach 9.6 million by 2050, tripling the current figure (Yahya et al., 2020). In China, the burden of COPD is anticipated to grow substantially due to factors such as an ageing population, high rates of cigarette smoking, and pervasive air pollution (Zhou et al., 2019). The Global Burden of Disease Study highlights a significant increase in COPD prevalence in China, which rose by 67.8%, from 27.75 million cases in 1990 to 45.17 million cases in 2019. This represents a nearly two-thirds increase over this period, indicating a markedly upward trend in COPD prevalence (GBD, 2020; Zheng et al., 2020).

COPD stands out as a significant contributor to mortality in numerous countries. The rise in COPD-related deaths can be primarily attributed to the widespread prevalence of smoking, a decline in mortality from other prevalent causes (such as ischemic heart disease and infectious diseases), the ageing global population, particularly in high-income nations, and the absence of effective disease-modifying treatments. According to data from the Global Burden of Disease Study from 204 countries and territories in 2017, the mortality rate due to COPD was estimated at 42 per 100,000 (constituting 4.72% of all-cause deaths) (GBD, 2020). By 2060, increased smoking rates in low-income countries and an ageing population

were estimated to result in more than 5.4 million deaths per year from COPD and related diseases (World Health Organization, 2022).

2.2 COPD and environmental risk factors

2.2.1 Cigarette smoking

The pathophysiology of COPD related to cigarette smoking is illustrated in Figure 2.2. Smoking triggers the activation of macrophages, which subsequently release various signalling molecules. These signalling molecules further activate neutrophils, leading to the release of proteases and oxidants that cause damage to the lung parenchyma (Wood & Stockley, 2006). Such damage results in the destruction of alveolar walls, contributing to the development of emphysema, a major pathological manifestation of COPD. Additionally, smoking directly activates epithelial cells, which stimulates the proliferation and activation of fibroblasts. This fibroblast activation and proliferation result in fibrosis, characterised by excessive deposition of connective tissue within the lung tissue. The fibrotic process contributes to the development of small airway disease, another key pathological feature of COPD (Wood & Stockley, 2006).

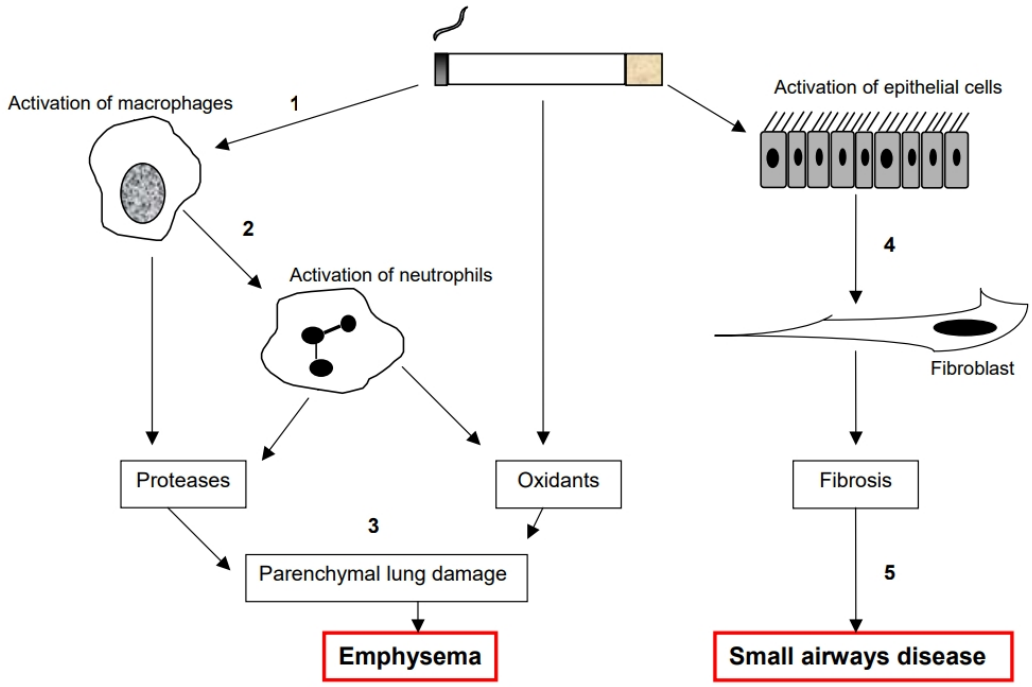

Figure 2.2 The pathophysiology of the cigarette causing COPD (Source from Wood & Stockley, 2006)

Smokers exhibit a higher incidence of respiratory symptoms and pulmonary dysfunction compared to non-smokers. Additionally, smokers experience a more pronounced annual decline in FEV_1 and face an elevated mortality rate from COPD (Song et al., 2024). However, less than 50% of heavy smokers suffer from COPD (Salawati et al., 2020). It is estimated that half of the global cases of COPD are caused by risk factors other than tobacco, so other pathogenic factors must be considered (Yang et al., 2022). A 2012 International Tobacco Control Malaysia report reported a drastic increase in smoking in adult men (46.4%) and a slight increase in women (1.6%), which may increase the prevalence of COPD in Malaysia (Gea et al., 2015). Genetic factors contribute to altering the risk of COPD among smokers, but additional risk factors should also be considered. Factors such as sex and societal influences can play a role in determining whether an individual engages in smoking or encounters particular occupational exposures. Socio-economic status

may be related to birth weight, which may affect lung growth and development, thus affecting susceptibility to COPD (Bardsen et al., 2022).

2.2.2 Biomass exposure

Cigarette smoking has been identified as a significant risk factor for COPD for more than five decades, primarily due to research conducted in high-income countries. However, with the emergence of studies from Low- and Middle-Income Countries (LMICs), it became evident that non-smoking risk factors played a more crucial role in these regions (Li et al., 2023c; Brakema et al., 2019). While cigarette smoking continues to be the predominant risk factor for COPD in high-income countries, accounting for over 70% of cases, its contribution in LMICs ranges from 30% to 40% of the total burden (Yang et al., 2022). Considering that LMICs contribute to over 85% of the global burden of COPD, non-smoking risk factors now surpass 50% of the overall burden worldwide (Yang et al., 2022).

When burned in open fires or inefficient stoves, wood, animal dung, crop residues, and coal can significantly elevate household air pollution levels (Balmes, 2019). Wood burning, particularly when incomplete, generates substantial amounts of smoke and particulate matter ($PM_{2.5}$ and PM_{10}). These particulates can penetrate the respiratory system and enter the lungs, leading to chronic exposure in individuals with COPD. Certain individuals may exhibit increased susceptibility to these particulates due to genetic predispositions. Epigenetic regulation, mediated through microRNAs (miRNAs), can influence gene expression and may contribute to an individual's susceptibility to COPD. Prolonged exposure to particulate matter results in lung inflammation and oxidative damage. This inflammation and oxidative stress cause deterioration of lung tissue, impairing respiratory function and contributing to

the progression of COPD (Ortiz-Quintero et al., 2022; Ogunkunle & Ahmed, 2021). Figure 2.3 shows the pathophysiology of woodsmoke causing COPD. In LMICs, exposure to household air pollution is linked to an increased risk of acquiring COPD (Mortimer et al., 2022). However, the extent to which household air pollution versus other poverty-related exposures explain the association is unclear (Gan et al., 2013). Biomass and coal serve as the primary energy source for cooking, heating, and various household requirements for nearly three billion people globally, indicating a substantial population at risk of COPD on a global scale (Assad et al., 2015).

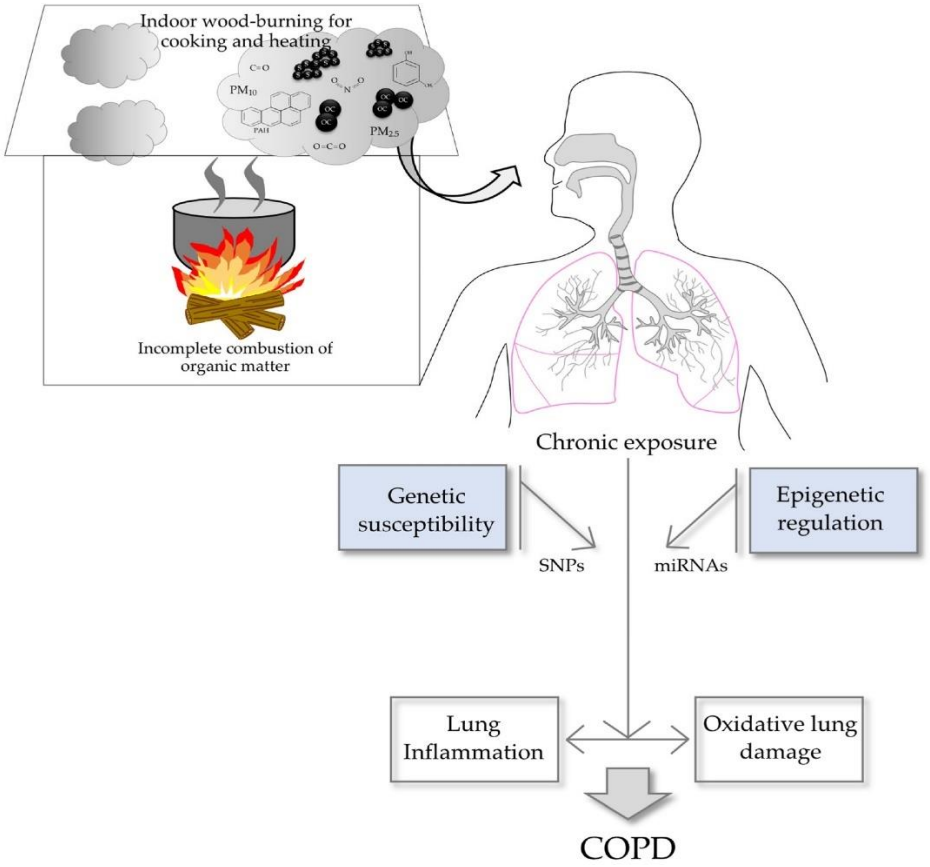

Figure 2.3 The pathophysiology of woodsmoke causing COPD (Source from Ortiz-Q uintero et al., 2022)

2.2.3 Occupational exposure

Occupational exposures, encompassing organic and inorganic dust, chemical agents, and fumes, represent an environmental risk factor for COPD that is often underestimated (Paulin et al., 2015). People inhaling high pesticide concentrations are more likely to get respiratory symptoms, airway blockage, and COPD (Faruque et al., 2021). A cohort study based on the United Kingdom Biobank population identified certain occupations, such as sculptors, gardeners, and warehouse workers, linked to an elevated risk of COPD among individuals who have never smoked and do not have asthma (De Matteis et al., 2019). In a cross-sectional observational study, it was shown that self-reported exposure to workplace dust and fumes is correlated with heightened airflow obstruction and respiratory symptoms, as well as increased emphysema and gas trapping assessed through computed tomography scans, in both men and women (Marchetti et al., 2014).

According to a population-based cohort study in Stockholm, Sweden found that the population attributable fraction for COPD from occupational exposure to particles was 10.6% among men and 6.1% among women (Grahn et al., 2021). Moreover, a longer duration of occupational exposure is significantly related to COPD. A hospital-based quantitative cross-sectional study among the Bangladeshi population showed that 20.6% of participants with shorter duration (1–9 years) of cumulative exposure years developed COPD compared to 51.5% of participants with longer duration (>9 years) cumulative exposure years (Sumit et al., 2020). The risk associated with occupational exposures in less regulated regions of the world is likely considerably more significant than what is reported in studies conducted in Europe and North America.

2.2.4 Air pollutants and COPD

Air pollution generally includes particulate matter (PM), ozone, nitrogen or sulfur oxides, heavy metals, and various greenhouse gases. It is a significant global contributor to COPD, accounting for approximately 50% of the attributable risk for COPD in LMICs (Institute for Health Metrics and Evaluation, 2022). In non-smokers, air pollution is the leading known risk factor for COPD (Global Burden of Disease of 2019 Risk Factors Collaborators, 2020). The respiratory risk posed by air pollution to individuals is contingent on the dose, and there are no discernible "safe" thresholds, even in nations with low ambient air pollution levels. Prolonged exposure to $PM_{2.5}$ and nitrogen dioxides markedly hampers lung growth in children (Guo et al., 2018), accelerates pulmonary function decline in adults and increases the risk for COPD, especially among those with additional risk factors for COPD (Bourbeau et al., 2022). Poor air quality from air pollution also increases the risk of COPD exacerbations, hospitalisations and mortality (Li et al., 2016). Thus, reducing indoor and outdoor air pollution is a crucial goal in preventing and managing COPD.

A study conducted in the Greater Kuala Lumpur area of Malaysia revealed that an increase of 10 $\mu g/m^3$ in the air pollution index significantly affects hospital admissions for chronic respiratory diseases among urban residents (Morrissey et al., 2015). Additionally, a retrospective study spanning from 2010 to 2014 in Kuala Lumpur indicated that exposure to trace gases (CO, NO_2, SO_2, O_3, and PM_{10}) was associated with increased respiratory hospitalisations, with SO_2 identified as a major factor contributing to hospital admissions for COPD exacerbations (Tajudin et al., 2019). China, a rapidly developing country with severe air pollution issues, air pollution-related mortality ranks among the highest globally (Manisalidis et al., 2020). The country faces complex and serious atmospheric pollution challenges

(Song et al., 2017). Exposure to pollution particles, termed as particulate matter (PM), has a strong correlation with both the prevalence and exacerbation of COPD. A study conducted in Shanghai, China, found that particles less than 0.5 μm in diameter are significantly associated with COPD mortality (Peng et al., 2020).

The prevalence of COPD is strongly correlated with levels of air pollution. In Changde, China, air pollution appears to be more severe compared to Kota Bharu, Malaysia. Data from 2023 indicates that Changde, located in Hunan Province, experienced an average Air Quality Index (AQI) of 105, categorised as "Unhealthy" (AQI 101–200), over three months of the winter season (November–January). The maximum daily average AQI during this period reached 325, which is classified as "Hazardous" (AQI 301–500) (Changde Air Quality Index Monthly Statistics, 2024).

In contrast, data for Kota Bharu, Malaysia, reveal that the highest daily maximum mean Air Pollution Index (API) recorded was 120, which falls within the "Unhealthy" category (API 100–200) during the period from 2010 to 2016 (Payus et al., 2022). This comparison highlights a more severe air pollution scenario in Changde, which could contribute to a higher prevalence of COPD.

2.2.5 Climate and COPD

The mortality hazard due to the high variability of the summertime temperature ratio increased for COPD patients over 65 years (Abu Hassan et al., 2014). One study analysed urban heat-related mortality in New York City and concluded that demographic changes and the population's adaptation to heat greatly influence future mortality risk (Petkova et al., 2017). The authors found a rapid adaptation to heat since the 1970s, possibly due to increased access to air-conditioning. Identifying COPD patients most at risk for climate-related

exacerbations enables climate-adapted prevention through patient guidance and treatment. Given global climate changes, discovering vulnerabilities and implementing adaptive measures will be increasingly important (Hoffmann et al., 2018).

Cigarette smoking, dust, chemicals inhaled, air pollution, and respiratory tract infection have been identified as key determinants for the development of COPD (GOLD, 2020). Moreover, COPD is associated with several comorbidities, such as cardiovascular disease, skeletal muscle dysfunction, osteoporosis, anxiety, and depression (Hansel et al., 2016). Several studies have already investigated the relationship between COPD and the environment. Mean temperatures are closely and independently related to the number of hospitalisations for COPD. A study performed in Bavaria, Germany, showed an increase of 1% in outpatient visits for COPD for each Fahrenheit degree decrease (Almagro et al., 2015). These results are similar to those of three other studies done in Germany and Taiwan, which found an increase of 0.8% in outpatient consultations for COPD exacerbations for each 1°C decrease in temperature and an increment of emergency room consultations in the colder months (Ferrari et al., 2012; Kurai et al., 2013; Tseng et al., 2013).

Numerous pieces of evidence have found that short-term exposure to ambient air pollution can increase the risk of adverse health, ranging from sub-health status to death, especially respiratory disorders. Short-term exposure to sulphur dioxide (SO_2), nitrogen dioxide (NO_2), and particulate matter with a diameter of 10 micrometres or less (PM_{10}) is strongly linked to a higher risk of COPD death (Schraufnagel et al., 2019). According to a season-stratified case-cross study, there are different associations between air pollution and COPD in China. For every $1g/m^3$ increase in

NO_2 concentration, the number of hospitalised patients with acute COPD increased by 0.9%, suggesting that NO_2 may be a risk factor for cases of COPD hospital admission in the spring. Autumn risk variables include $PM_{2.5}$ and SO_2. For every 1 g/m^3 increase in $PM_{2.5}$ concentration, the number of inpatients with COPD increased by 0.5 %, whereas the number of inpatients increased by 0.6 % for every 1 g/m^3 increase in SO_2 concentration. The predominant air pollutant in winter that increased the number of hospitalised COPD patients was $PM_{2.5}$; for every 1 g/m^3 rise in $PM_{2.5}$ concentration, the number of inpatients with acute COPD increased (Qu et al., 2018).

Local and transboundary smoke-haze has been a persistent issue in Malaysia (Che Samsuddin et al., 2018). Notably, during the 2015 El Niño phenomenon, smoke-haze originating from fires in Indonesia significantly impacted Malaysia. Recorded PM_{10} concentrations were 45.0 $\mu g/m^3$ and 47.0 $\mu g/m^3$ at semi-urban (Muar) and urban (Cheras) sites, respectively, prior to the smoke-haze event. During the haze episode, PM_{10} concentrations surged to 358 $\mu g/m^3$ and 415 $\mu g/m^3$ at these sites, reflecting an extremely unhealthy air quality index (Che Samsuddin et al., 2018). The adverse health effects of smoke-haze are predominantly linked to respiratory conditions, including COPD (Mohammad et al., 2022). Table 2.2 shows the results of previous studies on the relationship between COPD and environmental conditions, including studies conducted in China (Chen et al., 2016; Hang et al., 2018; Liu et al., 2021b; Lin et al., 2009; Mu et al., 2017; Qiu et al., 2018; Zheng et al.,2020) and Malaysia (Jaafar et al., 2021).

The most recent data concerning the prevalence of COPD in Malaysia dates back to 2010, whereas the most recent data for China is from 2019. Updated information is essential for a comprehensive understanding of COPD trends.