Complex Interventions to Address Chronic Respiratory Diseases and Tobacco Smoking in a Lower-Middle Income Setting

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Thesis Title and Abstract | Declarations | Inclusion of Publications Statement | Corrected Thesis and Responses

Thesis Title

Complex Interventions to Address Chronic Respiratory Diseases and Tobacco Smoking in a Lower-Middle Income Setting

Thesis Abstract

Chronic respiratory disease (CRD), including chronic obstructive pulmonary disease (COPD), asthma, and less common respiratory diseases, is one of the four major noncommunicable diseases worldwide. Tobacco smoking is a major, avoidable risk factor for CRD. In low- and middle-income countries, there are important barriers preventing people affected by CRD from gaining access to effective, evidence-based prevention and disease management. In Vietnam, little is known about the gap between evidence-based practice and actual clinical management for CRD and cigarette smoking. This thesis aims to assess the current practice for CRD and tobacco smoking in the Vietnamese healthcare system and to evaluate the feasibility of two interventions to reduce the burden of CRD and tobacco smoking.

The first part of the thesis includes two cross-sectional studies conducted at all four levels of healthcare facilities in Vietnam. In the first study, I used a syndromic approach to assess patients visiting healthcare facilities due to respiratory symptoms. The findings suggested that COPD and asthma were often misdiagnosed and more than half of patients with the diseases did not receive maintenance inhaled medicines for airways disease. In the second study, we found a high prevalence of current smoking among male patients seeking healthcare. The majority of those who attempted to quit had never used any evidence-based method to help them quit.

The second part of the thesis reports pilot studies for two trials that were conducted in three rural district hospitals in Hanoi. The first trial assessed the feasibility of a novel stepped approach to treatment of patients with undifferentiated CRD (asthma and/or COPD) using inhaled budesonide-formoterol. Our data collected over 12 months follow-up period suggested that this intervention is feasible in a rural setting in Vietnam. The second trial focused on tobacco smoking and the interventions included the implementation of smoke-free hospital policy, brief advice from doctors, and follow-up counselling phone calls and text messaging. We found a high rate of self-reported smoking cessation. However, many of the participants did not consent to biochemical verification of their quit status, limiting the interpretation of the trial.

Finally, I conducted a process evaluation to assess various aspects of implementing the intervention for CRD that may affect patients' outcomes. The process evaluation shows barriers and challenges to implementing the components of the intervention, such as insufficient inhaler education from pharmacists and underutilisation of management plan by patients. The findings from this process evaluation will help to improve the implementation of interventions for COPD and asthma in Vietnam.

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Publication Details #1

Full Title:	The cascade of care in the diagnosis and treatment of chronic obstructive pulmonary disease: a systematic review and meta-analysis
Authors:	Huang WC, Tsao L, Lee IP, Wu JP, Lin CY, Kuo CW, Hu HT, Palagyi A, Vu VG, Marks GB, Fox GJ
Journal or Book Name:	International Journal of Chronic Obstructive Pulmonary Disease
Volume/Page Numbers:	
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Status:	submitted
The Candidate's Contribution to the Work:	WCH formulated the research questions, led the literature search and data extraction, conducted the analysis, and wrote the manuscript.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 2.1. This section summarises the gaps between evidence-based recommendations and real-world practice for COPD using observational studies. The systematic review identified substantial gaps in the main components of care for patients with COPD, including diagnosis using spirometry, pharmacotherapy, smoking cessation, vaccination, and pulmonary rehabilitation.

Publication Details #2

Full Title:	A syndromic approach to assess diagnosis and management of patients presenting with respiratory symptoms to healthcare facilities in Vietnam
Authors:	Huang WC, Fox GJ, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Jan S, Negin J, Le TTL, Marks GB
Journal or Book Name:	ERJ Open Research
Volume/Page Numbers:	2021;7(1):00572-2020
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Status:	published
The Candidate's Contribution to the Work:	WCH formulated the research questions, conducted the data analysis, and wrote the manuscript.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 3.2. This sub-chapter addresses the first research objective of the thesis. In the article, I applied the syndromic approach to show the prevalence and management of common respiratory conditions among patients seeking healthcare to all four levels of the Vietnamese healthcare system.

Publication Details #3

Full Title:	Smoking behaviour among adult patients presenting to health facilities in four provinces of Vietnam
Authors:	Huang WC, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Freeman B, Jan S, Negin J, Marks GB, Fox GJ
Journal or Book Name:	BMC public health

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The Candidate's Contribution to the Work:	WCH formulated the research questions, conducted the data analysis, and wrote the manuscript.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 4. This chapter addresses the second research objective of the thesis. I used data from the VCAPS1 study to show the prevalence of smoking and related behaviours among patients seeking healthcare to all four levels of the Vietnamese healthcare system.

Publication Details #4

Full Title:	Stepped treatment algorithm using budesonide-formoterol for chronic respiratory diseases: a single arm interventional study
Authors:	Huang WC, Fox GJ, Pham NY, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Marks GB
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Volume/Page Numbers:	
Date Accepted/Published:	
Status:	submitted
The Candidate's Contribution to the Work:	WCH designed the study, conducted the analysis, and wrote the manuscript.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 5.1. This sub-chapter addressed the third research objective of the thesis. This study assessed the feasibility of an intervention that aimed to reduce exacerbations among patients with CRD visiting district hospitals in Vietnam.

Publication Details #5

Full Title:	A smoking Quitline integrated with clinician counselling at outpatient health facilities in Vietnam: a single-arm prospective cohort study
Authors:	Huang WC, Marks GB, Pham NY, Nguyen TA, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Fox GJ
Journal or Book Name:	BMC Public Health
Volume/Page Numbers:	
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Status:	submitted
The Candidate's Contribution to the Work:	WCH designed the study, conducted the analysis, and wrote the manuscript.
Location of the work in the thesis and/or how the work is incorporated in the thesis:	Chapter 6. This sub-chapter addressed the fourth research objective of the thesis. This study assessed the feasibility of an integrated smoking cessation intervention in assisting quitting smoking.

Candidate's Declaration

I confirm that where I have used a publication in lieu of a chapter, the listed publication(s) above meet(s) the requirements to be included in the thesis. I also declare that I have complied with the Thesis Examination Procedure.

Declaration

Unless otherwise noted in the text and figures, all research was carried out by the author at the Woolcock Institute of Medical Research Vietnam and Sydney between March 2018 and Sep 2021.

Human ethics approval for this project was obtained from the Human Research Ethics Committee at the University of Sydney and the Institutional Review Board of the Bach Mai Hospital, Vietnam.

This thesis is submitted to the University of New South Wales in fulfillment of the requirements for the degree of Doctor of Philosophy.

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Wan-Chun Huang
MD, MPH, DTMH

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This has been a great journey of my life, a great journey that was created by lovely people around me in the past few years.

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Publications Arising from This Work

Published and submitted manuscripts

1. Huang WC, Tsao L, Lee IP, Wu JP, Lin CY, Kuo CW, Hu HT, Palagyi A, Vu VG, Marks GB, Fox GJ. The cascade of care in the diagnosis and treatment of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Submitted to International Journal of Chronic Obstructive Pulmonary Disease.

2. Huang W-C, Fox GJ, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Jan S, Negin J, Le TTL, Marks GB. A syndromic approach to assess diagnosis and management of patients presenting with respiratory symptoms to healthcare facilities in Vietnam. ERJ Open Research. 2021;7(1):00572-2020. doi: 10.1183/23120541.00572-2020.

3. Huang WC, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Freeman B, Jan S, Negin J, Marks GB, Fox GJ. Smoking behaviour among adult patients presenting to health facilities in four provinces of Vietnam. BMC public health. 2021;21(1):845. Epub 2021/05/03. doi: 10.1186/s12889-021-10880-z.

4. Huang WC, Fox GJ, Pham NY, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Marks GB. Stepped treatment algorithm using budesonide-formoterol for chronic respiratory diseases: a single arm interventional study. Submitted to PLOS ONE.

5. Huang WC, Marks GB, Pham NY, Nguyen TA, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Fox GJ. A smoking Quitline integrated with clinician counselling at outpatient health facilities in Vietnam: a single-arm prospective cohort study. Submitted to BMC Public Health.

List of abbreviations

ACO	asthma-COPD overlap
AIC	Akaike information criterion
AICc	corrected Akaike information criterion
AUC	area under the receiver operating characteristic curve
COPD	chronic obstructive pulmonary disease
CRD	chronic respiratory disease
DALYs	disability-adjusted life-years
FeNO	fractional exhaled nitric oxide
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroid
LABA	long-acting beta-agonist
LAMA	long-acting muscarinic antagonist
LASSO	least absolute shrinkage and selection operator
LMICs	low- and middle-income countries
MRC	Medical Research Council
NCDs	non-communicable diseases
NRT	nicotine replacement therapies
PAL	Practical Approach to Lung Health
SABA	short-acting beta-agonist
VCAPS	Vietnam COPD, Asthma and Prevention of Smoking
WHO	World Health Organization

Abstract

Chronic respiratory disease (CRD), including chronic obstructive pulmonary disease (COPD), asthma, and less common respiratory diseases, is one of the four major noncommunicable diseases worldwide. Tobacco smoking is a major, avoidable risk factor for CRD. In low- and middle-income countries, there are important barriers preventing people affected by CRD from gaining access to effective, evidence-based prevention and disease management. In Vietnam, little is known about the gap between evidence-based practice and actual clinical management for CRD and cigarette smoking. This thesis aims to assess the current practice for CRD and tobacco smoking in the Vietnamese healthcare system and to evaluate the feasibility of two interventions to reduce the burden of CRD and tobacco smoking.

The first part of the thesis includes two cross-sectional studies conducted at all four levels of healthcare facilities in Vietnam. In the first study, I used a syndromic approach to assess patients visiting healthcare facilities due to respiratory symptoms. The findings suggested that COPD and asthma were often misdiagnosed and more than half of patients with the diseases did not receive maintenance inhaled medicines for airways disease. In the second study, we found a high prevalence of current smoking among male patients seeking healthcare. The majority of those who attempted to quit had never used any evidence-based method to help them quit.

The second part of the thesis reports pilot studies for two trials that were conducted in three rural district hospitals in Hanoi. The first trial assessed the feasibility of a novel stepped approach to treatment of patients with undifferentiated CRD (asthma and/or COPD) using inhaled budesonide-formoterol. Our data collected over 12 months follow-up period suggested that this intervention is feasible in a rural setting in Vietnam. The second trial focused on tobacco smoking and the interventions included the implementation of smoke-free hospital policy, brief advice from doctors, and follow-up counselling phone calls and text messaging. We found a high rate of self-reported smoking cessation. However, many of the participants did not consent to biochemical verification of their quit status, limiting the interpretation of the trial.

Finally, I conducted a process evaluation to assess various aspects of implementing the intervention for CRD that may affect patients' outcomes. The process evaluation shows barriers and challenges to implementing the components of the intervention, such as insufficient inhaler education from pharmacists and underutilisation of management plan by patients. The findings from this process evaluation will help to improve the implementation of interventions for COPD and asthma in Vietnam.

Table of Contents

Chapter 1. Burden of chronic respiratory disease and tobacco smoking

"Chronic respiratory disease remains, for the moment, an acceptable epidemic [1]"
The quote depicts the global action toward the disease, despite the recognition being one of the four major non-communicable diseases by the United Nations General Assembly in 2011 [2].

1.1. Burden of chronic respiratory disease

Burden of chronic respiratory disease worldwide

Chronic respiratory disease (CRD) includes a range of diseases of airways and other structure of the lungs. Among these diseases, chronic obstructive pulmonary disease (COPD) and asthma are the most prevalent. Less common CRD include bronchiectasis, occupational lung diseases, and pulmonary hypertension. According to the United Nations and the World Health Organization (WHO), CRD is one of the four major groups of noncommunicable diseases, along with cardiovascular diseases, cancers, and diabetes, that pose an enormous burden to health systems and people affected by these diseases [3].

CRD is among the leading causes of death and disability worldwide. A recent study using data from Global Burden of Disease describes the burden of CRD [4]. It shows that 544.9 million people had CRD in 2017. The number of individuals affected has increased by almost 40% when compared to 1990. The global prevalence of CRD was estimated to be 7.1%. COPD and asthma, being the most prevalent CRD, affect 3.9% and 3.6% of the global population. Death and disability-adjusted life-years (DALYs) caused by COPD and asthma together accounted for 6.6% of all-cause deaths and 4.2% of all-cause DALYs worldwide, respectively. Geographically, South Asia and Southeast Asia were the regions with the highest mortality rates due to COPD and asthma. A report from the WHO estimates that more than 90% of deaths from COPD occur in low- and middle-income countries (LMICs) [5].

Burden of chronic respiratory disease in Vietnam

In Vietnam, a lower-middle income country in Southeast Asia, COPD and asthma are

important challenges. A modelling study estimated that the prevalence of moderate to severe COPD among people 30 years and older in Vietnam was 6.7% [6]. A survey in northern Vietnam found that the prevalence of COPD was 7.1% among adults [7]. Another population-based survey showed an 8.1% prevalence of COPD among never-smokers aged 40 years or older [8]. For asthma, the prevalence was shown to be 5.6% in adults and 13.9% in school children [9, 10]. Based on a review of noncommunicable diseases by the Vietnam Ministry of Health, CRD accounted for approximately 6% of all deaths and 4.7% of total DALYs across the country [11].

Comprehensive estimates of the economic burden from CRD have yet been made in Vietnam. One study estimated that inpatient treatment for COPD cost $US 68.9 million per year [12]. Vo *et al.* conducted a cost analysis of COPD using electronic records from two provincial hospitals in Vietnam. The analysis showed that costs from pharmaceuticals accounted for more than 50% of total direct medical costs for COPD [13].

1.2. Burden of tobacco smoking

Burden of tobacco smoking worldwide

Despite abundant evidence of the harmful effects of tobacco smoking on human health and the initiation of the WHO Framework Convention on Tobacco Control in 2005, tobacco smoking remains a leading preventable risk factor for premature mortality and chronic diseases worldwide. The Global Burden of Disease estimated the worldwide prevalence of daily smoking was 25% for men and 5.4% for women in 2015 [14]. In the same year, around 11.5% of global deaths were attributed to tobacco smoking. Even though there was an overall decline in the prevalence per capita of daily smoking globally over the past two decades, the annualised rate of decline in smoking prevalence has slowed in many countries since 2005 [14, 15].

Tobacco smoking in Vietnam

In Vietnam, tobacco use remains widespread, particularly in the male population. The Global Adult Tobacco Survey Vietnam was a population-based survey representative of the general population that has been conducted twice, in 2010 and 2015. According to the survey, the

prevalence of current smoking in 2015 was 22.5% (45.3% for men, 1.1% for women), marginally decreased from 23.8% (47.4% for men, 1.4% for women) in 2010. Secondhand smoke exposure at home was reported by 59.9% for adults and 48% for children aged 13-15 years. Even within health facilities, 18.4% of adults who visited healthcare facilities in the past 30 days reported being exposed to secondhand smoke [16, 17]. It was also estimated that 16.9% of all deaths and 8.8% of DALYs in 2010 were attributable to tobacco smoking. Most of the deaths and DALYs lost due to smoking were associated with non-communicable diseases (NCDs), including CRD [11, 18].

1.3. Challenges of managing chronic respiratory disease in low- and middle-income countries

An overview of clinical management for chronic respiratory disease

COPD and asthma share several characteristics. Patients with COPD or asthma often have cough, dyspnoea, wheezing, chest tightness, or sputum production. Both diseases are characterised by chronic airway inflammation that may lead to exacerbations, a status of acute worsening of respiratory symptoms that requires a change in treatment [19-21]. Spirometry or measurement of peak expiratory flow is generally required to establish the diagnosis and assess disease progression. Symptom control and prevention of exacerbations are the goals for the management of COPD and asthma. To achieve these goals, patients with these diseases are treated with inhaled medicines, which may include short-acting bronchodilator, long-acting beta-agonist (LABA), long-acting muscarinic antagonist (LAMA), and inhaled corticosteroid (ICS) [20, 21]. Two treatment approaches of using inhaled medicines exist. The first approach is daily maintenance use, which is indicated for all LABAs, LAMAs, and ICSs. The other is an as-needed approach, which is intended for breakthrough symptoms. Drugs commonly used as-needed include SABAs and formoterol, a rapid-onset LABA often used in combination with an ICS [20].

Apart from pharmacotherapy, reducing risk factor exposure is a key component of clinical management. Common risk factors include cigarette smoking, environmental tobacco smoke, and air pollution. As cigarette smoking is a major risk factor for poor clinical outcome of both diseases, smoking cessation is recommended for every patient with COPD or asthma

who smoke [20, 21].

COPD is diagnosed with the presentation of respiratory symptoms, a history of exposure to risk factors for the disease, and the presence of airflow obstruction on spirometry that is often defined as post-bronchodilator forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) less than 0.7 or less than the lower limit of normal value [21-23]. Patients with COPD should be treated with an inhaled bronchodilator, or a combination of a LABA and a LAMA if highly symptomatic. ICS is indicated for patients with a blood eosinophil count ≥ 300 cells/µL or patients who experienced frequent or severe exacerbations [21]. Figure 1.1. shows the initial treatment and subsequent treatment adjustment recommended by Global Initiative for Chronic Obstructive Lung Disease (GOLD), a well-recognised international body that publishes guidelines for diagnosis and management of COPD.

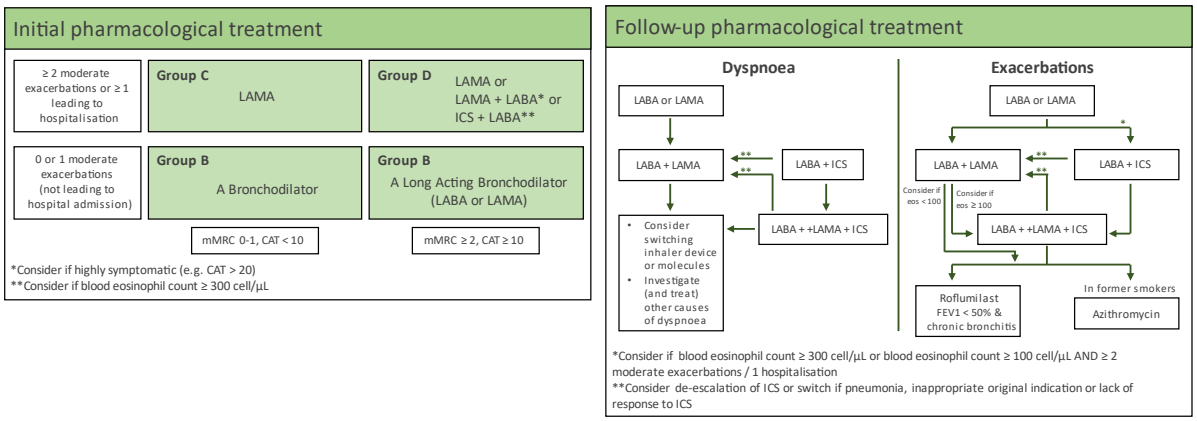

Figure 1.1. Pharmacological treatment recommended by GOLD 2021 [21]

The diagnosis of asthma is often based on the report of respiratory symptoms that vary over time and the observation of variable airflow obstruction [20]. A typical presentation of asthma is symptoms that often occur in the early morning or at night. Other common patterns include symptoms triggered by viral infections, allergen exposure, or changes in weather. Variable airflow obstruction can be detected by a bronchodilator response in spirometry (increase in FEV1 of > 12% and > 200mL) following the administration of a short-acting beta-agonist (SABA), a bronchial challenge test, or repeated spirometry or peak expiratory flow. As opposed to COPD, patients with asthma should always be treated with ICS. The combination of ICS and LABA is the most common pharmacotherapy for asthma.

LAMA is only used for patients whose disease cannot be controlled by ICS-LABA combination. Global Strategy for Asthma Management and Prevention published by Global Initiative for Asthma (GINA) is a well-cited report. Treatment recommendation in the report is a stepwise approach [20]. Figure 1.2 shows the latest update of the recommendations.

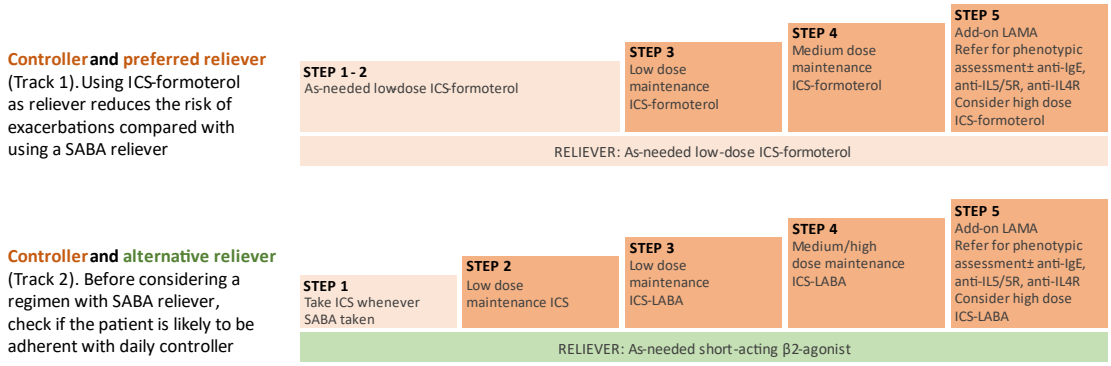

Figure 1.2. Stepwise treatment approach recommended by GINA 2021 [20]

Challenges of managing chronic respiratory disease

First, there is currently a lack of public health targets for CRD from health authorities. The WHO Global Monitoring Framework introduced nine targets and 25 indicators for NCDs. This standardised international framework was adopted at the 66th World Health Assembly in 2013 to enable accurate estimates of trends in chronic disease over time and between settings [24]. Targets for reductions in the prevalence have been set for 2025, with a baseline of 2010. Targets and indicators related to CRD and tobacco smoking are shown in Table 1.1. Among the targets, however, none was specific for CRD [25]. By contrast, targets were set for raised blood pressure, diabetes, and drug therapy to prevent heart attacks and strokes. The lack of attention and specific targets is an impediment to agenda prioritisation and allocating resources for CRD, despite the substantial burden shown in previous sections.

Table 1.1. Targets and indicators from the World Health Organization Global Monitoring Framework that are related to chronic respiratory disease and tobacco smoking

Targets for 2025	
Target 1	A 25% relative reduction in the overall mortality from cardiovascular diseases, cancer, diabetes, or chronic respiratory diseases
Target 5	A 30% relative reduction in prevalence of current tobacco use in persons aged 15+ years

Target 9	An 80% availability of the affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities
Indicators	
Indicator 1	Unconditional probability of dying between ages of 30 and 70 from cardiovascular diseases, cancer, diabetes or chronic respiratory diseases
Indicator 9	Prevalence of current tobacco use among adolescents
Indicator 10	Age-standardized prevalence of current tobacco use among persons aged 18+ years
Indicator 19	Availability and affordability of quality, safe and efficacious essential NCD medicines, including generics, and basic technologies in both public and private facilities

Another barrier to managing CRD in LMICs is the lack of availability of accurate diagnostic testing. Confirming a diagnosis of airway disease requires spirometry, which has been reported to be unavailable in resource-limited settings [25, 26]. A survey in Spain showed that 84.6% of primary care centres and 94.1% of secondary care centres performed spirometry [27]. By contrast, spirometry was available at only 24.4% of 45 hospitals in Uganda and 29.4% of 68 tertiary hospitals in Nigeria [28, 29]. Without a proper diagnosis, patients with CRD will not receive the treatment they need.

A lack of standardised data to assess the prevalence and burden of COPD and asthma, resulted from low availability of spirometry, is a key limitation. The Burden of Obstructive Lung Disease Study and the Latin American Project for Research in Pulmonary Obstruction Study have provided valuable information about the prevalence of COPD in several LMICs [30, 31]. However, much more remains to be done to achieve better assess the burden of CRD in LMICs.

Limited access to inhalers, the main medicines used for treating patients with COPD and asthma, is another important barrier. A cross-sectional study involved 52 LMICs showed the availability of beclomethasone in public hospitals was only 19% and that of budesonide was 16% [32]. In another study of eight LMICs, primary care facilities in four countries were not able to provide inhaled ipratropium [33]. Even with the highest availability in Sri Lanka, only 30% of primary care facilities could provide this drug.

Similar to drug availability, affordable inhaled medicines remain a major challenge in many LMICs. The report by Cameron *et al.* showed that buying one generic salbutamol inhaler in a private pharmacy would equate to up to 5 days' wages for the lowest-paid government worker in some LMICs [34]. Another study found an affordability of the ICS beclomethasone similar to that of salbutamol reported by Cameron *et al.* in 91% of the LMICs with available data [32]. Nevertheless, for generic ICS drug budesonide, the price ranged from less than one day's wage to more than 50 days' wage for one inhaler. Data regarding the cost and affordability of other inhaled medicines, such as LAMAs and combinations, are scarce and require further investigation [25, 35].

Finally, the cost of diagnosis and treatment is an important consideration when allocating healthcare resources. However, there is little information about the costs of managing CRD in LMICs [36]. A Markov decision-analytic model suggested that the introduction of portable spirometric screening for patients with chronic bronchitis was cost-effective in the primary care setting of China [37]. When compared to usual care, the use of portable spirometer costed ¥ -1,766 (around $273) per quality-adjusted life year gained (0.37 higher quality-adjusted life year and ¥647 lower cost, i.e. the use of spirometry was dominant - lower cost and more effective). Stanciole *et al.* assessed the cost-effectiveness of interventions (spirometer not included) for COPD and asthma in sub-Saharan Africa and Southeast Asia [38]. Among ten interventions, only ICSs for mild persistent asthma, influenza vaccine for COPD, and inhaled bronchodilators for COPD stage II were dominant as assessed by incremental cost effectiveness ratio. However, the authors acknowledged the considerable uncertainty caused by unavailable epidemiological parameters in some countries of the regions. Also, the cost-effectiveness of drug therapy was largely determined by its local price. More research and contextualization of the analysis to national levels are necessary to provide more information to guide health policy.

Inspired by the Global Drug Facility for tuberculosis, the Asthma Drug Facility was initiated by the International Union Against Tuberculosis and Lung Disease in 2006 to address the challenges of asthma in LMICs [39, 40]. The scheme was designed to assist obtaining quality-assured, affordable inhalers. Apart from drug procurement, standardised asthma

management guidelines and training were also developed. The Asthma Drug Facility was able to achieve a reduction of 50% in yearly treatment costs for severe asthma in its pilot project countries [41]. However, the scheme was suspended few years after its establishment due to a lack of ongoing funding. This highlights the necessity of a financial strategy and commitment from global agencies and national governments to sustain a model that is proven effective.

1.4. Challenges to assist quitting smoking in low- and middle-income countries

Reduction in exposure to risk factors is an important component for management of COPD and asthma. Given that cigarette smoking is a major modifiable risk factor, the issue of assisting smoking cessation should be addressed as well when we seek to reduce the burden of CRD.

An overview of smoking cessation interventions

MPOWER is a policy package endorsed by the WHO to assist the implementation of effective interventions to reduce the burden of tobacco smoking [42]. The "O" component of MPOWER stands for offering support to quit smoking. Table 1.2 shows common evidence-based clinical interventions for nicotine dependence [43, 44]. Brief clinician-delivered advice is often delivered as the 5A approach: Ask about tobacco use, Advise to quit, Assess willingness to make a quit attempt, Assist in quit attempt, and Arrange follow-up. The combination of some of these interventions may increase the odds of quitting. For example, behavioural interventions coupled with nicotine replacement therapy (NRT) has been shown to be more effective than NRT alone [45].

Table 1.2 Evidence-based interventions to assist quitting smoking [43, 44]

Delivery modality	Intervention
Non-pharmacological interventions	Self-help materials, brief clinician-delivered advice, behavioural therapy or face-to-face counselling, tobacco quitlines, text message services, web-based interventions, smartphone applications
Nicotine replacement therapy	Nicotine patch, nicotine gum, nicotine lozenge, nicotine nasal spray, nicotine inhaler
Pharmacotherapy	Bupropion, varenicline, cytosine

Challenges to assist quitting smoking

Article 14 of the WHO Framework Convention on Tobacco Control states that signatories shall implement appropriate measures to promote cessation and help tobacco users to quit. Recommended approaches included brief advice at primary care level, national toll-free tobacco quitlines, and cost-covered NRT [46]. The benefits of quitting smoking were evident for patients with CRD and is recommended in international guidelines for patient management [47, 48]. These recommendations apply to both high-income countries and LMICs. In line with the recommendations, a recent systematic review found that NRT, behavioural counselling and brief advice were effective in assisting smoking cessation in LMICs [49].

Despite the recommendations and evidence, national policies and implementation of strategies to reduce tobacco use remain suboptimal in many LMICs. As indicated in the 2019 WHO Report on the Global Tobacco Epidemic [50], only six middle-income countries and one low-income country offer comprehensive smoking cessation support. Among the 59 countries where none of the MPOWER measures has been adopted, 83% were LMICs. Furthermore, 67% of middle-income countries and almost all low-income countries had no national toll-free quitline. The report also showed that, even though more than two-thirds of the member states made NRTs available to smokers, only less than one third covered the costs either partially or fully. Given the higher cost of NRTs and other medications relative to income, affordability is a gap for using these medications to assist quitting smoking in LMICs [51].

Apart from access to quitline and medications, integration of cessation counselling into healthcare practice is a common challenge. Such challenge is rooted in several other factors, such as knowledge deficit, tobacco use by healthcare providers leading to reluctance to offer quit advice, and not considering cessation as part of the responsibility of healthcare providers [52].

1.5. Conclusion

The burden of CRD and tobacco smoking remain enormous in LMICs and should not be ignored. Health policies and implementation of strategies for both conditions are suboptimal in many LMICs, despite the clear evidence in treating CRD and offering help to quit smoking. Sustainable approaches and responses from the public health sectors, multilateral organisations and civil societies are required to address the unacceptable epidemic of CRD, and the health burden from tobacco smoking.

In the next chapter, I will discuss the gap between current practice in LMICs and evidence-based practice, which will then lead to the research studies of this thesis that sought to address the gap in CRD and smoking cessation in Vietnam.

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Chapter 2. Actions taken: how big is the gap?

Despite high-quality evidence for strategies to prevent and treat CRD, a wide gap remains between policy and practice for both CRD and tobacco smoking. GOLD and GINA are two well-known international bodies that publish regularly updated recommendations on clinical care for patients with COPD and asthma, respectively [1, 2]. Numerous reviews and guidelines based on research evidence are also widely accessible for healthcare professionals to assist patients quit smoking [3-6]. In Chapter 1, the challenges of managing CRD and smoking in LMICs have been discussed. In this chapter, I will review the evidence for implementing evidence-based approaches to managing CRD and helping quit smoking, with a focus on LMICs and Vietnam.

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2.1. Real-world management of chronic respiratory disease

Evaluation of COPD care using a cascade of care approach

Preface

This section contains the unaltered full text of the following manuscript submitted for publication:

> Huang WC, Tsao L, Lee IP, Wu JP, Lin CY, Kuo CW, Hu HT, Palagyi A, Vu VG, Marks GB, Fox GJ. The cascade of care in the diagnosis and treatment of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Submitted to International Journal of Chronic Obstructive Pulmonary Disease.

Appendix 2.1 of this thesis contains the supplementary appendix for this article. WCH formulated the research questions, led the literature search and data extraction, conducted the analysis, and wrote the manuscript.

Contribution of this section to the thesis

This section summarises the gaps between evidence-based recommendations and real-world practice for COPD using observational studies. The systematic review identified substantial gaps in the main components of care for patients with COPD, including diagnosis using spirometry, pharmacotherapy, smoking cessation, vaccination, and pulmonary rehabilitation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major global health threat that causes enormous disability and mortality. According to the World Health Organization (WHO)'s Global Health Estimates, COPD was the third leading cause of death and seventh leading cause of disability adjusted life years in 2019 [1]. Optimal care of patients with COPD requires a multidisciplinary approach that involves drug treatment, non-pharmacological therapy, and behaviour change.

To improve clinical care, GOLD was established in 2000 [2]. Annually updated GOLD guidelines define the standard of care for patients with COPD. National guidelines developed for local needs are also available in many countries [3].

Despite the burden of COPD to health system and the availability of evidence-based guidance, studies have shown sub-optimal diagnosis and management of COPD in many settings [4-7]. For example, a recent survey conducted in 19 countries showed 36.1% of patients diagnosed with COPD did not have airflow limitation [5]. Studies also found a lack of access to spirometry in primary care, hospitals, and even specialist care, which makes diagnosis even more challenging [8, 9]. Moreover, poor adherence to recommended pharmacotherapy has been reported [6].

Optimal management of COPD involves the implementation of multifaceted evidence-based recommendations, including smoking cessation and inhaled medicines [2]. Factors associated with poor adherence to these recommendations have been studied before [10, 11]. Nevertheless, most studies focused on one aspect and integrative assessments of COPD care remain limited.

The "cascade of care" is a systematic framework for tracking the progress of patients along the continuum of care. It has been applied to understand, identify and address gaps in the care of patients treated for a number of infectious conditions [12-14]. A recent study assessed the gaps along the care continuum for latent tuberculosis infection by meta-analysing studies from both high-income and low and middle-income countries (LMICs) [15].

Few studies have used the cascade of care framework to evaluate management of patients with chronic diseases [16-19]. For example, Ali *et al.* showed the gaps in glycaemic control, blood pressure control, low-density lipoprotein cholesterol control, and smoking for patients with diabetes [16]. The framework has not been used to assess the appropriateness of routine care for COPD.

Therefore, we aimed to characterise the progression of patients with COPD through the cascade of care by undertaking a systematic review and meta-analysis of the published literature. Specifically, we evaluated the proportion of patients who were not managed in accordance with recommended approaches for diagnosis, engagement in care and treatment adherence.

Material and methods

Search strategy and selection criteria

We undertook five systematic reviews and meta-analyses of observational studies describing management of patients with COPD. The five discrete systematic reviews of the main components of care include: (a) diagnosis using spirometry, (b) pharmacotherapy, (c) smoking cessation, (d) vaccination, and (e) pulmonary rehabilitation. Included articles were published in English from 1 January 2000 to December 2018. We searched MEDLINE, Embase, CINAHL, Global Health, and the Cochrane Library. Inclusion criteria are presented in Table 1. The search strategy is shown in Supplementary Table S1.

For each literature search, two authors independently screened the articles for inclusion (Diagnosis: CWK, CYL; Pharmacotherapy: IPL, JPW; Smoking cessation: WCH, HTH; Vaccination: WCH, LT; Pulmonary rehabilitation: CWK, CYL). Discordant results were resolved by consensus or discussion with a third author. Duplicate data were removed. To identify additional relevant articles, we searched reference lists of identified full texts from this search. Articles considered eligible for another component were also collected and assessed by the responsible authors.

We excluded conference abstracts, case-control studies, before-and-after studies, reviews,

editorials, and letters. The control arms of randomised trials of COPD treatment were excluded since additional efforts to retain patients in care for the trial differed substantially from routine clinical practice. Studies that did not report outcomes for patients without exacerbations were excluded. The study protocol was registered on PROSPERO (available at: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42017081965).

Data analysis

Data from the included full-text articles were extracted using a predesigned spreadsheet by the same two authors who screened the articles for inclusion. The two authors independently extracted data in duplicate for 10% of articles, and compared for concordance, to ensure consistency of data extraction. Data from all remaining articles were extracted by one author and checked by the other author against source documents. Collected data included years of data collection, country and income level determined by the World Bank, study design, study settings, and number of participants and proportion for each identified step in the cascade of care. The definition of each step in the cascade is shown in Table 1. We labelled the five components of COPD management alphabetically and used number to indicate the constituent steps within each component. The proportion of patients diagnosed with COPD on spirometry (Component A) was stratified by the definition of abnormal (lower limit of normal or fixed FEV1/FVC ratio of 0.7). Adherence to maintenance inhalers (ie Step B4) was defined as either a proportion of days covered of at least 0.8, or medication possession ratio of at least 0.8. Factors associated with non-completion of the steps assessed by adjusted multivariate analysis in the included articles were also gathered. Factors and their direction of relationships were summarised and classified using the WHO taxonomy [20, 21]. For studies that repeated the same measurement over time in the same population, for example, influenza vaccine coverage, data from the last date of measurement were used.

Pooled proportions of participants completing each step of the cascade, and their associated 95% confidence limits, were estimated using random effects meta-analyses using PROC Nlmixed in SAS® (v9.4, SAS Institute, Cary Corp. NC. USA) [22]. For pharmacotherapy (Component B) and pulmonary rehabilitation (Component E), the proportion remaining at that step was multiplied by the proportion remaining after the preceding step to estimate

the cumulative losses. Meta-analyses were performed where there were at least two eligible studies. Between-study heterogeneity was estimated using the I^2 statistic. The quality of included studies and risk of bias was assessed using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute of the National Institutes of Health [23].

RESULTS

Study selection and study characteristics

Results of the five literature searches are summarised in Table 2. PRISMA diagrams for each of the searches are shown in Supplementary Figure S1-S5. Our search results identified 2465, 4555, 9074, 4642, and 1473 records for diagnosis (Component A), pharmacotherapy (Component B), smoking cessation (Component C), vaccination (Component D), and pulmonary rehabilitation (Component E), respectively. The numbers of articles included in the five meta-analyses within each of these components were 18, 32, 15, 48, and 36. Studies from LMICs accounted for only a minority of included studies, with the exception of diagnostics studies (Table 2).

Cascade of care

Out of 18 studies included in the meta-analysis for COPD diagnosis (Component A), the prevalence of airflow limitation was available for 15 studies for studies defined by fixed ratio and 8 studies using lower limit of normal.

Table 1. Inclusion criteria for each step of the cascade of care

Literature search	Step of the cascade	Study inclusion criteria
Diagnosis (Component A)	A1. Respiratory symptoms present, among those with airflow obstruction	1. Population-based cross-sectional studies 2. Reported prevalence of airflow obstruction defined from spirometry, either fixed ratio of less than 0.7, or below the lower limit of normal 3. Reported prevalence of respiratory symptoms at the time of the survey (where respiratory symptoms were reported separately, the symptom with the highest proportion was used)
	A2. Ever diagnosed with COPD, among those with airflow obstruction	
	A3. Ever diagnosed with COPD, among those with airflow obstruction and respiratory symptoms	
Pharmacotherapy (Component B)	B1. Prescribed any inhaled medicine for COPD	1. Observational studies assessing patients with COPD 2. Prescription of inhaled medicines described 3. Reported proportion or number of patients prescribed with inhaled medicines
	B2. Prescribed any maintenance inhaler for COPD	
	B3. Adhered to maintenance inhalers for 12 months	1. Observational studies that follow-up patients with COPD for at least 12 months 2. Adherence assessed using proportion of days covered or medication possession ratio 3. Proportion or number of patients with adherence provided, at least at 12 months
Smoking cessation (Component C)	C1. Received any cessation intervention among COPD patients who are current smokers	1. Observational studies assessing patients with COPD 2. Status of smoking behaviour at baseline available 3. Reported proportion, or number, of participants provided with a smoking cessation service 4. Studies assessing only nicotine replacement therapy or medications were excluded
	C2. Advised to quit smoking among COPD patients who are current smokers	
Vaccination	D1. Received influenza vaccine	1. Observational studies assessing patients with COPD

(Component D)	D2. Received pneumococcal vaccine	2. Reported proportion, or number, of participants vaccinated against influenza or pneumococcal infection
Pulmonary rehabilitation (Component E)	E1. Pulmonary rehabilitation suggested or referred for pulmonary rehabilitation	1. Observational studies assessing patients with COPD 2. Definition of adherence described 3. Reported proportion, or number, of participants who were referred for or adhered to pulmonary rehabilitation programme 4. Studies evaluating home-based rehabilitation programme were excluded 5. Studies assessing adherence but reported only average adherence were excluded
	E2. Started pulmonary rehabilitation programme	
	E3. Adhered to pulmonary rehabilitation programme	

Table 2. Results of literature search

Literature search	Records identified	Full-text articles assessed for eligibility	Studies included in meta-analysis	Included studies with extractable data from low- and middle-income countries, n/N (%)
Diagnosis (Component A)	2465	111	18	7/18 (38.9%)
Pharmacotherapy (Component B)	4555	107	32	3/32 (9.4%)
Smoking cessation (Component C)	9074	61	15	1/15 (6.7%)
Vaccination (Component D)	4630	117	48	5/48 (10.4%)
Pulmonary rehabilitation (Component E)	1471	106	36	3/36 (8.3%)

Among general population who had airflow limitation measured on spirometry, around 57.9% (95% CI 45.9 – 69.0, I^2 = 98.4%, Step A1) had prevalent respiratory symptoms and 16.5% (95% CI 10.6 – 24.7, I^2 = 96.1%, Step A2) reported a prior diagnosis with COPD, chronic bronchitis or emphysema by a health professional (Figure 1a and Table 3). Only 29.7% (95% CI 13.1 – 54.3, I^2 = 99.3%, Step A3) of people who had both airflow limitation and respiratory symptoms had been diagnosed prior to the survey. The proportion of patients with respiratory symptoms was lower among those with airflow limitation defined by the lower limit of normal, in comparison to airflow limitation defined by a fixed proportion. The proportions of Step A1 and A2 were similar in high-income countries and LMICs.

Among patients diagnosed with COPD, 87.4% (95% CI 79.5 – 92.6, I^2 = 99.9%, Step B1) received inhalers (Figure 1b and Table 3) and maintenance inhalers were prescribed to 76.1% (95% CI 61.8 – 86.2, I^2 = 100%, Step B2) of patients.

Regarding adherence to maintenance inhaler therapy, only 30.9% (95% CI 18.3 – 47.1, I^2 = 100%, Step B3a) of patients given maintenance inhalers achieved satisfactory adherence defined by proportion of days covered. The proportion with satisfactory adherence defined by medication possession ratio was 29.7% (95% CI 20.3 – 41.3, I^2 = 99.8%, Step B4b). The results were equivalent to 19.1% of all patients with COPD for proportion of days covered and 19.3% for the medication possession ratio (Figure 1b).

Meta-analysis of the 15 studies involving smoking cessation showed that 66.8% (95% CI 50.0 – 80.2, I^2 = 99.8%, Step C1) had ever been offered a form of cessation support (Figure 1c). In the eight studies that provided data about doctors' smoking cessation advice, 72.3% (95% CI 61.2 – 81.2, I^2 = 95.5%, Step C2) of smoking patients were advised to quit smoking. Influenza and pneumococcal vaccine were given to 58.1% (95% CI 51.7 – 64.3, I^2 = 99.9%, Step D1) and 37.9% (95% CI 24.9 – 53.0, I^2 = 99.9%, Step D2) of patients, respectively.

Figure 1d shows the cascade steps for the pulmonary rehabilitation component of this review. Among patients with COPD, only 20.4% (95% CI 9.2 – 39.3, I^2 = 99.9%, Step E1) of patients had ever been recommended or referred for pulmonary rehabilitation and 80.8% (95% CI 71.8 – 87.4, I^2 = 98.9%, Step E2) started the programme (equivalent to 14.2% of all

patients with COPD). Adherence to a rehabilitation programme, according to individual study definitions, occurred in 70.3% (95% CI 64.5 – 75.6, I^2 = 97.0%, Step E3) of eligible patients, comprising a total of 11.6% of all patients with COPD. Figure 2 shows the overall proportion of patients with proper diagnosis and management that healthcare providers should achieve.

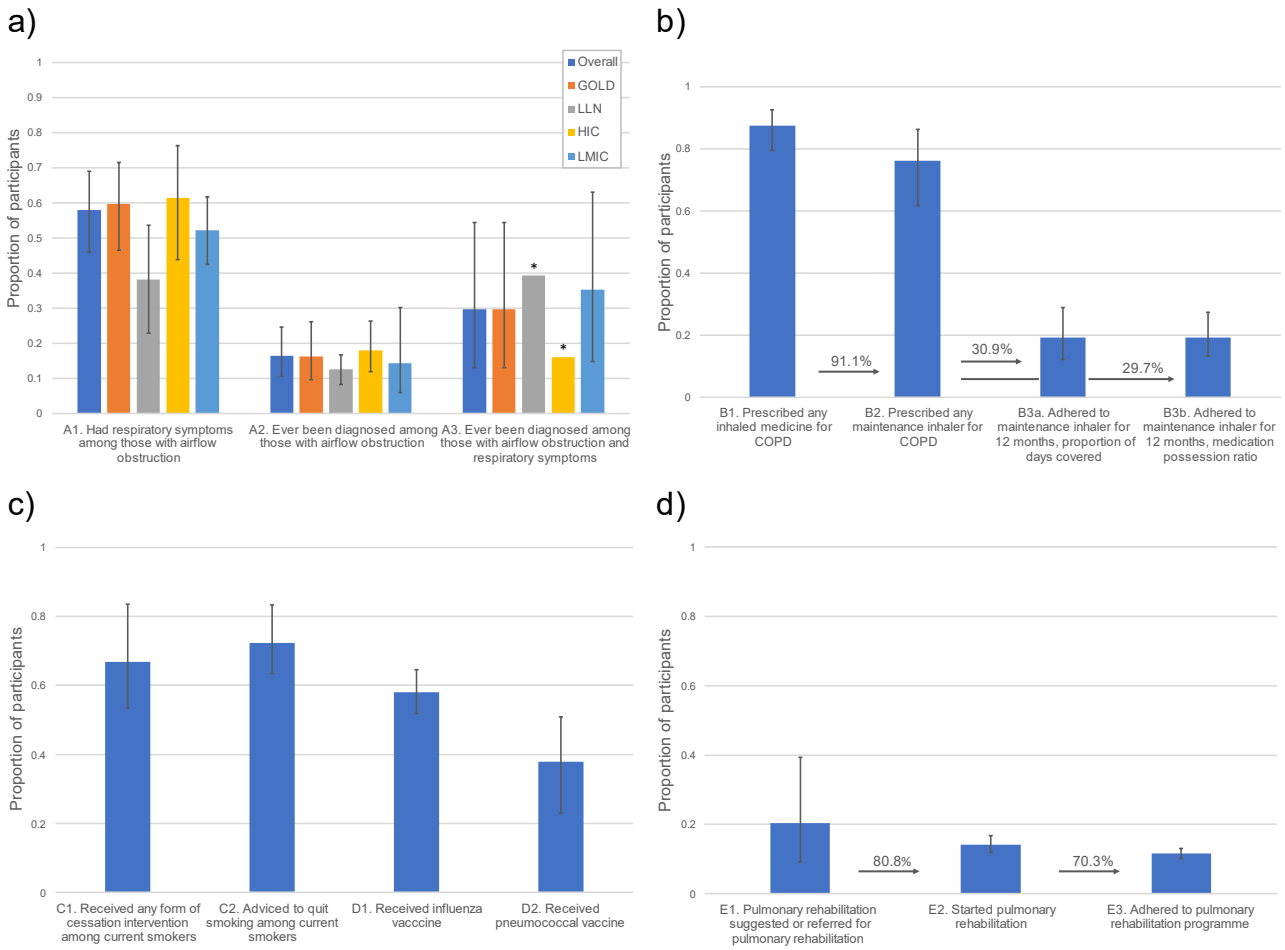

Figure 1. Cascade of care for chronic obstructive pulmonary disease. a) Diagnosis (Component A), b) Pharmacotherapy (Component B), c) Smoking cessation (Component C) and vaccination (Component D), d) Pulmonary rehabilitation (Component E). GOLD, Global Initiative for Chronic Obstructive Lung Disease; HICs, high-income countries; LMICs, low- and middle-income countries; LLN, lower limit of normal. *Only one study

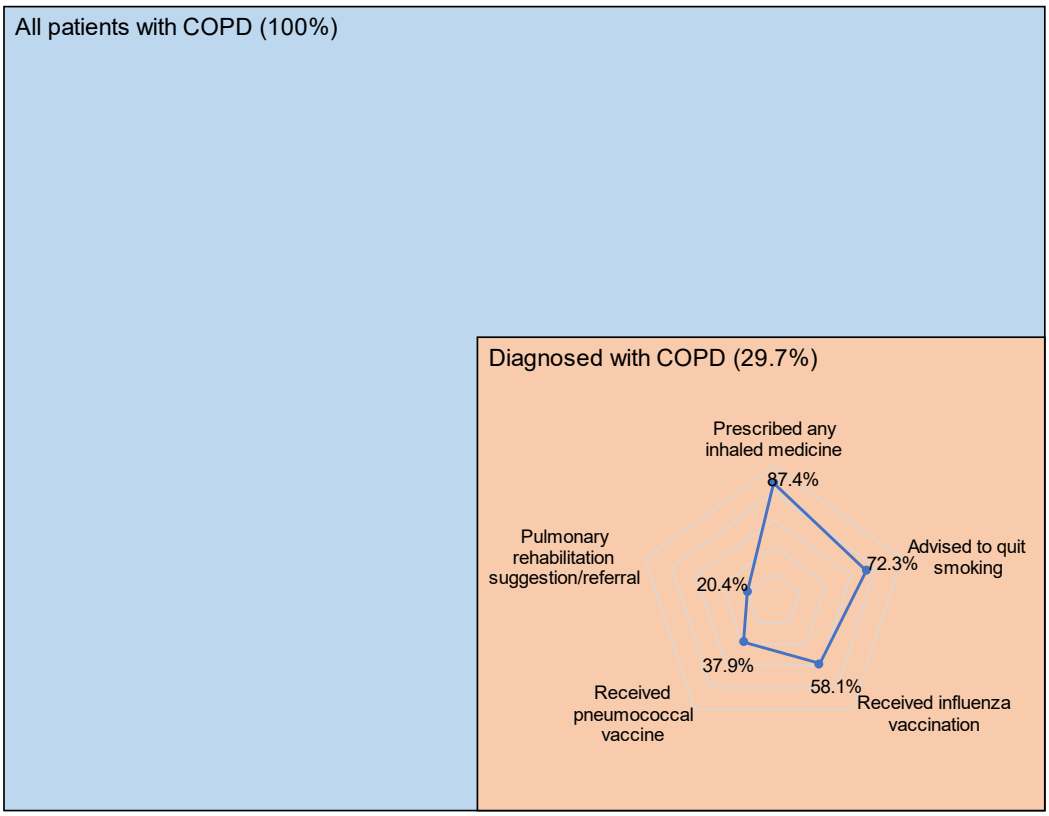

Figure 2. Proportion of optimal management for patients with chronic obstructive pulmonary disease. COPD, chronic obstructive pulmonary disease

Figure 3 shows the proportion of studies that found specific risk factors to be associated with completion of each step in the cascade. For example, all of the 10 articles assessed the association between age and influenza vaccine found younger patients with COPD were less likely to take the vaccine (Step D1). Some factors, such as sex, had varying results of relationship with the steps among the articles. Risk factors that were assessed in only one component of the cascade, or in less than three included studies, are listed in Supplementary Table S2.

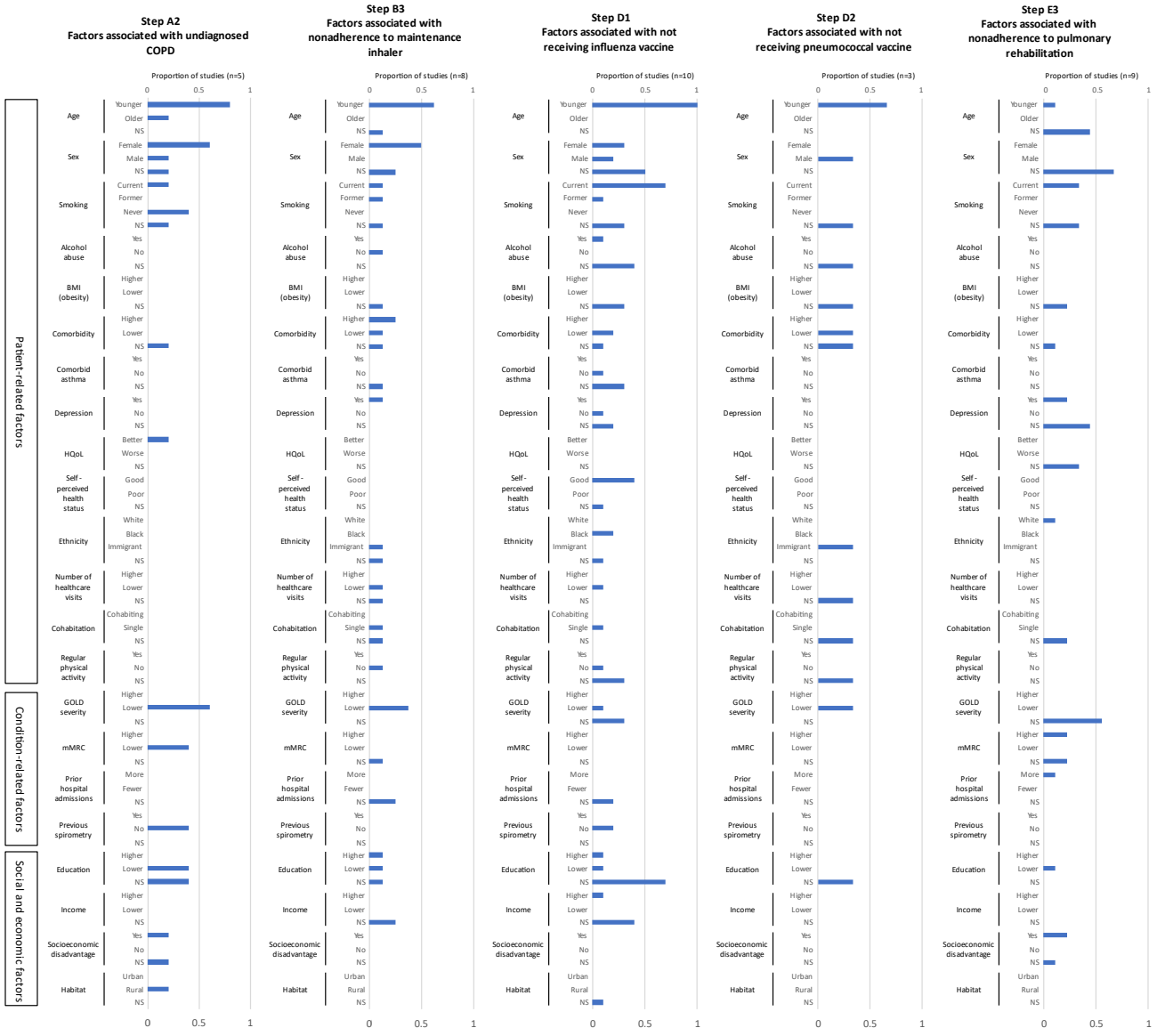

Figure 3. Factors associated with completion of each step of the cascade. Factors assessed in only one component or in less than three articles were listed in Supplementary Table S2. BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HQoL, health-related quality of life; mMRC, modified Medical Research Council scale; NS, nonsignificant.

Table 3. Pooled estimates of the proportion of patients progressing through each step of the cascade of care

Step in the cascade	Number of included studies	Proportion completing each step (numerator/denominator)	Definition of the numerator and denominator for calculating each proportion (n/N)	Pooled proportion (95% CI)	I^2
Diagnosis (Component A)					
A1. Had respiratory symptoms among those with airflow obstruction	14	3,829/7,673	Participants with respiratory symptoms and airflow limitation/participants with airflow limitation	57.9% (45.9 – 69.0)	98.4%
A2. Ever diagnosed with COPD among those with airflow obstruction	13	1,734/12,227	Participants with airflow limitation ever diagnosed with COPD, chronic bronchitis, or emphysema/participants with airflow limitation	16.5% (10.6 – 24.7)	96.1%
A3. Ever diagnosed with COPD among those with airflow obstruction and respiratory symptoms	3	604/1,176	Participants with respiratory symptoms and airflow limitation ever diagnosed with COPD, chronic bronchitis, or emphysema/ participants with respiratory symptoms and airflow limitation	29.7% (13.1 – 54.3)	99.3%
Pharmacotherapy (Component B)					
B1. Prescribed any inhaled medicine for COPD	18	172,014/246,660	Participants with COPD who were prescribed any inhaled medicine/participants with COPD	87.4% (79.5 – 92.6)	99.9%
B2. Prescribed any maintenance inhaler for COPD*	16	117,222/163,211	Participants with COPD who were prescribed any maintenance inhaler/participants with COPD who	91.1% (81.8 – 95.9)†	100%

Step in the cascade	Number of included studies	Proportion completing each step (numerator/denominator)	Definition of the numerator and denominator for calculating each proportion (n/N)	Pooled proportion (95% CI)	I^2
			were prescribed any inhaled medicine		
B3a. Adhered to maintenance inhaler for 12 months, PDC*	9	83,034/193,733	Participants who achieved good adherence defined by PDC/participants with COPD who used any maintenance inhalers	30.9% (18.3 – 47.1)‡	100%
B3b. Adhered to maintenance inhaler for 12 months, MPR*	6	23,359/72,328	Participants who achieved good adherence defined by MPR/participants with COPD who used any maintenance inhalers	29.7% (20.3 – 41.3)‡	99.8%
Smoking cessation (Component C)					
C1. Received any cessation intervention among current smokers	15	12,267/26,384	Participants with COPD who were current smokers ever received any cessation intervention/participants with COPD who were current smokers	66.8% (50.0 – 80.2)	99.8%
C2. Advised to quit smoking among current smokers	8	4,343/5,920	Participants with COPD who were current smokers ever been advised to quit smoking/participants with COPD who were current smokers	72.3% (61.2 – 81.2)	95.5%
Vaccination (Component D)					
D1. Received influenza vaccine	47	157,365/302,239	Participants with COPD ever received influenza vaccine/participants with COPD	58.1% (51.7 – 64.3)	99.9%

Step in the cascade	Number of included studies	Proportion completing each step (numerator/denominator)	Definition of the numerator and denominator for calculating each proportion (n/N)	Pooled proportion (95% CI)	I^2
D2. Received pneumococcal vaccine	21	90,284/159,655	Participants with COPD ever received pneumococcal vaccine/participants with COPD	37.9% (24.9 – 53.0)	99.9%
Pulmonary rehabilitation (Component E)					
E1. Pulmonary rehabilitation suggested or referred for pulmonary rehabilitation	10	16,956/88,954	Participants with COPD ever been suggested or referred for pulmonary rehabilitation/participants with COPD	20.4% (9.2 – 39.3)	99.9%
E2. Started pulmonary rehabilitation[*]	11	9,474/11,072	Participants with COPD been suggested or referred who started pulmonary rehabilitation/participants with COPD ever been suggested or referred for pulmonary rehabilitation	80.8% (71.8 – 87.4)[§]	98.9%
E3. Adhered to pulmonary rehabilitation programme[*]	21	5,659/8,295	Participants with COPD who started and adhered to pulmonary rehabilitation/participants with COPD who started pulmonary rehabilitation	70.3% (64.5 – 75.6)[¶]	97.0%

Abbreviations: COPD, chronic obstructive pulmonary disease; MPR, medication possession ratio; PDC, proportion of days covered

[*]Proportion remaining at that step was multiplied by the proportion remaining after the preceding step to estimate the cumulative losses, as shown in Figure 1b and Figure 1d

[†]Equivalent to 76.1% (95% CI 61.8 – 86.2) shown in Figure 1b

[‡]Equivalent to 19.1% (95% CI 12.1 – 28.9) and 19.3% (95% CI 13.3 – 27.3) shown in Figure 1b

[§]Equivalent to 14.2% (95% CI 11.9 – 16.8) shown in Figure 1d

[¶]Equivalent to 11.6% (95% CI 10.2 – 13.1) shown in Figure 1d

Quality assessment and risk of bias

Supplementary Table S3 presents the characteristics of the included studies. Quality assessment of these studies is shown in Supplementary Table S4. Most studies were rated as having good or fair quality.

Potential sources of bias and heterogeneity were examined. Nine articles (6.8%) had participation rate less than 50% and 47 articles (35.3%) did not specify participation rate. The majority of included studies in the step of spirometric diagnosis (Component A) were either related to the Burden of Obstructive Lung Disease study or followed the same methodology. However, the age range and assessment of respiratory symptoms and the inclusion criteria and definitions of COPD varied across studies. In the analysis of the cascade of inhaled pharmacotherapy use (Component B), seven studies were excluded because the specific drug combinations were not reported (Supplementary Figure S2). For example, if a study reported that 90% of patients received short-acting bronchodilators and 70% received long-acting bronchodilators, it was unclear how many patients took only short-acting bronchodilators and how many had neither. Some studies evaluated the use of inhalers among a mixed population of patients with COPD and asthma without reporting the outcomes of each separately. For vaccines (Component D), 29 (60.4%) articles reported participants' responses about vaccination history while other articles analysed data from doctors, medical records, or claim database. Finally, the nature of the pulmonary rehabilitation programmes offered and definition of adherence applied differ considerably among the included studies (Component E).

DISCUSSION

Evidence-based approaches to COPD diagnosis and management will only benefit patients if they are adopted in clinical practice. This systematic review has demonstrated substantial gaps in care for patients along the care continuum for COPD, using data from real-world observational studies. Around two-third of people with fixed airflow limitation and respiratory symptoms had not previously been diagnosed with COPD. One in four patients with COPD did not receive maintenance inhalers, while only a small proportion of patients adhered to prescribed inhalers. Many smokers with COPD did not receive smoking cessation

interventions, such as brief advice from their doctors. We found that vaccination coverage against influenza and pneumococcal infection was poor, and pulmonary rehabilitation was underutilised. Together, these findings highlight substantial gaps between policy and practice.

The first step in the care continuum was the accurate spirometric diagnosis of patients with presumptive COPD. Most epidemiological studies defined COPD by airflow obstruction on spirometry alone and did not report the presence of respiratory symptoms. Our analysis suggests that symptom screening, followed by spirometry, should be expanded to increase the detection of symptomatic COPD. On the other hand, treatment for asymptomatic airflow obstruction remains controversial. Recent studies showed that people with asymptomatic airflow obstruction had a higher risk of exacerbations and pneumonia, and poorer exercise tolerance when compared to people without airflow obstruction [24, 25]. More studies are required to understand the progression of disease among individuals with asymptomatic airflow obstruction and to identify whether screening and treatment should be recommended.

This study also showed poor adherence to recommendations for inhaled therapy by both physicians and patients. Many factors are likely to explain the reasons for poor medication adherence, including limited availability (particularly in resource-limited settings), high medication costs, lack of instructions for use, and insufficient knowledge of the healthcare providers [26]. Concerningly, we found the majority of patients prescribed maintenance therapy were not adherent after 12 months. Adherence to treatment was worse among patients with COPD and asthma in comparison to patients with other non-communicable diseases such as hypertension and heart failure [27]. Pragmatic solutions are urgently needed to address the drivers of non-adherence in order to prevent exacerbations and mortality, and reduce waste of healthcare resources [28].

Quitting smoking is a top priority for patients with COPD because of the substantial benefit of smoking cessation upon disease progression. However, our search yielded only a small number of observational studies documenting the uptake of smoking cessation interventions by patients with COPD. Only one included observational study reported the

outcomes of smoking cessation interventions in this population. In this study, among 328 patients with COPD who were current smokers at baseline, 71.2% (198/278) and 61.6% (148/240) remained smoking at 1-year and 2-year follow-up, respectively [29]. Two surveys in the same population of patients with COPD showed just a 2.3% reduction in smoking prevalence (28.3% to 26%) over 10 years [30]. The results of our review suggested that smoking cessation among patients with COPD is poorly characterised in real-world practice, and requires further research.

The influenza and pneumococcal vaccines have been shown to prevent serious illness and community-acquired pneumonia in patients with COPD [31, 32]. Many international and national authorities recommend that individuals with COPD should receive annual influenza and pneumococcal vaccines. The target coverage rate for influenza vaccine set by the WHO and European Union is 75% of at-risk groups, including patients with COPD [33]. A recent report by European Centre of Disease Control showed that influenza vaccine coverage rate from 2015 to 2018 among individuals with chronic medical conditions was available in only seven member states, with the highest at 60.5% in Ireland in 2017 – 2018 influenza season – a finding similar to our pooled proportion. With regards to pneumococcal vaccine, most countries lack a coverage target for patients with chronic illnesses. We found the uptake of pneumococcal vaccine was less than the 60% immunization coverage for high-risk population aged 19–64 years or the 90% target for adults ≥ 65 years set by the U.S. Healthy People 2020 plan [34]. Further evidence is needed to guide public health interventions and health policies related to pneumococcal vaccines in populations with COPD.

Pulmonary rehabilitation, proven to reduce symptoms and improve health-related quality of life, was also underused. We found the biggest gap at the referral stage; only around 20% of patients were referred to a pulmonary rehabilitation programme. Even though pulmonary rehabilitation is not indicated for every patient with COPD, the findings still suggest a substantial unmet need. The low rate of referral may result from various reasons, such as a lack of available programme or patients' unawareness of benefits. Randomised trials have shown the equal effectiveness of home-based or community-based programme, as compared to hospital-based programme [35, 36]. Further evidence about how to increase the uptake and completion of rehabilitation programmes for patients with COPD is urgently

needed.

We identified several factors contributing to non-completion of steps of the cascade. These can help direct future efforts to improve adoption of evidence-based approaches. Several factors were important in our evaluated interventions. A number of included studies found patients with younger age had a higher risk of missed diagnosis, poor adherence to inhalers and not receiving vaccines. However, most identified risk factors were patient-related factors and condition-related factors; few studies reported health care team and system-related factors [37-40].

This study has several limitations. First, similar to other meta-analyses of observational studies, differences in inclusion criteria, measurement of outcomes, and definitions for adherence between studies led to a high degree of heterogeneity in our meta-analyses [15, 22]. Second, low participation rates and data obtained solely by participants' self-report in some included articles may introduce misclassification bias. Third, we did not include studies published in languages other than English. This may affect the generalizability of our findings.

Conclusion

In conclusion, this systematic review provides a comprehensive analysis of real-world COPD care. The five systematic literature searches capture the key components of patient management. This approach of multiple related literature searches enabled us to assess and include more studies relevant to each of the components. To our knowledge, this study is the first to apply the cascade of care to real practice of care for COPD. The findings provide important insights that informs future policies and actions to address the growing global burden of COPD.

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Disclosure

The author reports no conflicts of interest in this work.

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Real-world management for asthma

Key elements of asthma management include pharmacotherapy, patient education and self-care, avoidance of allergen exposure, and vaccinations against common respiratory pathogens. Observational studies have identified room for improvement in all these elements of care. There are several problems in the management of people with asthma that are also common to patients with COPD, including access to diagnostic tests, availability and affordability of respiratory medicines, vaccine uptake, and adherence to inhalers [1-3].

One important issue specific to asthma management is the overuse of SABA, which has been shown to be associated with an increased risk of exacerbation and mortality [4, 5]. The over-reliance of SABA as a symptom reliever is rooted in patients' attachment to SABA's rapid activity in alleviating their symptoms. This has been reinforced by formal recommendations that patients use as-needed SABA whenever they have symptoms [6, 7]. A recent study showed a prevalence of SABA overuse (≥ 3 SABA canisters/year) of 9% to 32% among asthmatic patients in five European countries [8]. A systematic review had a similar finding that 17% to 24.3% of adults used ≥ 3 SABA canisters in a year [9]. As asthma is a disease of airway inflammation, the use of SABA alone temporarily relieves symptoms without addressing inflammation in airways that is responsible for the pathogenesis of asthma. Overuse of SABA causes a down-regulation of beta-receptor and reduced response, leading to greater use for unresolved symptoms [10]. Increased risk of exacerbation and even mortality may occur if patients continue to use SABA to "treat" their asthma [4, 5]. To address the underlying airway inflammation that causes symptoms, patients should be taking ICS, instead of repeated SABA use. Hence, the GINA guidelines have recommended against the use of SABA alone for patients with asthma since 2019 [11].

Observations about management of chronic respiratory disease in LMICs and Vietnam

Though the available evidence is limited, studies from LMICs provide an insight that helps understand the gap between optimal evidence-based recommendations and the reality of clinical practice in the care of CRD. A cohort study in Uganda followed 449 patients (median age 33 years; interquartile range 20 – 48) with asthma. This study found that 59.6% of patients experienced at least one exacerbation in one year and 11 (2.4%) asthma-related death in two years. Among the cohort, only 32.7% were on ICS at baseline [12]. The rates of

exacerbation and mortality were much higher than observations from developed countries [13-15]. Another cohort study in Egypt assessed treatment adherence of patients with COPD. Of 1,311 enrolled patients, 48.1% stopped inhaled medicines within one year after study enrolment [16]. Observations from specialist centres in four Latin American countries revealed that, among 594 patients aged ≥ 12 years, only 43.4% achieved optimal asthma control, defined as a score of ≥ 20 on Asthma Control Test (ACT) [17]. The result was similar to studies from specialist care in Turkey (51.5%) and South Africa (47.2%) [18, 19]. The studies indicated that clinical management and outcomes of patients with CRD in these developing settings need to be improved.

Several studies have assessed the management of asthma in Vietnam. A survey of primary care physicians in Vietnam showed a low level of knowledge about GINA recommendations [20]. Among 201 primary care physicians, only 49.8% of used spirometry and 24.4% used ACT in routine practice. Around 21% of the physicians had no correct answer to five scenarios of classifying asthma control levels based on GINA guidelines. Despite the recommendation against LABA monotherapy, 70% of the respondents used LABA alone to treat their patients. Another survey conducted at a university hospital in Southern Vietnam showed a suboptimal level of asthma control among 308 patients aged 12 years and older [21]. Among the patients, 96.4% were given ICSs but 40.9% had an ACT score of less than 20. A high proportion of uncontrolled asthma was also found in another survey of 322 patients [22]. In this study, 59.6% of patients had an ACT score of less than 20 and 83.5% had poor knowledge of self-care, assessed by the Asthma Self-Management Questionnaire.

Studies have demonstrated that clinical care for COPD in Vietnam, like care for people with asthma, remains suboptimal. A survey evaluated knowledge of COPD care of 461 doctors working at provincial hospitals and district hospitals [23]. Only 23.5% of the respondents were able to stage disease severity according to GOLD 2011 criteria correctly; 85.7% of the doctors did not guide their patients on using the inhaler devices. Another study assessed inhaler technique and adherence to treatment of 70 patients with COPD at a national hospital in northern Vietnam [24]. Less than a third of patients had good inhaler technique – 22.7% for metered-dose inhalers, 30.4% for dry powder inhalers and 31.8% for soft-mist inhalers. Half of the participants were found to be poorly adherent to inhaler therapy (score

≤ 45 in 10-item Test of Adherence to Inhaler). Data from a study conducted in nine countries in the Asia-Pacific region showed that 57% of patients with COPD in Vietnam had at least one exacerbation in the past year, which was the second highest among the countries [25].

Overall, available literature from LMICs and Vietnam showed suboptimal disease control, limited knowledge about management of CRD among doctors, low utilisation of spirometry, and low levels of adherence to evidence-based treatment recommendations.

Evidence about interventions to improve care for patients with CRD in Vietnam

Few studies have evaluated the effectiveness of interventions to improve care for patients with CRD in Vietnam. One recent randomised controlled trial showed that a 30-minute counselling session with a hospital pharmacist significantly improved patients' quality of life over three months among patients with COPD treated at a university hospital in Southern Vietnam [26]. Participants who received the intervention also had a lower rate of poor inhaler technique as compared to the control group. A research team conducted a pre- and post-intervention study of a pharmacist-led programme that consisted of inhaler technique training and individual counselling for patients with COPD enrolled in a university hospital. The authors found that the intervention significantly improved inhaler technique, medication adherence, and quality of life [27, 28]. Another simulated patient study from the same research team showed that a 4-hour training session about asthma management, delivered to community pharmacists, was effective in improving counselling performance [29]. These two studies in Vietnam demonstrated the role of clinical pharmacists in improving the care and outcomes of patients with CRD.

Mind the gap, and calls to fill it

Putting together the burden of CRD and observations from clinical practice in LMICs, a substantial unmet need exists. Effective and cost-effective interventions suitable for LMICs are needed. More robust epidemiological and clinical reports are also desirable for future monitoring and evaluation. A recent review put forward a number of priorities to address CRD in LMICs, including research topics, capacity building, and health system strengthening [1]. In 2019, the COPD Assembly of the Asia Pacific Society of Respirology published a position statement. The statement emphasised the differences in clinical characteristics of

patients with COPD in Asian countries and those in Western countries. The statement gave recommendations related to the features of Asian patients with COPD (Table 2.1) [30]. The Global Asthma Report 2018 also suggested: "Governments, health services and allied researchers should develop new ways to target and deliver asthma care in diverse health systems and contexts, and gather evidence of costs and outcomes, cost-effectiveness, affordability and feasibility [31]."

Table 2.1. Distinctive features of COPD in Asia and recommendations from the COPD Assembly of the Asia Pacific Society of Respirology

Feature	Recommendation
Low awareness, underdiagnosis, and undertreatment	• Public relations campaigns are needed to improve the low rate of awareness of COPD in Asia.
Low utilisation of pulmonary function testing	• The importance of pulmonary function test should be emphasized to general practitioners. • Governmental interventions are needed to improve the low pulmonary function testing rate in Asia.
Low inhaler use	• The importance of inhalers should be taught to both general practitioners and patients. • Governmental interventions are needed to improve the low rate of inhaler use in Asia.
High smoking prevalence	• Physicians should provide counsel and offer nicotine replacement and pharmacological products. • Asian governments should implement a tobacco control policy.
Air pollution exposure	• Air pollution level should be monitored and COPD patients kept informed. • COPD patients should avoid going outside when the air pollution level is high. • Asian countries should collaborate on implementing an air pollution policy.
Biomass smoke exposure	• A history of biomass smoke exposure should be taken.
Low Body Mass Index	• Potential adverse effects of drugs should be monitored closely in patients with low Body Mass Index. • A lower dose of roflumilast and inhaled corticosteroid may be considered for patients with a low Body Mass Index.
Bronchiectasis	• Inhaled corticosteroid needs to be prescribed with caution in COPD combined with bronchiectasis
Tuberculosis-destroyed lung	• Long-acting bronchodilators can be considered for patients with tuberculosis-destroyed lung. • A diagnosis of tuberculosis should be considered before and

	during inhaled corticosteroid use.
Parasitic infections	• Parasitic infections should be ruled out in patients with high blood eosinophil counts.

2.2. Offering assistance to quit smoking: observations from low- and middle-income countries

Tobacco smoking is a major risk factor for COPD and asthma. Interventions to assist smoking cessation play a critical role in managing patients with the diseases. This section describes smoking-related behaviour and evidence of smoking cessation interventions in LMICs.

Global Adults Tobacco Survey

Two studies evaluated smoking-related behaviour in LMICs using data from Global Adults Tobacco Survey 2010. The first study showed that the percentage of smokers in 16 LMICs who had tried to quit in the past 12 months varied largely, from 11.6% in China to 47.9% in Thailand [32]. They also found low proportions of smokers using any form of recommended cessation assistance to help them quit, with the highest country being only 27%. The other study showed that 81.7% of current smokers in 14 LMICs were in the precontemplation stage of the transtheoretical model, i.e. no intention to quit within the next six months [33]. The findings suggested that most smokers in LMICs did not intend to quit and the adoption of methods to assist with smoking cessation was low.

In Vietnam, Global Adult Tobacco Survey was conducted in 2010 and 2015 [34, 35]. Table 3 compares some of the main indicators related to smoking cessation. The prevalence of current smoking decreased slightly from 23.8% to 22.5%, with no statistical significance. More smokers had been asked about smoking status and suggested to quit by a healthcare provider in 2015. However, quit rates were similar in the two surveys. Among smokers who attempted to quit in the past 12 months, the proportion who had used NRT was much lower in 2015 than in 2010. Prescription medicines and counselling/advice were rarely used, with no statistical difference between the two years. Finally, the cost of manufactured cigarettes was lower in 2015 than in 2010.

Table 3. Comparison between Global Adults Tobacco Survey 2010 and 2015 in Vietnam

	2010 survey	**2015 survey**
Prevalence of current smoking, percentage (95% CI)		
Men	47.4 (45.4 – 49.4)	45.3 (43.1 – 47.5)
Women	1.4 (1.0 – 2.1)	1.1 (0.7 – 1.6)
Overall	23.8 (22.7 – 24.9)	22.5 (21.3 – 23.8)
Cessation, percentage (95% CI)		
Ever smokers who quit smoking	29.3 (27.2 – 31.4)	29.0 (26.9 – 31.3)
Smokers asked about their smoking status by a healthcare provider*	34.9 (30.9 – 39.1)	45.6 (41.2 – 50.1)
Smokers being advised to quit smoking by a healthcare provider*	29.7 (25.8 – 34.0)	40.5 (36.3 – 45.0)
Cessation methods used among smokers who attempted to quit in the past 12 months, percentage (95% CI)		
Nicotine replacement therapy	24.4 (21.3 – 27.8)†	3.0 (1.9 – 4.8)
Prescription medications	0.4 (0.1 – 1.4)	0.3 (0.1 – 1.1)
Counselling/advice	3.0 (2.1 – 4.4)	2.3 (1.3 – 4.2)
Economics		
Average amount of money spent on a pack of 20 manufactured cigarettes (adjusted for inflation)	VND 12,700‡	VND 11,800
Cost of 100 manufactured cigarettes, percentage of GDP per capita	2.7%	2.5%

*Among current smokers and former smokers who have been abstinent for less than 12 months, and who visited a healthcare provider during the past 12 months

†The much higher percentage of nicotine replacement therapy in 2010 as compared to 2015 might be due to misclassification of regular chewing gum (not included in 2010 survey) to nicotine replacement therapy in 2010. The percentage of regular chewing gum in 2015 survey was 17.3% (95% CI 14.4 – 20.7).

‡At the 2015 price

Smoking cessation interventions in LMICs

There is growing evidence supporting tobacco cessation interventions in LMICs, even in places with the most limited resources. A systematic review of randomised controlled trials found that NRT, behavioural counselling and brief advice were efficacious in assisting smoking cessation in LMICs [36]. Low-cost cessation interventions include oral cytosine [37, 38], integrating brief advice into routine healthcare encounters [39], and national automated text message programmes [40].

However, it is arguable that evidence-based interventions developed in high-income countries are equally effective and applicable in LMICs. Studies have suggested that smoking

cessation interventions might require substantial local adaptation in order to be implemented in LMICs. Asfar *et al*. conducted a process evaluation of their behavioural intervention. They found that self-monitoring, nicotine fading exercise and social support enhancement learnt from more developed nations were not useful in Syria [41]. Likewise, two studies from Pakistan and Syria did not show the added benefit of pharmacotherapy to behavioural support in "real-world" clinical settings [42, 43]. Another study found that pharmacological therapies, particularly bupropion, nicotine patches, and nicotine gum, were cost-effective in preventing death and disease caused by tobacco use in Seychelles (being a middle-income country at the time the study, but becoming a high-income country after 2010) [44]. Nevertheless, the authors also suggested these medicines should be made available at "significantly reduced prices" to be cost-effective in lower income developing countries.

Evidence about assisting smoking cessation in Vietnam

Little evidence is available about observations of smokers receiving smoking cessation advice and interventions from healthcare workers in Vietnam. One recent qualitative study assessed barriers to smoking cessation for HIV-infected people who inject drugs [45]. The study found that those who made quit attempts were generally not motivated by advice from their HIV care providers' advice. Also, counselling from HIV care providers was inconsistent, short, and limited by insufficient provider knowledge.

Several studies have evaluated different smoking cessation interventions in Vietnam. Village health worker cessation counselling, added to advice from community health centre, significantly reduced 6-month biochemically-verified abstinence when compared to advice from community health centre alone (10.5% vs. 25.7%; $p < 0.001$) [46]. A survey of 469 smokers who called a free quitline operated by Bach Mai Hospital, Hanoi, showed that 31.6% claimed to have successfully quit smoking and 5.1% had been abstinent for 6-months or more [47]. In another study, of 602 adult smokers who had intention to quit in 12 months, 72% expressed willingness to use a text-messaging cessation service [48]. The findings from these studies suggested that interventions outside of healthcare settings may be accepted by smokers and effective in assisting cessation.

Following the announcement of Decision 1315/QĐ-TTg (ratification of the Plan for the Implementation of the Framework Convention on Tobacco Control) in 2009, a pilot before-and-after study evaluated the effect of implementing smoke-free hospital policy in nine hospitals [49]. After implementing the policy, the prevalence of self-reported smoking among healthcare workers significantly decreased, and smoking was more likely to be observed outside buildings and cafeterias. Nevertheless, despite decreased airborne concentrations of nicotine, nicotine was still detected in the air of all the monitored areas in the hospitals. Upon search, no further study investigating the implementation of smoke-free hospital in Vietnam was found. Strategies for implementing the enforcement of the smoke-free hospital policy in Vietnam are needed.

The steps ahead to smoke-free

The WHO Global Monitoring Framework set a global target of a 30% reduction in the prevalence of current smoking in 2025, compared with 2010 levels [50]. According to an analysis of global survey data, many countries will not achieve the target based on the projected prevalence if current trends remain unchanged [51]. This is likely to be the case in Vietnam where smoking prevalence declined marginally from 23.8% to 22.5% between 2010 and 2015.

Over the past decade, the Vietnamese government has enacted laws to control tobacco use, including Decision 1315/QĐ-TTg in 2009 and Directive 05/CT-BYT (strengthening the implementation of Law on Prevention and Control of Tobacco Harm in health section) in 2013 [52, 53]. Nevertheless, findings from Global Adults Tobacco Survey have suggested that even though more smokers were asked about smoking and advised to quit by healthcare providers, the use of smoking cessation methods among smokers was low. Also, the lower cost of manufactured cigarettes in 2015 than in 2010 did not serve as an incentive to quit smoking. A lot remains to be done in Vietnam to reduce smoking prevalence and prevent diseases associated with tobacco use, such as CRD.

2.3. The Vietnamese health system

This section provides an overview of the Vietnamese health system and its challenges, which

informed the design of the studies included in this thesis. Figure 2.1 shows the structure of the Vietnamese public health system [54-56]. Public healthcare facilities are organised into four levels: national (central) hospitals, provincial hospitals, district hospitals, and commune health centres. District hospitals and commune health centres are considered the grassroots level of healthcare and provide service to an average of about 120,000 and 10,000 people in the local communities, respectively. In 2016, almost 82% of the Vietnamese population was covered by public health insurance [57].

The healthcare system in Vietnam faces many challenges at the grassroots level, particularly at commune health centres. According to the Joint Annual Health Review 2015[58], commune health centres can only perform 52.2% of the services determined by the national classification of technical services intended to be performed at commune health centres. This was caused by the shortage of essential medicines, lack of medical devices, shortage of appropriately qualified personnel, and inadequate training of healthcare workers. Limited and ineffective curative care service at the grassroots health network has led to overcrowding at higher-level hospitals [58, 59].

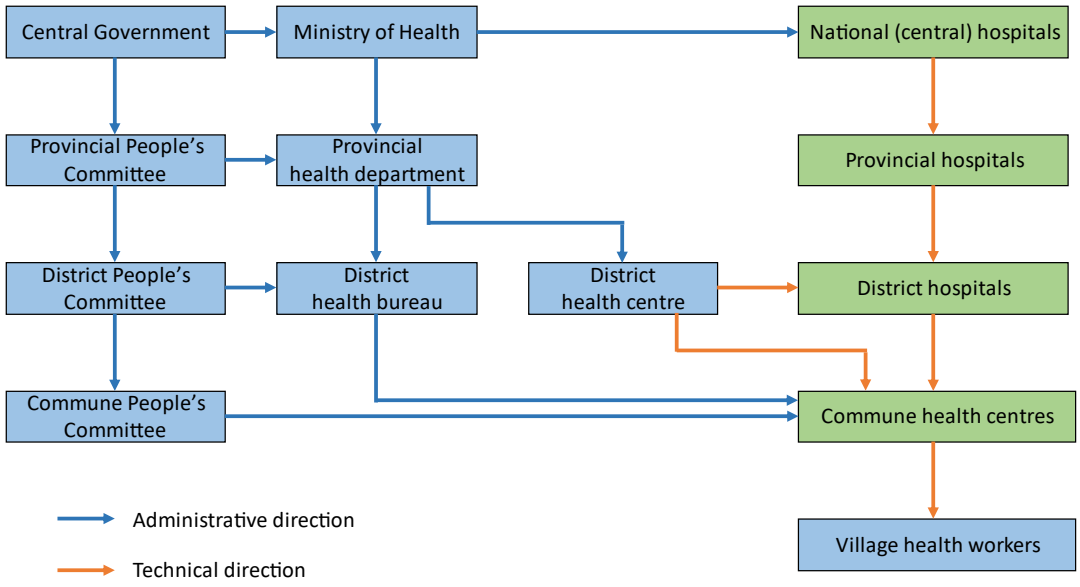

Figure 2.1. Structure of the Vietnamese health system [54-56]

2.4. Overview of VCAPS study and the research setting

The Vietnam COPD, Asthma and Prevention of Smoking (VCAPS) study is a programme of research aiming to understand and reduce the burden of CRD and tobacco smoking in healthcare settings in Vietnam. The VCAPS study consists of four main parts. The VCAPS 1 study was a prospective cohort study that contributed to an understanding of respiratory diseases and smoking behaviour among patients presenting to health facilities. The current practices and attitudes regarding disease management and tobacco control were evaluated in the VCAPS2 study. The VCAPS3 study served as a pilot study assessing the feasibility of two interventions that were hypothesised to reduce exacerbations of CRD and to assist quitting smoking. The findings of the VCAPS3 study informed the design of the VCAPS4 study, a 2*2 cluster randomised controlled trial that evaluated the effectiveness of a stepped approach to CRD management and a smoking cessation intervention integrated within the healthcare system.

VCAPS1 study and VCAPS2 study were conducted at all four levels of healthcare facilities in order to be representative of the actual practice in the Vietnamese healthcare system. The interventions of the VCAPS3 and the VCAPS4 studies were intended to reach a wider patient population without posing an even higher burden to central and provincial hospitals if the interventions were to be scaled up. The grassroots level facilities were considered. However, commune health centres generally provide preventive services and treatment for acute infections and common ailments [56]. Services for NCDs at commune health centres were limited [60]. A survey of 89 commune health centres showed that only 40% of these centres provided care for CRD [61]. Therefore, the interventions were designed to be implemented in district hospitals.

2.5. Research objectives

The literature review suggested that little is known about the management of CRD in Vietnam. Most studies assessed doctors' knowledge about recommendations from international guidelines. There were few interventional studies, which were carried out in national or university hospitals. In terms of smoking cessation, evidence from Vietnam suggested that counselling from village health workers and quitlines may be effective in

assisting cessation. However, observations of actual practice for smoking cessation in healthcare settings is lacking.

The research in this thesis used the VCAPS study as its platform. The research objectives of this thesis include:

1. To describe the prevalence and management of common respiratory conditions, including CRD, among patients seeking healthcare to all four levels of the Vietnamese healthcare system.
2. To describe the prevalence of smoking and related behaviours among patients seeking healthcare to all four levels of the Vietnamese healthcare system.
3. To assess the feasibility of an intervention aiming to reduce exacerbations among patients with CRD visiting district hospitals.
4. To assess the feasibility of an integrated smoking cessation intervention in assisting quitting smoking.

Chapter 3 and chapter 4 of the thesis address the first two objectives using data from the VCAPS1 study. Chapter 5 to 7 address the latter two objectives. Chapter 5 and chapter 6 describe the two interventions and findings from the VCAPS3 study. Chapter 7 contains a process evaluation for the intervention for CRD in the VCAPS3 study.

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Chapter 3. Syndromic approach for patients with respiratory conditions

3.1. Syndromic approach and Practical Approach to Lung Health

Syndromic approaches to disease management

A syndrome is a group or cluster of symptoms and objective observations that commonly occur together. A syndromic approach, or syndromic management, refers to treating patients based on the presenting syndrome, rather than a definitive diagnosis, which may not be apparent at the time of initial presentation. It is particularly suited to circumstances where a definitive diagnosis may be difficult or expensive to reach or where it may be delayed for a considerable time period and, where safe and effective management can be implemented based on the syndromic diagnosis alone. For example, pneumonia can be treated based on a clinical or radiological (syndromic) diagnosis without identifying the aetiology. Since the 1980s, WHO has been promoting syndromic approaches to the management of acute diarrhoea and acute respiratory infections in children, and sexually transmitted diseases at primary care level [1, 2]. The syndromic approach has been widely studied and adapted for sexually transmitted diseases in many LMICs [3, 4].

Practical Approach to Lung Health

In light of the burden of respiratory illnesses and insufficient tuberculosis case detection globally, the WHO developed "Practical Approach to Lung Health (PAL)" in the early 2000s [5]. The aim of PAL was to improve the quality of respiratory care in primary care settings and the efficiency of respiratory service delivery within health systems in LMICs. PAL uses a syndromic approach with an emphasis on tuberculosis, pneumonia, and CRD.

Following the development of PAL, a number of studies have evaluated the effect of adopting PAL into clinical practice [6]. In Bishkek, Kyrgyzstan, researchers found a one-third decrease in referrals to hospitals, specialists, or for diagnostic tests from family doctors after training in PAL techniques [7]. Antibiotic prescription among patients with acute upper respiratory infections also decreased by 34.6%. On average, the cost of drug prescriptions for each patient with respiratory conditions reduced by 32.2%.

In South Africa, an integrated syndromic respiratory disease guideline, called PAL for South Africa, was made available after adapting the PAL approach to the local barriers and facilitators to health care access, relevant local policies, and medical literature [8]. PAL for South Africa, combined with educational outreach sessions delivered to nurse practitioners, achieved higher rates of tuberculosis case detection and prescription of inhaled corticosteroids to patients with asthma, when compared with usual care in a cluster randomised controlled trial [9].

Similar to the findings from Kyrgyzstan and South Africa, improved clinical and economic outcomes following implementing PAL were observed in studies conducted in other countries (Table 3.1).

In the following section, I describe the application of a syndromic approach to diagnosis in patients presenting with respiratory symptoms, using data from the VCAPS1 study implemented across the four levels of the Vietnamese healthcare system.

Table 3.1. Studies applying Practical Approach to Lung Health [6]

Outcome		**Countries where study conducted**
Diagnosis	Increase in diagnosis of CRD	Algeria, Chile, Jordan, Morocco, Kyrgyzstan, South Africa, Tunisia, Syria
	Improvement in TB case detection	Algeria, Bolivia, Morocco, South Africa, Syria, Tunisia South Africa, Algeria
Treatment	Decrease in drug prescription, particularly antibiotics and adjuvant drugs	Algeria, Bolivia, El Salvador, Jordan, Kyrgyzstan, Morocco, Nepal, Syria, Tunisia
	Increase in inhaled corticosteroids prescription	Algeria, Chile, Jordan, Kyrgyzstan, Morocco, South Africa, Syria, Tunisia
Managerial	Increase in respiratory disease management in primary care and decrease in referral to upper health level	Bolivia, El Salvador, Guinea, Jordan, Kyrgyzstan, South Africa
Economic	Reduction in the average cost of drug prescription per respiratory patient	Algeria, Bolivia, Jordan, Kyrgyzstan, Morocco, Syria, Tunisia

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3.2. Application of the syndromic approach in Vietnam

preface

This sub-chapter contains the unaltered full text of the following published article:

> Huang WC, Fox GJ, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Jan S, Negin J, Le TTL, Marks GB. A syndromic approach to assess diagnosis and management of patients presenting with respiratory symptoms to healthcare facilities in Vietnam. ERJ Open Research. 2021;7(1):00572-2020. doi: 10.1183/23120541.00572-2020.

Appendix 2.2 of this thesis contains the supplementary appendix for this article. WCH formulated the research questions, conducted the data analysis, and wrote the manuscript.

Contribution of this sub-chapter to the thesis

This sub-chapter addresses the first research objective of the thesis. In the article, I applied the syndromic approach to show the prevalence and management of common respiratory conditions among patients seeking healthcare to all four levels of the Vietnamese healthcare system.

Introduction

Respiratory diseases are common reasons for presentation to healthcare facilities worldwide and impose a large burden upon the health system [1, 2]. The prevalence of chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD) and asthma, has been rising globally, with an increase in deaths due to these diseases [3]. Lower respiratory tract infection (LRTI) and tuberculosis also remain major causes of mortality, especially in low- and middle-income countries (LMICs) [2, 4].

In many settings, the diagnosis and management of chronic respiratory diseases remains suboptimal. Incorrect diagnostic pathways contribute to inappropriate treatment decisions [5], and poor outcomes. Many patients who are labelled as having COPD, or its related entities emphysema or chronic bronchitis, lack demonstrable airflow obstruction on spirometry [6]. On the other hand, population-based surveys in diverse locations demonstrate that many people with airflow limitation measured on spirometry have never been formally diagnosed with COPD or asthma [7, 8].

A correct diagnostic label should lead to the initiation of treatment that is beneficial to patients. For example, some patients with COPD will benefit from treatment with inhaled corticosteroids, whilst others do not [9, 10]. This latter group includes some patients who develop excess pneumonia as a result of treatment with inhaled corticosteroids [11, 12]. There is evidence that markers reflecting underlying eosinophilic inflammation are useful for identifying those likely to benefit from ICS [9]. Other therapies are effective for selected patient groups: bronchodilators will most benefit patients with respiratory symptoms who have airflow limitation [13, 14], while antimicrobial agents will be beneficial when bacterial infection is present. Accurate diagnostic decision-making is essential to ensure that the right treatment is given to the right patient.

Inappropriate treatment decisions for respiratory diseases are common in many healthcare systems [15-17]. Strategies have been developed to improve decision-making for respiratory diseases [18-20], including the World Health Organization-recommended “Practical Approach to Lung Health” that aims to improve the quality of care for patients with

respiratory symptoms at first-level health facilities [1]. This symptom-based approach does not require extensive diagnostic testing, and has been shown to be feasible in resource-limited settings [21-24]. Once respiratory syndromes have been correctly identified, optimal therapeutic approaches can be adopted [21, 25].

In Vietnam, the clinical characteristics of patients presenting with respiratory symptoms to different levels of healthcare have not been well-characterised. Similarly, the correlation between diagnosis and treatment for respiratory diseases is poorly understood. Given the incomplete implementation of evidence-based strategies shown in previous studies [16, 26, 27], we hypothesised that a simple syndromic approach can be used to assess the quality of care in a healthcare system and may improve patient care.

The aim of this study was to establish syndromic diagnoses for a representative sample of patients presenting with respiratory symptoms to healthcare facilities in Vietnam using a simple, standardised diagnostic approach and to compare this syndromic diagnosis with the clinical diagnosis and treatment decisions made by local healthcare workers.

Methods

Study design

We implemented an observational study with a baseline survey, diagnostic tests and a follow-up assessment at 4 weeks.

Study setting

The study was conducted in four provinces of Vietnam, a middle-income country in Southeast Asia with a population of 96 million people. The four provinces comprised two in the north (Hanoi Capital and Thanh Hoa Province) and two in the south (Ho Chi Minh City and Ca Mau Province).

Patients were recruited from health facilities at all four levels of the Vietnamese health system: central (national) hospitals, provincial hospitals, district hospitals and commune health centres.

Sampling of study sites and participants

Major central and provincial hospitals in each province were included. In addition, four district hospitals were selected by random sampling within each of the four provinces. Two commune health centres from each selected district were also chosen by random sampling. The probability of each facility being chosen was proportional to the populations of the districts and communes within which the health facilities were located. Within each central and provincial hospital, departments in which patients with respiratory diseases were routinely managed were included. At district hospitals, patients were recruited at outpatient clinics.

Recruitment commenced at each site on a randomly selected day of the week. Consecutive patients, aged 5 years old and above, who attended the study sites for clinical assessment and all inpatients in participating wards during the recruitment period were listed in an enumeration logbook. The age, gender, current respiratory symptoms, and smoking status of all patients were recorded.

Sample size was calculated from estimating the prevalence of COPD in different levels of facilities. We expected the prevalence of COPD among patients seeking healthcare with respiratory symptoms would be 15%. With a precision of 5% and an alpha of 0.05, assuming approximately 20% loss to follow-up at the 4-week visit, we aimed at recruiting 250 individuals for follow-up per category.

Eligibility and consent

Enumerated patients who met the eligible criteria were selected at random to participate in the study. Patients aged 5 years old and above presenting to the facility with at least one respiratory symptom (dyspnoea, cough, wheezing, and/or chest tightness) that occurred within the previous 24 hours were eligible. Patients who were unable to complete the survey due to communication difficulties, who were resident in another province, or who were known to be pregnant were ineligible. For outpatients, the sampling fraction was calculated before the commencement of recruitment, based upon the number of individuals who could be seen by study staff within one day, as a proportion of the average number of

daily patients attending the clinic over the preceding 6 month period. Recruitment of patients continued until the recruitment target was reached at each site.

In order to assess potential selection bias, patients who declined to participate were asked to complete a brief 'minimal data questionnaire' that included their demographic details. Eligible participants were asked to give written informed consent. Participants completing the minimal data questionnaire were asked to provide verbal consent only.

Study measurements

Data collected from consenting participants during the baseline survey included age, gender, body weight, body height, presenting symptoms, highest level of education attainment, current occupation, smoking habit, comorbidities, and the Common Cold Questionnaire [28]. Anteroposterior chest radiograph and full blood count with white blood cell differential count were also obtained. Patients aged 50 years or more with dyspnea had blood collected for brain natriuretic peptide (BNP) or N-terminal pro-BNP (NT-proBNP). The cut-points for elevated BNP, NT-proBNT, neutrophilia, and eosinophilia are shown in Table 1. Patients with cough for more than 2 weeks had their sputum tested for *M. tuberculosis* using GeneXpert MTB/RIF® (Cepheid). Diagnoses made and treatment administered by the treating clinician were also recorded.

Trained technicians performed spirometry using EasyOne® Air spirometer (ndd Medizintechnik) according to American Thoracic Society / European Respiratory Society guidelines [34]. Participants performed the procedure with no salbutamol administered at the baseline visit. At the 4-week visit, measurements were made before and 15 minutes after administration of 400 micrograms of salbutamol via a metered-dose inhaler with spacer.

An external reviewer independent from the study interpreted the results of spirometry following a consensus statement for office spirometry from the National Lung Health Education Program [35]. Spirometry results with a quality of A to C were considered valid and included in the analysis. We excluded results with a quality of D and F (criteria shown in Supplementary Table S1).

Chest radiographs performed at the facilities were reviewed independently by two experienced respiratory physicians. The readers recorded the presence of airspace opacity, cardiomegaly, and pulmonary venous hypertension based on the definitions in Supplementary Table S2. Disagreements in interpretation between the two physicians were resolved by consensus discussion. A third respiratory physician adjudicated where consensus could not be reached.

Healthcare workers did not have access to the above diagnostic tests performed for this study if the tests were not performed as a part of their clinical investigation.

Syndromic diagnoses

Eight syndromes were defined, *a priori*, using data from the survey and the diagnostic test described above (Table 1). We used the Global Lung Function Initiative 2012 reference value to determine the lower limit of normal [36]. For each syndrome their defining features and recommended treatment, based on international guidelines, are shown in Table 1.

Statistical methods

Prevalence estimates and associated 95% confidence limits were calculated for participants who completed the baseline survey. Patients with missing data or lost to follow-p were classified according to the data that were available. Kappa statistics were used to evaluate the agreement between the predefined syndromes and the diagnostic labels given by healthcare workers at the facilities. Analyses were conducted using SAS® (v9.4, SAS Institute, Cary Corp. NC. USA). R Statistical Software (v4.0.0, Foundation for Statistical Computing, Vienna, Austria) with UpSetR package [37] was used to visualize concurrences of syndromes in the participants.

Ethical approval

The study was approved by the Human Research Ethics Committee at the University of Sydney, and the Institutional Review Board of the Bach Mai Hospital, Hanoi, Vietnam.

Table 1. Criteria used to define the eight respiratory syndromes

Syndrome	Criteria	Treatment and management relevant to the analysis
Fixed airflow limitation (COPD) without eosinophilia	Post-bronchodilator FEV1/FVC < lower limit of normal AND no eosinophilia* at presentation	Long-acting bronchodilators, SABA [29]
Fixed airflow limitation (COPD) with eosinophilic inflammation	Post-bronchodilator FEV1/FVC < lower limit of normal AND eosinophilia* at presentation	Long-acting bronchodilators, ICS, SABA [29]
Reversible airflow limitation (asthma)	FEV1 increases by > 200ml and > 12% of the baseline value after inhaling a bronchodilator	ICS, long-acting bronchodilators [30]
Other airflow limitation	FEV1/FVC < lower limit of normal on baseline spirometry for those without measure of post-bronchodilator spirometry	May benefit from bronchodilators; consider post-bronchodilator spirometry
Lower respiratory tract infection	Focal or localised air-space consolidation on chest X-ray AND neutrophilia†	Antibiotics
Tuberculosis	Positive GeneXpert result for sputum sample	Anti-tuberculosis agents
Heart failure	Cardiomegaly‡ on chest X-ray AND one or more signs of pulmonary venous hypertension on chest X-ray OR elevated BNP/pro-BNP level§	Diuretics for volume overload [31]
Upper respiratory tract infection (common cold)	Moderate symptoms in at least 2 of the 4 categories, OR mild symptoms in 3 or more categories, OR mild symptoms in one category plus a cough in Common Cold Questionnaire [28] with symptoms last ≤ 10 days AND none of the above 7 syndromes	Symptomatic treatment

BNP: brain natriuretic peptide; COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; ICS: inhaled corticosteroids; SABA: short-acting beta-agonists

*Eosinophilia [29]: Eosinophil count > 0.3 $\times 10^9$/L;

†Neutrophilia [32]: neutrophil count > 6.3 $\times 10^9$/L;

‡Cardiothoracic ratio > 0.55;

§Elevated BNP/pro-BNP level [33]: BNP level > 400 pg/mL; Pro-BNP level > 450 pg/mL for subjects aged < 50 years, Pro-BNP level > 900 pg/mL for subjects aged 50 - 75 years, Pro-BNP level > 1,800 pg/mL for subjects aged > 75 years.

Results

From September 2017 to October 2018, we screened 13,157 patients for inclusion in the study (Figure 1). Among 3,163 patients who met the eligibility criteria, 1,617 were randomly selected and invited to participate in the study. Following selection, 977 patients (including 878 outpatients and 99 inpatients) agreed and completed the baseline survey. Among them, 635 (65%) had chest X-rays and 673 (68.9%) had valid baseline spirometry. At the four-week follow-up, 935/977 (95.7%) patients completed the survey and 607/977 (62.1%) performed valid spirometry.

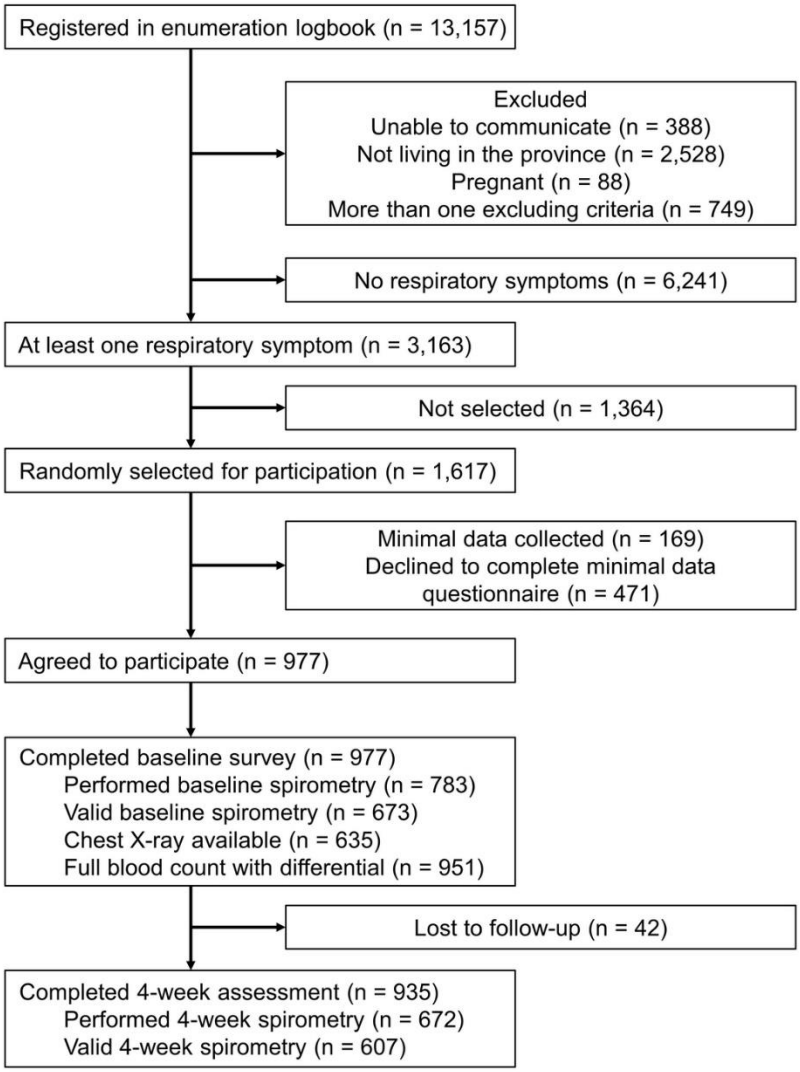

Figure 1. Consort diagram of participant recruitment

The median age of the cohort was 59 years (interquartile range: 47 – 67 years). Nearly two thirds were male, the majority of whom were current or ex-smokers (Table 2). Only 6/325 (1.9%) of female patients were current or former smokers. Supplementary Table S3 compares the demographic characteristics of participants and non-participants.

Table 3 shows the prevalence of the pre-defined syndromes in study cohort. More than one in five of the cohort (198/977, 20.3%) had fixed (post-bronchodilator) airflow limitation consistent with a diagnosis of COPD. Among these, 41.9% (83/198) had associated peripheral blood eosinophilia. Only 2.7% of patients had reversible airflow limitation, consistent with asthma. Another 4.0% of participants exhibited airflow limitation on baseline spirometry but did not have short-acting beta-agonist (SABA) administered so reversibility could not be assessed.

Findings consistent with LRTI and tuberculosis accounted for 8.4% and 1.4% of patients, respectively. Patients who had none of the above syndromes but who fitted the criteria for upper respiratory tract infection (URTI) constituted 16.4% of the sample and further 48.1% of the cohort did not meet the criteria for any of the pre-defined syndromes.

Among the 977 participants, 56 (5.7%) met the criteria for two concurrent syndromes. Another 1 patient (0.1%) met the criteria for three syndromes concurrently. Figure 2 shows the numbers of patients with one or more of the syndromes. The most common combination of syndromes were (i) fixed airflow limitation without eosinophilia and a LRTI (11 patients), and (ii) fixed airflow limitation without eosinophilia and heart failure (10 patients).

The prevalence of fixed airflow limitation and heart failure increased with age (Table 4). By contrast, patients presenting with URTI and those whose symptoms could not be attributed to any pre-defined syndrome were more likely to be young people.

Table 2. Demographics of patients presenting to healthcare facilities with respiratory symptoms

	All participants (n=977)	Central/Provincial facilities (n=487)	District facilities (n=405)	Commune facilities (n=85)
Age, median (IQR)	59 (47 - 67)	57 (42 - 66)	60 (50 - 67)	61 (52 - 68)
Male gender, n (%)	643 (65.8)	333 (68.4)	250 (61.7)	60 (70.6)
Body Mass Index, median (IQR)*	21.7 (19.0 - 24.1)	20.8 (18.4 - 23.6)	22.4 (20.2 - 24.6)	21.7 (19.4 - 24.1)
Highest education level, n (%)†				
Primary	365 (38.6)	178 (38.5)	156 (39.0)	31 (36.9)
Secondary	480 (50.7)	224 (48.5)	208 (52.0)	48 (57.2)
University	92 (9.7)	54 (11.7)	33 (8.3)	5 (6.0)
Unknown/No answer	9 (1.0)	6 (1.3)	3 (0.8)	0 (0.0)
Comorbidity, n (%)†				
Heart disease	150 (15.9)	80 (17.3)	60 (15.0)	10 (11.9)
Hypertension	285 (30.1)	115 (24.9)	141 (35.3)	29 (34.5)
Diabetes	74 (7.8)	36 (7.8)	30 (7.5)	8 (9.5)
Asthma, asthmatic bronchitis, or allergic bronchitis	142 (15.0)	73 (15.8)	55 (13.8)	14 (16.7)
COPD	93 (9.8)	50 (10.8)	38 (9.5)	5 (6.0)
Chronic bronchitis	175 (18.5)	88 (19.1)	68 (17.0)	19 (22.6)
History of tuberculosis	119 (12.6)	63 (13.6)	41 (10.3)	7 (8.3)
Smoking history, n (%)†				
Male				
Current smoker	318 (51.2)	165 (52.1)	113 (46.1)	40 (67.8)
Ex-smoker	169 (27.2)	89 (28.1)	68 (27.8)	12 (20.3)
Never smoked	134 (21.6)	63 (19.9)	64 (26.1)	7 (11.9)
Female				

Current smoker	3 (0.9)	1 (0.7)	1 (0.7)	1 (4.0)
Ex-smoker	3 (0.9)	2 (1.4)	1 (0.7)	0 (0.0)
Never smoked	319 (98.1)	142 (97.9)	153 (98.7)	24 (96.0)
Geographic region, n (%)				
Northern Vietnam	568 (58.1)	321 (65.9)	205 (50.6)	42 (49.4)
Southern Vietnam	409 (41.9)	166 (34.1)	200 (49.4)	43 (50.6)

IQR: interquartile range; COPD: chronic obstructive pulmonary disease

*9 missing values

†31 paediatric patients less than 15 years old not asked

Table 3. The prevalence of the syndromic diagnoses, according to the study algorithm, among patients presenting to healthcare facilities with respiratory symptoms

Syndromic diagnosis	All health facilities (n=977)		Central/Provincial health facilities (n=487)		District health facilities (n=405)		Commune health facilities (n=85)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Fixed airflow limitation (COPD) without eosinophilia	115 (11.8)	9.8 - 13.8	55 (11.3)	8.5 - 14.1	46 (11.4)	8.3 - 14.5	14 (16.5)	8.6 - 24.4
Fixed airflow limitation (COPD) with eosinophilia	83 (8.5)	6.8 - 10.2	37 (7.6)	5.2 - 10.0	37 (9.1)	6.3 - 11.9	9 (10.6)	4.1 - 17.1
Reversible airflow limitation (asthma)	26 (2.7)	1.7 - 3.7	10 (2.1)	0.8 - 3.3	13 (3.2)	1.5 - 4.9	3 (3.5)	0.7 - 10.0
Other airflow limitation*	39 (4.0)	2.8 - 5.2	16 (3.3)	1.7 - 4.9	20 (4.9)	2.8 - 7.1	3 (3.5)	0.0 - 7.5
Lower respiratory tract infection	82 (8.4)	6.7 - 10.1	68 (14.0)	10.9 - 17.0	14 (3.5)	1.7 - 5.2	0 (0.0)	-
Tuberculosis	14 (1.4)	0.7 - 2.2	14 (2.9)	1.4 - 4.4	0 (0.0)	-	0 (0.0)	-
Heart failure	46 (4.7)	3.4 - 6.0	36 (7.4)	5.1 - 9.7	10 (2.5)	1.0 - 4.0	0 (0.0)	-
Upper respiratory tract infection (common cold)†	160 (16.4)	14.1 - 18.7	71 (14.6)	11.4 - 17.7	78 (19.3)	15.4 - 23.1	11 (12.9)	6.6 - 22.0
None of above syndromes†‡	470 (48.1)	45.0 - 51.2	220 (45.2)	40.8 - 49.6	203 (50.1)	45.3 - 55.0	47 (55.3)	44.7 - 65.9

COPD: chronic obstructive pulmonary disease

*Airflow limitation on initial spirometry without measure of post-bronchodilator spirometry

†Includes patients without chest X-ray, spirometry, or both

‡With none of the other syndromes

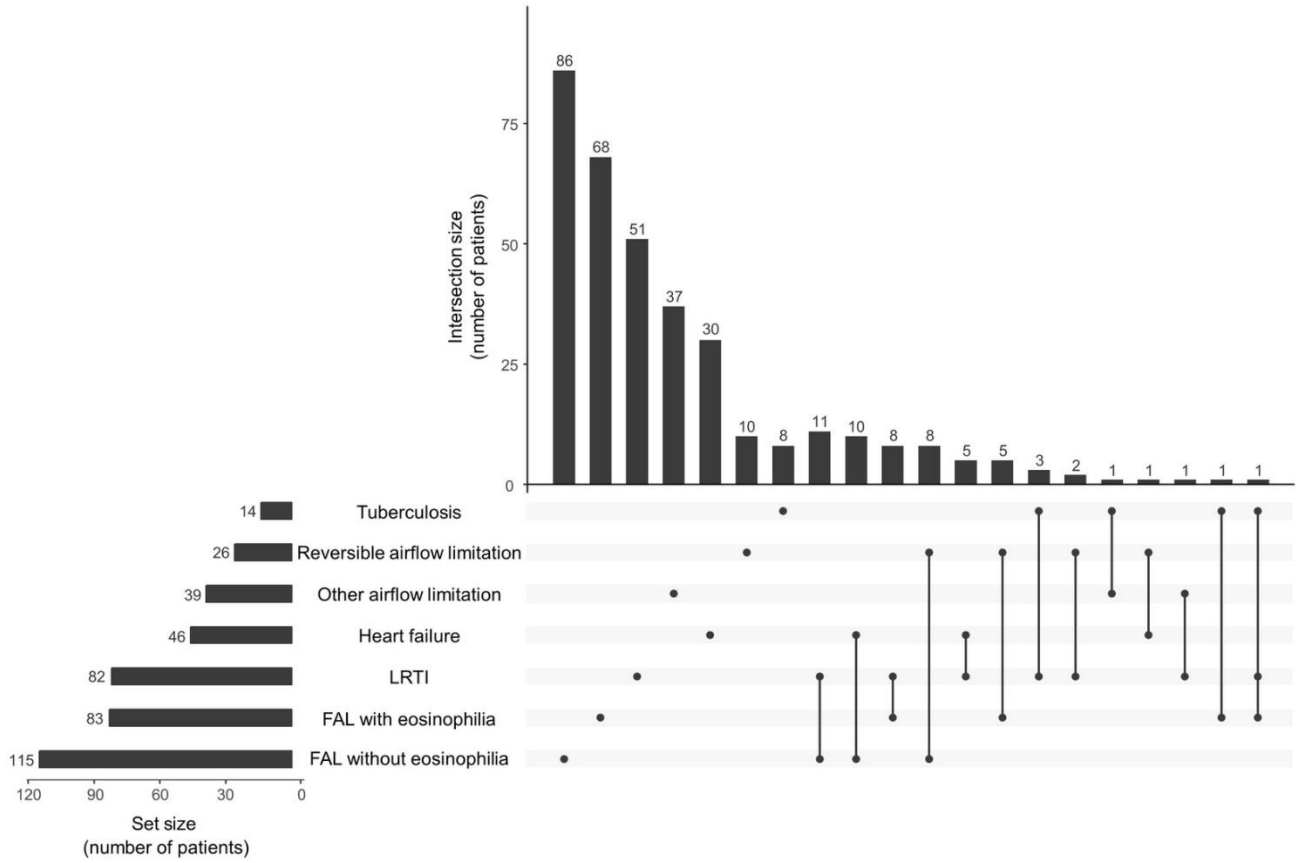

Figure 2. Overlap of syndromes among enrolled participants with respiratory symptoms.

The set size represents the number of patients with the syndrome next to it. The intersection size represents the number of patients with one (one dot) or more (connected dots) of the syndromes. For example, among 115 patients who had FAL without eosinophilia, 86 had this syndrome alone and 11 also had LRTI. LRTI, lower respiratory tract infection; FAL, fixed airflow limitation.

Table 4. Prevalence of syndromic diagnoses by age group

Syndromic diagnosis	Age 15 - 34 years (n=102)		Age 35 - 54 years (n=235)		Age 55 - 74 years (n=513)		Age >= 75 years (n=96)	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
Fixed airflow limitation (COPD) without eosinophilia	1 (1.0)	0 - 2.9	15 (6.4)	3.3 - 9.5	82 (16.0)	12.8 - 19.2	15 (15.6)	8.4 - 22.9
Fixed airflow limitation (COPD) with eosinophilia	1 (1.0)	0 - 2.9	14 (6.0)	2.9 - 9.0	53 (10.3)	7.7 - 13.0	15 (15.6)	8.4 - 22.9
Reversible airflow limitation (asthma)	3 (2.9)	0 - 6.2	5 (2.1)	0.3 - 4.0	15 (2.9)	1.5 - 4.4	2 (2.1)	0 - 4.9
Other airflow limitation*	8 (7.8)	2.6 - 13.1	9 (3.8)	1.4 - 6.3	18 (3.5)	1.9 - 5.1	2 (2.1)	0 - 4.9
Lower respiratory tract infection	13 (12.8)	6.3 - 19.2	10 (4.3)	1.7 - 6.8	48 (9.4)	6.8 - 11.9	10 (10.4)	5.1 - 18.3
Tuberculosis	4 (3.9)	0.2 - 7.7	4 (1.7)	0.1 - 3.4	6 (1.2)	0.2 - 2.1	0 (0.0)	-
Heart failure	0 (0.0)	-	8 (3.4)	1.1 - 5.7	29 (5.7)	3.7 - 7.7	9 (9.4)	3.5 - 15.2
Upper respiratory tract infection (common cold)†	25 (24.5)	16.2 - 32.9	52 (22.1)	16.8 - 27.4	61 (11.9)	9.1 - 14.7	9 (9.4)	3.5 - 15.2
None of above syndromes†‡	53 (52.0)	42.3 - 61.7	125 (53.2)	46.8 - 59.6	238 (46.4)	42.1 - 50.7	42 (43.8)	33.8 - 53.7

31 paediatric patients less than 15 years old not included; COPD: chronic obstructive pulmonary disease

*Airflow limitation on initial spirometry without measure of post-bronchodilator spirometry

†Includes patients without chest X-ray, spirometry, or both

‡With none of the other syndromes

Among 115 patients with fixed airflow limitation and no eosinophilia, only 34.8% were diagnosed with COPD by treating doctors (Table 5). Only one of 14 (7.1%) patients with fixed airflow limitation assessed at the commune health centres was correctly diagnosed with COPD. Overall, the agreement between the presence of fixed airflow limitation (with or without eosinophilia) and a clinician diagnosis of COPD was poor (Kappa = 0.31, 95% CI: 0.23 – 0.38). The agreement between the presence of reversible airflow limitation and a clinical diagnosis of asthma was even worse (Kappa = 0.16; 95% CI: 0.08 – 0.25). Agreement was also poor for the diagnoses of LRTI (Kappa = 0.32; 95% CI: 0.15 – 0.49), tuberculosis (Kappa = 0.06; 95% CI: -0.01 – 0.13), and heart failure (Kappa = 0.15; 95% CI: 0.02 – 0.28). Among 630 patients with URTI or none of the syndromes, 173 (27.5%) received at least one diagnostic label for a disease for which drug therapy would be indicated, including COPD, asthma, heart failure, pneumonia, and tuberculosis. The clinical diagnoses for the 129 patients with none of the syndromes who were given none of the relevant labels are provided in Supplementary Table S4.

Table 6 shows the proportions of patients with each syndrome who were prescribed medications during their attendance at the healthcare facilities. Less than half of patients with fixed airflow limitation were given long-acting bronchodilators (85/198, 42.9%) and a minority of patients with either reversible airflow obstruction or fixed airflow obstruction with eosinophilia were prescribed inhaled corticosteroids (30/109, 27.5%). No patients attending commune health centres were prescribed maintenance inhaled medicines and only one out 26 patients with fixed or reversible airflow limitation received a SABA inhaler. Table 6 also shows that antibiotics were prescribed to more than half of the patients, even among those with syndromes for which this treatment is unlikely to be beneficial, such as those with only common cold and patients with none of the defined syndromes. The proportion of patients prescribed an antibiotic was similar across all facilities.

Table 5. The relationship between study-defined respiratory syndromes and diagnoses given by treating doctors

A. All facilities		Diagnoses by healthcare workers							
Syndromic diagnosis	N	COPD n (%)	Asthma n (%)	Pneumonia n (%)	Tuberculosis n (%)	Heart failure n (%)	Bronchitis n (%)	Common cold n (%)	None of the labels n (%)
Fixed airflow limitation (COPD) without eosinophilia	115	**40 (34.8)**	19 (16.5)	17 (14.8)	3 (2.6)	0 (0.0)	33 (28.7)	9 (7.8)	16 (13.9)
Fixed airflow limitation (COPD) with eosinophilia	83	**39 (47.0)**	11 (13.3)	7 (8.4)	3 (3.6)	1 (1.2)	15 (18.7)	4 (4.8)	15 (18.1)
Reversible airflow limitation (asthma)	26	5 (19.2)	**6 (23.1)**	2 (7.7)	0 (0.0)	2 (7.7)	7 (26.9)	5 (19.2)	5 (19.2)
Other airflow limitation*	39	3 (7.7)	7 (18.0)	2 (5.1)	0 (0.0)	0 (0.0)	16 (41.0)	7 (18.0)	10 (25.6)
Lower respiratory tract infection	82	20 (24.4)	2 (2.4)	**23 (28.1)**	12 (14.6)	3 (3.7)	16 (19.5)	2 (2.4)	20 (24.4)
Tuberculosis	14	1 (7.1)	0 (0.0)	5 (35.7)	**8 (57.1)**	0 (0.0)	1 (7.1)	0 (0.0)	3 (21.4)
Heart failure	46	14 (30.4)	7 (15.2)	11 (23.9)	3 (6.5)	**5 (10.9)**	12 (26.1)	4 (8.7)	5 (10.9)
Upper respiratory tract infection (common cold)†	160	12 (7.5)	13 (8.1)	7 (4.4)	5 (3.1)	1 (0.6)	56 (35.0)	**57 (35.6)**	27 (16.9)
None of above syndromes†‡	470	50 (10.6)	40 (8.5)	46 (9.8)	10 (2.1)	3 (0.6)	163 (34.7)	65 (13.8)	**129 (27.5)**

B. Central/provincial health facilities		Diagnoses by healthcare workers							
Syndromic diagnosis	N	COPD n (%)	Asthma n (%)	Pneumonia n (%)	Tuberculosis n (%)	Heart failure n (%)	Bronchitis n (%)	Common cold n (%)	None of the labels n (%)
Fixed airflow limitation (COPD) without eosinophilia	55	**21 (38.2)**	12 (21.8)	7 (12.7)	2 (3.6)	0 (0.0)	17 (30.9)	2 (3.6)	6 (10.0)
Fixed airflow limitation (COPD) with eosinophilia	37	**23 (62.2)**	3 (8.1)	5 (13.5)	3 (8.1)	0 (0.0)	3 (8.1)	0 (0.0)	7 (18.9)

Reversible airflow limitation (asthma)	10	2 (20.0)	**2 (20.0)**	1 (10.0)	0 (0.0)	2 (20.0)	2 (20.0)	3 (30.0)	1 (10.0)
Other airflow limitation*	16	0 (0.0)	6 (37.5)	1 (6.3)	0 (0.0)	0 (0.0)	4 (25.0)	2 (12.5)	6 (37.5)
Lower respiratory tract infection	68	19 (27.9)	1 (1.5)	**21 (30.9)**	11 (16.2)	3 (4.4)	9 (13.2)	1 (1.5)	18 (26.5)
Tuberculosis	14	1 (7.1)	0 (0.0)	5 (35.7)	**8 (57.1)**	0 (0.0)	1 (7.1)	0 (0.0)	3 (21.4)
Heart failure	36	13 (36.1)	6 (16.7)	11 (30.6)	3 (8.3)	**4 (11.1)**	6 (16.7)	0 (0.0)	4 (11.1)
Upper respiratory tract infection (common cold)†	71	9 (12.7)	10 (14.1)	2 (2.8)	5 (7.0)	1 (1.4)	20 (28.2)	**16 (22.5)**	15 (21.1)
None of above syndromes†‡	220	33 (15.0)	33 (15.0)	31 (14.1)	10 (4.6)	2 (0.9)	51 (23.2)	16 (7.3)	**62 (28.2)**
C. District health facilities		Diagnoses by healthcare workers							
		COPD	Asthma	Pneumonia	Tuberculosis	Heart failure	Bronchitis	Common cold	None of the labels
Syndromic diagnosis	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fixed airflow limitation (COPD) without eosinophilia	46	**18 (39.1)**	7 (15.2)	6 (13.0)	1 (2.2)	0 (0.0)	14 (30.4)	6 (13.0)	4 (8.7)
Fixed airflow limitation (COPD) with eosinophilia	37	**16 (43.2)**	8 (21.6)	1 (2.7)	0 (0.0)	1 (2.7)	9 (24.3)	4 (10.8)	3 (8.1)
Reversible airflow limitation (asthma)	13	3 (23.1)	**4 (30.8)**	1 (7.7)	0 (0.0)	0 (0.0)	5 (38.5)	2 (15.4)	1 (7.7)
Other airflow limitation*	20	3 (15.0)	1 (5.0)	1 (5.0)	0 (0.0)	0 (0.0)	11 (55.0)	5 (25.0)	2 (20.0)
Lower respiratory tract infection	14	1 (7.1)	1 (7.1)	**2 (14.3)**	1 (7.1)	0 (0.0)	7 (50.0)	1 (7.1)	2 (14.3)
Tuberculosis	0	-	-	-	**-**	-	-	-	-
Heart failure	10	1 (10)	1 (10)	0 (0.0)	0 (0.0)	**1 (10)**	6 (60)	4 (40)	1 (10.0)
Upper respiratory tract infection (common cold)†	78	3 (3.9)	3 (3.9)	4 (5.1)	0 (0.0)	0 (0.0)	32 (41.0)	**38 (48.7)**	9 (11.5)
None of above syndromes†‡	203	17 (8.4)	6 (3.0)	10 (4.9)	0 (0.0)	1 (0.5)	96 (47.3)	38 (18.7)	**49 (24.1)**
D. Commune health facilities		Diagnoses by healthcare workers							
		COPD	Asthma	Pneumonia	Tuberculosis	Heart failure	Bronchitis	Common	None of

Syndromic diagnosis	N							cold	the labels
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fixed airflow limitation (COPD) without eosinophilia	14	**1 (7.1)**	0 (0.0)	4 (28.6)	0 (0.0)	0 (0.0)	2 (14.3)	1 (7.1)	6 (42.9)
Fixed airflow limitation (COPD) with eosinophilia	9	**0 (0.0)**	0 (0.0)	1 (11.1)	0 (0.0)	0 (0.0)	3 (33.3)	0 (0.0)	5 (55.6)
Reversible airflow limitation (asthma)	3	0 (0.0)	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (100.0)
Other airflow limitation*	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	2 (66.7)
Lower respiratory tract infection	0	-	-	**-**	-	-	-	-	-
Tuberculosis	0	-	-	-	**-**	-	-	-	-
Heart failure	0	-	-	-	-	**-**	-	-	-
Upper respiratory tract infection (common cold)†	11	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	4 (36.4)	**3 (27.3)**	3 (27.3)
None of above syndromes†‡	47	0 (0.0)	1 (2.1)	5 (10.6)	0 (0.0)	0 (0.0)	16 (34.0)	11 (23.4)	**18 (38.3)**

COPD: chronic obstructive pulmonary disease

Bolded text indicates patients in whom the syndromic diagnosis and healthcare worker diagnosis were in agreement

*Airflow limitation on initial spirometry without measure of post-bronchodilator spirometry

†Includes patients without chest X-ray, spirometry, or both

‡With none of the other syndromes

Table 6. Treatment provided to patients with the syndromic diagnoses

A. All facilities Syndromic diagnosis	N	Systemic corticosteroids n (%)	Inhaled corticosteroids n (%)	Long-acting bronchodilators n (%)	Short-acting beta-agonist n (%)	Antibiotics n (%)	Anti-tuberculosis n (%)	Diuretics n (%)
Fixed airflow limitation (COPD) without eosinophilia	115	47 (40.9)	30 (26.1)	48 (41.8)	17 (14.8)	75 (6.2)	0 (0.0)	5 (4.4)
Fixed airflow limitation (COPD) with eosinophilia	83	29 (34.9)	25 (30.1)	37 (44.6)	10 (12.1)	44 (53.0)	2 (2.4)	5 (6.0)
Reversible airflow limitation (asthma)	26	8 (30.8)	5 (19.2)	7 (26.9)	1 (3.9)	16 (61.5)	0 (0.0)	3 (11.5)
Other airflow limitation*	39	7 (18.0)	7 (18.0)	8 (20.5)	2 (5.1)	20 (51.3)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	82	31 (37.8)	19 (23.2)	23 (28.1)	1 (1.2)	52 (63.4)	1 (1.22)	7 (8.5)
Tuberculosis	14	1 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)	6 (42.9)	3 (21.4)	0 (0.0)
Heart failure	46	21 (45.7)	11 (23.9)	15 (32.6)	7 (15.2)	32 (70.0)	0 (0.0)	12 (26.1)
Upper respiratory tract infection (common cold)†	160	50 (31.3)	18 (11.3)	28 (17.5)	8 (5.0)	104 (65.0)	2 (1.3)	0 (0.0)
None of above syndromes†‡	470	113 (24.0)	62 (13.2)	91 (19.4)	24 (5.1)	271 (57.7)	4 (0.9)	21 (4.5)
Overall	977	283 (29.0)	161 (16.5)	235 (24.1)	66 (6.8)	586 (60.0)	10 (1.0)	49 (5.0)

B. Central/provincial health facilities Syndromic diagnosis	N	Systemic corticosteroids n (%)	Inhaled corticosteroids n (%)	Long-acting bronchodilators n (%)	Short-acting beta-agonist n (%)	Antibiotics n (%)	Anti-tuberculosis n (%)	Diuretics n (%)
Fixed airflow limitation (COPD) without eosinophilia	55	28 (50.9)	24 (43.6)	26 (47.3)	6 (10.9)	37 (67.3)	0 (0.0)	3 (5.5)
Fixed airflow limitation (COPD) with	37	18 (48.7)	18 (48.7)	18 (48.7)	5 (13.5)	20 (54.1)	1 (2.7)	2 (5.4)

eosinophilia								
Reversible airflow limitation (asthma)	10	4 (40.0)	2 (20.0)	2 (20.0)	0 (0.0)	7 (70.0)	0 (0.0)	3 (30.0)
Other airflow limitation*	16	2 (12.5)	6 (37.5)	5 (31.3)	1 (6.3)	7 (43.8)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	68	26 (38.2)	18 (26.5)	20 (29.4)	1 (1.5)	41 (60.3)	1 (1.5)	5 (7.4)
Tuberculosis	14	1 (7.1)	1 (7.1)	0 (0.0)	0 (0.0)	6 (42.9)	3 (21.4)	0 (0.0)
Heart failure	36	16 (44.4)	10 (27.8)	14 (38.9)	6 (16.7)	24 (66.7)	0 (0.0)	11 (30.6)
Upper respiratory tract infection (common cold)†	71	23 (32.4)	14 (19.7)	17 (23.9)	6 (8.5)	42 (59.2)	2 (2.8)	0 (0.0)
None of above syndromes†‡	220	51 (23.2)	54 (24.6)	58 (26.4)	20 (9.1)	121 (55.0)	3 (1.4)	13 (5.9)
Overall	487	151 (31.0)	134 (27.5)	145 (29.8)	41 (8.4)	283 (58.1)	8 (1.6)	33 (6.8)
C. District health facilities		Systemic corticosteroids	Inhaled corticosteroids	Long-acting bronchodilators	Short-acting beta-agonist	Antibiotics	Anti-tuberculosis	Diuretics
Syndromic diagnosis	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fixed airflow limitation (COPD) without eosinophilia	46	14 (30.4)	6 (13.0)	22 (47.8)	10 (21.7)	27 (58.7)	0 (0.0)	2 (4.4)
Fixed airflow limitation (COPD) with eosinophilia	37	11 (29.7)	7 (18.9)	19 (51.4)	5 (13.5)	19 (51.4)	0 (0.0)	3 (8.1)
Reversible airflow limitation (asthma)	13	4 (30.8)	3 (23.1)	5 (38.5)	1 (7.7)	9 (69.2)	0 (0.0)	0 (0.0)
Other airflow limitation*	20	4 (20.0)	1 (5.0)	3 (15.0)	1 (5.0)	11 (55.0)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	14	5 (35.7)	1 (7.1)	3 (21.4)	0 (0.0)	11 (78.6)	0 (0.0)	2 (14.3)
Tuberculosis	0	-	-	-	-	-	-	-
Heart failure	10	5 (50.0)	1 (10.0)	1 (10.0)	1 (10.0)	8 (80.0)	0 (0.0)	1 (10.0)
Upper respiratory tract infection (common cold)†	78	25 (32.1)	4 (5.1)	11 (14.1)	1 (1.3)	55 (70.5)	0 (0.0)	0 (0.0)

None of above syndromes[†‡]	203	48 (23.7)	8 (3.9)	33 (16.3)	4 (2.0)	120 (59.1)	1 (0.5)	8 (3.9)
Overall	405	110 (27.2)	27 (6.7)	90 (22.2)	23 (5.7)	248 (61.2)	1 (0.3)	16 (4.0)

D. Commune health facilities		Systemic corticosteroids	Inhaled corticosteroids	Long-acting bronchodilators	Short-acting beta-agonist	Antibiotics	Anti-tuberculosis	Diuretics
Syndromic diagnosis	N	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Fixed airflow limitation (COPD) without eosinophilia	14	5 (35.7)	0 (0.0)	0 (0.0)	1 (7.1)	11 (78.6)	0 (0.0)	0 (0.0)
Fixed airflow limitation (COPD) with eosinophilia	9	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (55.6)	1 (11.1)	()
Reversible airflow limitation (asthma)	3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other airflow limitation[*]	3	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (66.7)	0 (0.0)	0 (0.0)
Lower respiratory tract infection	0	-	-	-	-	-	-	-
Tuberculosis	0	-	-	-	-	-	-	-
Heart failure	0	-	-	-	-	-	-	-
Upper respiratory tract infection (common cold)[†]	11	2 (18.2)	0 (0.0)	0 (0.0)	1 (9.1)	7 (63.6)	0 (0.0)	0 (0.0)
None of above syndromes[†‡]	47	14 (29.8)	0 (0.0)	0 (0.0)	0 (0.0)	30 (63.8)	0 (0.0)	0 (0.0)
Overall	85	22 (25.9)	0 (0.0)	0 (0.0)	2 (2.4)	55 (64.7)	1 (1.2)	0 (0.0)

COPD: chronic obstructive pulmonary disease

[*]Airflow limitation on initial spirometry without measure of post-bronchodilator spirometry

[†]Includes patients without chest X-ray, spirometry, or both

[‡]With none of the other syndromes

Discussion

In the study we applied a syndromic approach to assess the diagnosis and treatment provided across all levels of the Vietnamese healthcare system. We showed that many people presenting to health facilities with respiratory symptoms had either no defined respiratory syndrome or had only URTI. Furthermore, those who did have well-defined syndromes, such as fixed or reversible airflow limitation, a LRTI, tuberculosis or heart failure were often not diagnosed with the condition at the facility. The use of specific therapies, such as inhaled medicines and antibiotics, were poorly correlated with the presence of the relevant syndrome.

The agreement between the syndromic diagnosis we made based on a simple, standardised assessment and the diagnostic label applied by the attending clinicians was poor. This highlights the importance of utilising simple tests, particularly spirometry, to facilitate accurate diagnosis at all levels of the health system.

The benefit of applying a standardised diagnostic approach extends from diagnosing disease to appropriate prescription of treatment. The proportion of patients with fixed airflow limitation given inhaled long-acting bronchodilators and the proportion of patients with reversible airflow limitation given inhaled corticosteroids were both low. This is consistent with a recent cross-sectional survey which revealed a low level of knowledge and implementation of the GINA guidelines 2015 among primary care physicians in Vietnam [16]. Using spirometry to obtain evidence of airflow obstruction would more likely result in the appropriate targeted pharmacotherapy being given to patients [38].

In contrast to the underuse of inhaled medicines, inappropriate prescription of antibiotics and systemic corticosteroids occurred at all levels of facilities. We found a substantial proportion of patients with a URTI, or with no defined respiratory syndrome, were provided with antibiotics. The use of systemic corticosteroids might be justified by the presence of exacerbation of COPD or asthma in some patients. However, the proportion of patients given corticosteroids was high even among patients without evidence of airflow limitation.

Our findings give rise to important questions that can be addressed by future studies. The findings of poor correlation between pre-defined syndromes and the diagnosis and treatment applied by the treating doctors, indicate that implementing a syndromic approach may improve patient care. The syndromic approach is of the most value where the capacity to implement a complex diagnostic algorithm is limited, such as within community health facilities. An optimal syndromic pathway to diagnosis and management must also balance the needs and capacity of the local system in each setting. Secondly, given the difficulties in obtaining inhaled medicines and maintaining follow-up for chronic respiratory diseases in resource-limited settings, tailored pragmatic interventions coupling with the syndromic approach need to be considered. Following the introduction of an intervention, the approach can also be used to evaluate the impact of the intervention.

This approach provides a simple assessment of burden of respiratory diseases and will ensure an acceptable quality of patient care, while allowing for health-system barriers to diagnosis and treatment decisions. The approach can be adapted for other LMICs. Further studies are necessary to demonstrate the benefits of applying such approaches in different clinical settings.

This study has a number of strengths. We enrolled a randomly selected representative sample of patients at all four levels of health facilities in four provinces of Vietnam. This allows us to generalise our findings to urban and rural settings across Vietnam. Secondly, we defined the syndromes independently of the treating clinicians using a simple, standardised algorithmic approach. This allowed us to evaluate the diagnostic decision-making and evaluate the appropriateness of treatment against objective criteria.

There were several limitations. First, diagnostic tests, such as spirometry and chest X-ray were not available for all participants. A minority of patients did not have a spirometry result of acceptable quality. For these patients a definite syndromic diagnosis could not be made. Second, some patients with asthma may had a normal spirometry result and a negative bronchodilator response upon presentation. This may explain the low prevalence of asthma observed in our study. Finally, the study sample may slightly under-represent the proportion of patients attending commune level facilities, in comparison to higher level facilities [39].

In conclusion, this study identified a substantial discordance between standardised syndromic diagnoses of respiratory disease and the diagnoses reached within the health system in Vietnam. Increased access to spirometry, and possibly other objective measures including radiology and biomarkers, may assist in the implementation of locally-relevant syndromic approaches to management. This would be an important element of strategies for reducing the burden of chronic lung disease in resource-limited settings.

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Chapter 4. Smoking behaviours among patients seeking healthcare

Preface

This chapter contains the unaltered full text of the following published article:

> Huang WC, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Freeman B, Jan S, Negin J, Marks GB, Fox GJ. Smoking behaviour among adult patients presenting to health facilities in four provinces of Vietnam. BMC public health. 2021;21(1):845. Epub 2021/05/03. doi: 10.1186/s12889-021-10880-z.

Appendix 2.3 of this thesis contains the supplementary appendix for this article. WCH formulated the research questions, conducted the data analysis, and wrote the manuscript.

Contribution of this chapter to the thesis

This chapter addresses the second research objective of the thesis. I used data from the VCAPS1 study to show the prevalence of smoking and related behaviours among patients seeking healthcare to all four levels of the Vietnamese healthcare system.

Background

Tobacco smoking remains the leading preventable risk factor for chronic disease and premature death in both developed and developing countries [1]. Reducing the prevalence of smoking is a high priority in global health [2].

Evidence-based strategies have been shown to reduce smoking prevalence in many settings. The MPOWER framework [3], endorsed by the World Health Organization (WHO), is a package intended to assist implementation of effective interventions. The O refers to offering help to quit tobacco use, such as quit advice from health professionals, cessation medications, and quit lines.

Health facilities provide a setting in which smokers may be amenable to smoking cessation efforts, as they often present with symptoms caused by smoking-related health conditions. Smoking cessation interventions are effective when tailored to patients in various healthcare settings, such as primary care, emergency room, and inpatient department [4]. The WHO, which coordinates the implementation of the Framework Convention on Tobacco Control, has also highlighted the importance of smoking cessation efforts in health care settings [5,6].

Despite wide recognition of effectiveness and the promulgation of government policies, there is limited implementation of cessation programmes in many healthcare settings [7-10]. In Vietnam, the government enacted a comprehensive Law on Prevention and Control of Tobacco Harms in 2012. This was followed by the Vietnamese government's Directive 05/CT-

BYT that reinforces the delivery of cessation services within facilities at all levels of the healthcare system. However, there is little evidence about the extent to which smokers receive support to quit smoking during routine attendance at healthcare facilities.

A 2015 population-based survey found current smoking prevalence of 45.3% among males and 1.1% among females in Vietnam [11]. More than half of current smokers surveyed were considering quitting. The majority of those who attempted to quit in the past 12 months did not seek assistance. The prevalence of smoking among patients attending healthcare facilities, their preparedness to quit, and their access to effective smoking cessation interventions have not been well-characterised.

This study aimed to evaluate the behaviours related to smoking among patients seeking healthcare, including prevalence of smoking and past quit attempts. It also aimed to determine the attitudes towards quitting smoking among patients who were smokers.

Methods

Design and study setting

We performed a cross-sectional survey within 46 government health facilities selected from four Provinces of Vietnam. This Southeast Asian country is a middle-income country with a population of 96 million people. The public healthcare system is organised into four levels: central (national) hospitals, provincial hospitals, district hospitals and commune health centres. This study was undertaken in four of Vietnam's 63 provinces, including two in the

north of Vietnam (the capital, Hanoi, and Thanh Hoa Province) and two in the south (Ho Chi Minh City and Ca Mau Province). Participants were recruited from health facilities at all four levels of the health system in each province.

Sampling of study sites

Major central and provincial hospitals in each province were included. In addition, four district hospitals were randomly selected in each province. Within each selected district, two commune health centres were also selected by random sampling. The probability of each facility being chosen was proportional to the populations of the districts and communes within which the health facilities were located. Within each central and provincial hospital, one department was selected by convenience sampling from among the wards or clinics in which patients with respiratory diseases were managed, or smokers were routinely assessed. At district hospitals, patients were recruited on outpatient clinics.

Selection of study participants

Eligible patients were aged 15 years and over attending selected study sites. Patients were ineligible if they were unable to complete the survey due to substantial communication difficulties, lived in another province, or were known to be pregnant.

Study participants were selected at random from among the following groups of patients attending the selected healthcare facilities: (i) Consecutively presenting outpatients presenting with any medical condition (with a sampling fraction determined based upon the

recruitment capacity of study staff) ; (ii) Consecutively presenting outpatients with one or more respiratory symptoms (dyspnoea, cough, wheezing, and/or chest tightness); and (iii) Inpatients with any medical condition at participating hospitals on the day of the survey. The age and gender of patients in each group were recorded in a registration book. From among patients listed in the registration book, a random sample was selected and invited to participate in the study.

All eligible participants selected to be included in the study were asked to give written informed consent. In order to assess potential selection bias, patients who declined to complete the full survey were asked to provide verbal consent and complete a “minimal data questionnaire” that included their age and gender.

Questionnaire

Data collected for the full survey included age, gender, body weight, height, current and past smoking behaviours, current tobacco products, history of advice to quit smoking from healthcare providers, quit attempts in the last 12 months, smoking cessation services used in the last 12 months, and preparedness to stop smoking. Other details that were collected included past medical history, comorbidities, the highest level of educational attainment and current occupation. The questionnaire was developed based on published questionnaires [12,13].

Statistical methods

The prevalence of smoking and associated 95% confidence intervals were calculated from the proportion of all enumerated individuals presenting to health facilities who reported smoking within the preceding 30 days. Multiple imputation was used to impute missing values for smoking status, using age and gender as the observed data [14]. We separated males and females in the analysis of smoking prevalence, because the Global Adult Tobacco Survey (GATS) 2015 showed a significant disparity in the prevalence of smoking among males and females in the general population [11]. The standardised prevalence ratio was determined by comparing the differences in smoking rate among the study population and the general population, based upon population estimates from the GATS [11]. The confidence limits for the standardised prevalence ratio were obtained by bootstrapping. Comparisons were undertaken using chi-square test for categorical variables and analysis of variance for continuous variables. Analyses were conducted using SAS® (v9.4, SAS Institute, Cary Corp. NC. USA).

Ethical issues

Ethical approval was provided by the Human Research Ethics Committee of the University of Sydney (2017/511), and the Institutional Review Board of the Bach Mai Hospital, Hanoi, Vietnam. Participants aged 18 and over provided written informed consent. Adolescents between 15 and 18 year of age provided verbal assent, and their parents provided written informed consent.

Results

Prevalence of smoking

Study participants were recruited between September 2017 and October 2018. Table 1 shows the prevalence of smoking by gender, age groups and levels of facility. Among 11,245 enumerated patients who visited health facilities during the observation period, the prevalence of current smoking was 18.6% (95% CI: 17.8% – 19.4%) overall, and 34.6% (95% CI: 33.2% – 36.0%) among men and 1.1% (95% CI: 0.8% – 1.3%) among women. Male patients aged 25 to 64 years were more likely to smoke than those younger than 25 years or older than 65 years. The prevalence among male patients visiting commune health centres (42.2%, CI: 36.7 – 47.7%), and district hospitals (39.3%, CI: 37.1 – 41.4%) was higher than that among patients visiting central/provincial hospitals (31.0%, CI: 29.2 – 32.8%). The prevalence among female patients was higher at commune health centres (4.4%, CI: 1.9 – 6.9) when compared to central/provincial hospitals (0.8%, CI: 0.5 – 1.2) and district hospitals (0.9%, CI: 0.5 – 1.3).

Table 1. Proportion of current smoking among patients presenting to health facilities, by age, sex and health system level

		All facilities (46 facilities) N = 9,700				Central/provincial hospital (8 facilities) N = 4,890				District hospital (16 facilities) N = 4,287				Commune health centre (22 facilities) N = 523			
		Male N = 4,620		Female N = 5080		Male N = 2,373		Female N = 2,517		Male N = 1,956		Female N = 2,331		Male N = 291		Female N = 232	
		n/N	% (95% CI)*	n/N	% (95% CI)*	n/N	% (95% CI)*	n/N	% (95% CI)*	n/N	% (95% CI)*	n/N	% (95% CI)*	n/N	% (95% CI)*	n/N	% (95% CI)*
All age		1,595/4,620	34.6 (33.2 – 36.0)	53/5,080	1.1 (0.8 – 1.3)	699/2373	31.0 (29.2 – 32.8)	21/2517	0.8 (0.5 – 1.2)	771/1,956	39.3 (37.1 – 41.4)	20/2331	0.9 (0.5 – 1.3)	125/291	42.2 (36.7 – 47.7)	12/232	4.4 (1.9 – 6.9)
Age group (years)	**15-24**	51/250	24.0 (18.3 – 29.6)	3/319	1.0 (-0.1 – 2.1)	17/119	20.2 (12.3 – 28.1)	0/145	0	27/115	25.8 (17.6 – 34.0)	1/154	0.8 (-0.7 – 2.2)	7/16	43.1 (18.3 – 67.8)	2/20	9.1 (-)†
	25-34	170/428	40.2 (35.8 – 44.7)	8/580	1.4 (0.5 – 2.4)	82/213	39.4 (33.3 – 45.5)	4/283	1.4 (0 – 2.8)	78/184	42.7 (35.6 – 49.7)	2/244	1.0 (-0.3 – 2.3)	10/31	32.8 (16.7 – 48.9)	2/53	3.6 (-1.3 – 8.4)
	35-44	186/489	38.1 (33.8 – 42.4)	11/622	1.8 (0.7 – 2.8)	95/238	39.4 (33.5 – 45.4)	4/305	1.3 (-)†	79/201	39.1 (32.4 – 45.9)	6/293	2.0 (0.4 – 3.6)	12/50	24.9 (12.8 – 37.0)	1/24	3.5 (-3.3 – 10.4)
	45-54	322/765	40.4 (37.0 – 43.9)	12/838	1.4 (0.6 – 2.2)	137/380	35.6 (31.1 – 40.1)	3/411	0.7 (-0.1 – 1.6)	160/339	45.9 (40.6 – 51.3)	6/389	1.5 (0.3 – 2.7)	25/46	51.4 (37.5 – 65.3)	3/38	6.4 (-0.6 – 13.5)
	55-64	495/1,203	39.6 (37.0 – 42.2)	8/1,218	0.7 (0.2 – 1.1)	206/586	34.7 (31.0 – 38.3)	5/552	0.9 (0.1 – 1.7)	253/553	45.3 (41.2 – 49.4)	3/618	0.5 (-0.1 – 1.1)	36/64	54.4 (42.3 – 66.5)	0/48	1.8 (-1.8 – 5.5)
	65+	371/1,486	26.1 (24.0 – 28.3)	11/1,503	0.7 (0.3 – 1.2)	162/837	22.5 (19.8 – 25.2)	5/821	0.6 (0.1 – 1.1)	174/564	30.1 (27.1 – 34.9)	2/633	0.4 (-0.1 – 0.9)	35/84	40.7 (30.4 – 51.0)	4/49	7.0 (0.4 – 13.6)

*Pooled proportions. Missing values for smoking status were estimated for 1,544 individuals using multiple imputation, with 95% confidence limits calculated based upon imputed values.

†Between-imputation variance is zero

The standardised prevalence ratio of smoking among the population in the healthcare facilities was 0.80 (95% CI: 0.74 – 0.87) when compared with an age-matched sample from the general population reported in the GATS in 2015 [11]. When compared to a gender-matched sample from the GATS 2015, the prevalence of smoking was also lower in the healthcare facility sample – the prevalence ratio of current smoking was 0.77 (95% CI: 0.73 – 0.81).

Selection and demographics of participants

Figure 1 shows a flowchart of participant selection. A random sample of current smokers (1,044 out of 1,434 smokers) was selected to complete the full survey. Among these smokers, 748 (71.6%) completed the full survey. Among 623 participants who had respiratory symptoms but did not smoke, 170 were former smokers and 22 of them quit smoking within the past 12 months.

The majority (99.3%) of the 748 current smokers who completed the full survey were men. The median age was 57 years (interquartile range: 46 - 65). Approximately one in three (32.2%) current smokers lived with another smokers. In Additional file 1, Supplementary Table S1 shows the demographic characteristics of the 748 current smokers who completed the full survey. Supplementary Tables S2 and S3 compare the demographic characteristics of participants and non-participants who were current smokers. Supplementary Table S4 shows tobacco products used by the 748 current smokers.

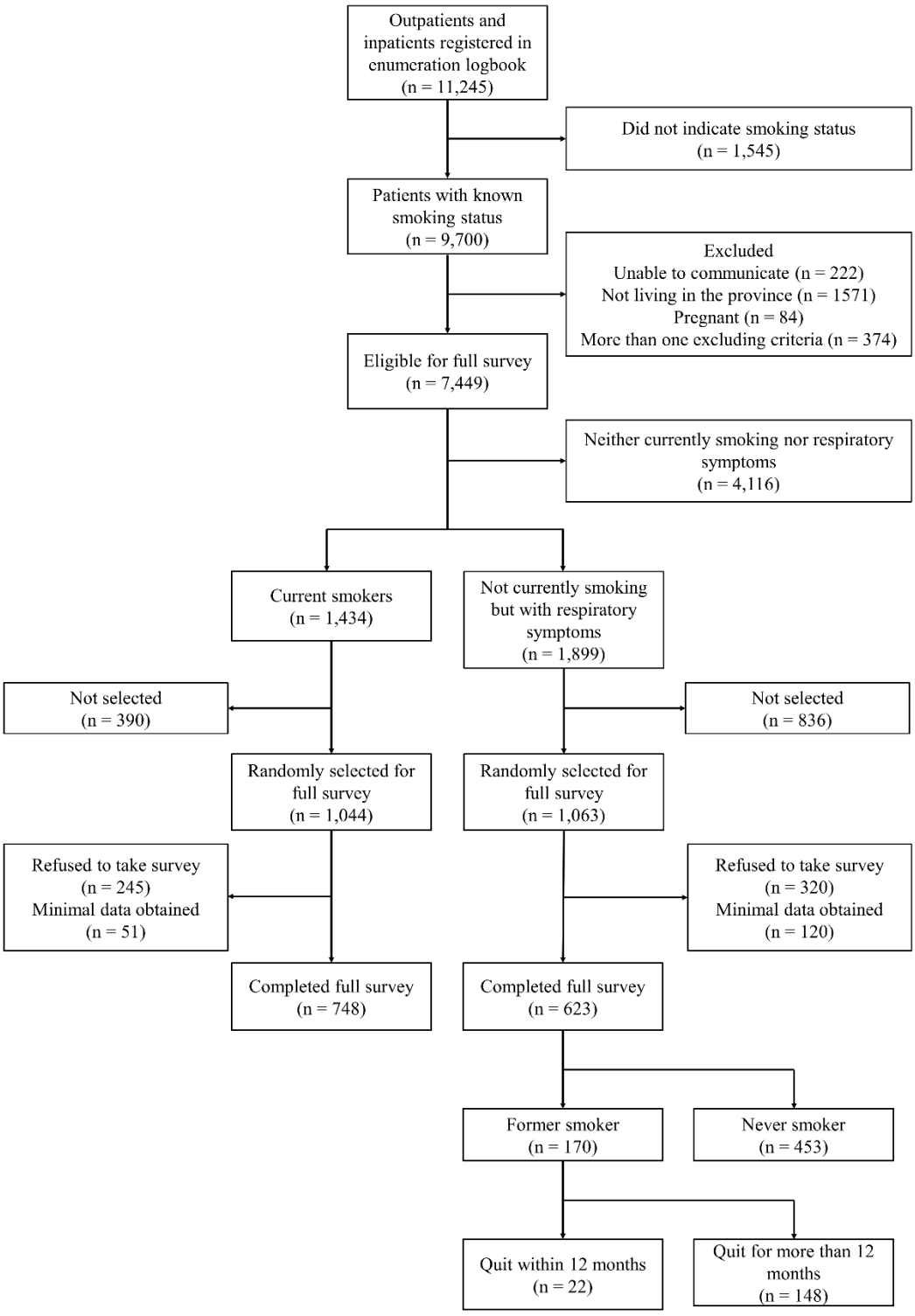

Figure 1. Consort diagram of participant recruitment

Smoking cessation attempts

Among 748 current smokers who completed the full survey, 254 (34%) reported having been asked if they smoked tobacco by a healthcare provider in the last 12 months, 494 (66%) reported having not been asked. During this time, 260 (34.8%) current smokers had tried to quit. Among the 254 patients who had been asked about smoking by a healthcare provider, 229 (90.2%) had been advised to quit by a healthcare provider and 103 (40.6%) had tried to stop smoking in the previous 12 months. Among the 494 patients who have not been asked about their smoking habits, 157 (31.8%) patients had tried to quit in the previous 12 months. Compared to current smokers who had not asked about smoking by a healthcare provider, those who had been asked had a higher chance of attempting to quit (40.6% vs 31.8%, p = 0.017).

Table 2 shows the proportion of participants who had used smoking cessation interventions among those who had tried to quit in the previous 12 months: including the 260 current smokers and 22 ex-smokers who had successfully quit within the past 12 months. The majority who had made quit attempts had done so without using any form of cessation assistance. Counselling had been used by 5 (1.9%) current smokers and nicotine replacement therapy had been used by 26 (10%) current smokers. Prescription medicines other than nicotine replacement therapy, traditional medicines, quit line, and smokeless tobacco had been used by less than 1% of current smokers. Among the 22 patients who successfully quit in the previous 12 months, only one reported having received counselling.

Table 2. Reported use of smoking cessation interventions among patients completing full survey who attempted to quit in the prior 12 months

	Currently smoking n = 260	Not currently smoking n = 22	Total n = 282
Method of smoking cessation used in past 12 months (n, %)*			
Smoking cessation counselling	5 (1.9)	1 (4.5)	6 (2.1)
Nicotine replacement therapy	26 (10.0)	0 (0)	26 (9.2)
Other prescription medications (e.g. varenicline)	2 (0.8)	0 (0)	2 (0.7)
Traditional medicines	1 (0.4)	0 (0)	1 (0.4)
A quit line or a telephone support line	1 (0.4)	0 (0)	1 (0.4)
Use of smokeless tobacco	1 (0.4)	0 (0)	1 (0.4)
None of above methods used (n, %)	230 (88.5)	21 (95.5)	251 (89.0)

*Patients may have used more than one method.

Table 3. Preparedness to quit smoking among current smokers completing full survey, by health system level*

	All facilities (46 facilities) n = 632	Central/provincial hospital (8 facilities) n = 234	District hospital (16 facilities) n = 344	Commune health centre (12 facilities) n = 54
Plans to quit within the next month (n, %)	116 (18.4%)	71 (30.3%)	39 (11.3%)	6 (11.1%)
Plans to quit within the next 12 months (n, %)	66 (10.4%)	28 (12.0%)	32 (9.3%)	6 (11.1%)
Plans to quit someday, but not next 12 months (n, %)	172 (27.2%)	45 (19.2%)	114 (33.1%)	13 (24.1%)
Not currently interested in quitting (n, %)	250 (39.6%)	78 (33.3%)	147 (42.7%)	25 (46.3%)
Unknown/refused to answer (n, %)	28 (4.5%)	12 (5.1%)	12 (3.5%)	4 (7.4%)

*116 missing values

Stages of change

The stages of change among current smokers are shown in Table 3. When asked about readiness to quit, 116/632 (18.4%) current smokers wanted to quit within the next month. The proportion of patients wanting to quit in the next month was higher at central/provincial hospitals (71/234, 30.3%) than those visiting district hospitals (39/344, 11.3%, $p < 0.001$) and commune health centres (6/54, 11.1%, $p = 0.004$). Nevertheless, almost 40% of these current smokers did not consider quitting at all, with the proportion highest at commune health centres (25/54, 46.3%) and lowest at central/provincial facilities (78/234, 33.3%).

Discussion

This survey of patients from 46 health facilities in 4 provinces of Vietnam shows a high prevalence of smoking among male patients seeking healthcare. Current smokers who were asked about smoking by a healthcare provider were more likely to make quit attempts than those not asked. Smoking cessation aids and assistance were generally not used by smokers who attempted to quit. Current smokers visiting central/provincial hospitals were more inclined to quit, yet almost four in ten current smokers seeking healthcare were not interested in quitting smoking.

This study is the first to measure the prevalence of smoking among patients presenting to all four levels of Vietnam's government healthcare system. Our finding on substantial sex difference is consistent with previously reported data in many low- and middle-income countries (LMICs) [15] and those collected among patients with HIV in Vietnam [16]. The higher prevalence among male patients aged 25 to 64 years is also in keeping with population-wide data [11]. Even though the high ratio of males to females among smokers in South East Asia and Western Pacific regions has been well documented, a recent scoping review found few research articles on the association between masculinity and smoking behaviour [17]. This association and effective interventions specifically for male smokers remain to be studied, especially in countries where male-to-female ratio of smoking prevalence is high.

Identifying patients who smoke by healthcare providers may increase the likelihood of quitting. A meta-analysis found that a system to screen tobacco use in healthcare settings significantly increases the chance of clinical intervention [18]. In our analysis, the majority of current smokers who had been asked about smoking behaviour also received advice to quit from healthcare providers. We also observed a higher proportion of attempting to quit among current smokers who had been asked about smoking by medical professionals than those who had not been asked. Nevertheless, only about one third of the current smokers in our study had been asked about their smoking behaviour in the past 12 months and a high proportion of current smokers did not want to quit. The findings warrant the implementation of screening for tobacco use and quit advice in healthcare facilities in Vietnam, particularly commune health centres where prevalence of current smoking is the highest.

After identifying smokers in healthcare settings, the establishment of other system-based approaches might increase the chance of quitting. This may include capacity building activities for healthcare workers, a reminder system to prompt cessation discussion with the patients [19], and incorporating cessation as a routine part of care management for patients admitted to hospitals [20,21]. Optimal management for following up patients after discharge should be considered as well. The lower prevalence of current smoking in healthcare settings than in the general population, coupled with the finding that a third of current smokers lived with another smoker, suggests the importance of smoking cessation activities beyond the healthcare system. According to the GATS 2015, more than half of current smokers were considering quitting but less than one third of them ever visited to a healthcare provider during the previous 12 months [11]. An analysis from the same survey showed high secondhand smoke exposure in public places [22]. We agree with the recommendation from the GATS 2015 that the national cessation programme should be strengthened in order to better reach those smokers who do not access healthcare. A recent study showed a positive result about the toll-free quit line run by Bach Mai Hospital [23]. Currently, this quit line provides around 10 follow-up counselling calls over 12 months. Provision and promotion of similar quit line services to the entire country will benefit those who are not reached by healthcare-based interventions. Similarly, mobile phone-based tobacco cessation interventions (mCessation) may achieve effective and cost-effective

results in Vietnam and other LMICs [24,25]. A cluster randomised controlled trial evaluating the effectiveness of a smoking cessation intervention that incorporates mCessation is currently underway (registration number: ACTRN12620000649910). Other measures, such as community-based cessation interventions and implementation of smoke-free environment, may also increase smokers' motivation to stop smoking. Another ongoing cluster randomised controlled trial attempted to assess the effectiveness of involving community health workers in smoking abstinence [26]. Further studies to evaluate the effectiveness and cost-effectiveness of different interventions, both healthcare-based and non-healthcare-based, are desirable.

We demonstrated a very low rate of utilisation of smoking cessation services among patients who made quit attempts in the past 12 months. This finding was similar to a cross-sectional survey among 321 men calling the quit line service run by Bach Mai Hospital [27]. Only less than 5% of these male smokers used direct counselling, nicotine replacement therapy, or medicines (bupropion/varenicline) before calling the quit line. An important barrier to accessing this service includes the lack of awareness of the phone number by smokers, which could be addressed by increasing funding for health promotion in Vietnam, and including the Quitline number on the packages of tobacco products [28].

Our analysis also showed differences in willingness to quit among patients at different levels of health facility. This finding, along with the differences in prevalence of smoking across sex, age groups, and levels of facility, indicates the need to tailor evidence-based smoking cessation interventions to the local context. An example to achieve this is the "Ottawa Model for Smoking Cessation", a systematic approach to tobacco dependence management delivered for patients attending healthcare settings [21].

The strength of this study is inclusion of participants from all levels of the health system in four geographically distinct provinces of Vietnam, increasing its generalisability. We also used standardised questionnaires to assess current smoking behaviours, and contact with tobacco control services. However, our study sample may slightly under-represent the proportion of patients attending commune level facilities – in comparison to higher level facilities [29].

This study has a number of important policy implications. First, the low proportion of current smokers been asked about smoking habits highlights the need for a screening system to identify patients who smoke that can be integrated into routine practice. Second, the intervention to support quit smoking in the healthcare facilities should be tailored to patients' characteristics and capacity of the facility. Third, even though cessation medications are effective in assisting smokers quit, these medications are expensive and not readily available in Vietnam. Policies to provide cessation medications covered by public health insurance that are cost-effective will be necessary to further reduce smoking prevalence.

Further research is required to address several questions. How smokers acquire information about cessation services and access assistance in Vietnam is still not clear. For example, the quit line operated by Bach Mai Hospital is the first national quit line service that has been available since 2015. It is desirable to know that smokers did not use this service because they were not aware of the service or they did not consider it helpful. A recent systematic review of randomised controlled trials showed that nicotine replacement therapy, behavioural counselling and brief advice are effective interventions in LMICs [30]. Nevertheless, implementing these interventions in healthcare settings remains a big challenge in many LMICs [31]. A flexible model to include evidence-based smoking cessation services into clinical practice in different levels of health facilities should also be established. Finally, it is needed to study the role of health authorities in supervising the implementation, which is critical to maintain the sustainability of the model.

Conclusions

In conclusion, smoking is common among male patients presenting to healthcare facilities in Vietnam. Formal smoking cessation supports are rarely used by smokers attempting to quit. This is a population likely to benefit from a structured smoking cessation programme based on effective models of care.

Declarations

Ethics approval and consent to participate

Ethical approval was provided by the Human Research Ethics Committee of the University of Sydney (2017/511), and the Institutional Review Board of the Bach Mai Hospital, Hanoi, Vietnam. Participants aged 18 and over provided written informed consent. Adolescents between 15 and 18 year of age provided verbal assent, and their parents provided written informed consent.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None declared.

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Authors' contributions

WCH and GJF analysed and interpreted the data. WCH wrote the manuscript. All authors reviewed and commented on the manuscript. GJF, GBM, and TAN conceptualised the study

idea. GJF, GBM, QCN, VNN, BF, SJ, and JN designed the study. NYP led the project implementation. TAN, VGV GCN, and VNN assisted research activities and resources. GJF and GBM obtained funding for the study. All authors have read and approved the manuscript.

Acknowledgements

Not applicable

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Chapter 5. A novel approach for patients with chronic respiratory disease

5.1. A stepped treatment algorithm using budesonide-formoterol

Preface

This sub-chapter contains the unaltered full text of the following manuscript submitted for publication

> Huang WC, Fox GJ, Pham NY, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Marks GB. Stepped treatment algorithm using budesonide-formoterol for chronic respiratory diseases: a single arm interventional study. Submitted to PLOS ONE.

Appendix 2.4 of this thesis contains the supplementary appendix for this article. WCH designed the study, conducted the analysis, and wrote the manuscript.

Contribution of this sub-chapter to the thesis

This sub-chapter addressed the third research objective of the thesis. This study assessed the feasibility of an intervention that aimed to reduce exacerbations among patients with CRD visiting district hospitals in Vietnam.

Introduction

Chronic respiratory diseases (CRD), including chronic obstructive pulmonary disease (COPD) and asthma, poses an enormous burden to health systems worldwide [1]. COPD and asthma are obstructive lung diseases that share common characteristics, such as treatment with inhalers, chronic airway inflammation, and exacerbations that are recognised by acute worsening of pulmonary function and respiratory symptoms.

Despite available evidence-based guidelines and cost-effective interventions, gaps exist between these approaches and actual clinical practice. Observational studies from different healthcare settings showed a low level of adherence to treatment recommended by guidelines, and insufficient awareness among physicians of optimal patient management [2-6]. Poor adherence to inhalers among patients has also been observed in various settings [7, 8]. There are major barriers to treatment for CRD in low- and middle-income countries (LMICs), including lack of access to diagnostic tests, limited human resources, and unavailability of medications [9-11].

Novel and pragmatic approaches should be considered to improve the uptake of effective medications in resource-limited settings. Recently, randomised trials have shown that inhaled budesonide-formoterol (IBF) in a single device, used as-needed, was as effective as daily maintenance inhaled corticosteroids in preventing exacerbations for mild and moderate asthma [12-14]. It is unclear if a similar approach can be used to achieve disease control for patients with all forms of obstructive lung diseases, including both asthma and COPD.

The aim of the study was to assess the feasibility of a pragmatic intervention that entails a stepped therapeutic approach using IBF for patients with CRD presenting to local healthcare facilities. We also aimed to determine the proportion of enrolled patients with at least one exacerbation during a 12-month follow-up period.

Materials and methods

Study design and setting

This single-arm interventional study was conducted in three rural district hospitals in Hanoi, Vietnam. In Vietnam, district hospitals deliver care to populations of around 100,000 people and their local communities [15].

Training for healthcare workers

Before the enrolment, healthcare workers from the three facilities participated in a training programme for study implementation, including recruit and follow-up participants, undertake patient education, administer inhaled medicine and perform spirometry and fractional exhaled nitric oxide (FeNO) testing. The study started at each facility with a run-in period that lasted for a week. During this period, research staff attended the facility to supervise the healthcare workers and deliver in-service training.

Screening for CRD

Patients aged ≥ 12 years who presented to the facility with at least one of cough, dyspnea, wheeze, or chest tightness and had a history of at least one prior episode of respiratory symptoms that had required attendance at a healthcare facility within the past two years were screened.

The screening procedure included spirometry and a respiratory symptom questionnaire (RSQ) [16]. We performed spirometry using handheld EasyOne® Air spirometer (ndd Medizintechnik) according to American Thoracic Society/European Respiratory Society guidelines [17]. Spirometry results with a quality of "A" to "C" were considered valid[18]. Research staff assessed the quality of spirometric recordings during the run-in period and at site visits every two weeks.

Airflow limitation was defined as a pre-bronchodilator FEV_1/FVC ratio < 0.7 or a peak expiratory flow < 0.8 of predicted value, if a valid FEV_1/FVC result was not achieved. The RSQ includes nine questions assessing symptoms related to asthma in the past four weeks. A score of ≥ 3/9 gives a specificity of more than 90% and a sensitivity of around 70-80% for identifying individuals with a history of asthma in the last year or bronchial hyperresponsiveness determined by provocation test[16]. A score of ≥ 3/9 on the RSQ was defined as probable asthma.

Patients referred for screening meeting all the following criteria were eligible for the therapeutic intervention: (a) having either airflow limitation, probable asthma, or both, (b) an alternative diagnosis, such as tuberculosis or pneumonia, was considered by clinicians to be unlikely to explain the symptoms, and (c) intended to live in Hanoi for the next 12 months. We excluded those who were (a) unable to provide consent, (b) allergic to budesonide or formoterol, and (c) pregnant women. Enrolled patients had a complete blood count with white cell differential count and FeNO measured at baseline. FeNO levels were categorised as low (<25 parts per billion, ppb), intermediate (25-50 ppb), and high (>50 ppb) [19].

Stepped treatment algorithm and clinical follow-up

Patients enrolled for treatment were advised to use IBF (dry powder inhaler, 160µg/4.5µg per dose) according to a stepped algorithm. At step 1, patients used the inhaler only as required for relieving symptoms. At step 2, patients used the inhaler twice daily and, in addition, as required for relief of symptoms. At step 3, patients were referred for assessment by a specialist at provincial-level facility. Clinic doctors were advised to refer patients if considered necessary, such as a severe exacerbation that required more intensive management than was available at the district level.

All participants received an information leaflet about CRD and a management plan at the time of enrolment. Pharmacists in the district hospitals instructed participants how to use the inhaler when they dispensed the patient's first device. Afterwards, pharmacists checked and, if necessary, corrected inhaler technique each time a participant returned to collect a new inhaler device.

Every patient started at step 1 of treatment. Participants were asked to return to the clinic four weeks later for assessment. After the 4-week visit, the treating doctors decided the schedule of further appointments based on their judgement.

At each follow-up assessment, the treating doctors evaluated participants' adherence to treatment based upon device counters, reassessed inhaler technique and determined their

symptoms and exacerbations. Treatment was escalated to a higher step if the participant demonstrated ongoing symptoms consistent with poor control, or had exacerbation(s), since the last visit, that was not due to poor adherence or incorrect inhaler technique. Poor symptom control was defined as a score of < 20 in a symptom questionnaire modified from the Asthma Control Test (replacing asthma with respiratory symptoms in the questionnaire) [20].

Study outcomes

The primary objective of the study was to evaluate the feasibility of the intervention. First, we estimated the proportion of participants who completed each step in a pre-specified 'cascade of care' in the treatment of CRD. Steps in the cascade included: (1) patients who attended the health facilities, presenting with respiratory symptoms consistent with CRD, (2) patients who initiated diagnostic assessment, (3) patients who completed spirometry or peak expiratory flow test, (4) patients completing diagnostic assessment who were diagnosed with CRD, (5) patients with CRD who commenced IBF, according to the algorithm, (6) patients who attended re-assessment 4 weeks after initiation of therapy, (7) patients who were adherent to recommended treatment after treatment commencement up to 3, 6, 9, and 12 months.

Research staff enumerated consecutive patients visiting the health facility with respiratory symptoms during the run-in period. The average number of people presenting to the facility per day meeting eligibility criteria during the run-in period was then used to estimate the number of participants at the first step of the cascade.

We assessed treatment adherence (step 7 of the cascade) by comparing the treatment step recommended by doctor and participants' actual use. A participant was defined as "use IBF as recommended" if the participant complied with doctor's recommendation at that time point. "Adherent to IBF" was defined as using IBF, whatever doing frequency, at that time point and previous contacts. "Adherent to recommended treatment step" was defined as complying with doctor's recommendation at that time point and previous contacts.

The secondary objective of the study was to determine the proportion of participants who

had at least one exacerbation during the follow-up period. We defined an exacerbation as acute worsening of respiratory symptoms that resulted in (a) a healthcare visit, (b) a diagnosis of exacerbation by a physician, or (c) a prescription of systemic corticosteroids.

Research staff called the participants 4 weeks, 3 months, 6 months, 9 months, and 12 months following enrolment to collect data. A patient was considered lost to follow-up if two or more consecutive follow-ups were missed.

Statistical methods

We described the characteristics of participants using frequencies, means with standard deviation, and medians with interquartile ranges. Comparative analyses were performed using multivariable logistic regression, with model covariates determined using a causal diagram (S1 Fig). Missing values for smoking status were imputed for the model analysis using age, sex, and level of education as the observed data. The effects of interest included baseline FeNO, baseline blood eosinophil count, and treatment adherence. Treatment adherence was scored on a scale of zero to four, with four indicating the use of IBF as recommended at all four phone calls (3, 6, 9, and 12 months) and zero none of these time points. Analyses were conducted using SAS® (v9.4, SAS Institute, Cary Corp. NC. USA).

Sample size

The targeted sample size of participants enrolled for intervention was 300, with 100 from each hospital. As we expected 30% of patients to have at least one exacerbation within 12 months, this sample size allowed us to estimate the proportion of patients experiencing one or more exacerbations within a 95% confidence interval of ± 5.2%.

Consent and ethical approval

Patients who were eligible for screening provided verbal consent before screening procedure. Patients who met the eligible criteria for intervention gave written informed consent.

The study was approved by the Human Research Ethics Committee at the University of

Sydney (protocol number: 2018/769), and the Institutional Review Board of the Bach Mai Hospital, Hanoi, Vietnam (approval number: 3497/QD-BM). The study was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619000554167).

Results

Fig 1 shows the CONSORT diagram of the study. From March 2019 to July 2019, 479 patients were screened and initiated diagnostic assessment. Among them, 468 (97.7%) completed lung function and 391 (81.6%) had valid spirometry results (Fig 2). Among 333 (71.2%) patients diagnosed with CRD, 313 (94%) started the treatment algorithm. Based upon estimates obtained during the run-in period, the number of recruited patients comprised 9.6% of patients who visited the facilities with respiratory symptoms consistent with CRD.

The median age of the 313 patients was 65 years (interquartile range: 56 – 72 years, Table 1). Females accounted for 24.3% of the sample. Among 256 patients with an acceptable spirometry result, 230 (89.8%) had airflow limitation. Of 274 patients who had FeNO measured at baseline, 89 (32.5%) had an intermediate level and 60 (21.9%) had a high level.

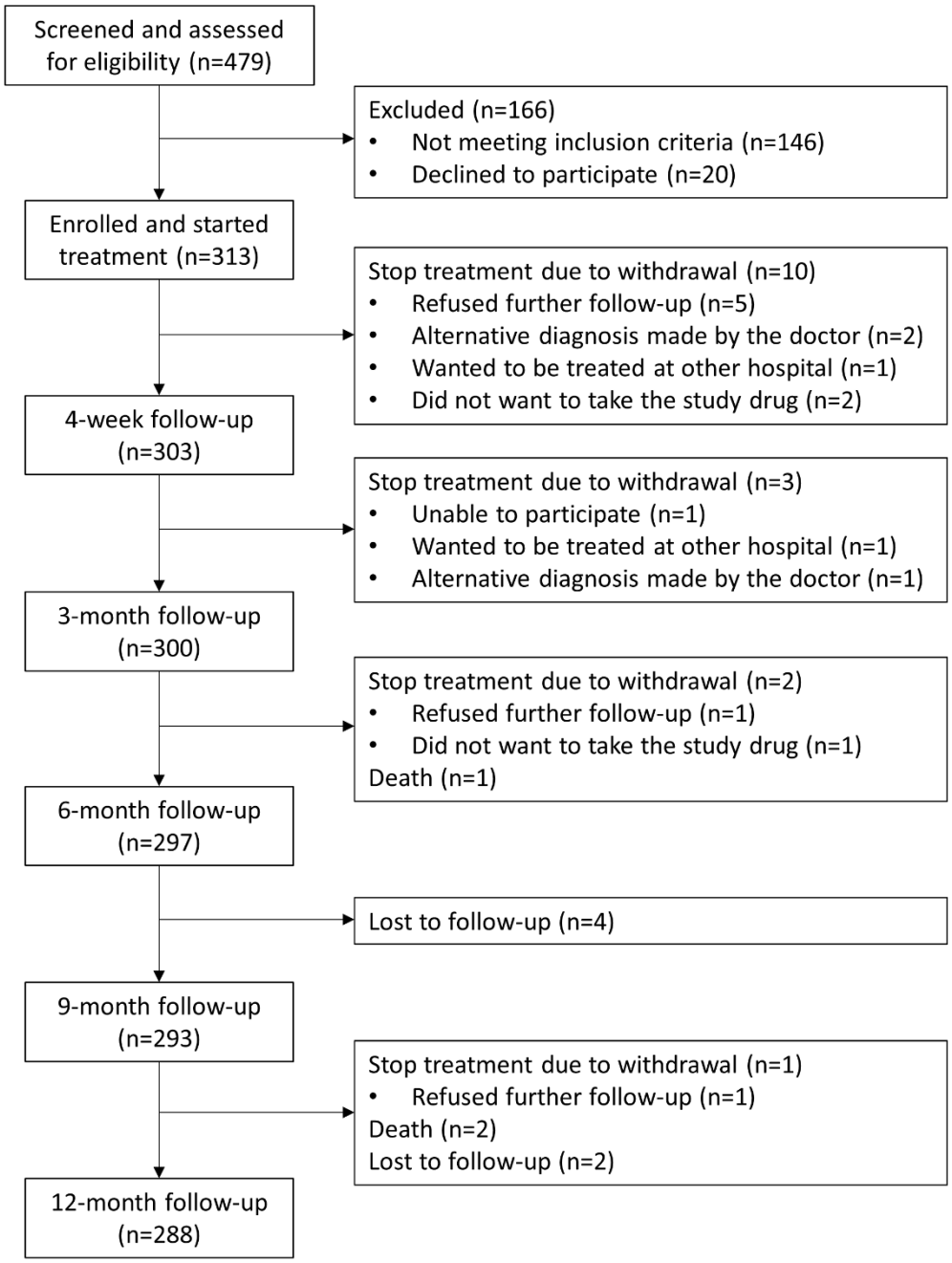

Fig 1. CONSORT diagram.

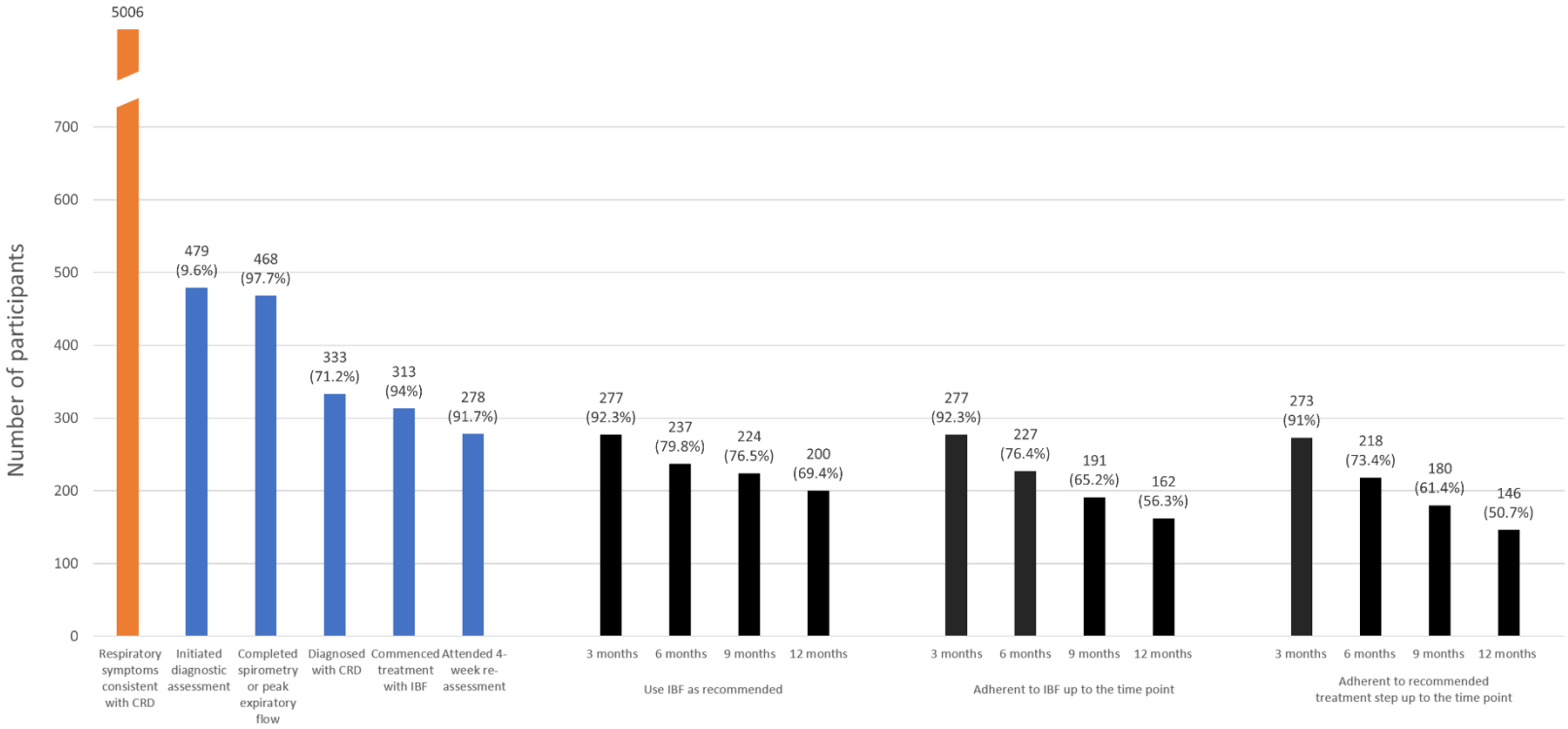

Fig 2. Proportion of patients completing each step of the cascade of intervention.

CRD, chronic respiratory diseases; IBF, inhaled budesonide-formoterol

Table 1. Baseline characteristics of study participants

Characteristic	All participants
Total	313 (100)
Median age, years (IQR)	65 (56 – 72)
Female sex	76/313 (24.3)
Current smoking (n=247)	86/247 (34.8)
Comorbidity	
Hypertension	66 (21.1)
Diabetes	18 (5.8)
Coronary artery disease	5 (1.6)
Heart failure	4 (1.3)
Gastrointestinal reflux disease	26 (8.3)
Baseline lung function*	
FEV_1, litres (SD) (n=256)	1.25 (0.6)
FVC, litres (SD) (n=256)	2.2 (0.76)
FEV_1/FVC (n=256)	55.4 (12.1)
FEV_1/FVC < 0.7 (n=256)	230/256 (89.8)
Peak expiratory flow, %pred. (SD) (n=50)	50.6 (23.1)
Peak expiratory flow %pred. < 0.8 (n=50)	45/50 (90.0)
Eosinophil count, 10^9/L (IQR) (n=296)	0.27 (0.12 - 0.55)
FeNO, parts per billion (IQR) (n=274)	26 (16 - 44)
Low level (< 25)	125 (45.6)
Intermediate level (25 – 50)	89 (32.5)
High level (> 50)	60 (21.9)
Highest level of education attained (n=306)	
Less than primary education	33 (10.8)
Primary education	65 (21.2)
Secondary education	195 (63.7)
University degree, or equivalent, or higher	13 (4.3)

Data are median (IQR), n/N (%), or mean (SD).
FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; SD, standard deviation
*Pre-bronchodilator

Following enrolment, 278/303 (91.7%) participants attended the 4-week assessment (Fig 2). Twelve months after enrolment, 56.3% and 50.7% of participants were still adherent to IBF and to recommended treatment step, respectively.

The cumulative proportion of patients with an exacerbation, as defined, is shown in Fig 3. During the 12-month follow-up period, 56.3% of participants developed acute respiratory symptoms that required at least one visit to healthcare facility (47.2% if excluding private pharmacy visits). The proportion of participants diagnosed with one or more exacerbations and receiving systemic corticosteroids over the 12-month period was 35.4% and 15.3%, respectively.

Fig 4 shows the prevalence of nonadherence to treatment. The proportion of patients who reported feeling well without using IBF and the proportion who reported using step1 treatment among those suggested to use step 2, both increased over time. Around 1% of patients continued maintenance treatment, but with a daily dose of less than that recommended for step 2 treatment.

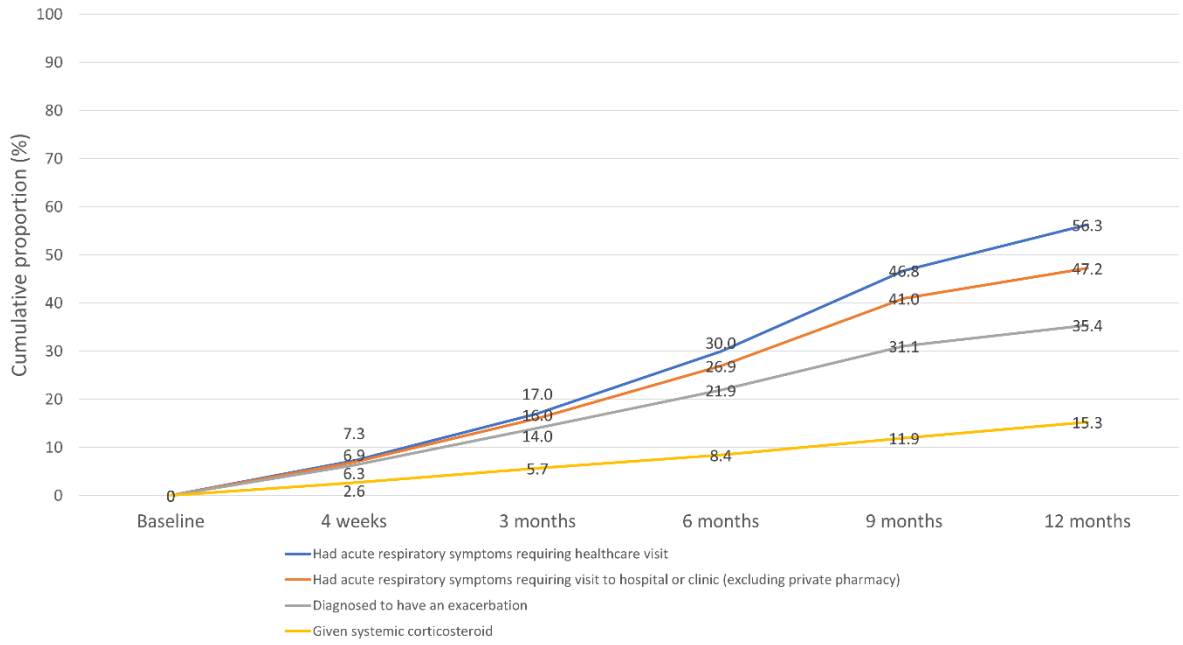

Fig 3. Proportion of participants with at least one exacerbation over study period.

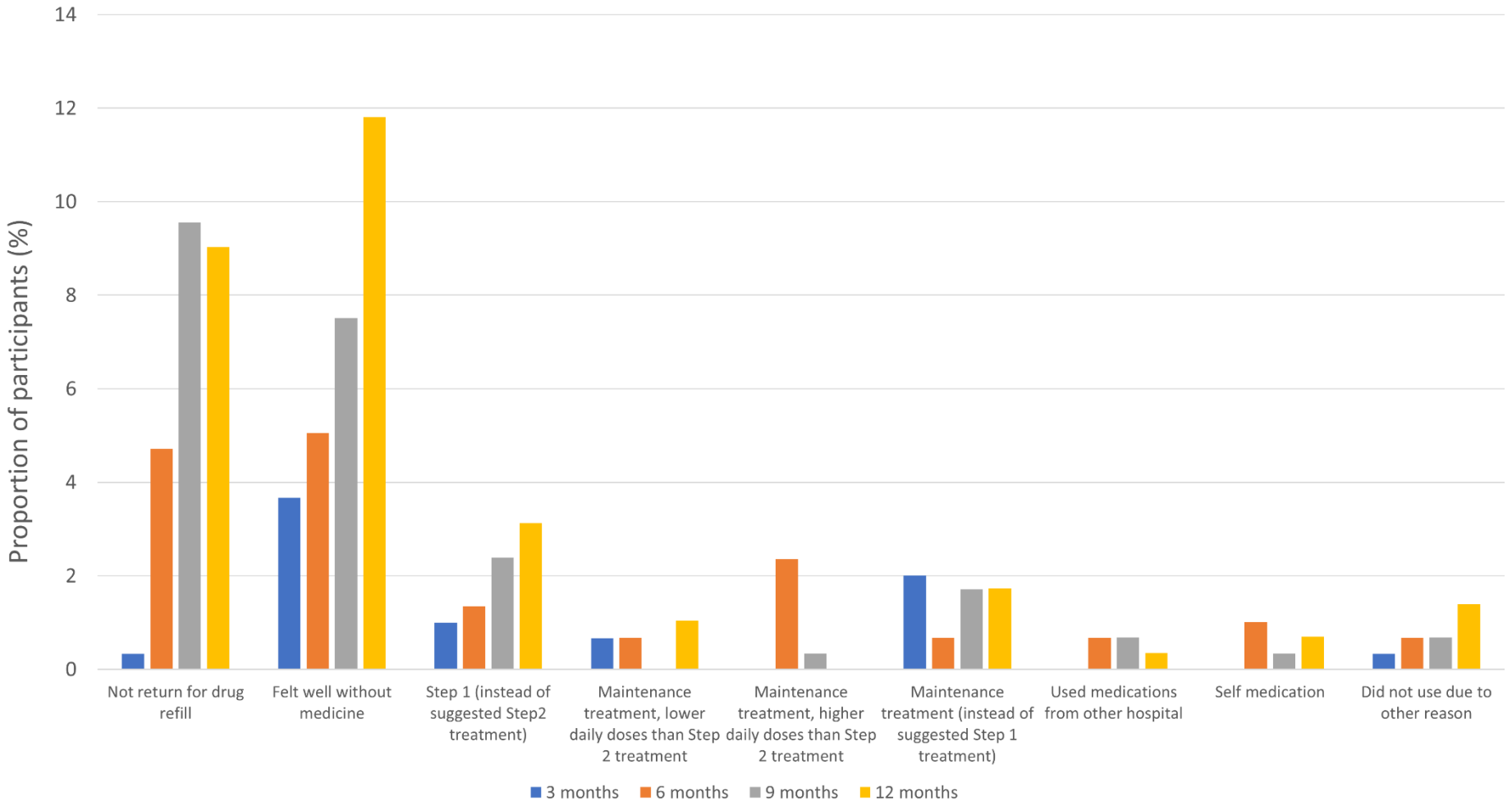

Fig 4. Patterns of nonadherence to treatment.

The associations between exacerbations and effects of interest after adjustment are shown in Table 2. No association was found between exacerbation and the values of baseline FeNO or blood eosinophils. Treatment adherence was associated with a lower odds of visit to hospital or clinic (odds ratio = 0.712, 95% CI = 0.582 – 0.871), a lower odds of diagnosis of exacerbation (odds ratio = 0.675, 95% CI = 0.536 – 0.85), and a lower odds of being given systemic corticosteroids (odds ratio = 0.484, 95% CI = 0.307 – 0.763).

Table 3 shows the average daily doses of IBF used by participants. Over the study period the mean daily number of doses ± standard deviation was 1.5 ± 1.2 doses and the median daily number of doses was 1.3 (interquartile range: 0.7 to 2.3) doses. Over the period from enrolment to the date of the last drug dispensing, these values were 2.3 doses ± 1.2 and 2.1 doses (interquartile range: 1.4 – 3.0 doses), respectively. The proportion of patients with an average daily budesonide dose exceeding 800µg was 3.8% over the entire study period and 8.8% over the period from enrolment to date of last drug dispensing.

Table 2. Logistic regression models of risk of developing exacerbations

Effect of interest	**Outcome**	**Adjusted odds ratio (95% CI)**	**Covariates adjusted according to causal diagram**
Baseline FeNO level* (intermediate vs low)	Visit to hospital or clinic	1.649 (0.932 – 2.916)	Baseline blood eosinophil count, smoking status
	Diagnosis of exacerbation by a physician	1.219 (0.673 – 2.210)	
	Given systemic corticosteroids	0.988 (0.453 – 2.152)	
Baseline FeNO level*	Visit to hospital or clinic	1.685 (0.875 –	

(high vs low)		3.242)	
	Diagnosis of exacerbation by a physician	1.627 (0.797 – 3.321)	
	Given systemic corticosteroids	2.268 (0.717 – 7.178)	
Baseline blood eosinophil count	Visit to hospital or clinic	1.173 (0.532 – 2.586)	Baselin FeNO level, smoking status
	Diagnosis of exacerbation by a physician	1.310 (0.560 – 3.065)	
	Given systemic corticosteroids	2.158 (0.585 – 7.958)	
Treatment adherence[†]	Visit to hospital or clinic	0.712[§] (0.582 – 0.871)	Age, smoking status
	Diagnosis of exacerbation by a physician	0.675[§] (0.536 – 0.850)	
	Given systemic corticosteroids	0.484[§] (0.307 – 0.763)	

FeNO, fractional exhaled nitric oxide

[*]Low level, <25 ppb; intermediate level, 25-50 ppb; high level, >50 ppb

[†]Scored on a scale of zero to four, with four indicating the use of inhaled budesonide-formoterol as recommended at all four phone calls (3, 6, 9, and 12 months) and zero none of these time points

[§]Statistically significant

Table 3. Average daily doses of budesonide-formoterol (N = 288)

Method of calculation[*]	**Mean daily doses (SD)**	**Median daily doses (IQR)**	**Maximum average daily doses**	**Proportion with 5-8 daily doses**[§]
Total study period (365 days)	1.5 (1.2)	1.3 (0.7 – 2.3)	5.3	3.8%
Between first (date of enrolment) and last inhaler dispensing[†]	2.3 (1.2)	2.1 (1.4 – 3.0)	6.9	8.8%

[*]Two different methods used because doses used between the day the last inhaler dispensed and the last day of study were not known

†Excluding patients who had only one inhaler dispensed

§200 μg budesonide per dose

Throughout the study period, three deaths were reported. Two of them stopped IBF about 5 weeks and 3 months before their death. The third patient had several exacerbations but declined the recommendation of referral to a provincial hospital. Another patient had an episode of intraventricular haemorrhage leading to hospitalisation. None of the above adverse events was judged to be related to the study drug. One participant reported skin rash, which improved after discontinuing the study drug.

Discussion

In this study we showed the feasibility of a novel and pragmatic therapeutic algorithm used for patients with CRD, including both asthma and COPD. More than half of participants complied with the recommended treatment up to 12 months after enrolment. Adherence to recommended treatment was associated with a lower risk of exacerbation. However, baseline FeNO and blood eosinophil counts were not related to the subsequent risk of having an exacerbation. Only a small number of patents required an average daily dose of budesonide of over 800 μg. The frequency of exacerbations among the participants and the safety profile of the therapeutic algorithm were within the expected range for patients with CRD [21-24].

Diagnostic assessment using spirometry is essential to identify patients with CRD. In our

study, only 10% of patients with repeated respiratory symptoms underwent diagnostic assessment, suggesting a low rate of referral for spirometry in the facilities. Hence, many patients with CRD may have been missed. A recent cross-sectional survey showed more than 20% of patients with respiratory symptoms who attended district health facilities in Vietnam had either fixed or reversible airflow limitation [25], and would have potentially benefited from the treatment algorithm of this study. Other studies have also shown that misdiagnosis of COPD and asthma is common [26, 27]. Our study suggested that a portable spirometer can be effectively incorporated in clinical practice in a rural setting of LMICs to facilitate diagnosis and prompt proper treatment.

Poor adherence to inhaled medicine is a well-documented problem [28, 29]. A study of patients with COPD showed adherence could be as low as 13%, 12 months after starting maintenance treatment [30]. In our study, the proportion of participants remained adhering to suggested treatment was high compared to other published studies. Furthermore, the majority of patients who were nonadherent to treatment suggestions reported feeling well during follow-up, even with a self-directed dose reduction. Therefore, the observations support the feasibility of this treatment algorithm in this setting.

Increased FeNO and blood eosinophil counts at baseline were shown not associated with risk of exacerbations in our study, which was not consistent with evidence from studies in patients with COPD and asthma [31-33]. A recent trial assessing as-needed IBF in patients with mild asthma found a similar result [34]. From their analysis, benefits of as-needed IBF

over as-needed salbutamol for preventing exacerbations were independent of baseline blood eosinophil count or FeNO. Given that the two biomarkers are known predictors of response to inhaled corticosteroids [35-37], it is plausible that exacerbations were prevented through a pathway involving formoterol among patients with a low level of type 2 inflammation [34]. More studies are required to show the relationship between these biomarkers and exacerbations among patients using as-needed IBF. Furthermore, even though our study did not seek to distinguish COPD and asthma, studies evaluating effects of as-needed IBF in patients with COPD may help expand our understanding of management of CRD.

Even though the estimation of exacerbations might be affected by concomitant cardiorespiratory diseases, or underestimated due to patients' not reporting deterioration, we consider the proportion of exacerbation among participants within expected range. A prospective cohort in Uganda found 59.6% of patients with asthma experienced at least one exacerbation in a year [23]. Another study conducted in multiple Asia-Pacific countries reported 33.1% of patients with mild intermittent asthma and 58.6% of patients with severe persistent asthma required an emergency visit for respiratory condition during the previous year [22]. The PERCEIVE study showed 89% of people with COPD suffered from at least one episode of symptom flare-up within a year [24]. The exacerbation frequency in our population, alone with the adherence pattern, suggest the algorithm could be used in other similar settings. The effectiveness of the algorithm in reducing exacerbations and its safety are currently under investigation in Vietnam with a cluster randomised controlled trial (ACTRN12620000649910).

The study is novel in several ways. First, the treatment algorithm requires only one inhaled medicine. This could reduce the need for procuring multiple inhalers and prevent the problems of using various types of inhaler devices, such as poor technique and low adherence. Second, our population includes both patients with COPD and asthma. The algorithm does not require clinical staff be able to distinguish between the two entities, which is difficult in many clinical settings. Finally, the study was implemented in three rural district hospitals in Vietnam, indicating the potential utility of such algorithm in resource-limited areas and primary care.

This study has several limitations. First, the RSQ was originally designed for epidemiological studies [16] and its validity in directing therapy in clinical settings is not established. However, we found most patients enrolled had both airflow limitation and a high score in the questionnaire. Hence, it is unlikely that we inadvertently enrolled many patients without CRD. Second, data regarding exacerbation frequency was obtained from the participants and were not validated with medical records. Third, we did not assess the incidence of pneumonia and pulmonary tuberculosis, two possible adverse events of inhaled corticosteroids. Finally, current tools to assess symptom control were designed for either COPD or asthma. The validity of using these tools for a population constituted by different forms of obstructive lung diseases remains to be explored.

In conclusion, this novel therapeutic algorithm was feasible and tolerable for patients with

CRD in a rural healthcare setting. Further studies are required to establish the safety, effectiveness and cost-effectiveness of similar approaches in a range of settings.

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5.2. Predicting exacerbations among patients with chronic respiratory disease managed using a stepped treatment algorithm based on budesonide-formoterol

One of the main goals of treatment in patients with CRD is the prevention of disease exacerbations. An exacerbation is generally defined as an acute worsening of respiratory symptoms that requires a change in treatment (such as using a short course of systemic corticosteroids) [1-3]. Definitions based on healthcare utilisation, such as unplanned healthcare visits, emergency care, and hospitalisations, have also been used in medical literature [4, 5]. An exacerbation leads to reduced health-related quality of life, a higher risk of death, and extra clinical and economic burden to the health system. Identifying patients at high risk for exacerbations could assist clinicians in appropriately targeting preventative interventions.

A prediction model uses a combination of independent variables to predict a specified outcome. A prediction model is different from an explanatory model that aims to identify the causal linkages between exposures (independent variables) and the outcome of interest (dependent variable) [6]. As suggested in a recent review, "A significant statistical association is insufficient to establish a claim of prediction" [7]. A key difference between prediction and causal models is the selection of explanatory (or independent) variables. In the prediction model, the aim is to maximise the explanatory power of the model without the need to draw any causal inference about the explanatory variables. In the causal model, it is important to test a hypothesised causal pathway and consider the impact of biasing (or confounding) factors that affect the causal inference [8]. In Chapter 5.1, explanatory (or causal) modelling was used to explore the association between three independent characteristics and exacerbations. The aim of the analysis in this section was to construct a prediction model, without causal inference, that can identify patients with increased risk of exacerbation among those with CRD who started the stepped budesonide-formoterol treatment algorithm.

Literature review of prediction models for COPD and asthma

A recent systematic review evaluated 228 articles describing 408 prediction models in patients with COPD [9]. Among the included prediction models, mortality was the most

common endpoint (51%) and 10% assessed the risk of COPD exacerbation. This review identified several methodological weaknesses in the development of models, including internal validation, assessment of calibration, model presentation, approach to reduce overfitting, and external validation. The authors also commented on the necessity of evaluating safety, effectiveness, and cost-effectiveness of using these prediction models in clinical practice in future research.

Another review article identified 25 articles with 27 prediction models that predict exacerbations in COPD patients [10]. They found substantial heterogeneity in the number and type of predictors, statistical methods, and measures of prediction model performance. For example, only a third of the models were built upon a procedure for variable selection. Also, only 5 out of the 27 models reported performance related to discrimination and calibration. The authors concluded that a standard methodology should be adopted for developing prediction models.

Models predicting childhood asthma shared similar issues in study design [11]. In this review, 28 studies with 21 regression-based models and five machine learning models were identified. Three studies did not report any performance measure. Only less than 30% of the regression-based models and none of the machine learning models underwent external validation.

The increase in submissions related to prediction models led to the publication of guidance for respiratory, sleep, and critical care medicine researchers to improve the development and reporting of prediction models [12]. The authors identified common problems in the design and implementation of prediction model development. These include predictor selection, evaluation of model performance, validation, and elements that should be reported. Recommendations from this guidance, along with the TRIPOD Statement [13], were used to guide model construction and reporting in this section.

Source of data and participants

We used the data collected from the VCAPS3 study for this analysis. The study setting, eligibility criteria, and follow-up were explained in Chapter 5.1. Among 313 patients who

started the stepped budesonide-formoterol algorithm, 24 dropped out during the follow-up period, leaving 289 (92.3%) included in this analysis.

Model building and selection of variables

The base model included the following variables that were available at baseline: age, sex, smoking status, presenting symptoms, highest education attained, comorbidities, score of respiratory symptom questionnaire, tentative diagnosis of the treating doctor, blood eosinophil count, FEV1 % predicted value, FVC % predicted value, FEV1/FVC ratio, and FeNO level. Missing values in smoking status (20.8% missingness) were imputed. FeNO level was log transformed to fit normal distribution. We defined the outcome as one or more episodes of acute respiratory symptoms requiring hospital or clinic visits during the 12 months after enrolment. Logistic regression was used for model construction. We applied and compared three selection procedures: backward elimination, stepwise selection, and least absolute shrinkage and selection operator (LASSO) regularization. The model with the lowest Akaike Information Criterion (AIC) was selected as the final model for each of the selection procedures. Apart from AIC, we used area under the receiver operating characteristic curve (AUC) to assess model performance. Among the models from the three selection procedures, the one with the highest AUC was chosen. We applied bootstrapping on 500 resampled datasets for internal validation and the Hosmer-Lemeshow test to evaluate model calibration.

We intend to use the VCAPS4 study for external validation of the final model. The VCAPS4 study was a 2x2 cluster randomised controlled trial evaluating the effectiveness of the two interventions in the VCAPS3 study. The expected sample size for the CRD intervention of the VCAPS4 study was 3,393 (control and intervention arms combined). Because FeNO was not used in the VCAPS4 study, we also evaluated a second model that excluded FeNO in this chapter. Results of external validation were not available as the VCAPS4 study was ongoing at the time of submission.

Results of prediction models

The baseline characteristics of participants and the number of missing values are shown in Table 5.1. There were missing values in smoking status (20.8%), spirometry (17.3%), blood

eosinophil counts (4.8%), and FeNO levels (12.8%). Missing values in smoking status were imputed before entering the base model, using the same technique described in Chapter 5.1. Among the 289 participants, 135 (46.7%) had one or more exacerbations during the 12-month follow-up period.

Table 5.1. Baseline characteristics of the model derivation population

	Total (n=289)	Proportion of individuals with valid data, n (%)
Median age, years (IQR)	65 (56 – 72)	289 (100)
Female sex	71 (24.6)	289 (100)
Current smoking	78 (34.1)	229 (79.2)
Presenting symptom		
Cough	259 (89.6)	289 (100)
Dyspnoea	247 (85.5)	289 (100)
Wheezes	163 (56.4)	289 (100)
Chest tightness	77 (26.6)	289 (100)
Comorbidity		
Hypertension	61 (21.1)	289 (100)
Diabetes	17 (5.9)	289 (100)
Coronary artery disease	5 (1.7)	289 (100)
Heart failure	4 (1.4)	289 (100)
Gastrointestinal reflux disease	23 (8)	289 (100)
Score of respiratory symptom questionnaire (SD)	6 (4 – 7)	289 (100)
Spirometry*		
FEV1 % predicted value (SD)	53.9 (22.4)	239 (82.7)
FVC % predicted value (SD)	76.2 (21.1)	239 (82.7)
FEV1/FVC ratio	55.6 (12)	239 (82.7)
Blood eosinophil count, 10^9/L (IQR)	0.27 (0.13 – 0.57)	275 (95.2)
FeNO, parts per billion (IQR)	26 (16 – 42.5)	252 (87.2)
Highest level of education attained		
Less than primary education	30 (10.4)	289 (100)
Primary education	61 (21.1)	289 (100)
Secondary education	188 (65)	289 (100)
University degree, or equivalent, or higher	10 (3.5)	289 (100)
Tentative diagnosis of treating doctor		
COPD	239 (82.7)	289 (100)
Asthma	39 (13.5)	289 (100)
ACO	7 (2.4)	289 (100)
Not certain yet	4 (1.4)	289 (100)

Data are median (IQR), n/N (%), or mean (SD).
ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity;

IQR, interquartile range; SD, standard deviation
*Pre-bronchodilator

Table 5.2 shows the final models from the selection procedures. For both models in which FeNO was included and FeNO was excluded, backward elimination (Model 1 and Model 4) achieved the lowest AIC and highest AUC values. Model 1 (with FeNO) and Model 4 (without FeNO) were selected accordingly. The two models (Table 5.3) demonstrated a satisfactory fit to the data (Hosmer-Lemeshow test >0.05 in both models).

For Model 1, the AUC for predicting exacerbations was 0.72 (95% CI 0.65 – 0.78) and the bootstrapped AUC was 0.73 (95% CI 0.67 – 0.79). The AUC and the bootstrapped AUC for Model 4 was 0.70 (95% CI 0.63 – 0.77) and 0.72 (95% CI 0.66 – 0.78), respectively.

Table 5.2. Description of prediction models obtained from the selection procedures

Models	**Variable selection procedure**	**Final variable number**	**AIC**	**AICc**	**AUC**
FeNO included in base model					
Model 1	Backward	7	308.14	309.13	0.72
Model 2	Stepwise	3	311.68	311.86	0.66
Model 3	LASSO	2	320.63	320.74	0.61
FeNO not included in base model					
Model 4	Backward	6	310.06	310.87	0.70
Model 5	Stepwise	3	311.68	311.86	0.66
Model 6	LASSO	2	320.63	320.74	0.61

AIC, Akaike information criterion; AICc corrected Akaike information criterion; AUC, area under the receiver operating characteristic curve; FeNO, fractional exhaled nitric oxide; LASSO, least absolute shrinkage and selection operator

Table 5.3. Independent variables and associated parameters of the selected models for odds of 1 or more exacerbations during the 12-month period after enrolment

	Model 1			Model 4		
	Hosmer-Lemeshow test = 0.6948			Hosmer-Lemeshow test = 0.9454		
	Odds ratio			Odds ratio		
Variable	Estimate	95% CI	p-value	Estimate	95% CI	p-value
Sex						
Male	Ref			Ref		
Female	2.06	0.96 – 4.44	0.06	1.89	0.89 – 4.02	0.10
Log FeNO	0.82	0.67 – 1.00	0.05			
FVC, % predicted	0.98	0.97 – 0.99	0.03	0.99	0.97 – 1.00	0.05

value						
Score of respiratory symptom questionnaire	1.15	0.99 – 1.33	0.08	1.14	0.98 – 1.33	0.08
Hypertension	1.87	0.96 – 3.68	0.07	1.82	0.93 – 3.54	0.08
Diabetes	5.72	1.18 – 27.73	0.03	5.07	1.05 – 24.49	0.04
Tentative diagnosis of treating doctor at baseline						
COPD	Ref			Ref		
Asthma	0.27	0.10 – 0.78	0.02	0.28	0.10 – 0.79	0.02
ACO	2.39	0.39 – 14.63	0.35	2.26	0.38 – 13.42	0.37
Not certain yet	2.59	0.23 – 29.6	0.44	2.36	0.21 – 26.8	0.49
Intercept	2.38			1.02		

ACO, asthma-COPD overlap; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FVC, forced vital capacity

Discussion

In patients with CRD who started the stepped budesonide-formoterol intervention, a prediction model that incorporates clinical information and spirometry results can be used to identify patients who have an increased odds of exacerbations. The addition of FeNO into the model slightly improves the predictive ability of the model.

A number of alternative statistical methods can be used to select predictors when constructing a prediction model. However, consensus regarding the optimal approach is lacking. Traditional techniques include pre-specified theory-based selection, backward elimination, stepwise selection, forward selection, and selection based on bivariate association. Penalised regression methods were developed more recently to address overfitting, increase model stability, and improve accuracy. These penalised methods include LASSO, adaptive LASSO, Ridge, and Elastic-Net regularisation. We compared the performance of three techniques commonly used in prediction models in COPD and asthma [10, 14] and found better predictive value for the variable set selected using traditional backward elimination, compared with LASSO and stepwise selection. This finding suggests that comparison between different selection procedures may be necessary to optimise predictive modelling.

The discrimination of the selected models is comparable to prior models developed for COPD or asthma. The AUC from existing literature about models for predicting exacerbations among patients with COPD ranged from 0.53 to 0.79 [10]. Another review article showed a range of AUC from 0.5 to 0.94, with an overall 0.73 from meta-analysis, among 30 models for asthma exacerbations [14]. However, due to the high level of heterogeneity in the design of the studies included in these meta-analyses, the comparison provides only a broad sense of model performance of our analysis. Data from the VCAPS4 study will be used to evaluate the external validity of our models.

Inhaled medications have been shown to reduce exacerbation frequency. Therefore, treatment adherence is an important predictor of exacerbations. Patients with poor adherence to inhaled medicines are at higher risk of exacerbations [2, 3], as demonstrated in Chapter 5.1. As actual adherence to prescribed medications can only be observed prospectively, measures of adherence are rarely available at baseline to inform prediction models. The value of including treatment adherence in prediction models is thus limited. However, questionnaires assessing prior treatment adherence may be used as an alternative approach. For example, in a recent article describing a prediction model for severe exacerbations of asthma, the authors used the Medication Adherence Rating Scale to quantify adherence to inhaled corticosteroids. This was considered as a candidate predictor [15]. However, in their analysis, the Medication Adherence Rating Scale was not selected as one of the final predictors. The ability of adherence questionnaires at baseline to predict future exacerbation warrants further investigation.

There are some limitations in the development of this prediction model. First, the sample size was relatively small. Even though the results of bootstrapping indicated good internal validity, the wide confidence interval makes the estimates uncertain. Second, spirometry or FeNO results were not available in a minority of participants. We considered imputation inappropriate for these two variables and hence the number of observations with complete data was reduced. Third, the study was conducted in rural district hospitals in Hanoi, Vietnam, which may affect the generalizability of the results to other settings. Further external validation will be required.

In conclusion, the prediction models using clinical information and spirometry data, with or without FeNO, can identify patients at an increased risk of exacerbations among those who use the stepped budesonide-formoterol treatment. Validation of the models using data from a larger external cohort, the ongoing VCAPS4 study, should be undertaken to further assess the validity of the models.

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Chapter 6. A smoking cessation intervention beyond healthcare settings

Preface

This section contains the unaltered full text of the following manuscript submitted for publication:

> Huang WC, Marks GB, Pham NY, Nguyen TA, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Fox GJ. A smoking Quitline integrated with clinician counselling at outpatient health facilities in Vietnam: a single-arm prospective cohort study. Submitted to BMC Public Health.

Appendix 2.5 of this thesis contains the supplementary appendix for this article. WCH designed the study, conducted the analysis, and wrote the manuscript.

Contribution of this sub-chapter to the thesis

This sub-chapter addressed the fourth research objective of the thesis. This study assessed the feasibility of an integrated smoking cessation intervention in assisting quitting smoking.

Background

Tobacco smoking remains a leading cause of premature death and chronic diseases worldwide. Despite the abundant evidence to assist people quit smoking, poor reach and utilisation of smoking cessation interventions has been observed in many low and middle-income countries (LMICs) [1, 2].

Numerous barriers prevent the scale-up of smoking cessation interventions in resource-limited settings [3, 4]. These include competing time pressures and inadequate counselling skills of healthcare workers, personal tobacco use by doctors and a lack of support from senior clinical leaders [5]. Just one third of middle-income countries, and almost no low-income countries, have established telephone Quitlines [6]. Furthermore, nicotine replacement and other smoking cessation therapies are often unaffordable or unavailable [7].

Despite these challenges, recent evidence demonstrates the feasibility and effectiveness of low-cost smoking cessation interventions in LMICs. Such interventions include cytosine [8, 9], integrating brief advice into other existing healthcare services[3, 10], and text messaging for smokers [11, 12]. However, limited evidence is available about many promising interventions, including the combination of multiple cessation modalities.

The primary objective of the study was to assess the feasibility of a smoking cessation intervention that integrates brief advice from physician, follow-up counselling phone calls, and scheduled text messages within the Vietnamese health system. The secondary objective was to determine biochemically-verified quit rate among participants 12 months after enrolment.

Methods

Study design and setting

This single-arm intervention study was conducted in three rural district hospitals in Hanoi, Vietnam.

Vietnam is signatory to the World Health Organization Framework Convention on Tobacco Control since 2005. National legislation requires all public hospitals to implement a smoke-free program within their facilities [13]. Currently, there are two official toll-free Quitlines supported by Vietnam Tobacco Control Fund. One in northern Vietnam was established in 2015 and run by Bach Mai Hospital, a leading general hospital in Hanoi. The Quitline program is delivered by 10 certified counsellors [14]. The other one in Southern Vietnam was run by Gia Dinh People's Hospital since 2017.

The Vietnamese health system is organised according to four levels: central (national) hospitals, provincial hospitals, district hospitals, and commune health centres. District hospitals deliver healthcare to their local communities[15]. Outpatient clinics at district hospitals provide general consultations with basic blood tests and X-rays available.

Study population and selection criteria

We enrolled patients aged ≥ 12 years presenting to selected district facilities, as well as healthcare workers employed by these facilities. Participants meeting the following criteria were eligible for inclusion: (a) Had smoked at least 100 cigarettes in his/her lifetime, (b) Smoked cigarettes (defined as smoking at least one cigarette in the previous month), (c) Agrees to participate in the smoking cessation programme, (d) Able to communicate effectively, (e) Intends to be resident in the province for the next 12 months.

Intervention and follow-up

This study evaluated the implementation of a complex intervention. Before enrolment commenced, we engaged with hospital leaders to implement a smoke-free hospital policy, in accordance with national policy and guidelines [16, 17].

Training was provided to healthcare workers about the goals of smoke-free hospitals, and how to deliver brief advice using the '5As approach'. Written material were developed to assist with smoking cessation, based upon health promotion materials from the Ministry of Health in New South Wales, Australia [18, 19]. A Quitline was established at the Hanoi office of Woolcock Institute of Medical Research using the system of a telecommunication company. Quitline counsellors undertook a 3-day training programme by an external expert

and on-site training at the Quitline office run by Bach Mai Hospital [14]. Posters with Quitline information were placed in the consultation rooms and public places of the hospitals.

Healthcare workers could refer patients to the Quitline after obtaining verbal consent. People could also refer themselves by calling the toll-free Quitline. Healthcare workers who were current smokers were also invited to join the smoking cessation programme during the training.

The Quitline program included a scheduled one-way text message service that lasted for three months and nine counselling phone calls in 12 months. After each smoker was referred to the study Quitline (i.e. the doctor passed the smoker's contact info to the study Quitline), the Quitline counsellor called the smoker within 24 hours, excluding weekends and public holidays. During this baseline phone call, the Quitline counsellor assessed participants' eligibility, and enrolled them into the smoking cessation programme. The Quitline counsellor then collected information about study participants, provided counselling and encouraged each smoker to set a planned quit date, preferably within 14 days [20].

After the baseline phone call, the scheduled one-way text messages service started. The Quitline counsellor sent 64 text messages to a participant over a 3-month period. These messages included strategies to avoid smoking cues, deal with cravings, and encouragement (Supplementary Table S1 and Table S2 in Additional file 1 show the schedule and content of the text messages). Quitline counsellor called participants 1 week, 2 weeks, 3 weeks, 4 weeks, 3 months, 6 months, 9 months, and 12 months after baseline to provide cessation counselling. The Quitline operated during working hours. The scheduled text messaging service and the Quitline were both free of charge.

Study outcomes

The primary outcome measure was the proportion of enrolled smokers with biochemically-verified abstinence after 12 months. Individuals who stated they had not smoked in the previous 30 days were asked to submit urine for cotinine testing to verify abstinence.

Verification was based upon a test strip that detected the presence of cotinine in urine at a cut-off concentration of 200 ng/mL (Confirm BioSciences, CA. USA). The secondary outcome measures included (a) the proportion of individuals who self-reported not having smoked within the previous 30 days, at the time of the 12-month follow-up, and (b) the proportion of patients reporting at least one quit attempt lasting 30 days during the follow-up period.

Participation in the intervention was evaluated using a "cascade of care" approach. Pre-defined steps in the cascade for those attending health facilities were: (a) the number of smokers attending outpatient health services; (b) the proportion of smokers in the previous step who enrolled in the smoking cessation programme; (c) the proportion of those in the previous step who completed initial outpatient counselling and received smoking cessation material; (d) the proportion of enrolled smokers who reported making at least one quit attempt, lasting at least 30 days, during the 12-month follow-up period; (e) the proportion of enrolled smokers who reported being abstinent from smoking for at in the prior 30 days at 3, 6, 9, and 12 months after enrolment.

Research staff stayed at the registration counter and asked about current smoking status of consecutive patients visiting the health facility during a one-week run-in period. The average number of smokers presenting to the facility per day during this period was then used to estimate the number of smokers at the first step of the cascade.

Statistical methods

The characteristics of participants were analysed using descriptive statistics. Comparisons of selected baseline demographic characteristics among participants grouped by smoking status at 12 months were performed using chi-square test and analysis of variance for categorical and continuous variables, respectively. An exploratory analysis using multivariable logistic regression was done to identify factors associated with abstinence at 12 months. In the regression, Fagerström Test for Cigarette Dependence was grouped into high (7 – 10), moderate (4 – 6); and low (<4). The number of successful counselling phone calls was highly negatively skewed, and normalisation was not achieved. We grouped the number of phone calls made per participant as 8 or above, 6 to 7, and less than 6, according to quartiles. A p-value less than 0.05 was considered statistically significant. Analyses were

conducted using SAS® (v9.4, SAS Institute, Cary Corp. NC. USA).

Sample size

The sample size was calculated to estimate the proportion of people quitting smoking over a 12-month period. We expected 10% of lost to follow-up and 10% of participants to achieve smoking cessation at the end of the study. A sample size of 480 people (160 at each health facility) allowed us to estimate the quit rate within a 95% confidence interval of ± 2.8%. However, finally, we were able to recruit 218 participants and the quit rate was 5%, yielding a 95% confidence interval of ± 2.9%

Ethical issues

Healthcare workers obtained verbal consent from patients to receive brief counselling and to authorise their phone numbers to be sent to Quitline staff. Additional verbal consent was provided during the initial phone call, to enable data collection, participation in counselling and follow-up. Ethical approval was provided by the Human Research Ethics Committee at the University of Sydney (Protocol 2018/769), and the Institutional Review Board of the Bach Mai Hospital, Hanoi, Vietnam (Approval 3497/QD-BM).

RESULTS

Figure 1 shows the CONSORT diagram for recruitment to the study. Between May 2019 and January 2020, 431 individuals were referred to the Quitline, including 14 patients referred themselves by calling the Quitline, and 5 healthcare workers (Figure 2). Based upon estimates obtained from enumeration during the run-in period, about 17.6% of smokers visiting healthcare facilities on the dates of referral were referred to the study Quitline by healthcare workers. Among the 431 referred to the study Quitline, 221 (51.3%) meeting the eligibility criteria agreed to participate in the smoking cessation programme.

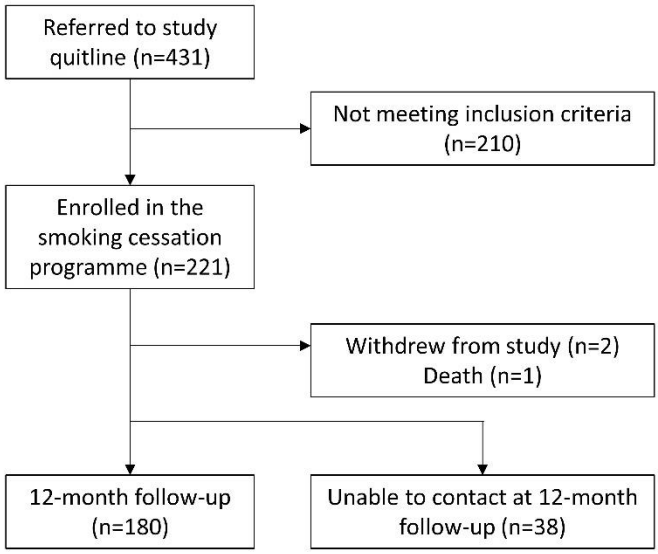

Figure 1. CONSORT diagram of the study

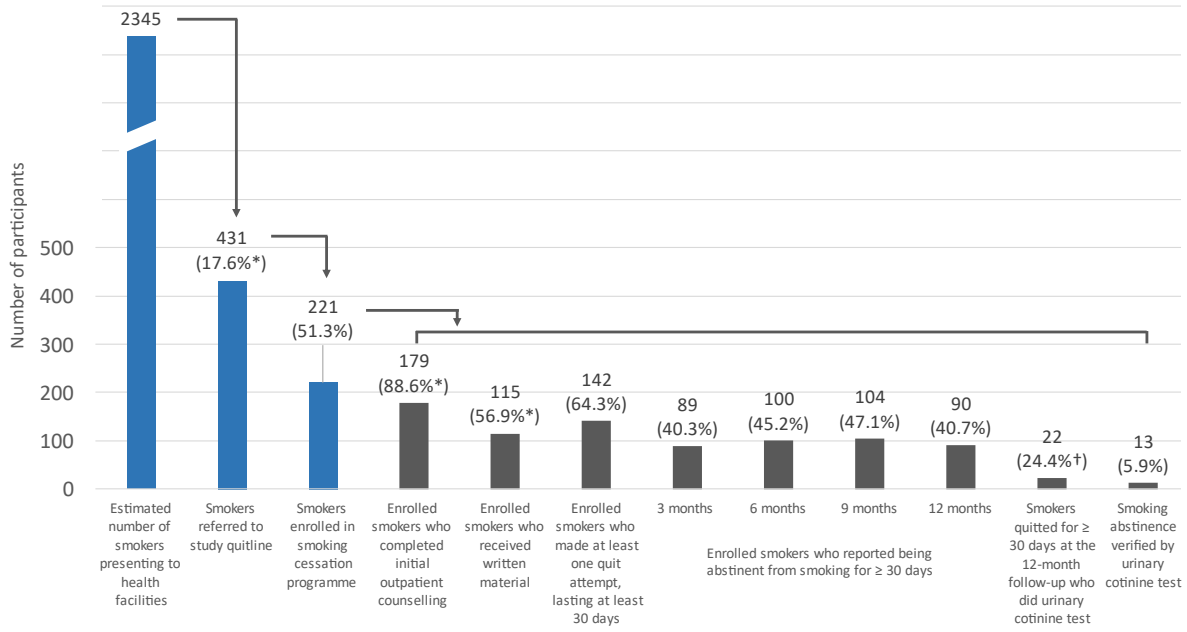

Figure 2. Proportion of smokers presenting to health facilities completing each step of the cascade. *Only patients referred by doctors included in the proportion calculation.

†Denominator is the 90 subjects with self-reported smoking abstinence at 12 months.

Among patients attending the Quitline, 179 (88.6%) reported that they received brief counselling by their doctor, and 115 (56.9%) received written smoking cessation material from the doctor (Figure 2). During the 12-month follow-up, 142 out of 221 enrolled subjects (64.3%) reported making at least one quit attempt that lasted at least 30 days. At the end of the study, 90 (40.7%) reported abstinence from smoking for at least 30 days. Among these, 22 (24.4%) agreed to take a urinary cotinine test, of which 13 (59% of those tested) returned a negative result. Overall, the proportion of verified quitters was 5.9% of those enrolled in the smoking cessation programme at 12 months.

Among the 221 enrolled smokers, 141 (63.8%) answered all 4 counselling phone calls within the first month and 117 (52.9%) answered all the 8 phone calls. The median number of successful phone calls made was 8 (interquartile range: 6 – 8).

Table 1 shows the baseline characteristics of the 221 enrolled smokers. All smokers were men, with a median age of 51 years (interquartile range: 38 – 61 years). The median score on the Fagerström Test for Cigarette Dependence was 6 (interquartile range: 4 – 8). The majority (73.8%) of smokers had attempted to quit at least once previously. Personal health was the main reason they expressed interest in quitting at the present encounter (95.5%). Only 4.1% referred to the expense of smoking as their reason to quit.

Table 2 compares the characteristics of participants by their final smoking status. Among all participant characteristics, the initial decision to specify a planned personal quit date was associated with an increase in successful quitting. Participants who set a personal quit date within 14 days from the baseline had a higher chance of quitting (still smoking vs. self-reported cessation, p=0.034; still smoking vs. biochemically-verified cessation, p=0.031).

Table 1. Baseline characteristics of smokers referred to the smoking Quitline

Characteristic	Total (n=221)
Demographic factors	
Age, median years (IQR)	51 (38 – 61)
Male sex, n (%)	221 (100)
Highest level of education attained, n (%)	
Less than primary	3 (1.4)
Primary	5 (2.3)
Lower secondary	92 (41.6)
Upper secondary	78 (35.3)
University degree, or equivalent, or higher	43 (19.5)
Smoking-related factors	
Median average number of cigarettes/day (IQR)*	20 (10 – 30)
Score on the Fagerström Test for Cigarette Dependence at baseline (IQR)*	6 (4 – 8)
Median years smoking (IQR)	25 (15 – 40)
At least one prior quit attempt, n (%)	163 (73.8)
Drink alcohol every day, n (%)	83 (37.6)
Drink caffeinated drinks every day, n (%)	157 (71.0)
Living with at least one other smoker, n (%)	53 (24.0)
Reasons given to quit, n (%)	
Personal health condition	211 (95.5)
Family's health	28 (12.7)
Expense	9 (4.1)

*63 missing values
IQR, interquartile range

Table 2. Comparison of characteristics by participants' smoking status at the end of study

Characteristic	Continuing to smoke at 12 months	Self-reported smoking cessation at 12 months	Biochemically-verified smoking cessation at 12 months
Total	128	77	13
Demographic factors			
Age, median years (IQR)	50 (37.5 – 59)	50 (38 – 61)	56 (51 – 61)
Highest level of education attained, n (%)			
Less than primary	2 (0.6)	1 (1.3)	0 (0)
Primary	2 (1.6)	3 (3.9)	0 (0)
Lower secondary	52 (40.6)	32 (41.6)	6 (46.2)
Upper secondary	47 (36.7)	25 (32.5)	6 (46.2)
University degree, or equivalent, or higher	25 (19.5)	16 (20.8)	1 (7.7)
Smoking-related factors			
Median average number of cigarettes/day (IQR)*	20 (10 – 30)	20 (10 – 30)	10 (5 – 17.5)
Score on the Fagerström Test for Cigarette Dependence (IQR)*	6 (5 – 8)	6 (5 – 7)	5 (2.5 – 6)
Median years smoking (IQR)	22 (15 – 40)	30 (15 – 40)	30 (30 – 36)
Ever attempted to quit in the past, n (%)	92 (71.9)	60 (77.9)	9 (69.2)
Drink alcohol every day, n (%)	44 (34.4)	33 (42.9)	3 (23.1)
Drink caffeinated drinks every day, n (%)	95 (74.2)	50 (64.9)	10 (76.9)
Living with at least one other smoker, n (%)	32 (25.0)	17 (22.1)	3 (23.1)
Reasons given to quit, n (%)			
Personal health condition	123 (96.1)	73 (94.8)	12 (92.3)
Family's health	15 (11.7)	11 (14.3)	2 (15.4)
Expense	8 (6.3)	1 (1.3)	0 (0)
Quitting-related factors			
Advised to quit by referral doctor, n (%)†	103 (87.3)	64 (90.1)	11 (100)
Received written material from referring doctor, n (%)‡	68 (57.6)	40 (56.3)	6 (54.6)
Days from baseline to target quit date, n (%)			
Less than 14 days	87 (68.5)	62 (79.5)	11 (100)
14 days or more, or did not commit to a target quit date	40 (31.5)	16 (20.5)	0 (0)
Number of successful counselling phone	7 (5 – 8)	8 (7 – 8)	8 (7 – 8)

calls, median (IQR)			

*63 missing values; †18 missing values

IQR, interquartile range

Table 3. Logistic regression showing factors associated with self-reported smoking cessation for at least 30 days at 12-month follow-up

	Odds of self-reported cessation at 12 months	
	Model 1	**Model 2**
Variables included in the model	Adjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Age, years	0.99 (0.95 – 1.04)	1.00 (0.96 – 1.04)
Highest level of education attained		
Lower secondary and less*	Reference	
Upper secondary	0.41 (0.16 – 1.04)	0.63 (0.31 – 1.30)
University degree, or equivalent, or higher	0.87 (0.27 – 2.76)	1.09 (0.42 – 2.81)
Average number of cigarettes/days	1.03 (0.98 – 1.08)	-
Fagerström Test for Cigarette Dependence		
Low (<4)	Reference	-
Moderate (4-6)	1.44 (0.42 – 4.89)	-
High (7-10)	0.36 (0.09 – 1.46)	-
Years smoking (for each additional year)	0.99 (0.94 – 1.04)	1.01 (0.97 – 1.04)
Ever attempted to quit in the past	1.39 (0.50 – 3.85)	1.29 (0.62 – 2.66)
Drink alcohol every day	1.11 (0.47 – 2.59)	1.35 (0.71 – 2.58)
Drink caffeinated drinks every day	0.62 (0.24 – 1.61)	0.74 (0.37 – 1.50)
Living with at least one other smoker	1.22 (0.41 – 3.63)	0.92 (0.42 – 1.99)
Reasons given to quit (Yes vs. No)		
Personal health condition	0.47 (0.06 – 3.57)	1.17 (0.22 – 6.28)
Family's health	0.69 (0.13 – 3.64)	2.08 (0.68 – 6.38)
Expense	0.21 (0.02 – 2.62)	0.20 (0.02 – 1.84)
Advised to quit by referral doctor	1.23 (0.31 – 4.89)	1.36 (0.46 – 4.00)
Received written material from referral doctor	0.97 (0.40 – 2.35)	0.83 (0.44 – 1.56)
14 days or more, or did not decide a target quit date	Reference	Reference
Less than 14 days	1.75 (0.69 – 4.43)	**2.23 (1.06 – 4.67)†**
Number of successful counselling phone calls		
5 calls of less	Reference	Reference
6 – 7 calls	**7.46 (1.53 – 36.24)†**	**3.86 (1.28 – 11.67)†**
All 8 calls	**12.17 (2.87 – 51.69)†**	**6.98 (2.50 – 19.49)†**

*Combined due to small numbers in less than primary and primary levels

†Statistically significant (p<0.05).

Results of the exploratory regression model of factors associated with self-reported smoking cessation are shown in Table 3. Smokers who had more successful counselling phone calls were more like to have quit (6 – 7 phone calls vs. five calls or less, odds ratio 7.46, 95% CI 1.53 – 36.24; all eight phone calls vs. five calls or less, odds ratio 12.17, 95% CI 2.87 – 51.69). We did a second model excluding Fagerström Test for Cigarette Dependence and average number of cigarettes per day, the two variables with a high proportion of missing values. The estimates in the second model were similar to the first model, except for days from baseline to personal quit date that became statistically significant in the second model. A personal quit date of less than 14 days from baseline were associated with a higher chance of self-reported cessation (odds ratio 2.23, 95% CI 1.06 – 4.67) when compared with ≥ 14 days or no target quit date. Because of the small number of biochemically-verified smoking cessation observations, a regression model was not performed to evaluate associations with confirmed cessation [21].

DISCUSSION

In the single-arm intervention study, we evaluated the feasibility of a smoking cessation intervention that recruited participants in three rural district hospitals in Vietnam. About half of smokers referred to the study Quitline were eligible and agreed to join the smoking cessation programme. More than half of participants answered all eight planned counselling phone calls. Two-third of participants made at least one quit attempt that lasted for more than 30 days. Around 40% of participants reported abstinence from smoking at the end of the study but only a small proportion of these self-reported quitters did urinary cotinine test. Overall, 5.9% of all participants achieved verified smoking cessation for more than 30 days 12 months after enrolment.

Quitline and text messaging are proven effective interventions to support smoking cessation. The low-cost nature made the two interventions suitable for widespread use, especially in resource-limited settings [10]. However, most Quitlines and text messaging require smokers to call or sign up first. In our study, the two interventions were combined as a smoking cessation programme operated by one Quitline centre, using existing infrastructure. The integration of the smoking cessation programme with brief advice provided by healthcare

workers and referral from hospitals to a centralised call facility provides a model that could readily be scaled up more widely. A high retention rate and high participation rate in counselling phone calls also demonstrated the feasibility of the intervention.

We found an association between number of successful counselling phone calls and self-reported quitting. In existing literature, the association between planned number of calls and quit rates is inconsistent. A recent Cochrane review found some evidence that interventions with three to six calls may be more effective than those offering only one call [22]. The authors suggested further studies directly comparing different numbers of counselling calls to consolidate the evidence. As the actual number of phone calls delivered may differ from planned number, as in our study, we also suggest research evaluating the effect and potential dose-response of number of counselling phone calls on quit rate.

Despite the strength of the integrated intervention, we found a low proportion of smokers at healthcare facilities were referred by healthcare workers to the study Quitline. This could be explained by several factors. First, not all doctors were willing to take part in the study and refer their patients to our Quitline. Second, doctors may have not advised their patients to quit due to high patient loads in the clinics or their lack of confidence on smoking cessation [23, 24]. There is evidence that even very brief advice can improve quit rates [25]. Doctors should be encouraged to talk with their patients about quitting smoking, even in very short time, and provide available resources.

We found few healthcare workers volunteered to participate in the programme as smokers. A previous survey from three large hospitals in Vietnam showed a 35.6% smoking prevalence among male health professionals and 23% among doctors [26]. Healthcare professionals' smoking behaviour may lead to less commitment to providing cessation suggestions, or less confidence in counselling [5]. Further studies are needed to evaluate the barriers to healthcare workers participating in smoking cessation interventions. Interventions targeted towards healthcare workers who are smokers should be considered in Vietnam, both for their health and for the benefit of their patients.

This study has some important policy implications. The Vietnamese government's Directive

05/CT-BYT in 2013 emphasised the importance of scaling up smoke free hospitals. This decision is supported by a guide for implementation, developed by the Vietnamese Committee on Smoking and Health, that has been piloted in nine hospitals across Vietnam [17, 27]. However, this policy has not yet been widely adopted. In our study, we encouraged the hospitals to strengthen smoke-free hospital, yet little was planned after study commencement. Further actions are needed to ensure proper implementation of Vietnamese regulations around smoking cessation within health facilities, and greater resourcing to support the smoke-free hospital policy.

The study has several limitations. First, a high proportion of participants who reported abstinence did not complete a urinary cotinine test at the end of study. Some of those who self-reported cessation may have not reported their smoking status correctly. Others may have refused due to the COVID-19 epidemic (99% of the study participants had their final contacts after March 2020). Second, it is possible that some infrequent smokers were misclassified due to the cotinine test strips, which give a single band result at a cut-off value. However, a false positive result due to environmental exposure to other sources of cotinine is unlikely, given the relatively high threshold of 200 ng/mL detected by the strips [28]. Third, were unable to implement a more comprehensive smoke-free hospital policy. Our research team will publish a formal qualitative assessment that was conducted recently on this topic. Finally, as this was a single-arm study, the effectiveness of the intervention cannot be determined. A cluster randomised controlled trial, with study design informed by this feasibility study, is currently ongoing to evaluate the effectiveness of the intervention in quitting smoking (ACTRN12620000649910).

CONCLUSIOINS

In conclusion, the integration of brief advice and referral from healthcare facility, Quitline counselling phone calls, and scheduled text messaging was feasible in rural hospitals in northern Vietnam. The scale-up of smoking cessation within hospitals, for both clinicians and patients, is an important priority within the local healthcare system.

List of abbreviations

LMICs: Low- and middle-income countries

Declarations

Ethics approval and consent to participate

Healthcare workers obtained verbal consent from patients to receive brief counselling and to authorise their phone numbers to be sent to Quitline staff. Additional verbal consent was provided during the initial phone call, to enable data collection, participation in counselling and follow-up. Ethical approval was provided by the Human Research Ethics Committee at the University of Sydney (Protocol 2018/769), and the Institutional Review Board of the Bach Mai Hospital, Hanoi, Vietnam (Approval 3497/QD-BM).

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None declared.

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Authors' contributions

GJF, GBM, and Thu Anh Nguyen conceptualised the study idea. WCH, GJF, GBM, QCN, VNN, SJ, and JN designed the study. NYP and Thuy Anh Nguyen coordinated the project implementation. Thu Anh Nguyen, VGV GCN, and VNN assisted research activities and resources. GJF and GBM obtained funding for the study. WCH and GJF analysed and interpreted the data. WCH wrote the manuscript. All authors reviewed and commented on

the manuscript.

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Not applicable

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Chapter 7. Process evaluation of the stepped treatment algorithm

The overall aim of the VCAPS study was to characterise the current practice related to CRD and smoking cessation in healthcare facilities and propose interventions that can be implemented and scaled up in Vietnam. To achieve this aim, it is critical to also evaluate local context and associated barriers and facilitators in order to understand if the interventions would work outside of study settings, and how the interventions should be strengthened to improve implementation and effectiveness of the interventions. This chapter shows how I applied process evaluation to the VCAPS3 study to identify modifiable factors that affect the implementation and effectiveness of the CRD intervention.

Healthcare experiences of patients with chronic respiratory diseases in Vietnam

The nature of healthcare provided to patients with CRD has not been well characterised in Vietnam. In Chapter 3, I showed that more than half of patients with airflow obstruction did not receive inhaled medicines from healthcare facilities or providers. A recent qualitative study explored the pathways patients with asthma or COPD in Vietnam utilise to access health care [1]. The authors conducted in-depth interviews with 41 patients with COPD, asthma, or asthma-COPD overlap. They found that patients generally visited multiple healthcare facilities before a definitive diagnosis was made at a provincial hospital or a national hospital. Several factors associated with access to healthcare were identified, including participants' knowledge of their respiratory conditions, availability of social support, costs of healthcare services, public health insurance coverage, distance to healthcare facilities, and attitude toward healthcare providers.

Chapter 5 shows the feasibility of a treatment algorithm using inhaled budesonide-formoterol for patients with CRD visiting district hospitals (the VCAPS3 study). In this chapter, I aimed to further explore factors affecting implementation and the effects of the intervention on patients' clinical outcomes by using a process evaluation.

7.1. Implementation science, complex intervention, and process evaluation

Implementation science and complex intervention

Implementation science, or implementation research, is a research discipline that seeks to address the challenges of know-do gaps in real-world settings. Implementation science uses systematic research methods to improve knowledge translation, supporting quality improvement, and informing scale-up [2]. The emphasis of implementation science is a "dynamic adaptation to local context, stakeholders, local care resources, and end-user engagement in understanding how and why change processes work [3]."

A complex intervention is one that includes multiple interacting components and non-linear causal pathways [4]. Other definitions suggest that the complexity also involves the number and difficulty of behaviours required by healthcare providers or patients, and the flexibility in the intervention permitted when conducting the work [5]. Complex interventions follow theory driven processes, yet vary in forms when implemented in different contexts [6].

A randomised controlled trial in India evaluating the effectiveness of family-led rehabilitation after stroke in preventing death and dependency provides an example of the application of implementation science to the study of a complex problem and intervention [7]. The intervention followed the principles of implementation science. A pilot study determined the feasibility of the intervention before the randomised controlled trial [8]. The intervention was designed to be affordable when scaled-up. It was delivered in addition to the routine rehabilitation at the study sites. The intervention was a complex intervention, suggested by the multiple components described in the paper, including training family members to provide simplified evidence-based rehabilitation at home, impairment and disability assessment by a rehabilitation professional, joint goal setting with the patient and caregiver for activities of daily living, caregiver training for limb positioning, and encouragement of the practice of task-specific activities.

Process evaluation for implementation science

The UK Medical Research Council (MRC) defines process evaluation as a study that aims to provide a detailed understanding needed to inform policy and practice by examining implementation, mechanisms of impact, and contextual factors [9]. A process evaluation can be conducted during the feasibility stage, alongside the evaluation of effectiveness, or during the scale-up of an intervention.

Various approaches are available when conducting process evaluation for the implementation of a complex intervention. The UK MRC provided a guidance on evaluating complex intervention in 2008 and developed a well-cited process evaluation framework in 2015 (Figure 7.1) [5, 9]. Apart from the UK MRC process evaluation framework, researchers have developed different theories, models and frameworks to assess the process of implementation.

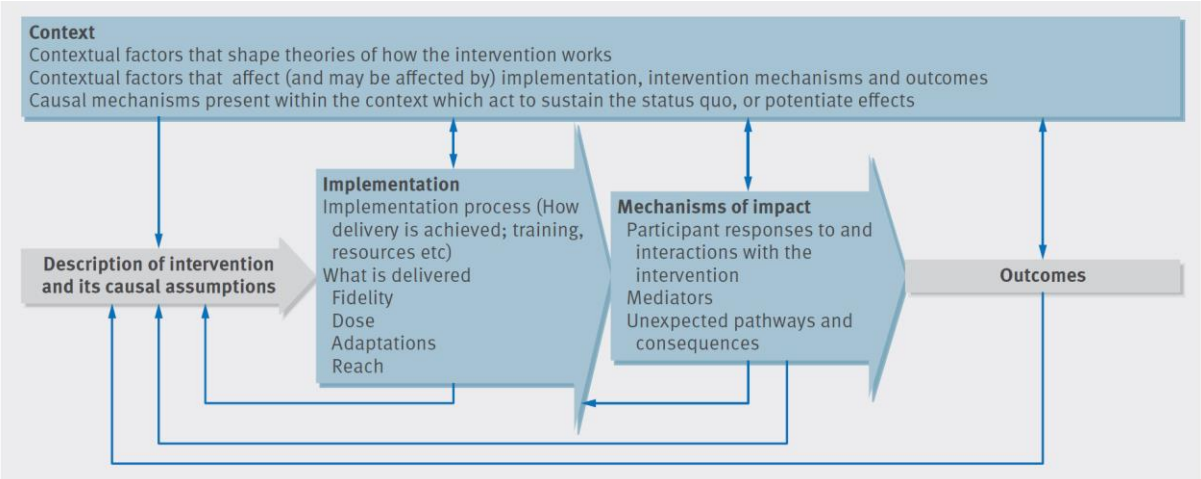

Figure 7.1. UK MRC process evaluation framework[9]

Nilsen classified these approaches into three categories according to the purpose of evaluation: (a) describing and/or guiding the process of translating research into practice, (b) understanding and explaining what influences implementation outcomes, and (c) evaluating implementation [10]. For example, the Canadian Institutes of Health Research Model of Knowledge Translation, in the first category, describes the cycle of the knowledge to application process [11]. Another example is the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework in the third category that assesses five dimensions of implementation endeavours [12]. The RE-AIM framework has been widely applied in different fields, including disease management [13]. Lemanske *et al.* used the RE-AIM framework to assess the implementation of a school-based asthma management plan comprised of four components for children with asthma [14]. Examples of indicators for the RE-AIM framework in this study include the number of schools trained in the program (Reach), number of school days missed for children with asthma as compared to that for

children without asthma (Effectiveness), and number of schools approached and number using the program (Adoption).

7.2. Material and Methods

Description of intervention in the VCAPS3 study

The intervention in the VCAPS3 study was a complex intervention that centred around the stepped budesonide-formoterol. Figure 7.2 describes the components of the intervention that, directly or indirectly, have an impact on the risk of exacerbations. For instance, the availability of spirometry could confirm the diagnosis of CRD and avoid misdiagnosis and treatment delay. Another example is inhaler technique. An inadequate inhaler technique leads to ineffective drug delivery and subsequent poor disease control. Therefore, the stepped budesonide-formoterol inhaler treatment should be provided together with other measures to maximise the effect of the drug.

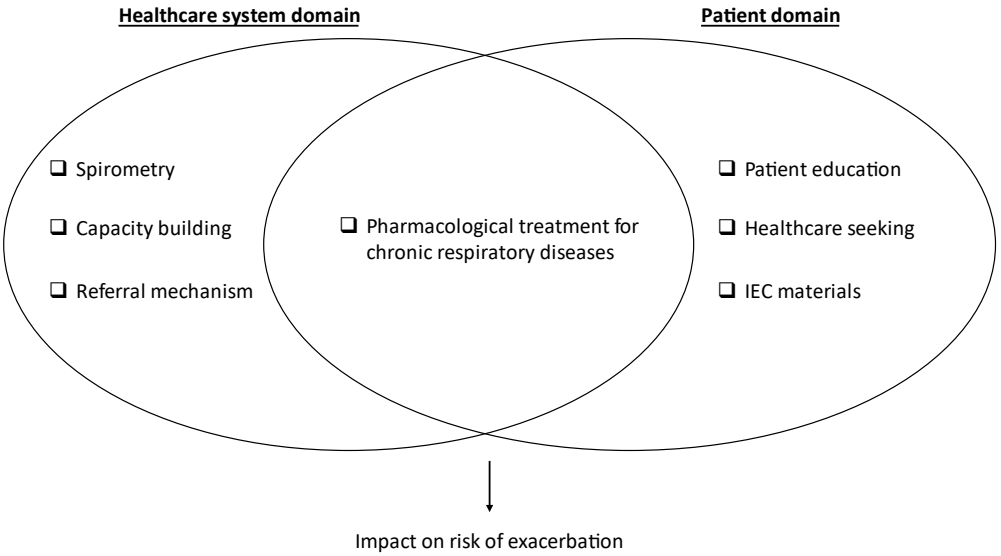

Figure 7.2. The intervention implemented in the VCAPS3 study

Framework and source of data for process evaluation

I adapted the RE-AIM framework for this process evaluation. Table 7.1 show the indicators that I defined for the five dimensions of the RE-AIM framework. Both quantitative and qualitative data were used for this process evaluation. The results of quantitative data have been shown in Chapter 5, including exacerbations of CRD and a cascade of care that measured the proportions of patients lost in each step along the cascade. Qualitative data

contained semi-structured interviews with patients enrolled in the VCAPS3 study. The semi-structured interviews were a qualitative sub-study of the VCAPS3 that aimed to explore patients' experience and opinions about the intervention, and to identify modifiable factors that may influence patients' adherence to the intervention. Reports from monitoring visits were also reviewed to identify relevant issues. In addition, we interviewed doctors working in the three hospitals involved in the VCAPS3 study one year after completion of the study to understand how their practice has changed.

Table 7.1. RE-AIM framework and associated indicators for the implementation of the VCAPS3 intervention

Dimension	**Indicator**	
Reach	Quantitative data	• The number of hospitals with available spirometry and maintenance inhalers before and during the study • The proportion of individuals meeting the criteria for screening who were referred for screening • The proportion individuals meeting the criteria for treatment who were enrolled
	Qualitative data	• Patients' opinion and experience of access to healthcare and medications, and factors associated with access
Effectiveness	Quantitative data	• The impact of the CRD intervention on the outcome. The outcome refers to the proportion of individuals enrolled in the CRD intervention reporting one or more acute exacerbations over the study period.
	Qualitative data	• Patients' subjective descriptions about disease control and health-related quality of life
Adoption	Quantitative data	• The number of doctors within the district hospitals that adopt the CRD intervention
	Qualitative data	• Doctors' opinion toward the intervention
Implementation	Quantitative data	• The proportion of individuals who completed lung function test among those referred for screening • The proportion of individuals who had valid spirometry results among those referred for screening • The proportion of individuals returned for the scheduled follow-up four weeks after enrolment.
	Qualitative data	• The level of fidelity to the various components of the CRD intervention (Figure 7.2), including consistency of delivery as intended and adaptations

		made. Examples include provision of inhaler technique education, the use of IEC materials, and follow-up visits to the district hospitals
Maintenance	Quantitative data	• The number of hospitals with available spirometry and maintenance inhalers after completion of the study
	Qualitative data	• The extent to which the various components of the CRD intervention (Figure 7.2) becomes institutionalised or part of the routine organizational practices of district facilities. • Patients' preference for follow-up visits to hospitals

Recruitment and sampling of the qualitative sub-study

We recruited patients who had participated in the VCAPS3 study for at least three months for the qualitative sub-study. A purposive sampling strategy with maximum variation was applied to select the participants of this qualitative sub-study. We included adult patients from all three hospitals. Patient characteristics considered for maximum variation included sex, age, treatment step, baseline symptom score, and severity of airflow limitation. The intended sample size was 10 to 20 participants until thematic saturation was reached. We invited patients by phone calls and arranged face-to-face interviews.

Interviews and data collection

Participants were interviewed in Vietnamese in a quiet room in their registered hospitals. Three local Vietnamese research staff employed by the Woolcock Institute of Medical Research conducted the interviews using a semi-structured interview guide (Appendix 3). The three interviewers had previous experience conducting qualitative interviews. The investigators and the interviewers discussed the interview guide in advance to ensure a consistent understanding of the questions. The interviewers had no prior relationships with participants before the interview.

Interviews lasted from 22 to 75 minutes, with a median length of 35 minutes. Interviews were audio-recorded. A detailed English summary based on listening to the audio recordings was written up by the same interviewer. Verbatim Vietnamese transcripts were also generated from the audio recordings.

Qualitative data analysis

I analysed the interview summaries and the transcripts using reflexive thematic analysis [15], with assistance from one of the Vietnamese interviewers who had experience with thematic analysis. Reflexive thematic analysis, developed by Braun and Clarke, belongs to one of the three main types of thematic analysis. The emphasis of reflexive thematic analysis is to conceptualise themes as patterned meanings across the dataset, with the researcher being actively engaged in the process of analysis and interpretation. The philosophy of reflexive thematic analysis contrasts with the coding reliability thematic analysis that seeks to identify the "accurate and agreed" codes/themes within data [15].

I first familiarised myself with the data by reading the interview summaries and transcripts multiple times before a set of codes was generated. The coding data was charted together and examined to conceptualise themes. The themes and the thematic map were informed by discussions among the research team. The codes and themes were then revised after review and discussion with the Vietnamese interviewer. I applied the revised themes back to the dataset. Verbatim quotes that demonstrated the ideas of the themes were selected and translated to English by the Vietnamese interviewer. The coding process was done using NVivo (Version 12, QSR International, Doncaster, Australia).

Informed consent and ethics approval

We obtained verbal consent during the phone call invitation after explaining the purpose and procedure. The interviewer also obtained written consent before interviewing a participant.

This qualitative sub-study and the interview guide were approved by the human research ethics committee of the University of Sydney before commencement.

7.3. Results

Qualitative sub-study

Seventeen patients completed the semi-structured interview. The baseline characteristics of the participants are shown in Table 7.2. Four themes related to the components of the implementation were conceptualised from the reflexive thematic analysis (Figure 7.3). The

first three themes (i.e. trust and relationships, patient's experiences of clinical management, and treatment-related factors) interacted with each other and all of them affected patient behaviour. Table 7.3 shows the definition for each of the themes. These themes were elaborated further, in addition to the quantitative indicators, under the RE-AIM framework in the following sections.

Table 7.2. Characteristics of patients participating in the qualitative sub-study

Characteristics (n=17)	
Age, median (interquartile range)	54 (48 – 61)
Male sex, n (%)	12 (70.6)
Diagnosis at baseline, n (%)	
Chronic obstructive pulmonary disease	10 (58.8)
Asthma	7 (41.2)
Highest education attained, n (%)	
Less than primary education	2 (11.8)
Primary education	3 (17.7)
Lower secondary	10 (58.8)
Higher secondary	2 (11.8)

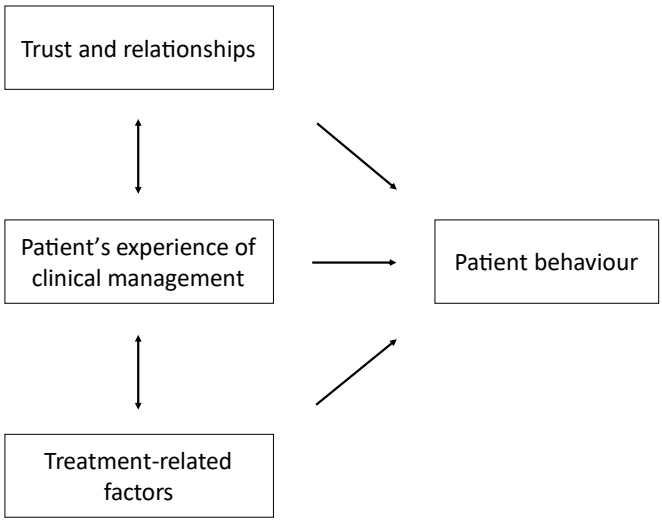

Figure 7.3. Themes conceptualised from the thematic analysis

Table 7.3. Definitions of the four themes conceptualised from the thematic analysis

Theme	**Definition**
Trust and relationships	Patient's trust in healthcare facilities and patient's relationships with healthcare workers, research staff, patient's family, and

	neighbours.
Patient's experience of clinical management	The clinical care patients received, such as examinations, health education from healthcare workers, self-care materials, and follow-up visits.
Treatment-related factors	Factors associated with drug therapy before and after study enrolment. These factors included perceived effectiveness of treatment, device attributes, and treatment burden.
Patient behaviour	Behaviours of patients that are associated with disease control. These include adherence to treatment recommendation, inhaler use, self-care, and healthcare seeking behaviour.

The findings of the process evaluation in relation to the intervention and contextual factors are summarised in Table 7.4.

Reach (access to healthcare and medications)

Most patients had access to healthcare and medications before joining the study, though the pathways patients went through varied among the interviewed participants. Participants described visiting different healthcare facilities to treat their respiratory conditions. These healthcare facilities included district hospitals, provincial hospitals, central hospitals, private clinics, and private pharmacies. Drug prescriptions from healthcare facilities included oral medicines, injections, and inhaled medicines (both budesonide-formoterol and other inhalers). However, less than half of the interviewed participants had experience using inhaled medicines before. Some patients also bought medicines, including antibiotics and inhalers, directly from private pharmacies, which were prevalent and readily accessible in Vietnam.

Table 7.4. Summary of the process evaluation findings using the RE-AIM framework

Dimension	Finding	
Reach	Healthcare seeking	• Overall good access to healthcare • Patients visit various healthcare facilities for their respiratory conditions • District hospitals more often visited than higher-level facilities due to distance and health insurance policy • High rate of consent to joining VCAPS3 among eligible patients
	Pharmacological treatment	• Poor access to maintenance inhalers before VCAPS3 • COPD/Asthma Management Programme is key for health insurance coverage for maintenance inhalers
	Spirometry	• Spirometer not routinely available in district hospitals • Low referral rate for spirometry testing in VCAPS3
Effectiveness	Pharmacological treatment	• Experience of ineffective therapies from different kinds of health facilities before joining VCAPS3 • Subjective improvement in symptoms, exacerbation rates, and healthcare-related quality of life after joining VCAPS3
	Patient education	• Effectiveness of study drug affected by inhaler education and inhaler technique
	Information, education, and communication materials	• Poor utilisation of the VCAPS3 materials by some patients, leading to nonadherence to recommended drug dosing
Adoption	Capacity building	• Being able to manage patients with CRD using maintenance inhaler was an incentive for doctors to participate in VCAPS3
	Pharmacological treatment	• Experience with VCAPS3 led to application for COPD/Asthma Management Programme in order to make maintenance inhalers available
Implementation	Capacity building	• Technicians could do spirometry with good quality following a short training course and 1-week on-site supervision • Pharmacists were able to incorporate inhaler education into routine practice
	Information, education,	• VCAPS3 materials were not well utilised by patients

	and communication materials	• Positive feedback from doctors about experience using diabetes and hypertension booklets provided insights for modifying VCAPS materials
	Pharmacological treatment	• Doctor's decision on treatment step escalation depended on multiple factors
	Patient education	• Pharmacists did not always assess inhaler technique of the patients • Patients could follow the instruction not to self-medicate from private pharmacies
	Healthcare seeking	• The majority of patients would return to registered district hospital for uncontrolled symptoms • Patients may seek examination at a higher-level facility by themselves due to low trust to district hospital
	Referral	• Patients may refuse to visit referral hospital due to long distance or experience of ineffective treatment from the referral hospital
Maintenance	Spirometry	• One participating district hospital cannot do spirometry testing even with a spirometer the test has not yet approved for health insurance coverage for this hospital
	Pharmacological treatment	• One participating district hospital has no maintenance inhalers available because their application to COPD/Asthma Management Programme is still awaiting approval
	Patient education	• Pharmacists in the three district hospitals declined to provide inhaler education after the study

Access to healthcare and medicines depended on several factors, including cost, distance to healthcare facilities, and support from family. In Vietnam, patients need a referral from their registered district hospital in order to seek healthcare at a higher-level facility. Patients who visit provincial/central hospitals without a referral will face higher out-of-pocket expenses to get examinations and treatment. Patients who cannot ride motorcycles rely on their families to come to the hospital, especially those who live in rural areas. Also, patients with chronic conditions managed through health insurance schemes preferred district hospitals for regular visits and drug prescriptions. One of the schemes is COPD/Asthma Management Programme, by which outpatients with COPD or asthma can receive inhalers regularly from the hospital [16]. Therefore, patients generally visited district hospitals more often because the cost was covered by public health insurance and district hospitals were close to their home.

Among the three hospitals in the VCAPS3 study, two had a spirometer and one had a supply of maintenance inhaled medicines for asthma before the study. During the study implementation, all three hospitals used the handheld spirometer and inhaled budesonide-formoterol that we provided for the VCAPS3 study.

Data from Chapter 5 showed a low rate of referral for spirometry. According to the estimation, less than 10% of patients with symptoms consistent with CRD were referred to do spirometry. Among those referred, more than 70% were diagnosed with CRD and the majority started the treatment. The findings suggested that doctors did not refer patients for spirometry according to the eligibility criteria. Instead, they referred patients based on their clinical impressions (i.e. referred patients with a tentative diagnosis of COPD or asthma). Even though a high proportion of patients was confirmed to have CRD, more may have been misdiagnosed with other diseases.

The acceptance rate for participation in the study was high. Only about six per cent of eligible patients declined to join. The majority of interviewed participants reported that the treating doctor introduced the study and encouraged them to join for the benefit of their health. One patient joined the study after his relative found out the information about this study on the Facebook page of the district hospital. Another patient was informed by a

neighbour. When talking about reasons for joining the study, apart from the suggestion from the doctor, free drugs and examinations was a common factor reported by the participants.

Effectiveness of treatment

Despite good access to healthcare and medicines, most interviewed participants shared negative experiences with previous treatment, even inhaled medicines. Patients described those drugs as not effective, only helped a little bit, or only reduced symptoms for a short period of time.

> A: "I was prescribed antibiotics and other drugs, but it was effective temporarily, only for a short period. I always had to use the medicine." (Male, 66 years)

After joining the study, 47% of patients experienced acute respiratory symptoms that required healthcare visit(s) to a hospital or clinic during the follow-up period. Even though the number was similar to observational studies of patients with COPD or asthma, we cannot determine the effectiveness of the intervention statistically due to its single-arm design. However, almost all participants in this qualitative sub-study reported an improvement in disease control, either less day-to-day respiratory symptoms or less frequent exacerbations, after joining the study. Participants also indicated that they experienced a reduced burden due to treatment and improved quality of life, leading to their willingness to continue the treatment. Patients' subjective descriptions indicated that the treatment in the VCAPS3 study was effective for them.

> A: "When I had the symptoms, I inhaled 1 puff immediately. This morning, I felt very good after inhaling. You see, I can go upstairs and go downstairs, can walk around the hospital, then came here [for the interview]. My health is much better now." (Male, 65 years)

The effectiveness of the treatment in the study might have been affected by other factors, as suggested from the qualitative data. These factors included incorrect inhaler technique, inadequate self-care (such as self-medication and not following the management plan), and lack of inhaler education by pharmacists. For example, one patient reported that he did not

find the study drug useful during the first month of the study when he was using the drug incorrectly. Following the instruction of inhaler technique at the four-week follow-up, his symptoms improved a lot. Another patient still used SABA prescribed by a central hospital along with the study drug after enrolment.

> A: "I have used few times, but I felt that I did not use it correctly . . . I have asked [the healthcare workers] when I returned to the clinic. I was instructed on the inhaler usage again, I practiced right after at the clinic. Since then, I have only used this drug [budesonide-formoterol] and no need to use other medicines." (Male, 57 years)

Adoption

Among doctors in the three hospitals treating patients with respiratory conditions, less than half actively worked with the research team in recruitment and patient follow-up. The rest did not participate in the study.

Doctors from the two hospitals where maintenance inhalers were not available before the study shared positive feedback about the intervention. Before the study, patients could only receive systemic corticosteroids and nebulisers when they developed exacerbations. Patients from the nearby communities had to visit other hospitals to get inhaled medicines. After participation, doctors could manage the majority of patients with CRD in their hospitals. This experience has led to their application for COPD/Asthma Management Programme in order to continue their care for patients with CRD after study completion.

Implementation

Before the study, leaders of the hospitals were engaged in order to gain their support for study implementation. At the one hospital where a spirometer was not available before, a separate room was designated for performing spirometry. Doctors, pharmacists, and technicians were made aware of their responsibilities during the training before study commencement. The research team also provided on-site supervision that lasted for one week at the beginning of the study.

Quantitative data showed that among patients referred for screening, 97.7% completed lung

function and 81.6% had valid spirometry results. More than 90% of enrolled patients returned for the 4-week follow-up re-examination.

As a part of the intervention, we provided written materials to patients, including a brochure and a management plan. The brochure contained basic health information about CRD, self-care, and an illustration of inhaler technique. The management plan, similar to an asthma action plan, explained how a patient should use the inhaler at different stages of disease control. Even though all interviewed participants indicated they received the materials from doctors, the majority either did not read the materials or could not read due to illiteracy. One patient believed the brochure was about smoking cessation. Another patient shared that he just followed the instructions from the doctor and did not pay attention to the content of the materials. However, during the interview, he gave the wrong information about the allowed daily dose, which was clearly stated in the management plan.

In the study, doctors decided and communicated the treatment step with their patients. Pharmacists were instructed to check and correct patient' inhaler technique when they dispense the drug to a patient. However, we found several issues related to inhaler use. Two interviewed participants misunderstood the maximum daily dose of budesonide-formoterol; one patient thought the maximum dose was five inhalations each day and the other thought he could only use the drug twice per day. Another patient used the study drug with the dosing frequency he was told at a higher-level hospital before he first received the drug in our study. Some patients from one hospital were not taught how to use inhaler when they received the inhaler from the hospital pharmacy. Even among those instructed, incorrect inhaler technique was still common when asked to show their steps of using the inhaler in front of the interviewer.

The study protocol did not dictate the frequency of follow-up after the 4-week re-examination. Most patients were instructed by their doctors to return when they run out of inhaler doses or if they still feel uncomfortable after using the study drug. During the interview, participants provided different perspectives regarding clinical follow-up. Some of them said that regular follow-up at the clinic was not necessary because of mild symptoms or because they can carry self-care properly. More of the participants believed that a regular

follow-up, such as monthly or every two months, helped to better monitor their condition. However, the preference for follow-up visits does not seem to reflect the patient's disease control but the patient's desire for feeling secure about their health.

A: "Regular examination is better, feels more save, and secure." (Female, 49 years)

With regard to implementation fidelity, we observed adaptations and inconsistency. One example was doctor's decision on escalating treatment step. During the follow-up, we noticed that the treating doctors did not escalate treatment for some patients who had an exacerbation. Upon further communications, the doctors provided justifications for their decision. First, some of the patients had an exacerbation due to poor inhaler technique, which the doctors corrected after noticing. Second, some other patients might have had exacerbations, but the exacerbations were less frequent or less severe compared to their conditions before the study. The doctors saw the clinical improvement and decided to continue the same treatment. Finally, for those who did not follow the treatment suggestions, the doctors reinforced the importance of compliance, instead of stepping up treatment immediately.

Another example was the referral to a higher-level facility. For patients who were not in proper control on Step 2 treatment, a referral for further evaluation was recommended in the protocol. We received reports from doctors that patients refused to visit the referral hospital. Two common reasons emerged from their conversations with patients. First, some patients did not consider their conditions so serious that visiting a distant hospital was necessary. The second one related to patients' past experience with the referral hospital. The treatment they received before from the referral hospital did not improve their symptoms. Therefore, these patients preferred to maintain the therapy from the district hospital.

As shown in the qualitative analysis, pharmacists in one hospital did not teach correct inhaler technique to some of their patients. During a monitoring visit, a pharmacist shared that sometimes they were too busy to check if patients could use the inhaler correctly. They gave the inhaler to a patient without assessment if that was not the first device dispensed to

that patient.

Patients' trust in the hospitals and relationships with the healthcare workers affected how they sought healthcare, even during the VCAPS3 study. Most interviewed participants followed the instruction to return to the district hospitals when their conditions were not stable. Some doctors from the three district hospitals called patients to check their health status and ask them to return for evaluation, even though this was not required by the study. Several patients shared that they stopped buying drugs from private pharmacy when they felt uncomfortable with their lung conditions after suggested by their doctors not to do so. However, there were also patients who worried about the quality of equipment in district facilities and described that they wanted extra examinations at a higher-level facility. One patient even visited a central hospital for examination without informing the doctor at the district hospital.

> A: "[If budesonide-formoterol is not effective] I would go to the hospital immediately to check my health status. For example, if I take medicine and I don't feel my symptoms are better or change, I have to check if my disease becomes worse, why the drug was not effective like before.
> Q: Would you immediately go to the local pharmacy to ask the pharmacist for drugs?
> A: No." (Male, 54 years)

Finally, research staff also played a role in affecting participants' behaviour. All patients in the VCAPS3 study received scheduled follow-up phone calls from research staff. In the calls, the research staff asked about exacerbations, symptom control, inhaler use, and reminded the patients to return to the clinic if their disease was not in good control. Most participants described the questions as easy to understand and felt happy and been cared for by the research staff. Participants also took the advice from the research staff to visit the district hospital for re-evaluation and treatment adjustment.

> A: "I was so happy when receiving the phone call. The staff asked me 'How is your health recently? How do you feel today?'" (Female, 69 years)

A: “The questions were easy to answer. The staff asked me ‘How do you use the study drug? How is your health condition recently, after participating in this study? How have your symptoms improved? We will contact you regularly, please keep contact with us . . .’ The staff really cares about my health condition.” (Male, 66 years)

Maintenance after the pilot study

Before the study was closed, we discussed with the three hospitals their plans on patients enrolled in the study and procurement, such as spirometers and inhaled medicines. Relevant information was collected during follow-up communications with doctors one year after study completion.

The hospital with no spirometer before the study received a spirometer sponsored by a pharmaceutical company after study completion. However, payment for spirometry in this hospital has not been approved to be covered by public health insurance. Spirometry test remains unavailable even though the device is there. The other two hospitals continue to perform the test as before.

Availability of maintenance inhalers differs among the three hospitals after the study. One hospital has budesonide-formoterol and fluticasone-salmeterol, but the doctors can only prescribe the inhalers to inpatients upon discharge. The hospital is still awaiting the result of their application for the COPD/Asthma Management Programme. Hence, all patients with CRD enrolled in this hospital are being treated at other hospitals. The second hospital has budesonide-formoterol and is included in the COPD/Asthma Management Programme. Doctors still treat and follow the majority of the VCAPS3 participants. The last hospital has made fluticasone-salmeterol available after their success in applying for COPD/Asthma Management Programme. Some patients from the study preferred to continue budesonide-formoterol after study completion. Since the hospital cannot provide budesonide-formoterol, part of these patients moved to another hospital and the remaining buy budesonide-formoterol themselves and continue to be followed at this hospital.

In terms of patient education, all pharmacists in the three hospitals only dispense drugs after the study. They no longer check inhaler technique and instruct patients, claiming that

this is not a responsibility of their job.

7.4. Discussion

The process evaluation using the RE-AIM framework confirmed the feasibility of the complex intervention in rural district hospitals in Hanoi, Vietnam. We found that implementing the intervention at district hospitals allowed a high reach to patients with CRD living in the communities around the hospitals. We also identified some factors that require special attention in order to improve patients' outcomes, such as insufficient use of management plan and inhaler education.

Our findings showed that access to inhaled medicines and prompt diagnosis, but not healthcare, was an issue in the Vietnamese health system. Most patients were able to seek healthcare at different levels, from private pharmacies to central hospitals. However, more than half of the interviewed patients had no prior experience of using inhaled medicines, suggesting that patients had either not been diagnosed with CRD or not provided with inhaled medicines due to unavailability in the health facilities. The findings were consistent with the results from Chapter 3 and the study describing healthcare pathways of patients with COPD or asthma [1].

The availability of inhaled medicines and spirometers in a public healthcare facility in Vietnam depends largely on the payment list of health insurance at that facility. To make both inhaled medicines and spirometry test institutionalised, the hospital needs approval for its' application for COPD/Asthma Management Programme. The inclusion of inhaled medicines in health insurance coverage will also reduce the financial burden to patients. A prerequisite of the approval is a 1-month training to the spirometry technician and at least one doctor from the hospital. They are required to undertake the training at a provincial hospital or a central hospital to ensure the quality of care [16]. The procedure may pose difficulties to district hospitals where human resource is often a challenge. There have been only 20-25% of district hospitals in Vietnam qualified for this programme since its establishment in 2011 (verbally reported by Secretary General of the Viet Nam Respiratory Society upon my inquiry in September 2021).

To improve diagnostic accuracy for patients with chronic or repeated respiratory symptoms, spirometry testing should be emphasised. The test can assist evaluating symptoms and screen individuals at risk of pulmonary disease [17]. The intervention was designed to identify and reach more patients with CRD at the grassroots level of the healthcare system. To achieve this objective and increase uptake of effective treatment during a scale-up, doctors should be encouraged to utilise spirometry more often when it is available.

Evidence has shown pharmacists' role in improving inhaler technique and medication adherence of patients with CRD [18, 19], yet we found a critical issue regarding inhaler education that should be addressed. After the study, pharmacists refused to offer inhaler education to patients and considered this not a duty of theirs. Challenges of pharmacists in the Vietnamese healthcare system have been studied, including shortage of pharmacists, insufficient competency, and lack of recognition of being medication counsellors [20, 21]. The coordination of clinical work in district hospitals is urgently needed to ensure the delivery of adequate patient care.

An important observation from the study was the suboptimal utilisation of educational materials to patients. The information in the management plan provided guidance about inhaler dosing at different levels of symptoms. Similar materials have been used widely for patients with asthma [22, 23]. One learning from the hospitals was the booklets for diabetes and hypertension. The booklets were designed to be carried by the patients as a record of self-monitoring, follow-up visits and drug prescriptions, which also included self-care information. The booklets have been used and found useful by doctors in the district hospitals. Even though there was no formal evidence, we decided to modify the materials and incorporate the messages in the management plan and follow-up records into the booklet for the VCAPS4 study.

Patient follow-up was another modification that we made for the VCAPS4 study. Upon exploration in the semi-structured interview, patients generally preferred regular re-evaluation by their doctors for better disease monitoring. The data also showed a high rate of presence to scheduled 4-week follow-up. The current policy in Vietnam requires patients

with chronic conditions to return monthly in order to get medications. In the VCAPS4 study, doctors were asked to schedule regular follow-ups every three months, i.e. four weeks, three months, six months, nine months, and 12 months. Patients' adherence to follow-up schedules and its association with clinical outcomes will be evaluated.

Treatment step escalation and referral to a higher-level facility was a decision of multiple factors, as suggested from the study. Given the complexity of the decision, external medical advisors with experience in the clinical care of CRD were contracted in the VCAPS4 study for consultation and review to ensure study compliance and patient safety.

One extra finding from the data about phone call communications is of value in the era of the COVID-19 pandemic. Most patients shared positive experiences talking with research staff over the phone calls. Patients also followed the advice to visit the district hospital when asked for. Doctors in the VCAPS3 study also called their patients to follow their conditions, even though not required by the study protocol. Given the public health measures for the COVID-19 epidemic globally, such as lockdown and social distancing, telemedicine has become an alternative approach for chronic diseases [24-27]. The effect of remote follow-up on the health of patients with CRD will be worthwhile investigating, especially for resource-limited areas or high burden areas.

Apart from this process evaluation for the pilot study, another process evaluation alongside the VCAPS4 study has been planned. The process evaluation will be carried out using the UK MRC framework and data collected from the VCAPS4 study and other VCAPS sub-studies (Figure 7.4). The results will inform policy and practice change in Vietnam, following the engagement with local stakeholders.

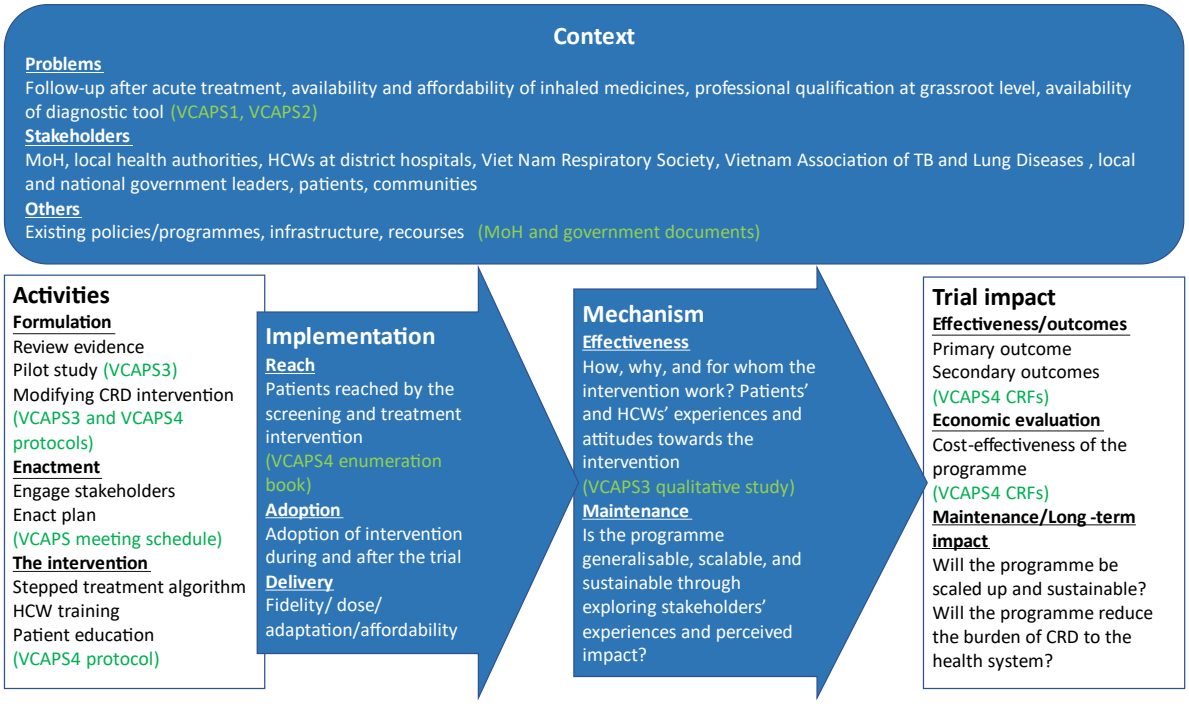

Figure 7.4. Logic model of the process evaluation for VCAPS4

In conclusion, this process evaluation shows barriers and challenges to implementing the components of the intervention. The VCAPS4 study and its associated process evaluation will provide more evidence to shape and facilitate scale-up.

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Chapter 8. General discussion and conclusion

The work in this thesis shows (a) epidemiological data on common respiratory conditions and tobacco smoking across four levels of healthcare facilities in Vietnam, and (b) findings from a pilot study evaluating the feasibility of interventions for CRD and smoking cessation. The findings from the thesis have informed the design of the VCAPS4 study and will provide a foundation for further studies addressing the issues of care for CRD and smoking in LMIC settings.

Chapter 3 of the thesis describes the prevalence and management of common respiratory diseases among patients seeking healthcare in Vietnam using a syndromic approach. The study showed a high prevalence of CRD that had been misdiagnosed. Other important findings included a low rate of inhaler prescriptions for patients with CRD and inappropriate use of systemic corticosteroids and antibiotics. The study was the first to show prevalence and gaps in the management for patients with respiratory symptoms among a representative sample of patients in Vietnam. The findings were supported by previous studies showing the lack of knowledge in patients management for CRD among doctors in Vietnam [1, 2]. The study suggested that a syndromic approach could be applied to assess the burden of respiratory diseases and the quality of patient care in a health system. The results also indicated an urgent need for strategies to improve care for CRD in Vietnam.

The study presented in Chapter 4 shows the prevalence of smoking and related behaviours among patients visiting healthcare facilities in Vietnam, using the same sampling method described in Chapter 3. We found a high prevalence of current smoking among male patients. Smokers who attempted to quit made little use of evidence-based cessation aids, such as counselling, nicotine replacement therapy, and quitlines. We also found that a high proportion of current smokers were not interested in quitting at all, especially in commune health centres. The findings suggested the potential of smoking cessation interventions targeting smokers seeking healthcare in Vietnam. However, even though there is governmental policy enforcing the delivery of cessation services in healthcare facilities, reports on the actual implementation are lacking. A systematic approach that can be

integrated into routine practice in Vietnamese healthcare facilities remains to be established.

The strength of the two studies in Chapter 3 and Chapter 4 is the representative sample from all four levels of healthcare facilities, which had not been done before in Vietnam. However, the small proportion of patients from commune health centres might have underrepresented this patient population.

In Chapter 5, I assessed the feasibility of the intervention to address the burden of CRD and used the data to build models to predict exacerbations among patients receiving the intervention. The intervention was pragmatic in nature, designed to be implemented in the grassroots level of healthcare facilities. It was novel in the stepped algorithm using a single inhaler and in deliberate absence of differentiation between COPD and asthma. Findings from the primary outcome and the cascade of care suggested the intervention was feasible in rural district hospitals in Vietnam. The exacerbation rate was comparable to observational studies of similar populations [3-5]. Adherence to recommended treatment was high up to the end of the study. Data on the average daily doses also showed that overuse of the study drug was uncommon. The prediction models used data collected at baseline to identify patients who may develop exacerbations after starting the treatment. The discrimination of the models was also comparable to those developed in previous studies for exacerbations of COPD or asthma. Data from VCAPS4 will further validate the models.

Chapter 6 describes the smoking cessation intervention designed to be integrated with routine practice in healthcare facilities. The intervention included brief advice from doctors, follow-up counselling phone calls, and scheduled text messages to support quitting. The study showed a high rate of successful counselling phone calls. We also found a good profile of quitting attempts during the follow-up period. However, the interpretation of the primary outcome (biochemically verified smoking cessation) was limited by the low proportion of urinary cotinine tests done by the participants. The novelty of the intervention was the integration between clinical care and quitline services. The active referral from hospitals could increase the reach of the quitline. The counselling phone calls and text messaging can be operated using existing infrastructure. Therefore, the intervention was considered

feasible and could be scaled up easily.

I also did a process evaluation of the intervention for CRD described in Chapter 5. Shown in Chapter 7, the process evaluation aimed to further assess the feasibility and understand the mechanisms of the intervention that were associated with the outcome. By using the RE-AIM framework, I showed issues that informed the study design of the VCAPS4 study. I also identified some barriers that we should pay attention to when the intervention, or a similar one, is to be implemented widely. For example, even though pharmacists were able to provide education on inhaler use to patients in the VCAPS3 study, pharmacists in the participating hospitals were reluctant to do so after the study. There is evidence about mistakes of using inhalers by patients and their association with reduced drug efficacy [6, 7]. Studies have also shown pharmacists' role in improving outcomes for patients with COPD in Vietnam [8, 9]. A model of care that can be sustained after study is needed to ensure the delivery of proper consultation for patients to use inhalers correctly.

We made several modifications to the interventions in the VCAPS4 study according to the observations in the two interventions in Chapter 5 and Chapter 6. In Chapter 7 I discussed the findings from the process evaluation and how the CRD intervention in the VCAPS4 study was made different from the feasibility study. The modifications discussed included changing the format of patient materials, arranging regular follow-up visits with doctors, and an extra role of external medical advisor for consultation and review of treatment step and potential safety concerns from excessive use of budesonide-formoterol. The objectives of the evaluation were to: (a) identify whether there is an alternative diagnosis and treatments required; (b) identify evidence of adverse effects, particularly respiratory infections; and (c) counsel patients with against excessive use. In terms of the smoking cessation intervention, we offered extra financial incentive to clinicians for patient referral in order to accelerate enrolment, as we observed low rate of referral leading to smaller actual sample size than planned in the feasibility study. Another observation from the feasibility study was low proportion of participants willing to come back to the clinic for abstinence verification (i.e. urinary cotinine test). Given the escalated COVID-19 epidemic in Vietnam over the past months, participants of the cluster RCT were allowed to take the test at home.

The two interventions in Chapter 5 and Chapter 6 are designed for district hospitals in order to reach a wider patient population. Once proved to be effective in the VCAPS4 study, the interventions could be adapted and scaled up to achieve the overall goal – reduce the burden of CRD and tobacco smoking.

Following the research work presented in this thesis, several recommendations can be made for future work. First, the smoking cessation intervention in the VCAPS study may benefit from a process evaluation, similar to the one shown in Chapter 7. The process evaluation can explore how brief advice and referral to the quitline can better fit in routine practice in district hospitals to increase uptake of the intervention. It can help to determine a proper frequency and schedule of phone calls and text messaging. Also, the content of phone call counselling and text messages may require refinements to meet the needs of smokers in Vietnam. Second, the features of patients with CRD in a specific setting should be considered when designing interventions. For example, the low utilisation of pulmonary function tests shown in the VCAPS3 study, which has also been indicated by the Asia Pacific Society of Respirology (Table 2.1), needs to be addressed [10]. Finally, a public health target for CRD from health authorities or multilateral agents could improve disease awareness among the public and healthcare workers. Healthcare resource re-allocation is also needed to drive the improvement in care for CRD. The optimal target and resource, especially during and after the COVID pandemic, requires communication and commitment from high-level authorities.

In conclusion, the studies presented in this thesis showed the epidemiological features of CRD and smoking among patients visiting all four levels of healthcare facilities in Vietnam. The two interventions designed to reduce the burden of CRD and tobacco smoking were feasible in a rural healthcare setting in Vietnam. The ongoing randomised controlled trial will demonstrate the effectiveness of the two interventions. We also expect further studies to evaluate similar interventions in other settings.

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Appendices

Appendix 1. Approval letters for the VCAPS3 study

Appendix 2. Supplementary appendices for publications in this thesis

2.1. Supplementary appendix for publication in Chapter 2

This section contains the supplementary appendix of the following manuscript submitted for publication:

Huang WC, Tsao L, Lee IP, Wu JP, Lin CY, Kuo CW, Hu HT, Palagyi A, Vu VG, Marks GB, Fox GJ. The cascade of care in the diagnosis and treatment of chronic obstructive pulmonary disease: a systematic review and meta-analysis. Submitted to International Journal of Chronic Obstructive Pulmonary Disease.

Supplementary Table S1. Literature search strategy

Diagnosis (Component A)	
Medline	
1.	exp Population/
2.	population.mp.
3.	community.mp.
4.	exp "Surveys and Questionnaires"/
5.	(survey$ or question$).mp.
6.	((pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$) adj3 (symptom$ or complain$)).mp.
7.	exp Spirometry/
8.	spirometr$.mp.
9.	((lung or pulmonary) adj3 function).mp.
10.	(Forced vital capacity or FVC or Forced expiratory volume in one second or FEV1).mp.
11.	1 or 2 or 3
12.	4 or 5
13.	7 or 8 or 9 or 10
14.	6 and 11 and 12 and 13
15.	limit 14 to yr="2000 - 2018"
Embase	
1.	'population'/exp
2.	'population'
3.	'community'
4.	'questionnaire'/exp
5.	survey* OR question*
6.	(pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*) NEXT/3 (symptom* OR complain*)
7.	'spirometry'/exp
8.	spirometr*
9.	(lung OR pulmonary) NEXT/3 function
10.	'forced vital capacity' OR fvc OR 'forced expiratory volume in one second' OR fev1
11.	#1 OR #2 OR #3
12.	#4 OR #5
13.	#7 OR #8 OR #9 OR #10
14.	#6 AND #11 AND #12 AND #13
15.	#14 AND [2000-2018]/py
Global Health	
1.	exp populations/
2.	population.mp.
3.	community.mp.
4.	exp surveys/
5.	(survey$ or question$).mp.
6.	((pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$) adj3 (symptom$ or complain$)).mp.
7.	spirometr$.mp.
8.	((lung or pulmonary) adj3 function).mp.
9.	(Forced vital capacity or FVC or Forced expiratory volume in one second or FEV1).mp.
10.	1 or 2 or 3
11.	4 or 5
12.	7 or 8 or 9
13.	6 and 10 and 11 and 12

14. limit 13 to yr="2000 - 2018"

CINAHL

1. (MH "Population+")
2. "population"
3. "community"
4. (MH "Surveys+")
5. survey* or question*
6. (pulmonary or lung* or airway* or airflow* or bronch* or respirat*) N3 (symptom* or complain*)
7. (MH "Spirometry")
8. spirometr*
9. (lung or pulmonary) N3 function
10. Forced vital capacity or FVC or Forced expiratory volume in one second or FEV1
11. S1 OR S2 OR S3
12. S4 OR S5
13. S7 OR S8 OR S9 OR S10
14. S6 AND S11 AND S12 AND S13
15. S14 Limiters - Date Published: 20000101-20181231

Cochrane

1. MeSH descriptor: [Population] explode all trees
2. (population)
3. (community)
4. MeSH descriptor: [Surveys and Questionnaires] explode all trees
5. (survey* or question*)
6. ((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) NEXT/3 (symptom* or complain*))
7. MeSH descriptor: [Spirometry] explode all trees
8. (spirometr*)
9. ((lung or pulmonary) NEXT/3 function)
10. (Forced vital capacity or FVC or Forced expiratory volume in one second or FEV1)
11. #1 OR #2 OR #3
12. #4 OR #5
13. #7 OR #8 OR #9 OR #10
14. #6 AND #11 AND #12 AND #13
15. #14 with Publication Year from 2000 to 2018, in Trials

Pharmacotherapy (Component B)

Medline

1. exp Pulmonary Disease, Chronic Obstructive/
2. Lung Diseases, Obstructive/
3. Chronic Obstructive Pulmonary Disease.mp.
4. COPD.mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. Emphysema$.mp.
7. (Chronic adj3 bronchitis).mp.
8. Chronic Obstructive Lung Disease.mp.
9. COLD.mp.
10. Chronic Obstructive Airway Disease.mp.
11. COAD.mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. administration, inhalation/
14. Bronchodilator agents/
15. Inhaler$.mp.
16. Inhalation$.mp.
17. Muscarinic Antagonists/
18. (muscarinic$ adj3 antagonist$).mp.
19. LAMA.mp.
20. Adrenergic Beta 2 Receptor Agonists/
21. (long$ adj3 beta$ adj3 agonist$).mp.
22. LABA.mp.
23. exp Adrenal Cortex Hormones/
24. (inhal$ adj3 (corticosteroid$ or steroid$ or glucocorticoid$)).mp.
25. ICS.mp.
26. Metered dose inhaler$.mp.
27. Dry powder inhaler$.mp.
28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. exp Patient Compliance/
30. exp "Treatment Adherence and Compliance"/
31. (adhere$ or nonadhere$ or non-adhere$).mp.
32. (complian$ or noncomplian$ or non-complian$).mp.
33. 29 or 30 or 31 or 32
34. 28 and 33
35. 12 and 34
36. limit 35 to yr="2000 - 2018"

Embase

1. 'chronic obstructive lung disease'/exp
2. 'obstructive airway disease'/de
3. 'chronic obstructive pulmonary disease'
4. 'copd'
5. obstruct* NEAR/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)
6. emphysema*
7. chronic NEAR/3 bronchitis
8. 'chronic obstructive lung disease'
9. 'cold'
10. 'chronic obstructive airway disease'
11. 'coad'
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. 'inhalational drug administration'/de
14. 'bronchodilating agent'/de
15. 'inhaler*'
16. 'inhalation*'
17. 'muscarinic receptor blocking agent'/de
18. muscarinic* NEAR/3 antagonist*
19. 'lama'
20. 'beta 2 adrenergic receptor stimulating agent'/de
21. long* NEAR/3 beta* NEAR/3 agonist*
22. 'laba'
23. 'corticosteroid'/exp
24. inhal* NEAR/3 (corticosteroid* OR steroid* OR glucocorticoid*)
25. 'ics'
26. 'metered dose inhaler*'
27. 'dry powder inhaler*'
28. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
29. 'patient compliance'/de
30. 'medication compliance'/de
31. adhere* OR nonadhere* OR 'non-adhere*'
32. complian* OR noncomplian* OR 'non-complian*'
33. #29 OR #30 OR #31 OR #32
34. #28 AND #33
35. #12 AND #34
36. #35 AND [2000-2018]/py

Global Health

1. exp chronic obstructive pulmonary disease/
2. Chronic Obstructive Pulmonary Disease.mp.
3. COPD.mp.
4. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
5. Emphysema$.mp.
6. (Chronic adj3 bronchitis).mp.
7. Chronic Obstructive Lung Disease.mp.
8. COLD.mp.
9. Chronic Obstructive Airway Disease.mp.
10. COAD.mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. inhalation/
13. bronchodilators/
14. Inhaler$.mp.
15. Inhalation$.mp.
16. (muscarinic$ adj3 antagonist$).mp.
17. LAMA.mp.
18. beta-adrenergic agonists/
19. (long$ adj3 beta$ adj3 agonist$).mp.
20. LABA.mp.
21. exp adrenal cortex hormones/
22. (inhal$ adj3 (corticosteroid$ or steroid$ or glucocorticoid$)).mp.
23. ICS.mp.
24. Metered dose inhaler$.mp.
25. Dry powder inhaler$.mp.
26. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27. exp Patient Compliance/
28. (adhere$ or nonadhere$ or non-adhere$).mp.
29. (complian$ or noncomplian$ or non-complian$).mp.
30. 27 or 28 or 29
31. 26 and 30
32. 11 and 31
33. limit 32 to yr="2000 - 2018"

CINAHL

1. (MH "Pulmonary Disease, Chronic Obstructive+")
2. (MH "Lung Diseases, Obstructive")
3. "chronic obstructive pulmonary disease"
4. "COPD"
5. obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
6. Emphysema*
7. Chronic N3 bronchitis
8. "Chronic Obstructive Lung Disease"
9. "COLD"
10. "Chronic Obstructive Airway Disease"
11. "COAD"
12. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
13. (MH "Administration, Inhalation")
14. (MH "Bronchodilator Agents")
15. Inhaler*
16. Inhalation*
17. (MH "Muscarinic Antagonists")
18. muscarinic* N3 antagonist*
19. "LAMA"
20. (MH "Adrenergic Beta-Agonists")
21. long* N3 beta* N3 agonist*
22. "LABA"
23. (MH "Adrenal Cortex Hormones+")
24. inhal* N3 (corticosteroid* or steroid* or glucocorticoid*)
25. "ICS"
26. Metered dose inhaler*
27. Dry powder inhaler*
28. S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27
29. (MH "Patient Compliance+")
30. "treatment adherence"
31. "treatment compliance"
32. adhere* or nonadhere* or nonadhere*
33. complian* or noncomplian* or noncomplian*
34. S29 OR S30 OR S31 OR S32 OR S33
35. S28 AND S34
36. S12 AND S35
37. S36 Limiters - Date Published: 20000101-20181231

Cochrane

1. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
2. MeSH descriptor: [Lung Diseases, Obstructive] this term only
3. (chronic obstructive pulmonary disease)
4. (COPD)
5. (obstruct* next/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*))
6. (emphysema*)
7. (Chronic next/3 bronchitis)
8. (chronic obstructive lung disease)
9. (COLD)
10. Chronic obstructive airway disease
11. COAD
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. MeSH descriptor: [Bronchodilator Agents] this term only
14. (inhaler*)
15. inhalation*
16. MeSH descriptor: [Muscarinic Antagonists] this term only
17. (muscarinic* next/3 antagonist*)
18. (LAMA)
19. MeSH descriptor: [Adrenergic beta-2 Receptor Agonists] this term only
20. (long* next/3 beta* next/3 agonist*)
21. (LABA)
22. MeSH descriptor: [Adrenal Cortex Hormones] explode all trees
23. (inhal* next/3 (corticosteroid* or steroid* or glucocorticoid*))
24. (ICS)
25. (Metered dose inhaler*)
26. (Dry powder inhaler*)
27. #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27
28. MeSH descriptor: [Patient Compliance] explode all trees
29. MeSH descriptor: [Treatment Adherence and Compliance] explode all trees
30. (adhere* or nonadhere* or non-adhere*)
31. (complian* or noncomplian* or non-complian*)
32. #29 OR #30 OR #31 OR #32

33. #28 AND #33
34. #12 AND #34
35. #34 with Publication Year from 2000 to 2018, in Trials

Smoking cessation (Component C)

Medline

1. exp Pulmonary Disease, Chronic Obstructive/
2. Lung Diseases, Obstructive/
3. Chronic Obstructive Pulmonary Disease.mp.
4. COPD.mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. Emphysema$.mp.
7. (Chronic adj3 bronchitis).mp.
8. Chronic Obstructive Lung Disease.mp.
9. COLD.mp.
10. Chronic Obstructive Airway Disease.mp.
11. COAD.mp.
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. smoking cessation.mp.
14. Smoking Cessation/
15. "Tobacco Use Cessation"/
16. ((quit$ or stop$ or ceas$ or cessation) adj5 (smoking or cigarette* or tobacco)).mp.
17. 13 or 14 or 15 or 16
18. 12 and 17
19. limit 18 to yr="2000 - 2018"

Embase

1. 'chronic obstructive lung disease'/exp
2. 'obstructive airway disease'/de
3. 'chronic obstructive pulmonary disease'
4. 'copd'
5. obstruct* NEAR/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)
6. emphysema*
7. chronic NEAR/3 bronchitis
8. 'chronic obstructive lung disease'
9. 'cold'
10. 'chronic obstructive airway disease'
11. 'coad'
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. 'smoking cessation'/de
14. 'smoking cessation'
15. (quit* OR stop* OR ceas* OR cessation) NEAR/5 (smoking OR cigarette* OR tobacco)
16. #13 OR #14 OR #15
17. #12 AND #16
18. #17 AND [2000-2018]/py

Global Health

1. exp chronic obstructive pulmonary disease/
2. Chronic Obstructive Pulmonary Disease.mp.
3. COPD.mp.
4. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
5. Emphysema$.mp.
6. (Chronic adj3 bronchitis).mp.
7. Chronic Obstructive Lung Disease.mp.
8. COLD.mp.
9. Chronic Obstructive Airway Disease.mp.
10. COAD.mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. smoking cessation/
13. smoking cessation.mp.
14. ((quit$ or stop$ or ceas$ or cessation) adj5 (smoking or cigarette* or tobacco)).mp.
15. 12 or 13 or 14
16. 11 and 15
17. limit 16 to yr="2000 - 2018"

CINAHL

1. (MH "Pulmonary Disease, Chronic Obstructive+")
2. (MH "Lung Diseases, Obstructive")
3. "chronic obstructive pulmonary disease"
4. "COPD"
5. obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
6. Emphysema*
7. Chronic N3 bronchitis
8. "Chronic Obstructive Lung Disease"

9. "COLD"
10. "Chronic Obstructive Airway Disease"
11. "COAD"
12. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
13. (MH "Smoking Cessation")
14. "smoking cessation"
15. ((quit* or stop* or ceas* or cessation) N5 (smoking or cigarette* or tobacco))
16. S13 OR S14 OR S15
17. ((S13 OR S14 OR S15) AND (S12 AND S16)) AND (S12 AND S16)
18. S17 Limiters - Date Published: 20000101-20181231

Cochrane

1. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
2. MeSH descriptor: [Lung Diseases, Obstructive] this term only
3. (chronic obstructive pulmonary disease)
4. (COPD)
5. (obstruct* next/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*))
6. (emphysema*)
7. (Chronic next/3 bronchitis)
8. (chronic obstructive lung disease)
9. (COLD)
10. Chronic obstructive airway disease
11. COAD
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. MeSH descriptor: [Smoking Cessation] this term only
14. (smoking cessation)
15. MeSH descriptor: [Tobacco Use Cessation] this term only
16. ((quit* or stop* or ceas* or cessation) next/5 (smoking or cigarette* or tobacco))
17. #13 OR #14 OR #15 OR #16
18. #12 AND #17
19. #18 with Publication Year from 2000 to 2018, in Trials

Vaccination (Component D)

Medline

16. exp Pulmonary Disease, Chronic Obstructive/
17. Lung Diseases, Obstructive/
18. Chronic Obstructive Pulmonary Disease.mp.
19. COPD.mp.
20. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
21. Emphysema$.mp.
22. (Chronic adj3 bronchitis).mp.
23. Chronic Obstructive Lung Disease.mp.
24. COLD.mp.
25. Chronic Obstructive Airway Disease.mp.
26. COAD.mp.
27. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
28. exp Influenza Vaccines/
29. ((influenza$ or flu$) adj3 (vaccin$ or immuni$ or inoculat$)).mp.
30. exp Pneumococcal Vaccines/
31. (Pneum$ adj3 (vaccin$ or immuni$ or inoculat$)).mp.
32. 13 or 14 or 15 or 16
33. 12 and 17
34. limit 18 to yr="2000 - 2018"

Embase

1. 'chronic obstructive lung disease'/exp
2. 'obstructive airway disease'/de
3. 'chronic obstructive pulmonary disease'
4. 'copd'
5. obstruct* NEAR/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)
6. emphysema*
7. chronic NEAR/3 bronchitis
8. 'chronic obstructive lung disease'
9. 'cold'
10. 'chronic obstructive airway disease'
11. 'coad'
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. 'influenza vaccine'/exp
14. (influenza* OR flu*) NEXT/3 (vaccin* OR immuni* OR inoculat*)
15. 'pneumococcus vaccine'/exp
16. pneum* NEXT/3 (vaccin* OR immuni* OR inoculat*)
17. #13 OR #14 OR #15 OR #16
18. #12 AND #17
19. #18 AND [2000-2018]/py

Global Health

1. exp chronic obstructive pulmonary disease/
2. Chronic Obstructive Pulmonary Disease.mp.
3. COPD.mp.
4. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
5. Emphysema$.mp.
6. (Chronic adj3 bronchitis).mp.
7. Chronic Obstructive Lung Disease.mp.
8. COLD.mp.
9. Chronic Obstructive Airway Disease.mp.
10. COAD.mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. ((influenza* or flu*) adj3 (vaccin* or immuni* or inoculat*)).mp.
13. (Pneum* adj3 (vaccin* or immuni* or inoculat*)).mp.
14. 12 or 13
15. 11 and 14
16. limit 15 to yr="2000 - 2018"

CINAHL

1. (MH "Pulmonary Disease, Chronic Obstructive+")
2. (MH "Lung Diseases, Obstructive")
3. "chronic obstructive pulmonary disease"
4. "COPD"
5. obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
6. Emphysema*
7. Chronic N3 bronchitis
8. "Chronic Obstructive Lung Disease"
9. "COLD"
10. "Chronic Obstructive Airway Disease"
11. "COAD"
12. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
13. (MH "Influenza Vaccine")
14. (influenza* or flu*) N3 (vaccin* or immuni* or inoculat*)
15. (MH "Pneumococcal Vaccine")
16. Pneum* N3 (vaccin* or immuni* or inoculat*)
17. S13 OR S14 OR S15 OR S16
18. S12 and S17
19. S18 Limiters - Date Published: 20000101-20181231

Cochrane

1. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
2. MeSH descriptor: [Lung Diseases, Obstructive] this term only
3. (chronic obstructive pulmonary disease)
4. (COPD)
5. (obstruct* next/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*))
6. (emphysema*)
7. (Chronic next/3 bronchitis)
8. (chronic obstructive lung disease)
9. (COLD)
10. Chronic obstructive airway disease
11. COAD
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. MeSH descriptor: [Influenza Vaccines] explode all trees
14. ((influenza* or flu*) next/3 (vaccin* or immuni* or inoculat*))
15. MeSH descriptor: [Pneumococcal Vaccines] explode all trees
16. (Pneum* next/3 (vaccin* or immuni* or inoculat*))
17. #13 OR #14 OR #15 OR #16
18. #12 AND #17
19. #18 with Publication Year from 2000 to 2018, in Trials

Pulmonary rehabilitation (Component E)

Medline

1. exp Pulmonary Disease, Chronic Obstructive/
2. Lung Diseases, Obstructive/
3. Chronic Obstructive Pulmonary Disease.mp.
4. COPD.mp.
5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
6. Emphysema$.mp.
7. (Chronic adj3 bronchitis).mp.
8. Chronic Obstructive Lung Disease.mp.
9. COLD.mp.
10. Chronic Obstructive Airway Disease.mp.
11. COAD.mp.

12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. Rehabilitation/
14. exercise therapy/
15. ((pulmon$ or respi$) adj5 (rehabilitat$ or train$)).mp.
16. 13 or 14 or 15
17. exp Patient Compliance/
18. exp "Treatment Adherence and Compliance"/
19. (adhere$ or nonadhere$ or non-adhere$).mp.
20. (complian$ or noncomplian$ or non-complian$).mp.
21. 17 or 18 or 19 or 20
22. 16 and 21
23. 12 and 22
24. limit 23 to yr="2000 - 2018"

Embase

1. 'chronic obstructive lung disease'/exp
2. 'obstructive airway disease'/de
3. 'chronic obstructive pulmonary disease'
4. 'copd'
5. obstruct* NEAR/3 (pulmonary OR lung* OR airway* OR airflow* OR bronch* OR respirat*)
6. emphysema*
7. chronic NEAR/3 bronchitis
8. 'chronic obstructive lung disease'
9. 'cold'
10. 'chronic obstructive airway disease'
11. 'coad'
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. 'rehabilitation'/de
14. 'kinesiotherapy'/de
15. (pulmon* OR respi*) NEXT/5 (rehabilitat* OR train*)
16. #13 OR #14 OR #15
17. 'patient compliance'/de
18. adhere* OR nonadhere* OR 'non-adhere*'
19. complian* OR noncomplian* OR 'non-complian*'
20. #17 OR #18 OR #19
21. #16 AND #20
22. #12 AND #21
23. #22 AND [2000-2018]/py

Global Health

1. exp chronic obstructive pulmonary disease/
2. Chronic Obstructive Pulmonary Disease.mp.
3. COPD.mp.
4. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.
5. Emphysema$.mp.
6. (Chronic adj3 bronchitis).mp.
7. Chronic Obstructive Lung Disease.mp.
8. COLD.mp.
9. Chronic Obstructive Airway Disease.mp.
10. COAD.mp.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. rehabilitation/
13. exercise/
14. ((pulmon$ or respi$) adj5 (rehabilitat$ or train$)).mp.
15. 12 or 13 or 14
16. exp Patient Compliance/
17. (adhere$ or nonadhere$ or non-adhere$).mp.
18. (complian$ or noncomplian$ or non-complian$).mp.
19. 16 or 17 or 18
20. 15 and 19
21. 11 and 20
22. limit 21 to yr="2000 - 2018"

CINAHL

1. (MH "Pulmonary Disease, Chronic Obstructive+")
2. (MH "Lung Diseases, Obstructive")
3. "chronic obstructive pulmonary disease"
4. "COPD"
5. obstruct* N3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)
6. Emphysema*
7. Chronic N3 bronchitis
8. "Chronic Obstructive Lung Disease"
9. "COLD"
10. "Chronic Obstructive Airway Disease"

11. "COAD"
12. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
13. (MH "Rehabilitation")
14. (MH "Therapeutic Exercise")
15. (pulmon* or respi*) N5 (rehabilitat* or train*)
16. S13 OR S14 OR S15
17. (MH "Patient Compliance+")
18. "treatment adherence"
19. "treatment compliance
20. adhere* or nonadhere* or nonadhere*
21. complian* or noncomplian* or noncomplian*
22. S17 OR S18 OR S19 OR S20 OR S21
23. S16 AND S22
24. S12 AND S23
25. S24 Limiters - Date Published: 20000101-20181231

Cochrane

1. MeSH descriptor: [Pulmonary Disease, Chronic Obstructive] explode all trees
2. MeSH descriptor: [Lung Diseases, Obstructive] this term only
3. (chronic obstructive pulmonary disease)
4. (COPD)
5. (obstruct* next/3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*))
6. (emphysema*)
7. (Chronic next/3 bronchitis)
8. (chronic obstructive lung disease)
9. (COLD)
10. Chronic obstructive airway disease
11. COAD
12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13. MeSH descriptor: [Rehabilitation] this term only
14. MeSH descriptor: [Exercise Therapy] this term only
15. ((pulmon* or respi*) next/5 (rehabilitat* or train*))
16. #13 OR #14 OR #15
17. MeSH descriptor: [Patient Compliance] explode all trees
18. MeSH descriptor: [Treatment Adherence and Compliance] explode all trees
19. (adhere* or nonadhere* or non-adhere*)
20. (complian* or noncomplian* or non-complian*)
21. #17 OR #18 OR #19 OR #20
22. #16 AND #21
23. #12 AND #22
24. #23 with Publication Year from 2000 to 2018, in Trials

Supplementary Table S2. Factors associated with completion of each step of the cascade identified using adjusted analysis in the included studies

Step of the cascade	Factors reported in the included studies*
Diagnosis (Component A)	
A1. Had respiratory symptoms among those with airflow obstruction	-
A2. Ever diagnosed with COPD among those with airflow obstruction	**Factors associated with undiagnosed COPD reported in included studies** Not heavy smoking (<30 pack-years)[1], lack of reported respiratory symptoms[2], did not have other thoracic diseases[3], did not have chronic bronchitis[3]
A3. Ever diagnosed with COPD among those with airflow obstruction and respiratory symptoms	-
Pharmacotherapy (Component B)	
B1. Prescribed any inhaled medicine	-
B2. Prescribed any maintenance inhaler	**Factors associated with not receiving maintenance inhalers reported in included studies** Less severe airflow limitation[4], lower mMRC score[4], not comorbid with asthma[4], lower annual exacerbation rate[4]
B3. Adhered to maintenance inhaler for 12 months	**Factors associated with nonadherence reported in included studies** Types of maintenance inhaler[†5,6], no prior use of ICS[5], no prior use of SABA[5], no oral corticosteroid co-medication[5], a general practitioner as first prescriber (vs pulmonologist)[5], lower number of prescriptions of COPD-related reliever medication[6],higher number of prescribed long-term medications[6], nonadherent to non-COPD medications[7], missed appointments[8], poor adherence to other inhalers[8], unemployed[9]
Smoking cessation (Component C)	
C1. Received any cessation intervention among current smokers	**Factors associated with not participating in smoking cessation programme** Older age[10], cohabitating (vs living alone)[10]
C2. Advised to quit smoking among current smokers	**Factors associated with not receiving smoking cessation advice** Uninsured (vs private health insurance coverage)[11], no usual source of care (vs doctor's office)[11], no comorbid chronic disease[11], less healthcare visits in past year[11]
Vaccination (Component D)	
D1. Received influenza vaccine	**Factors associated with not receiving influenza vaccine** Did not receive pneumococcal vaccine[12], did not have medications for COPD[13], did not have regular health check-up[14], routine check-up over 1 year prior[15], employment as the income source (vs unemployment insurance/worker's compensation/welfare/senior's benefits)[16], lower level of self-reported wealth[17], unmarried[14,17], no health insurance coverage[13,15], no diabetes[13,15,18], no coronary heart disease[15], presence of household children[15], deferred medical care due to cost[15], more unhealthy lifestyles[12]
D2. Received pneumococcal vaccine	**Factors associated with not receiving pneumococcal vaccine** Shorter duration of COPD[19], less comorbidities[20], nonadherent to seasonal influenza vaccines[19,20], lower functional social support[21]
Pulmonary rehabilitation (Component E)	
E1. Pulmonary rehabilitation suggested or referred for pulmonary rehabilitation	-
E2. Started pulmonary rehabilitation	**Factors associated with not starting pulmonary rehabilitation** Younger age[22], referred by inpatient COPD multidisciplinary team/inpatient physiotherapist/ community COPD clinic (vs consultant respiratory physician)[22]
E3. Adhered to pulmonary rehabilitation programme	**Factors associated with nonadherence to pulmonary rehabilitation** Higher baseline CAT score[23], lower Incremental Shuttle Walk Test distance/6 minutes walking distance[24-26], frailty status[25], using nebuliser[27],lower fat free mass index[28], good perception of effectiveness of the treatment[28], referred by general practitioner[22]

*Only factors not included in Figure 3

[†]Adherence to tiotropium better than LABA and ICS/LABA[5]; adherence to LAMA better than LABA[6]; adherence to LABA better than ICS and LABA/ICS[6]

Supplementary Table S3. Characteristics of studies included in the review

Diagnosis (Component A)

Reference	Author, year of publication	Years of study	Country	Study sample	Age range	Definition of airflow obstruction
1	Daldoul, 2013	?	Tunisia	661	≥ 40	FEV1/FVC <70%
2	Gemert, 2015	2012	Uganda	588	≥ 30	FEV1/FVC < LLN (GLI 2012)
3	Glaser, 2010	2003 – 2006	Germany	1,809	25 – 85	FEV1/FVC <70%; FEV1/FVC < LLN
4	Guerriero, 2015	2011 – 2012	Italy	1,236	18 – 79	FEV1/FVC <70%; FEV1/FVC < LLN (GLI 2012)
5	Karloh, 2018	2012 – 2013	Brazil	1,057	≥ 40	FEV1/FVC <70%
6	Lamprecht, 2015	2003 – 2012, 2003 – 2005, 2006 – 2007	Turkey, Norway, South Africa, China, Germany, Nigeria, Poland, USA, Portugal, UK, the Netherlands, the Philippines, India, Iceland, Austria, Tunisia, Australia, Estonia, Sweden, Canada, Venezuela, Mexico, Uruguay, Chile, Brazil, Spain, Colombia	30,874	≥ 40	FEV1/FVC < LLN
7	Lenoir, 2018	2014 – 2017	Switzerland	3,342	35 – 75	FEV1/FVC < LLN (GLI 2012)
8	Lindstrom, 2002	1992	Sweden	1,565	35 – 36, 50 – 51, 65 – 66	FEV1/VC <70% and FEV1 < 80% predicted
9	Lu, 2010	2003	China	20,245	≥ 40	FEV1/FVC <70%
10	Lundback, 2003	1996 – 1997	Sweden	1,237	46 – 47, 61 – 62, 76 – 77	FEV1/FVC <70%; FEV1/FVC <70% and FEV1 < 80% predicted
11	Methvin, 2009	?	USA	508	≥ 40	FEV1/FVC <70%
12	Miravitlles, 2009	2007	Spain	3,802	40 – 80	FEV1/FVC <70%
13	Murtagh, 2005	1999 – 2001	UK	722	40 – 69	FEV1/FVC <70% and FEV1 < 80% predicted
14	Nascimento, 2007	2002	Brazil	918	≥ 40	FEV1/FVC <70%
15	Pothirat, 2016		Thailand	574	≥ 40	FEV1/FVC <70%
16	Scholes, 2014	2010 – 2012	UK	7,879	40 – 95	FEV1/FVC <70%; FEV1/FVC < LLN
17	Waatevik, 2013	2003 – 2005	Norway	1,664	35 – 90	FEV1/FVC <70%
18	Wang, 2018	2012 – 2015	China	50,991	≥ 20	FEV1/FVC <70%; FEV1/FVC < LLN (Chinese reference values)

FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GLI, Global Lung Function Initiative; LLN, lower limit of normal

Pharmacotherapy (Component B)

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Definition of adherence
19	Allen-Ramey, 2012	2010	USA	Population-based survey	3,440	-

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Definition of adherence
20	Bogart, 2018	2011 – 2016	USA	Commercial claim database	14,635	PDC ≥ 0.8
21	Breekveldt-Postma, 2007	1998 – 2003	Netherlands	Drug dispensing records from community pharmacies linked to hospital discharge records	5,330	PDC ≥ 0.8
22	Casas, 2018	2016	Argentina, Chile, Colombia, Costa Rica, Guatemala, Mexico, and Uruguay	Specialist doctors	795	Test of Adherence to Inhalers
23	Corrado, 2012	2009	Italy	Pulmonary Units in university, general and county hospitals	4,094	-
24	Davis, 2017	2009 – 2014	USA	Claim database	13,657	PDC ≥ 0.8
25	Dhamane, 2016	2008 – 2012	USA	Claim database	14,117	PDC ≥ 0.8
26	Diette, 2015	2007 – 2008	USA	Claim database	55,361	-
27	Falk, 2016	1997 – 2013	Canada	Claim database	19,367	-
28	Green, 2015	before 2012	Canada	General practice	10,043	-
29	Gruffydd-Jones, 2016	1997 – 2013	UK	General practice research database	20,154	-
30	Gunen, 2015	2013	Turkey	Research hospitals, university hospitals, multidisciplinary state hospitals, and pulmonary diseases hospital	1610	-
31	Halpern, 2011	2004 – 2005	USA	Claim database	4,537	MPR ≥ 0.8
32	Hsieh, 2018	2012 – 2013	Taiwan	Hospitals	1,053	-
33	Ingebrigtsen, 2014	2003 – 2008	Denmark	Population-based survey with linkage to national registers	5,812	MPR > 0.8
34	Kim, 2017	2009 – 2013	South Korea	Claim database	9,086	MPR ≥ 0.8
35	Kuyucu, 2011	?	Turkey	Secondary and tertiary healthcare institutions and physician's offices	514	-
36	Laforest, 2012	2006 – 2008	France	Claim database	1,147	PDC ≥ 0.8
37	Maio, 2014		Italy	General practice	526	-
38	Make, 2012	2004 – 2005	USA	Claim database	51,072	MPR (only average adherence provided)
39	Monteagudo, 2017	2013	Spain	General practice	8,863	MPR between 0.8 and 1.2
40	Mueller, 2016	2010 – 2012	Germany	Claim database	45,937	MPR ≥ 0.8
41	Palmiotti, 2018	2015 – 2016	Italy	University hospitals, community hospitals, and territorial outpatient facilities	693	-
42	Price, 2014	2009 – 2013	UK	General practice research database	24,957	-
43	Raluy-Callado, 2015	2009 – 2013	UK	General practice	49,286	-

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Definition of adherence
44	Savaria, 2017	2003 – 2014	Canada	Claim database	113,435	PDC ≥ 0.8
45	Scalone, 2018	2013 – ?	Italy	Pulmonologist and internal medicine outpatient clinics	1,468	-
46	Sen, 2015	2010 – 2011	Turkey	Pulmonary outpatient clinics of university hospitals, research and training hospitals, state hospitals, and private hospitals	719	-
47	Tøttenborg, 2016	2008 – 2012	Denmark	Pulmonary outpatient clinics	13,369	PDC ≥ 0.8
48	Vestbo, 2014	2011	France, Germany, Italy, Spain, the UK, and the USA	Primary and secondary care	1,508	-
49	Vetrano, 2017	2002 – 2012	Italy	General practice research database	22,505	PDC ≥ 0.8
50	Wurst, 2014	2007 – 2009	USA	Claim database	3,268	PDC ≥ 0.8; MPR ≥ 0.8

MPR, medication possession ratio; PDC, proportion of days covered

Smoking cessation component

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Cessation intervention assessed
51	Bourbeau, 2008	2005	Canada	General practice	1,090	Smoking cessation advice, make follow-up appointment, drug therapy
52	Chavez, 2009	?	USA	University-based family medicine clinic	200	Counselling, Bupropion, Nicotine Replacement, Nicotine Patch, nicotine Gum, Nicotine Spray and Nicotine Inhaler
53	Henoch, 2016	2009 – 2012	Sweden	National register	7,810	Smoking cessation programme, patient education programme
54	Jones, 2008	2005 – 2006	UK	General practice	422	Nicotine gum, nicotine patches, referral to a smoking cessation clinic
55	Jouleh, 2018	2005 – 2006	Norway	Population-based survey and university hospital	335	Smoking cessation advice
56	Kalkhoran, 2018	2013 – 2014	USA	Population-based survey	1,312	Nicotine patch, gum, inhaler, nasal spray, lozenge, or pill; Chantix, varenicline, Wellbutrin, Zyban, or bupropion; counselling, a telephone help line or quit line, books, pamphlets, videos, a quit tobacco clinic, class, support group, or an internet or web-based programme
57	Kaufmann, 2015	2012	Switzerland	General practice	115	Smoking cessation advice, smoking cessation programme
58	Khan, 2017	2011 – 2015	UK	General practice	1,078	Smoking cessation advice, practical help
59	López Varela, 2008	?	Brazil, Mexico, Uruguay, Chile, Venezuela	Population-based survey	758	Smoking cessation advice, nicotine substitute, bupropion, others

38	Make, 2012	2004 – 2005	USA	Claim database	51,072	Claim for a smoking cessation intervention (medication or behavioural therapy)
60	Menezes, 2015	2012 – 2013	Brazil, France, Germany, Italy, Japan, Mexico, the Netherlands, Russia, South Korea, Spain, the UK, and the USA	Population-based survey	4,343	Smoking cessation advice
61	Rubio, 2017	2014 – 2015	Spain	Outpatient respiratory clinics	4,508	Specific intervention for smoking cessation
62	Schauer, 2016	2009 – 2010	USA	Population-based survey	2,339	Smoking cessation advice, self-help materials, class or programme/quitline/counselling, medication, scheduled any follow-up contacts
63	Tilert, 2015	2008 – 2011	USA	Population-based survey	3,177	Smoking cessation advice
64	Tøttenborg, 2013	2008 – 2011	Denmark	National register	15,264	Smoking cessation advice

Vaccination component

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Timing of influenza vaccine	Timing of pneumococcal vaccine
65	Abad-Arranz, 2018	2015 – 2016	Spain	General practice	4,307	Not reported	Not reported
66	Akturk, 2017	2013 – 2014	Turkey	University hospital, training hospitals, and public hospitals	296	Not reported	Not reported
67	Arinez-Fernandez, 2006	2003	Spain	General practice	10,711	-	In the past
51	Bourbeau, 2008	2005	Canada	General practice	1,090	Within 12 months	-
68	Britton, 2003	2000	UK	Population-based survey	400	Within last 12 months	-
69	Carrasco-Garrido, 2009	2003	Spain	General practice	10,711	In last campaign	In the past
70	Carreno-Ibanez, 2015	2010	Spain	Primary care database	93,797	2007-2010 campaigns and 2009 pandemic	In the past
71	Chapman, 2003	2000	Canada	Population-based survey	401	Within last 12 months	-
72	Chen, 2015	?	USA	Medical centres and specialist practices	282	In the last year	In the past
73	Chiatti, 2011	2004 – 2005	Italy	Population-based survey	5,935	In the last 12 months	-
74	Dal Negro, 2003	2000	Italy	Population-based survey	400	Within last 12 months	-
75	Eagan, 2016	2006 – 2007	Norway	Outpatient clinics of hospitals and private specialist practices	365	During the previous season	-
76	Feifer, 2002	1999 – 2000	USA	Survey to members of prescription benefit plans	1,036	During the previous year	In the past
77	Garrastazu, 2016	2011 – 2012	Spain	Population-based survey	899	2011-2012 campaign	Not reported
78	Halpern, 2003	2000	USA	Population-based survey	447	Within last 12 months	-
53	Henoch, 2016	2009 – 2012	Sweden	National register	7,810	Not reported	Not reported
79	Hsu, 2016	2012	USA	Population-based survey	36,811	Within last 12 months	-
80	Izquierdo, 2003	2000	Spain	Population-based survey	402	Within last 12 months	-
81	Jimenez-Garcia, 2005	2003	Spain	General practice	10,711	In the most recent	-

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Timing of influenza vaccine	Timing of pneumococcal vaccine
						campaign	
82	Jimenez-Garcia, 2009	2006 – 2007	Spain	Population-based survey	1,320	In the latest campaign	-
83	Jochmann, 2010	2007 – 2009	Swiss	General practice	615	Not reported	Not reported
55	Jouleh, 2018	2005 – 2006	Norway	Population-based survey	335	In the preceding year	-
57	Kaufmann, 2015	2012	Switzerland	General practice	115	2012	-
84	Kurmi, 2018	2013 – 2014	China	Community-based survey	1,586	In the last 12 months	In the last 12 months
35	Kuyucu, 2011	?	Turkey	Secondary and tertiary healthcare institutions and physician's offices	514	Not reported	Not reported
85	Kwong, 2007	2005	Canada	Population-based survey	5,752	Within last 12 months	-
59	Lopez Varela, 2008	?	Brazil, Mexico, Uruguay, Chile, and Venezuela	Population-based survey	758	In the preceding year	-
37	Maio, 2014		Italy	General practice	526	Not reported	Not reported
38	Make, 2012	2004 – 2005	USA	Claim database	51,072	Not reported	-
86	Martin, 2012	2009 – 2010	UK	General practice database	7,901	Not reported	Not reported
87	Mehuys, 2010	2008	Belgium	Community pharmacies	555	2007 - 2008 season	-
88	de Miguel-Diez, 2014	2006, 2009	Spain	Population-based survey	2,575	During the latest campaign	-
89	Miravitlles, 2008	2005 – 2006	17 countries, including Spain, Argentina, Ecuador, China	Multiple settings	833	In the last year	Not reported
39	Monteagudo, 2017	2013	Spain	Primary care database	8,863	Not reported	Not reported
90	Mowls, 2013	2011	USA	Population-based survey	16,309	In the past 12 months	-
91	Ozyurt, 2018	2014 – 2015	Turkey	Outpatient clinic of a tertiary centre	108	Within the last year	Within the last 5 year
41	Palmiotti, 2018	2015 – 2016	Italy	University hospital centres, community hospital centres and territorial outpatient facilities	693	Not reported	Not reported
92	Piperno, 2003	2000	France	Population-based survey	400	In the previous year	-
61	Rubio, 2017	2014 – 2015	Spain	Outpatient respiratory clinics	4,508	Not reported	Not reported
93	Santos-Sancho, 2012	2009	Spain	Population-based survey	1,309	In the previous season	-
94	Schembri, 2009	2001 – 2005	UK	General practice	3,343	Not reported	Not reported
95	Shin, 2017		Korea	Population-based survey	2,715	Within 1 year	-
96	Sundh, 2017	2011 – 2012	Sweden	Hospital-based secondary care units	373	Within the previous year	Within the previous 5 year
97	Tata, 2003	1991 – 1998	UK	General practice database	6,000	1 October to 30 April	-
98	Vila-Corcoles, 2007	2002 – 2005	Spain	General practice	1,298	Prior autumn	-

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Timing of influenza vaccine	Timing of pneumococcal vaccine
99	Vozoris, 2008	2003	Canada	Community-based survey	5,532	within the past year	-
100	Yu, 2011	2008 – 2009	Hong Kong	Specialist outpatient clinics and general practices	120	within the previous year	-
101	Wouters, 2003	2000	Netherlands	Population-based survey	415	Within last 12 months	-

Pulmonary rehabilitation component

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Duration/frequency of pulmonary rehabilitation	Definition of adherence
102	Al Moamary, M. S., 2010	2004 – 2008	Saudi Arabia	Pulmonary Rehabilitation Centre at a tertiary care teaching hospital	62	8-12 weeks/18-24 sessions	Completed 18 sessions
103	Almadana, 2017	2015	Spain	University hospital	57	12 weeks/36 sessions	At least 70% of sessions
104	Azarisman, 2008	2005 – 2006	Malaysia	University hospital	86	-	-
105	Bjoernshave, 2011	2008 – 2009	Denmark	Regional hospital	148	8 weeks/16 sessions	Completed the programme
51	Bourbeau, 2008	2005	Canada	General practice	1,090	-	-
106	Boutou, 2014	2012 – 2013	UK	Outpatient pulmonary rehabilitation programme	787	8-12 weeks/ 2 supervised sessions and 1 or more unsupervised home exercise sessions each week	At least 75% of the sessions
107	Braeken, 2017	2012 – 2014	Netherlands	University hospital	518	8 weeks of inpatient programme or 16 weeks of outpatient programme/ total 40 sessions	Completed the programme
108	Brown, 2016	1996 – 2013	USA	University hospital	440	Maximum 12 weeks/36 sessions	At least 8 consecutive weeks, completing 20 sessions
109	Busch, 2014	2007 – 2012	USA	Outpatient pulmonary rehabilitation programme	111	Twice a week for 20 - 36 total sessions	20 or more sessions
110	Corhay, 2012	2007 – 2008	Belgium	University pulmonary rehabilitation department	140	6 months/60 sessions	Completed the programme
111	Cote, 2005	?	USA	University hospital	246	8 weeks/24 sessions	Completed the programme
112	Evans, 2009	?	UK	University hospital	450	7 weeks/14 sessions	Completed the programme
113	Fischer, 2009	2005 – 2007	Netherlands	Pulmonary rehabilitation centre	217	12 weeks/3 days per week	Patients who stopped attending appointments before the end of the formal

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Duration/frequency of pulmonary rehabilitation	Definition of adherence
							rehabilitation programme and who missed the functionalfollow-up tests were non-completers
114	Garrod, 2006	?	UK	Primary or secondary care services	74	7 weeks/2 times per week	At least 10 sessions
115	Halding, 2017	2013 – 2014	Norway	Hospital	116	-	-
116	Hayton, 2013	2005 – 2010	UK	Outpatient pulmonary rehabilitation at a community hospital	711	8 weekly supervised sessions	6 sessions or more
117	Hogg, 2012	2008 – 2010	UK	Rehabilitation service in hospital and community settings	1,266	8 weeks/8 sessions (cohort recruitment programme) or 16 sessions (rolling recruitment programme)	at least 8 sessions on a rolling recruitment programme; at least 6 sessions on a cohort recruitment programme
118	Houchen-Wolloff, 2018	2000 – 2012	UK	Outpatient pulmonary rehabilitation at 2 hospital	1,515	7 weeks/2 times per week	Had any data recorded for a post-PR assessment
83	Jochmann, 2010	2007 – 2009	Switzerland	General practice	615	-	-
55	Jouleh, 2018	2005 – 2006	Norway	Population-based survey and university hospital	335	-	-
57	Kaufmann, 2015	2012	Switzerland	General practice	115	-	-
58	Khan, 2017	2011 – 2015	UK	General practice	1,078	-	-
35	Kuyucu, 2011	?	Turkey	secondary and tertiary healthcare institutions and physician's offices	514	-	-
119	Maddocks, 2016	2011 – 2015	UK	Pulmonary rehabilitation programme at a hospital	816	8 weeks/2 supervised and at least 1 additional home-based session each week	Completed the programme
37	Maio, 2014	?	Italy	General practice	526	-	-
86	Martin, 2012	2009 – 2010	UK	General practice database	7,901	-	-
89	Miravitlles, 2008	2005 – 2006	17 countries, including Spain, Argentina, Ecuador, China	Multiple settings	833	-	-
120	Moore, 2017	?	UK	General practice database	69,089	-	-
121	Oates, 2017	1996 – 2013	USA	Outpatient pulmonary rehabilitation programme at a university hospital	415	12 weeks/maximum 36 sessions	> 85% prescribed sessions

Reference	Author, year	Years of study	Country	Study setting/data source	Study sample	Duration/frequency of pulmonary rehabilitation	Definition of adherence
61	Rubio, 2017	2014 – 2015	Spain	Outpatient respiratory clinics	4,508	-	-
122	Sahin, 2018	2013 – 2017	Turkey	Pulmonary rehabilitation unit of a hospital	359	8 weeks	non-completion defined as those who did not start the program at all or did not come for 3 consecutive sessions
123	Scott, 2010	2000 – 2008	Canada	Pulmonary rehabilitation programme at a hospital	177	8 weeks/24 sessions	70% or more of sessions
124	Selzler, 2012	2005 – 2008	Canada	Outpatient pulmonary rehabilitation programme at a hospital	814	3 days per week for 6 weeks, or 2 days per week for 8 weeks	50% or more of sessions
64	Tøttenborg, 2013	2008 – 2011	Denmark	National register	15,264	-	-
125	Vagaggini, 2009	?	Italy	University hospital	96	8 weeks/16 sessions	Completed the programme
101	Yu, 2011	2008 – 2009	Hong Kong	Specialist outpatient clinics and general practices	120	-	-

Supplementary Table S4. Quality assessment of included studies using the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from the National Heart, Lung, and Blood Institute of the National Institutes of Health

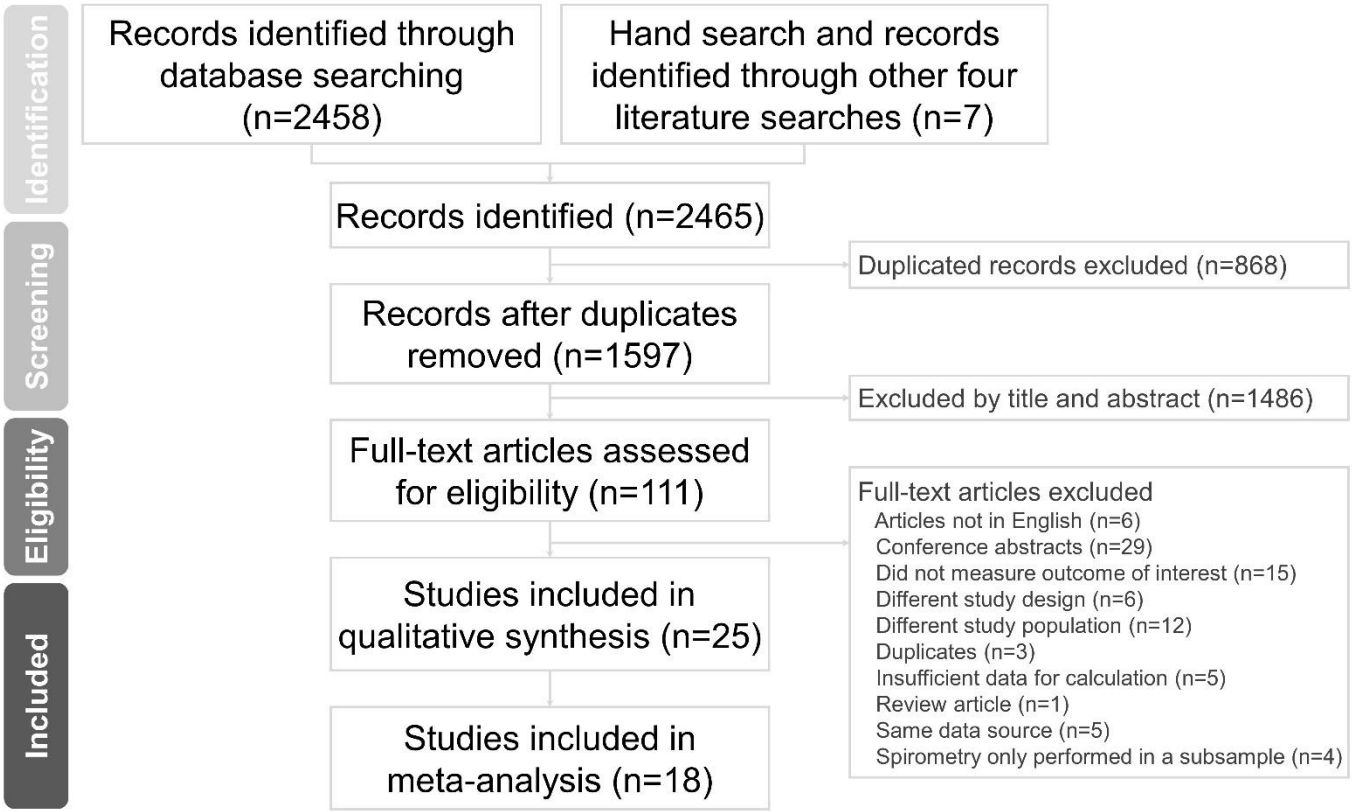
Reference	Author, year of publication	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall
1	Daldoul, 2013	Y	N	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	fair
2	Gemert,2015	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y	good
3	Glaser,2010	Y	Y	NR	Y	N	N	NA	N	Y	N	Y	NR	NA	N	fair
4	Guerriero,2015	Y	Y	N	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y	fair
5	Karloh,2018	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NR	NA	NA	good
6	Lamprecht,2015	Y	Y	NR	N	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
7	Lenoir,2018	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
8	Lindstrom,2002	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
9	Lu,2010	N	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	fair
10	Lundback,2003	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
11	Methvin,2009	Y	N	N	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	fair
12	Miravitlles, 2009	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y	good
13	Murtagh,2005	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NR	NA	N	fair
14	Nascimento,2007	Y	Y	NR	Y	Y	N	NA	N	Y	N	Y	NR	NA	N	fair
15	Pothirat,2016	Y	N	NR	Y	Y	N	NA	NA	Y	N	Y	NR	NA	N	fair
16	Scholes,2014	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
17	Waatevik,2013	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
18	Wang,2018	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y	good
19	Allen-Ramey,2012	Y	Y	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	fair
20	Bogart, 2018	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	Y	N	fair
21	Breekveldt-Postma, 2007	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NA	Y	Y	good
22	Casas, 2018	Y	Y	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	fair
23	Corrado, 2012	Y	Y	NR	Y	Y	N	NA	Y	Y	N	Y	NR	NA	N	fair
24	Davis, 2017	Y	Y	Y	Y	N	N	CD	Y	Y	N	Y	NA	Y	Y	fair
25	Dhamane, 2016	Y	Y	Y	Y	N	N	Y	NA	Y	N	Y	NA	Y	Y	fair
26	Diette, 2015	Y	Y	Y	Y	N	N	NA	NA	Y	N	Y	NA	NA	N	good
27	Falk, 2016	Y	Y	Y	Y	N	NA	NA	NA	NA	NA	Y	NA	Y	NA	poor
28	Green, 2015	Y	Y	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	fair
29	Gruffydd-Jones,2016	Y	Y	Y	Y	N	N	NA	Y	Y	Y	N	NA	NA	Y	fair
30	Gunen, 2015	Y	Y	NR	Y	Y	N	NA	Y	Y	N	Y	NR	NA	N	fair
31	Halpern, 2011	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NA	Y	Y	fair
32	Hsieh, 2018	Y	Y	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	fair
33	Ingebrigtsen,2014	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	fair
34	Kim, 2017	N	Y	Y	Y	N	N	CD	NA	Y	N	N	NA	Y	Y	fair
35	Kuyucu,2011	N	Y	NR	Y	N	N	NA	N	N	N	N	NR	NA	N	poor
36	Laforest, 2012	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NA	Y	Y	good
37	Maio, 2014	Y	N	N	Y	N	N	NA	Y	Y	N	N	NA	NA	Y	poor
38	Make,2012	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	NR	Y	N	good
39	Monteagudo,2017	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	NA	Y	Y	good

Reference	Author, year of publication	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall
40	Mueller, 2016	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NA	Y	Y	good
41	Palmiotti, 2018	N	Y	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	fair
42	Price, 2014	Y	Y	Y	Y	N	N	NA	NA	Y	N	Y	NA	NA	N	good
43	Raluy-Callado, 2015	Y	Y	Y	Y	N	N	NA	NA	Y	N	Y	NR	NA	N	good
44	Savaria, 2017	Y	Y	Y	Y	N	NA	NA	NA	NA	NA	Y	NA	Y	NA	fair
45	Scalone, 2018	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	NR	N	N	fair
46	Sen, 2015	Y	Y	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	fair
47	Tøttenborg, 2016	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NA	Y	Y	good
48	Vestbo,2014	Y	Y	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	fair
49	Vetrano, 2017	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NA	Y	Y	good
50	Wurst, 2014	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NR	Y	N	fair
51	Bourbeau,2008	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	good
52	Chavez,2009	Y	Y	Y	Y	N	NA	NA	NA	NA	NA	Y	NA	NA	NA	fair
53	Henoch,2016	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
54	Jones,2008	Y	Y	Y	N	N	NA	NA	NA	NA	NA	N	NA	NA	NA	fair
55	Jouleh,2018	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y	good
56	Kalkhoran,2018	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NA	NA	Y	fair
57	Kaufmann,2015	Y	Y	NR	Y	Y	CD	Y	N	Y	N	Y	NR	NA	NA	fair
58	Khan,2017	Y	Y	N	Y	N	N	NA	NA	N	N	N	NR	NA	Y	fair
59	López Varela,2008	Y	Y	Y	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y	good
60	Menezes,2015	Y	Y	Y	Y	Y	NA	NA	NA	NA	NA	Y	NA	NA	NA	fair
61	Rubio,2017	Y	Y	Y	Y	N	N	NA	N	Y	N	Y	NR	NA	N	Fair
62	Schauer,2016	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NA	NA	Y	fair
63	Tilert,2015	Y	Y	NR	Y	N	N	NA	Y	Y	N	N	NA	NR	Y	fair
64	Tøttenborg,2013	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	NR	NA	N	fair
65	Abad-Arranz, 2018	Y	Y	NR	N	N	N	NA	N	N	N	N	NR	NA	N	poor
66	Akturk,2017	Y	Y	NR	Y	N	N	NA	Y	N	N	N	NR	NA	N	Poor
67	Arinez-Fernandez,2006	Y	Y	NR	Y	Y	N	NA	Y	Y	N	N	NR	NA	Y	fair
68	Britton, 2003	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NR	NA	N	fair
69	Carrasco-Garrido,2009	Y	Y	NR	Y	Y	N	NA	NA	Y	N	Y	NR	NA	N	fair
70	Carreno-Ibanez,2015	Y	Y	Y	Y	N	CD	CD	Y	Y	Y	Y	NR	NA	Y	good
71	Chapman, 2003	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NR	NA	N	fair
72	Chen,2015	Y	Y	NR	Y	N	N	NA	Y	Y	Y	N	NR	N	Y	fair
73	Chiatti,2011	Y	Y	NR	Y	N	N	NA	Y	Y	N	N	NR	NA	Y	fair
74	Dal Negro, 2003	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NR	NA	N	fair
75	Eagan,2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NR	NR	Y	good
76	Feifer,2002	Y	Y	N	Y	N	N	NA	N	Y	N	Y	NR	NA	N	fair
77	Garrastazu,2016	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	NR	Y	Y	good
78	Halpern, 2003	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NR	NA	N	fair
79	Hsu, 2016	Y	Y	N	Y	N	N	NA	Y	N	N	N	NR	NA	Y	Fair
80	Izquierdo, 2003	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NR	NA	N	fair

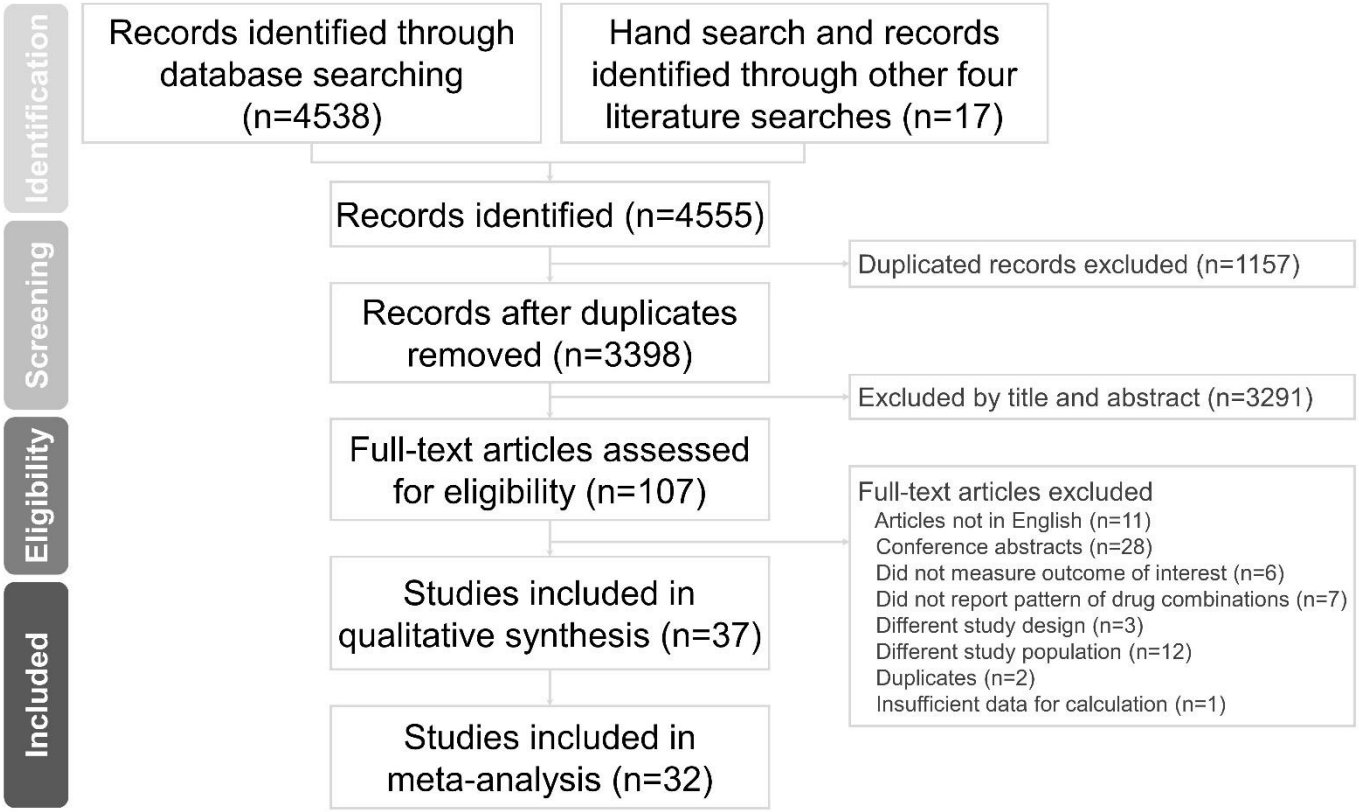
Reference	Author, year of publication	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall
81	Jimenez-Garcia,2005	Y	Y	NR	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y	fair
82	Jimenez-Garcia,2009	Y	Y	NR	Y	N	N	NA	Y	N	N	N	NR	NA	Y	Poor
83	Jochmann,2010	Y	N	NR	Y	N	N	NA	Y	Y	N	N	NA	NA	N	Fair
84	Kurmi, 2018	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	NA	fair
85	Kwong,2007	Y	Y	Y	Y	N	N	NA	Y	Y	N	N	NR	NA	Y	fair
86	Martin,2012	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	good
87	Mehuys,2010	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	fair
88	de Miguel-Diez,2014	Y	Y	NR	Y	N	N	NA	Y	N	N	N	NR	NA	Y	fair
89	Miravitlles, 2008	Y	N	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y	fair
90	Mowls, 2013	Y	Y	NR	Y	N	N	NA	NA	N	N	N	NR	NA	Y	Fair
91	Ozyurt, 2018	Y	N	NR	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	Fair
92	Piperno, 2003	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NR	NA	N	fair
93	Santos-Sancho,2012	Y	Y	NR	Y	Y	N	NA	Y	N	N	N	NA	NA	Y	fair
94	Schembri,2009	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	NR	NR	Y	good
95	Shin,2017	Y	Y	NR	Y	N	N	NA	Y	N	N	N	NR	NA	Y	fair
96	Sundh, 2017	Y	Y	NR	N	N	N	NA	Y	Y	N	Y	NR	NA	Y	fair
97	Tata,2003	Y	Y	Y	Y	Y	Y	Y	NA	Y	N	N	NA	NR	N	Fair
98	Vila-Corcoles,2007	Y	Y	NR	Y	N	Y	Y	NA	Y	Y	Y	NR	NR	Y	good
99	Vozoris,2008	Y	Y	NR	Y	N	N	NA	Y	Y	N	N	NA	NA	Y	good
100	Yu,2011	Y	Y	Y	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	good
101	Wouters, 2003	Y	Y	Y	Y	Y	N	NA	Y	N	N	N	NR	NA	N	fair
102	Al Moamary, M. S., 2010	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NR	Y	N	Fair
103	Almadana,2017	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	fair
104	Azarisman,2008	Y	Y	NR	Y	N	CD	CD	N	Y	N	Y	NR	NR	N	Fair
105	Bjoernshave,2011	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	NR	Y	N	fair
106	Boutou,2014	Y	Y	NR	Y	N	Y	Y	N	Y	N	Y	NR	Y	Y	fair
107	Braeken,2017	Y	Y	Y	Y	N	Y	Y	Y	N	N	Y	NR	Y	N	fair
108	Brown,2016	Y	Y	NR	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	fair
109	Busch,2014	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	Good
110	Corhay,2012	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	good
111	Cote,2005	Y	Y	NR	Y	N	Y	Y	NA	Y	N	Y	NR	Y	Y	good
112	Evans,2009	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	fair
113	Fischer,2009	Y	Y	Y	Y	N	Y	Y	Y	Y	NA	Y	NA	Y	Y	good
114	Garrod,2006	Y	N	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	good
115	Halding,2017	Y	N	N	Y	N	N	NA	Y	Y	N	Y	NR	NA	N	Fair
116	Hayton,2013	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	good
117	Hogg,2012	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	good
118	Houchen-Wolloff,2018	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	good
119	Maddocks,2016	Y	Y	NR	Y	Y	Y	Y	Y	Y	N	Y	NR	Y	Y	good
120	Moore,2017	Y	Y	Y	Y	N	Y	Y	NA	Y	N	Y	NR	Y	Y	good
121	Oates,2017	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	good

Reference	Author, year of publication	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall
122	Sahin,2018	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	good
123	Scott,2010	Y	Y	N	Y	N	Y	Y	Y	Y	N	Y	NR	Y	N	fair
124	Selzler,2012	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	N	Y	good
125	Vagaggini,2009	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y	NR	Y	Y	good

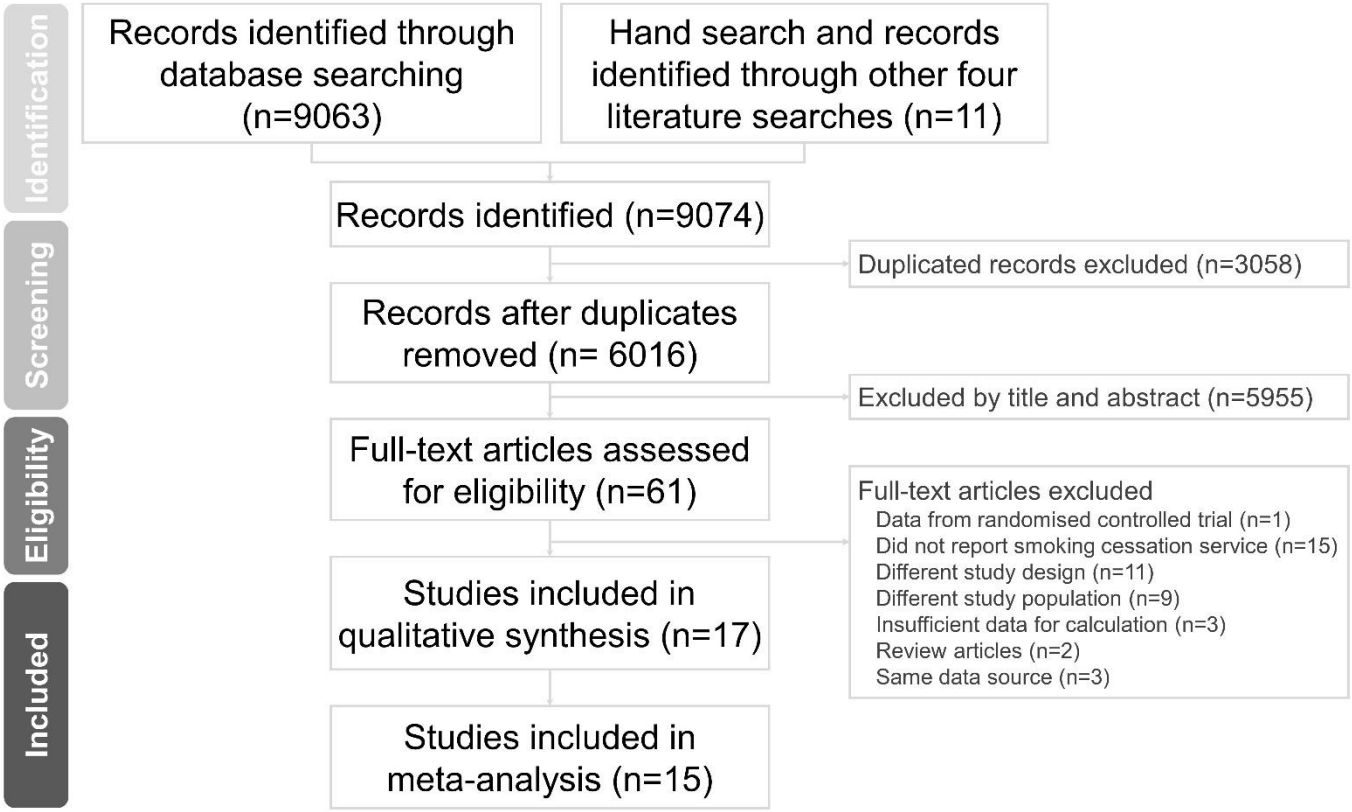
Supplementary Figure S1. PRISMA diagram of diagnosis (Component A).



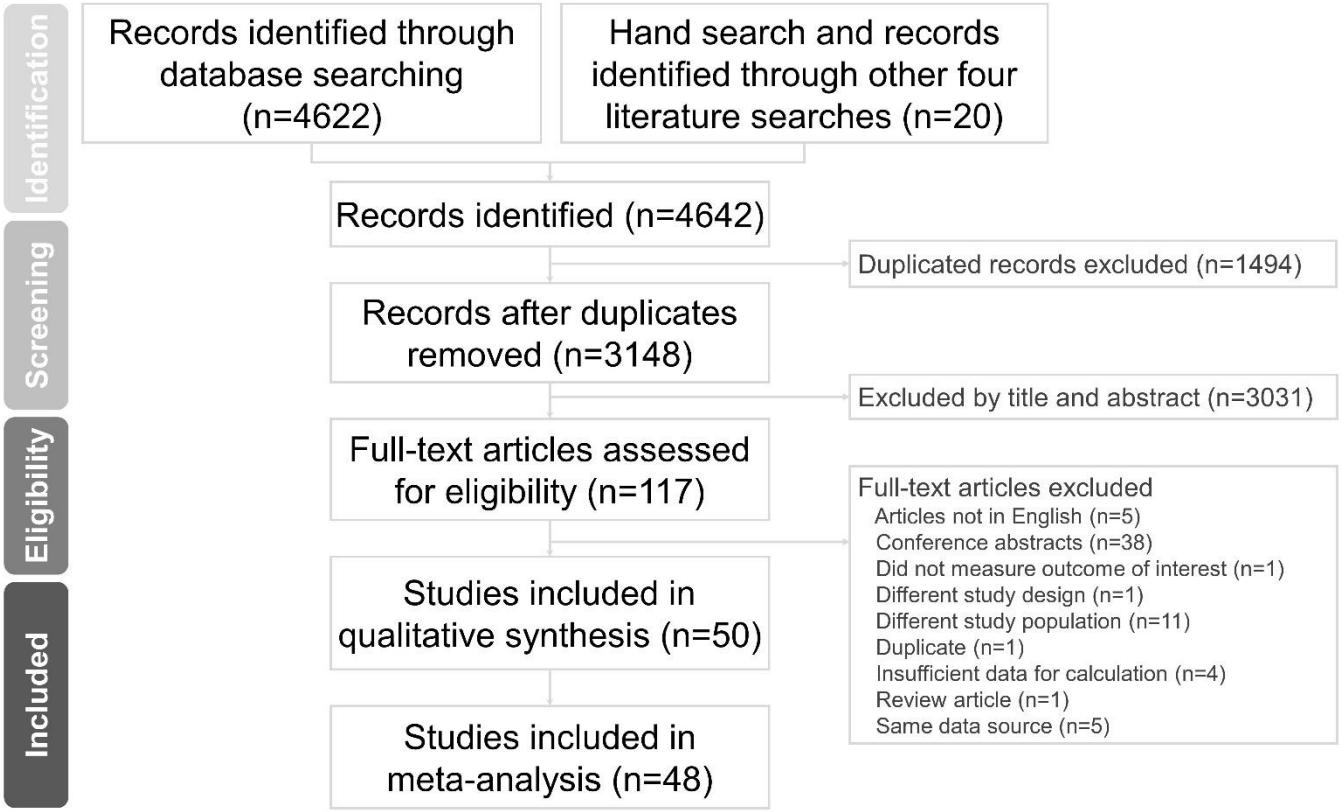
Supplementary Figure S2. PRISMA diagram of pharmacotherapy (Component B).



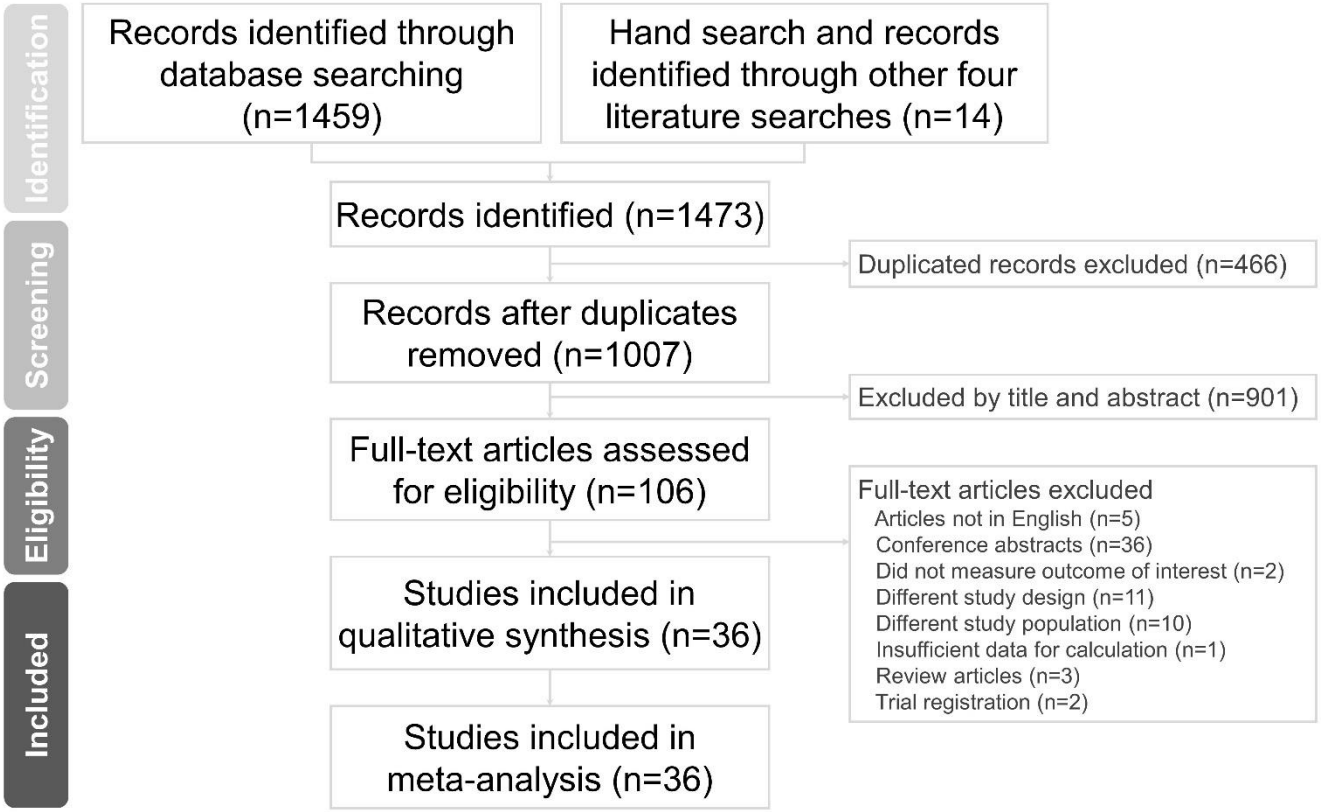
Supplementary Figure S3. PRISMA diagram of smoking cessation (Component C).



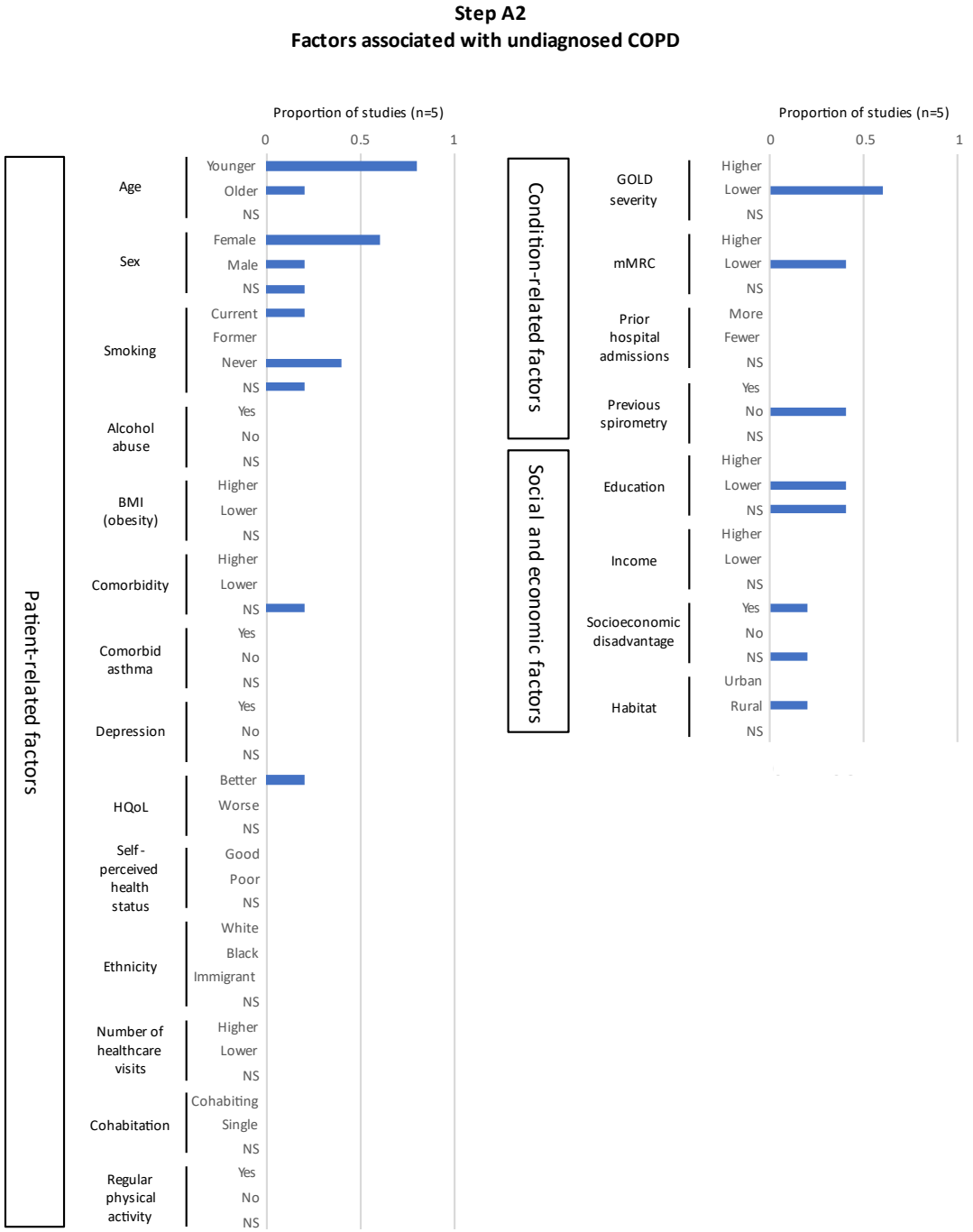
Supplementary Figure S4. PRISMA diagram of vaccination (Component D).



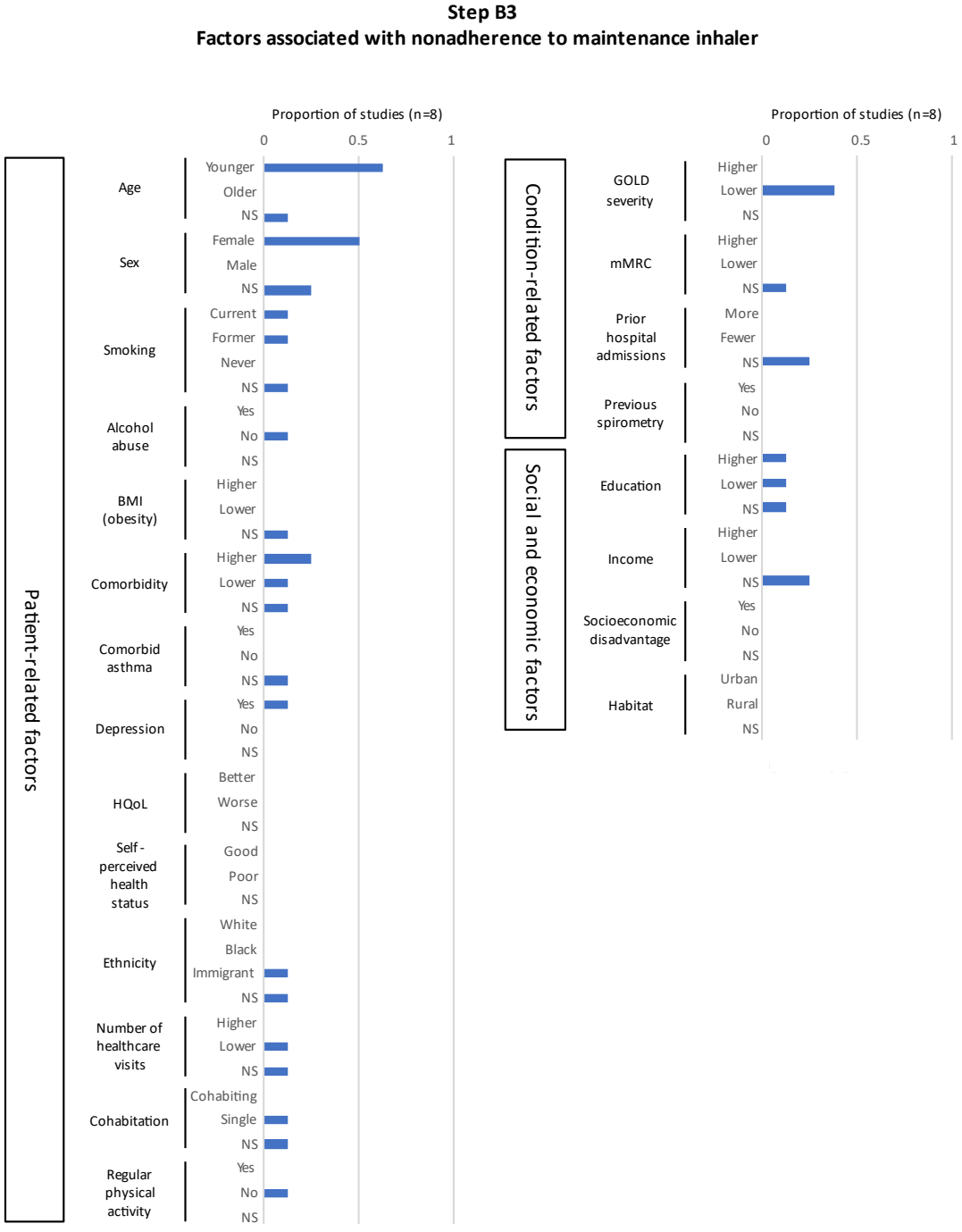
Supplementary Figure S5. PRISMA diagram of pulmonary rehabilitation (Component E).



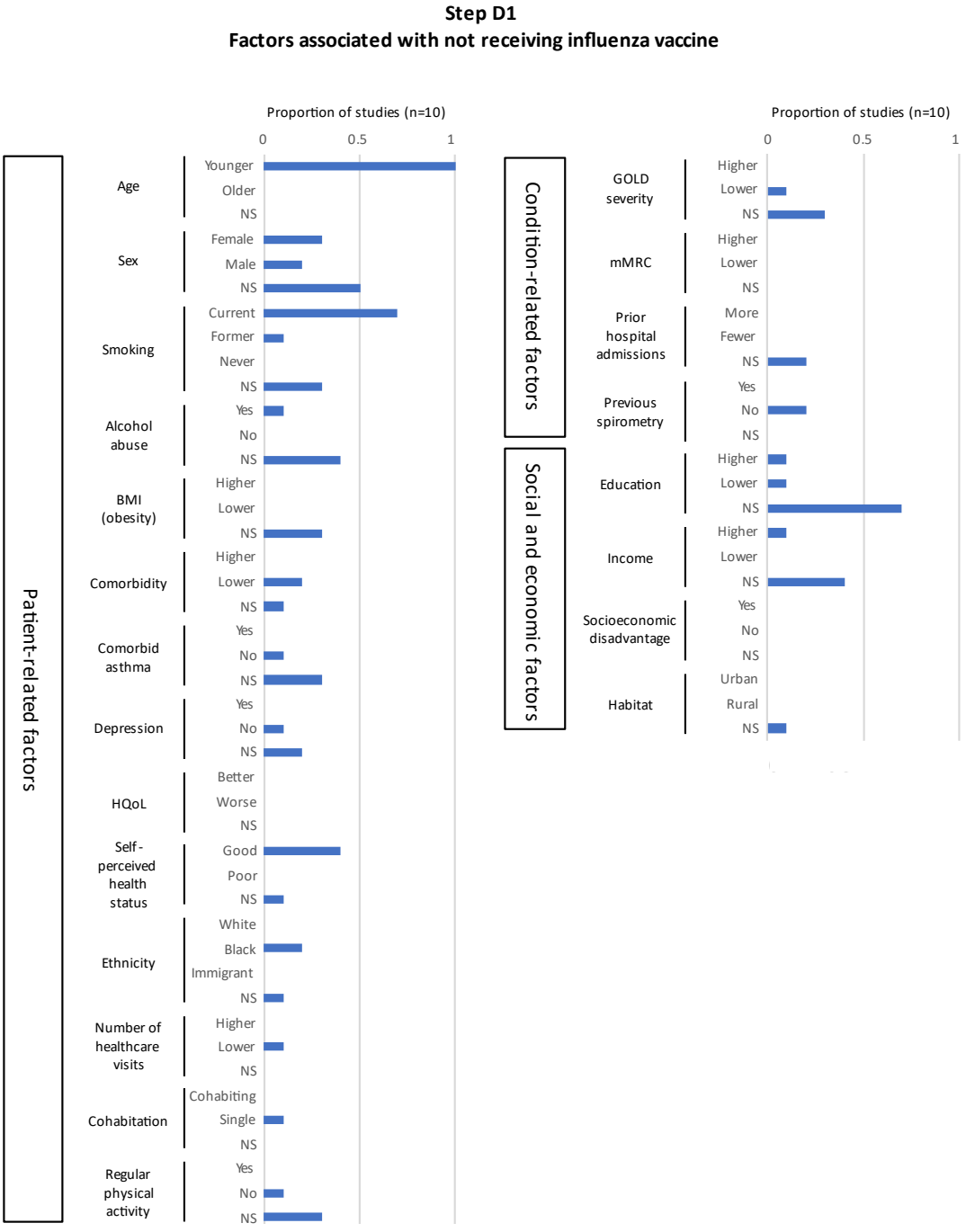
Supplementary Figure S6. Factors associated with undiagnosed chronic obstructive pulmonary disease. BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HQoL, health-related quality of life; mMRC, modified Medical Research Council scale; NS, nonsignificant.



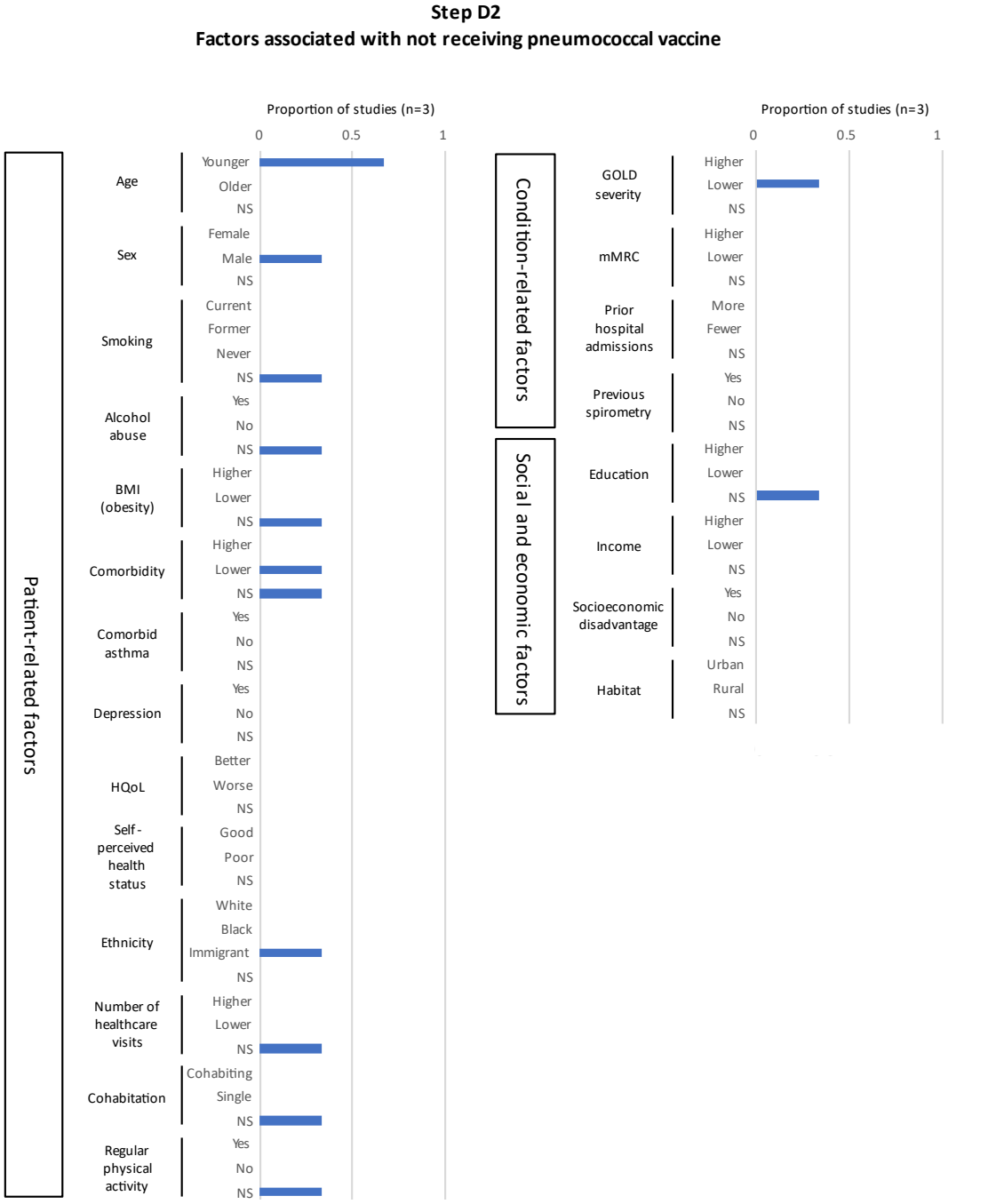
Supplementary Figure S7. Factors associated with nonadherence to maintenance inhaler. BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HQoL, health-related quality of life; mMRC, modified Medical Research Council scale; NS, nonsignificant.



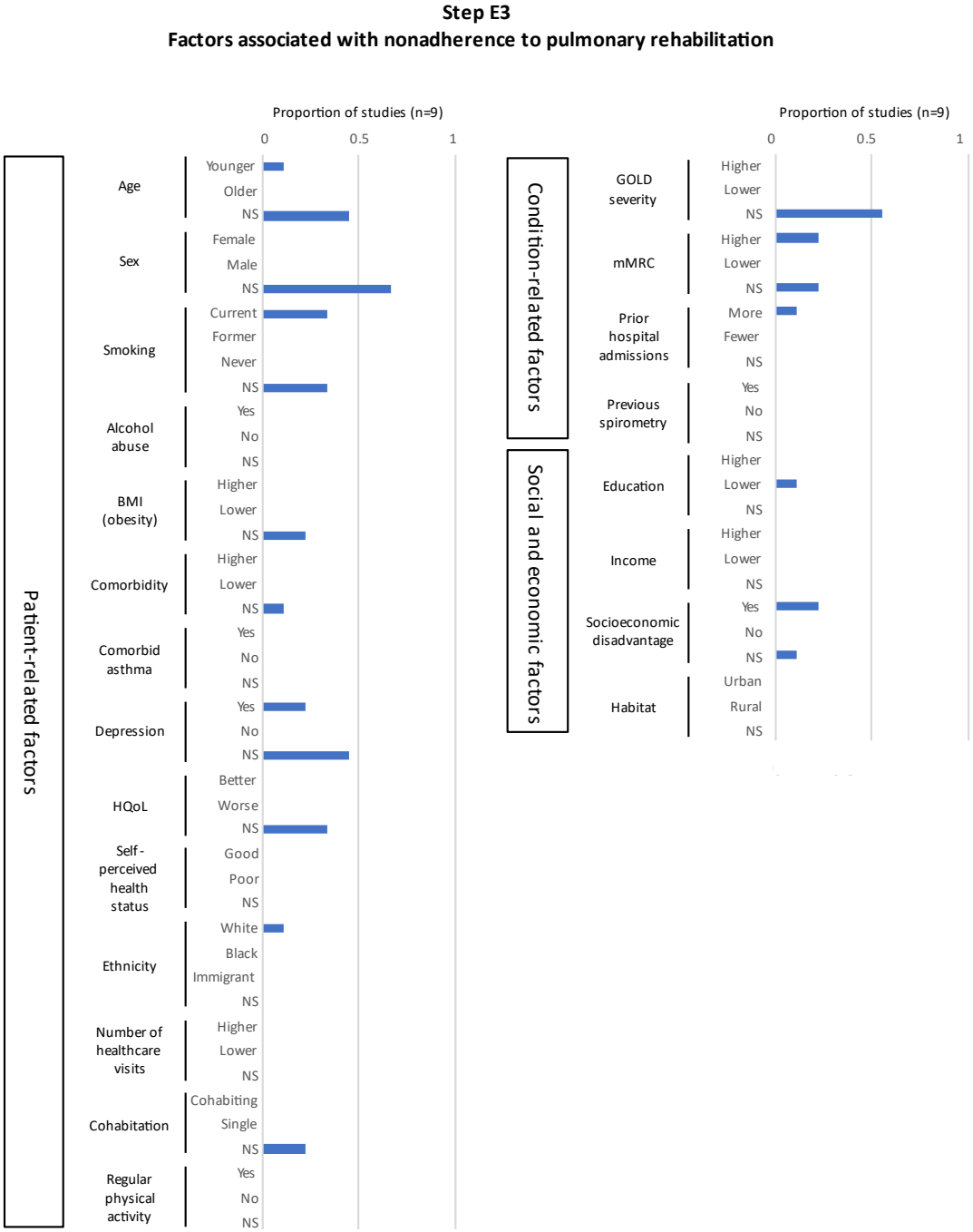
Supplementary Figure S8. Factors associated with not receiving influenza vaccine. BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HQoL, health-related quality of life; mMRC, modified Medical Research Council scale; NS, nonsignificant.



Supplementary Figure S9. Factors associated with not receiving pneumococcal vaccine. BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HQoL, health-related quality of life; mMRC, modified Medical Research Council scale; NS, nonsignificant.



Supplementary Figure S10. Factors associated with nonadherence to pulmonary rehabilitation. BMI, body mass index; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HQoL, health-related quality of life; mMRC, modified Medical Research Council scale; NS, nonsignificant.



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2.2. Supplementary appendix for publication in Chapter 3

This section contains the supplementary appendix of the following published article:

Huang W-C, Fox GJ, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Jan S, Negin J, Le TTL, Marks GB. A syndromic approach to assess diagnosis and management of patients presenting with respiratory symptoms to healthcare facilities in Vietnam. ERJ Open Research. 2021;7(1):00572-2020. doi: 10.1183/23120541.00572-2020.

Supplementary Table S1. Assessment of quality of spirometric testing

Rating	**Criteria**
A	At least 3 acceptable trials (for age 6 and under: 2 acceptable) AND the difference between the best two FEV1 and FVC values is equal to or less than 100mL (80mL if FVC < 1.0L; For age 6 and under: 80mL or 8% of FVC or FEV1 whichever is greater)
B	At least 3 acceptable trials (for age 6 and under: 2 acceptable) AND the difference between the best two FEV1 and FVC values is equal to or less than 150mL (100mL if FVC < 1.0L; For age 6 and under: 100mL or 10% of FVC or FEV1 whichever is greater)
C	At least 2 acceptable trials AND the difference between the best two FEV1 and FVC values is equal to or less than 200mL (150mL if FVC < 1.0L; For age 6 and under: 150mL or 15% of FVC or FEV1 whichever is greater)
D	At least 2 acceptable trials but the results are not reproducible according to 'C' OR only one acceptable trial.
F	No acceptable trial available

Supplementary Table S2. Operational definitions for chest X-ray interpretation

Chest X-ray finding	**Definition and description**
Air-space consolidation	The presence of a dense or confluent opacity occupying a portion or whole of a lobe or of the entire lung that may contain one or more of the following features: • Air bronchograms • Air-space nodules • Ill-defined or fluffy border • A silhouette sign The reader should indicate the location of the lesion.
Cardiomegaly	Cardiothoracic ratio > 0.55. The cardiothoracic ratio is calculated using the convention of measuring the thoracic diameter as the distance from the inner margin of the ribs at the level of the dome of the right hemidiaphragm and the cardiac diameter as the horizontal distance between the most rightward and most leftward margins of the cardiac shadow.
Pulmonary venous hypertension	The presence of one or more of the following: • Larger upper lobe vessels • Kerley's A or B lines • Increased prominence of “interstitial markings” • Enlargement and indistinctness of hila • Confluent acinar shadows (pulmonary alveolar oedema) • Perihilar alveolar filling • Lower lobe or more generalized alveolar filling The reader should describe what is seen from the list above.

Supplementary Table S3. Comparison between patients who completed the full survey, those who completed the minimal data questionnaire, and those who refused to participate at all healthcare facilities

	Baseline survey	**Minimal data collected**	**Declined to complete minimal data questionnaire**
Total	977	169	471
Male (n, %)	638 (65.3)	87 (51.5)	266 (56.5)
Age, years (mean, SD)	55.5 (17.1)	50.2 (20.5)	47.9 (22.7)

Supplementary Table S4. Other clinical diagnoses given by treating doctors for patients not meeting any of the predefined syndromes (n=129)

Diagnoses	**n (%)**
Pleural effusion	6 (4.7)
Lung tumour	4 (3.1)
Old tuberculosis	2 (1.6)
Myocardial infarction	2 (1.6)
Musculoskeletal pain	2 (1.6)
Lung abscess	2 (1.6)
Pneumothorax	1 (0.8)
Laryngeal cancer	1 (0.8)
Anterior mediastinal tumour	1 (0.8)
Subcutaneous emphysema and pneumomediastinum	1 (0.8)
Reported only patient's respiratory symptoms	20 (15.5)
Other non-respiratory diagnosis	59 (45.7)

Supplementary Table S5. Treatment provided to patients with a clinical diagnosis of bronchitis given by treating doctors

Diagnosis	n	Systemic corticosteroids	Inhaled corticosteroids	Long-acting bronchodilators	Short-acting beta-agonist	Antibiotics	Diuretics	Anti-tuberculosis
Bronchitis alone	243	80 (32.9)	5 (2.1)	27 (11.1)	1 (0.4)	205 (84.4)	6 (2.5)	0 (0)
COPD + bronchitis	12	8 (66.7)	6 (50)	8 (66.7)	1 (8.3)	9 (75)	1 (8.3)	0 (0)
Asthma + bronchitis	21	11 (52.4)	17 (81)	18 (85.7)	3 (14.3)	19 (90.5)	2 (9.5)	0 (0)

Supplementary references:

1. Webb WR, Higgins CB. Thoracic Imaging: Pulmonary and Cardiovascular Radiology. Lippincott Williams & Wilkins, Third Edition, 2017.
2. Wortham JM, Gray J, Verani J, Contreras CL, Bernart C, Moscoso F, Moir JC, Reyes Marroquin EL, Castellan R, Arvelo W, Lindblade K, McCracken JP. Using Standardized Interpretation of Chest Radiographs to Identify Adults with Bacterial Pneumonia—Guatemala, 2007–2012. *PloS one* 2015: 10(7): e0133257.
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2.3. Supplementary appendix for publication in Chapter 4

This section contains the supplementary appendix of the following published article:

Huang WC, Pham NY, Nguyen TA, Vu VG, Ngo QC, Nguyen VN, Freeman B, Jan S, Negin J, Marks GB, Fox GJ. Smoking behaviour among adult patients presenting to health facilities in four provinces of Vietnam. BMC public health. 2021;21(1):845. Epub 2021/05/03. doi: 10.1186/s12889-021-10880-z.

Supplementary Table S1. Demographics of current smokers completing full baseline survey, by level of healthcare facility

	All facilities (46 facilities) n = 748	**Central/provincial hospital (8 facilities) n = 277**	**District hospital (16 facilities) n = 408**	**Commune health centre (12 facilities) n = 63**
Age, years (median, IQR)	57 (46 - 65)	56 (42 - 64)	58 (48 - 65)	57 (48 - 65)
Male gender (n, %)	743 (99.3%)	276 (99.6%)	406 (99.5%)	61 (96.8%)
Education level (n, %)				
Less than primary	51 (6.8%)	18 (6.5%)	30 (7.4%)	3 (4.8%)
Primary	219 (29.3%)	89 (32.1%)	110 (27.0%)	20 (31.8%)
Lower secondary	283 (37.8%)	95 (34.3%)	161 (39.5%)	27 (42.9%)
Upper secondary	141 (18.9%)	49 (17.7%)	82 (20.1%)	10 (15.9%)
University degree, or equivalent, or higher	51 (6.8%)	24 (8.7%)	24 (5.9%)	3 (4.8%)
Unknown/No answer	3 (0.4%)	2 (0.7%)	1 (0.2%)	0 (0.0%)
Occupation (n, %)				
Indoor manual labourer	65 (8.7%)	24 (8.7%)	39 (9.6%)	2 (3.2%)
Outdoor manual labourer	68 (9.1%)	19 (6.9%)	45 (11.1%)	4 (6.3%)
Agricultural work	188 (25.1%)	69 (24.9%)	93 (22.9%)	26 (41.3%)
Retired	203 (27.1%)	72 (26.0%)	118 (29.0%)	12 (19.0%)
Unemployed	18 (2.4%)	5 (1.8%)	7 (1.7%)	6 (9.5%)
Other	206 (27.5%)	88 (31.8%)	105 (25.8%)	13 (20.6%)

Comorbidity (n, %)				
Heart disease	73 (9.8%)	25 (9.0%)	44 (10.8%)	4 (6.3%)
Hypertension	205 (27.4%)	58 (20.9%)	133 (32.6%)	14 (22.2%)
Diabetes	88 (11.8%)	21 (7.6%)	64 (15.7%)	3 (4.8%)
Asthma	45 (6.0%)	18 (6.5%)	19 (4.7%)	8 (12.7%)
COPD	30 (4.0%)	15 (5.4%)	14 (3.4%)	1 (1.6%)
Chronic bronchitis	67 (9.0%)	32 (11.6%)	25 (6.1%)	10 (15.9%)
Emphysema[*]	3 (0.5%)	1 (0.4%)	2 (0.5%)	0 (0.0%)
History of tuberculosis	65 (8.7%)	38 (13.7%)	20 (4.9%)	7 (11.1%)
Geographic area (n, %)				
Northern Vietnam	389 (52.0%)	150 (54.2%)	205 (50.2%)	34 (54.0%)
Hanoi	169 (22.6%)	66 (23.8%)	103 (25.2%)	0 (0.0%)
Thanh Hoa	220 (29.4%)	84 (30.3%)	102 (25.0%)	34 (54.0%)
Southern Vietnam	359 (48.0%)	127 (45.8%)	203 (49.8%)	29 (46.0%)
Ho Chi Minh City	143 (19.1%)	36 (13.0%)	102 (25.0%)	5 (7.9%)
Ca Mau	216 (28.9%)	91 (32.9%)	101 (24.8%)	24 (38.1%)
Had breathing problems that interfered with usual daily activities[†] **(n, %)**	52 (7.7%)	18 (7.6%)	31 (8.0%)	3 (5.3%)
Living with at least one other who smoked a cigarette, pipe or cigar in your home during the past two weeks (n, %)	241 (32.2%)	92 (33.2%)	131 (32.1%)	18 (28.6%)

IQR: interquartile range; [*]83 missing values; [†]69 missing

Supplementary Table S2: Comparison between current smokers who were included and those who were not included at all healthcare facilities

	Eligible, not selected	Eligible, selected
Total	390	1044
Male (n, %)	367 (94.1%)	1,027 (98.4%)
Age, years (mean, SD)	52.7 (15.4)	53.9 (14.5)

Supplementary Table S3: Comparison between current smokers who completed the full survey, those who completed the minimal data questionnaire, and those who refused to participate at all healthcare facilities

	Full baseline survey	Minimal data	Refused to participate
Total	748	51	245
Male (n, %)	741 (99.1)	50 (98.0)	236 (96.3)
Age, years (mean, SD)	54.7 (14.4)	51.4 (13.2)	51.7 (14.7)

Supplementary Table S4: Use of tobacco products among current smokers who completed the full survey

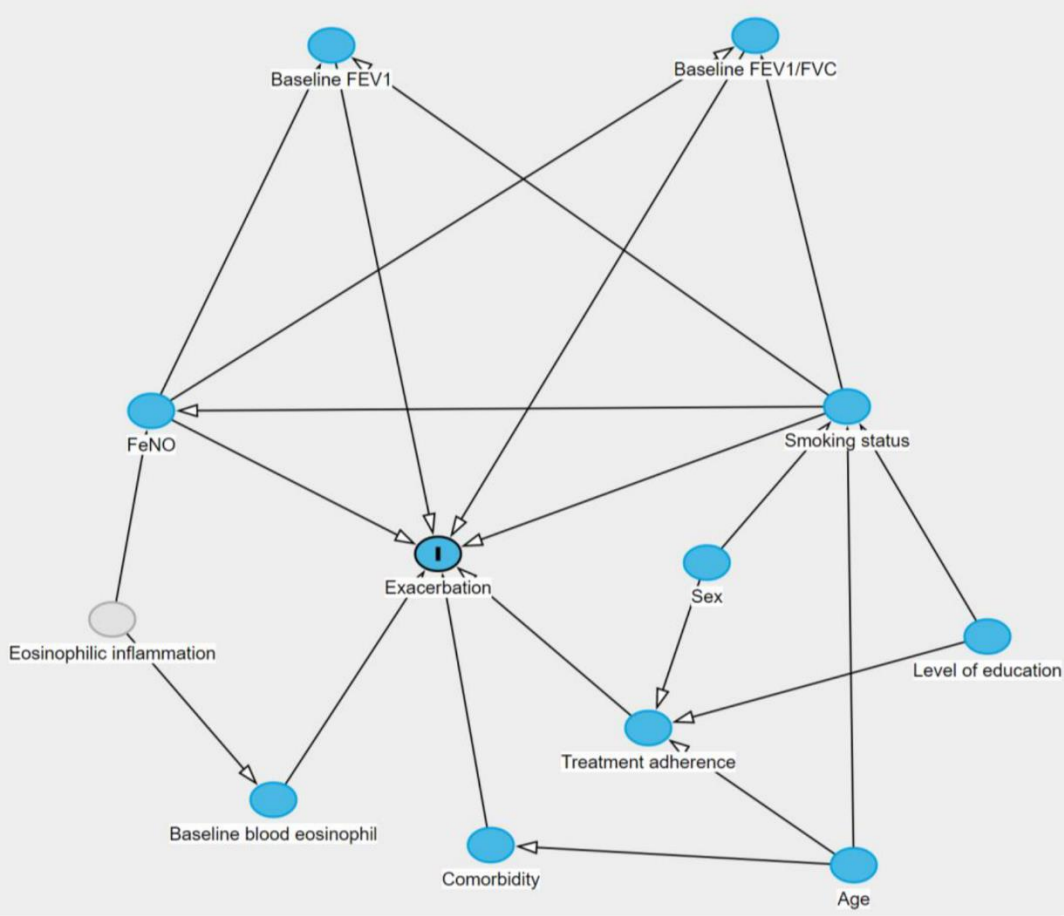
	Current smokers n = 748
Manufactured cigarettes (n, %)	550 (73.5%)

Hand-rolled cigarettes (n, %)	56 (7.5%)
Kreteks (n, %)	0 (0%)
Pipes full of tobacco (n, %)	0 (0%)
Cigars, cheroots, or cigarillos (n, %)	4 (0.5%)
Water pipes (n, %)	242 (32.4%)
Electronic cigarettes (n, %)	0 (0%)

2.4. Supplementary appendix for publication in Chapter 5

This section contains the supplementary appendix of the following manuscript submitted for publication:

Huang WC, Fox GJ, Pham NY, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Marks GB. Stepped treatment algorithm using budesonide-formoterol for chronic respiratory diseases: a single arm interventional study. Submitted to PLOS ONE.



S1 Fig. Casual diagram (directed acyclic graph) for logistic regression models evaluating factors associated with risk of exacerbations.

Figure produced from http://www.dagitty.net/dags.html

S1 File. TREND statement checklist.

Paper Section/Topic	Item No.	Descriptor	Reported? Pg#
TITLE and ABSTRACT			
Title and Abstract	1	• Information on how units were allocated to interventions	1
		• Structured abstract recommended	2
		• Information on target population or study sample	2
INTRODUCTION			
Background	2	• Scientific background and explanation of rationale	3
		• Theories used in designing behavioral interventions	NA
METHODS			
Participants	3	• Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	4-5
		• Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	4-5
		• Recruitment setting	4
		• Settings and locations where the data were collected	6-7
Interventions	4	• Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	4-6
		○ Content: what was given?	4-6
		○ Delivery method: how was the content given?	4-6
		○ Unit of delivery: how were subjects grouped during delivery?	NA
		○ Deliverer: who delivered the intervention?	4-6
		○ Setting: where was the intervention delivered?	4-6
		○ Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?	4-6
		○ Time span: how long was it intended to take to deliver the intervention to each unit?	NA
		○ Activities to increase compliance or adherence (e.g., incentives)	NA
Objectives	5	• Specific objectives and hypotheses	3
Outcomes	6	• Clearly defined primary and secondary outcome measures	6-7
		• Methods used to collect data and any methods used to enhance the quality of measurements	6-7
		• Information on validated instruments such as psychometric and biometric properties	6-7
Sample size	7	• How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	8
Assignment method	8	• Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	5
		• Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	NA
		• Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	NA
Blinding (masking)	9	• Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed	NA
Unit of Analysis	10	• Description of the smallest unit that is being analysed to assess intervention effects (e.g., individual, group, or community)	6-7
		• If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	NA
Statistical methods	11	• Statistical methods used to compare study groups for primary methods outcome(s), including complex methods for correlated data	7
		• Statistical methods used for additional analyses, such as subgroup analyses and adjusted analysis	7
		• Methods for imputing missing data, if used	7
		• Statistical software or programs used	7

RESULTS			
Participant flow	12	• Flow of participants through each stage of the study: enrollment, assignment, allocation and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	8-9
		○ Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study	8-9
		○ Assignment: the numbers of participants assigned to a study condition	8-9
		○ Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention	8-9
		○ Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition	8-9
		○ Analysis: the number of participants included in or excluded from the main analysis, by study condition	8-9
		• Description of protocol deviations from study as planned, along with reasons	NA
Recruitment	13	• Dates defining the periods of recruitment and follow-up	8
Baseline data	14	• Baseline demographic and clinical characteristics of participants in each study condition	9
		• Baseline characteristics for each study condition relevant to specific disease prevention research	NA
		• Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	NA
		• Comparison between study population at baseline and target population of interest	NA
Baseline equivalence	15	• Data on study group equivalence at baseline and statistical methods used to control for baseline differences	NA
Numbers analyzed	16	• Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	8-9
		• Indication of whether the analysis strategy was “intention to treat” or, if not, description of how non-compliers were treated in the analyses	NA
Outcomes and estimation	17	• For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	8-10
		• Inclusion of null and negative findings	10-11
		• Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	10-11
Ancillary analyses	18	• Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	10-12
Adverse events	19	• Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	12
DISCUSSION			
Interpretation	20	• Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	14-15
		• Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	13-14
		• Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	13
		• Discussion of research, programmatic, or policy implications	15
Generalizability	21	• Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study, and other contextual issues	14
Overall evidence	22	• General interpretation of the results in the context of current evidence and current theory	15

From: Des Jarlais, D. C., Lyles, C., Crepaz, N., & the Trend Group (2004). Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: The TREND statement. *American Journal of Public Health*, 94, 361-366. For more information, visit: http://www.cdc.gov/trendstatement/

2.5. Supplementary appendix for publication in Chapter 6

This section contains the supplementary appendix of the following manuscript submitted for publication:

Huang WC, Marks GB, Pham NY, Nguyen TA, Nguyen TA, Vu VG, Nguyen VN, Jan S, Negin J, Ngo QC, Fox GJ. A smoking Quitline integrated with clinician counselling at outpatient health facilities in Vietnam: a single-arm prospective cohort study. Submitted to BMC Public Health.

Supplementary Table S1. Text message schedule

Day	SMS type	Tailored information	SMS content
1	Admin	Male	Dear Mr. NAME, welcome to VCAPS smoking cessation intervention. Congratulations on your decision to manage your smoking. We are here to help you prepare
		Female	Dear Miss NAME, welcome to VCAPS smoking cessation intervention. Congratulations on your decision to manage your smoking. We are here to help you prepare
2	Admin	Quit date	Well done for setting up your quit date on DATE. Let's prepare for it together!
3	Strategy		From now on, don't smoke inside your home or inside your car. Go outside if you want to smoke.
4	Admin		Managing smoking works best when you're prepared. Stick with us. We'll show you some strategies to deal with cravings and difficult situations over the next few weeks.
5	Strategy	Answered Yes to the question "Do you drink coffee/tea/colas every day?"	We know you love drink coffee/tea/colas. Try to cut the drink in half. It helps reduce your discomfort after you stop smoking.

		Answered No to the question "Do you drink coffee/tea/colas every day?"	Avoid drink too much coffee/tea/colas. It will help you manage your smoking.
6	Strategy	Answered Yes to the question "Do you smoke water pipes?"	Do you smoke water pipes? Water pipes are not a safe alternative. If fact, water pipes might be worse to your health than manufactured cigarettes
		Answered No to the question "Do you smoke water pipes?"	There is no such thing as safe tobacco. Hand rolled cigarettes, waterpipes, and cigars carry the same health risks as manufactured cigarettes.
7	Encourage	Male	Smoking causes erectile dysfunction. You have made a right decision to manage your smoking.
		Female	Smoking can cause many diseases, including cancer, stroke, heart disease, and blindness. Feel proud of yourself for deciding to quit.
8	Strategy	Answered Yes to the question "Do you live with a smoker?"	Remember the smoking outside strategy? It applies to everyone living with you. No one smoke inside!
		Answered No to the question "Do you live with a smoker?"	Share with your family that you are quitting smoking. Someone might be willing to support and encourage you.
9	Strategy	Answered 30 minutes or less to the question "How soon after you wake up do you usually have your first smoke?"	If you want to smoke right after you wake up, it means your body is special and needs more assistance. Don't worry because we are here.
		Answered more than 30 minutes to the question "How soon after you wake up do you usually have your first smoke?"	Do you believe you can stop smoking? We do because our trained Quitline counsellors are ready to assist you.
10	Encourage		Isn't it good to your family that you start to do something to manage your smoking? Everyone in the family will become healthier.
11	Admin		Remember you can calll the VCAPS Quitline at 1800 6276 if you need help
12	Encourage	Overall progress not so good, indicated by the counsellor after the 1-week call	We know it is hard but it is a decision you will not regret. Keep getting the support you need and remind yourself of your reasons to stop smoking.
		Overall good progress, indicated by	You are on the right track! Stop smoking is hard but stay confident. You can do

		the counsellor after the 1-week call	this.
13	Strategy	Answered Yes to the question "Have you tried to quit smoking?"	Think about what strategies worked and what did not work well during your previous quit attempt. Use your past experience to help yourself.
		Answered No to the question "Have you tried to quit smoking?"	Be proud of yourself for deciding to stop smoking. Let's do it and make you a non-smoker.
14	Strategy		Think again your strategies to deal with cravings. If you don't have any strategy or are not sure about them, call the Quitline to get help.
15	Strategy		Knowing your triggers helps you learn how to deal with them. Talk to your Quitline counsellor and write down your top 3 triggers and your coping strategies.
16	Encourage		If you're feeling cranky it could be because you’re stopping smoking. This is only temporary. Call the Quitline if you need to talk about your mood.
17	Strategy	Answered Yes to the question "Do you drink alcohol every day?"	Would you like to reduce alcohol? It will help with your plan to stop smoking. And remember, don't smoke while you drink.
		Answered No to the question "Do you drink alcohol every day?"	It is good that you don't drink alcohol very often. Keep yourself away from alcohol.
18	Encourage	Overall progress not so good, indicated by the counsellor after the 2-week call	We know it is hard to persist. Believe in yourself and Keep getting the support you need to stop smoking.
		Overall good progress, indicated by the counsellor after the 2-week call	Good job! You are on the right track! Believe in yourself that you can become a nonsmoker.
19	Admin		Call the Quitline at 1800 6276 if you need assistance from the Quitline counsellor for dealing with cravings
20	Strategy	Answered Yes to the question "Do you roll your own cigarettes?"	Hand rolled cigarettes are not less harmful than ordinary cigarettes. They cause the same serious problems to your health.
		Answered No to the question "Do you roll your own cigarettes?"	Some people say hand rolled cigarettes are less harmful. It's not true.
21	Strategy	Answered Yes to the question "Are most of your friends smokers?"	It's not easy if you are surrounded by smoking friends. Can you find someone from your friends who also want to stop smoking?
		Answered No to the question "Are most of your friends smokers?"	Hang out with your friends in places where smoking is not allowed. It helps you manage your smoking.

22	Strategy		Urges for smoking often get away in few minutes. Get a quick exercise or eat a small snack.
23	Admin		Call the Quitline at 1800 6276 if you need help with your cravings or withdrawal symptoms
24	Strategy		Be careful when you go to a party or a smoking area. Do not let yourself slip. You have done so much.
25	Encourage	Participant indicated still smoking during the 3-week call	Stop smoking is difficult for some people. Let's keep trying. Call the Quitline if you are ready to choose a quit date.
		Participant indicated not smoking during the 3-week call	Congratulations on your progress! Keep your great work. We believe in you.
26	Strategy		Remember, no one can smoke inside your house or inside your car.
27	Encourage		You may feel strange when you stop smoking. This is withdrawal because your body is used to smoking. These feelings will go away in few weeks.
28	Strategy		Even the strongest cravings will go away after a few minutes. Focus on something else and remind yourself why you want to be smokefree.
29	Strategy		Researse beforehand in your mind how to resist if you are going to a place or party where people may offer you cigarettes.
30	Strategy		Gaining a few extra kilograms after stop smoking is normal. Eat healthy and exercise can prevent most of this weight gain.
31	Encourage		Can you see yourself as a nonsmoker? Trust yourself. You can make it happen.
32	Encourage	Participant indicated still smoking during the 4-week call	Stop smoking is difficult for some people. Let's keep trying. Call the Quitline if you are ready to choose a quit date.
		Participant indicated not smoking during the 4-week call	Congratulations on your progress! Keep your great work. We believe in you.
33	Strategy		If you are in a bad mood, talk about it with the Quitline counsellor or someone who supports you. Remember, your feelings matter.
34	Strategy		When you want to have just one cigarette, don’t think it's just one cigarette. Most people start regular smoking again after "just having one".
35	Encourage		Stay positive. Do not let things get you down. Your journey to a smokefree life might be a struggle, but looking back it will be well worth it.

37	Strategy		Don't let your friends smoke around you. Ask them to smoke outside or you can hang out with them in non-smoking places.
38	Encourage		Value your future. No matter when you quit, you are adding years to your life. You will not regret this.
40	Strategy		If you gain a lot of weight, go to see a doctor and seek medical advice.
42	Encourage		After you stop smoking, your lungs begin to improve and your heart attack risk begins to drop
44	Strategy		Practice in your head scenarios that might cause you to slip. Remember, do think it's just one cigarettes.
45	Admin		If you smoke again, call the Quitline at 1800 6276 to discuss the next step. Don't feel embarassed. We want to help you.
47	Encourage		Can you feel it? Urges are getting weaker and less frequent over time.
49	Encourage		Do you know how much money you spend on cigarettes? Think about what else you could do with that money.
51	Admin		We are sending less texts. But we are still here to help you.
53	Strategy		How well did your coping strategies work? Talk to the Quitline counsellor if your strategies were not helpful.
55	Encourage		Cigarettes never solved a problem for you. You did it yourself. You can do great things, so keep thinking positively
58	Encourage		There are so many benefits to being smokefree. What do you look forward to the most?
60	Strategy		No one smokes inside your house or inside your car. Anyone who wants to smoke should go outside.
62	Admin		Call the Quitline at 1800 6276 if you start smoking again. Our counsellor will discuss with you what we can do for you.
65	Strategy		How have you been feeling? Talk to your family or a friend if you are in a bad mood.
68	Encourage		You and your family are becoming healthier after you stop smoking. It's well worth it. Hang on to it.
72	Admin		Don't forget that you can call the Quitline at 1800 6276 if you need assistance.

76	Strategy		Don't forget your strategies for urges and difficult situations. Remind yourself and practice in your mind.
80	Encourage		Do you feel more comfortable and more confident after stop smoking? Feel proud of yourself for doing so much.
85	Admin		This is the last text. Good luck. You can still call the Quitline if you need support

Supplementary Table S2. Text message schedule around the target quit date

Day	SMS type	SMS content
1 day before	Strategy	Tomorrow is the day, you can do it and we are here to help. Review your coping strategies again.
Quit date	Admin	It's time to stop smoking. Call the quitline at 1800 6276 if you need any help.
1 day after	Strategy	Cravings to smoke only last for a few minutes. Take a quick walk or do a short exercise when you want to smoke.
2 days after	Strategy	Keep some sweet snacks in your purse or pocket. Take the snack instead of a cigarette next time you have a craving.
3 days after	Strategy	Avoid drink alcohol in the first 2 weeks will be helpful for managing your smoking.
4 days after	Strategy	Stress and anger are smoking triggers. If you're feeling stressed or upset. Call the quitline to get extra help. Or talk to your family or a friend.
5 days after	Encourage	"It always seems impossible until it is done." Never give up and don't be discouraged.
6 days after	Strategy	When you go out, choose non-smoking venues like the movies. This will help reduce your urges.
7 days after	Encourage	1 week smokefree! Do not look back now. Mark your calendar and do something special today to celebrate this milestone!

Appendix 3. Semi-structured interview guide for the VCAPS3 qualitative sub-study

Instructions and questions for the interview

Introduction and warm-up

Introducing yourself to the participant and explain the purpose of this interview. Remind the participant that the conversation will be audiotaped but their identification will remain confidential. During ice-breaking, the interviewer is suggested to talk about the participant's general health condition.

1. *Could you tell me about your health condition, particularly about your breathing?*

   Secondary questions and probes:

   a. How did you manage your disease before the study? How did you get treatment for your diseases before? How did you feel about it?

   c. How did you know about this study? Why did you decide to participate in the study?

Main questions

2. *How did you feel about the doctor's explanation about your lung problem?*

   Secondary questions and probes:

   a. Could you tell me what your lung disease is, according to what you have learned from the doctor?

   b. Could you describe to me what is said in the Chronic Respiratory Disease Management Plan? How have you been using it?

3. *How have you been using Symbicort since recruitment?*

Secondary questions and probes:

a. How do you find the pharmacist's instruction to use Symbicort?

b. Can you tell me if you have any difficulties to use Symbicort as suggested by the doctor? What can we do to prevent or reduce the troubles?

4. *How do you feel about the as-needed treatment?*

Secondary questions and probes:

What is good/not so good about it?

5. *How have you been feeling about your health since study recruitment?*

Secondary questions and probes:

a. How have your respiratory symptoms changed after using the medicine?

b. Have you ever had any flare-up after recruitment? What happened?

6. *What would you do if you did not feel comfortable with your respiratory condition?*

Secondary questions and probes:

a. What do you think about going to a local pharmacy for extra medicines?

b. Would you go to other hospital/doctor, instead of the original clinic, for check-up? If so, why?

7. *What do you do when you feel good and stable with your respiratory disease?*

Secondary questions and probes:

a. What might prevent you from coming back to the clinic for follow-up assessment?

b. If you could choose, do you prefer a regular follow-up or do you want to come back only when you fell ill? And why did you choose so?

8. *There have been some questionnaires that you were asked by our colleagues via phone*

calls. How do you find those questions?

Secondary questions and probes:

a. Were there questions difficult to understand or respond? Could you give me an example?

9. *How do your family or friends influence your disease management?*

Secondary questions and probes:

a. How do your family members (spouse, children) say about your disease and treatment? How do they support your treatment? Who takes you to the hospital?

b. Do you know any friend who has the same disease? What do you talk about the disease and the treatment?

Closing questions

The interviewee should be encouraged to express anything they would like to say about their experience in this study before ending the conversation.

10. *Could you tell me more about your experience in the study, something that we have not discussed?*

Thank and remind the participant about confidential nature.